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Association between maternal mRNA covid-19 vaccination in early pregnancy and major congenital anomalies in offspring: population based cohort study with sibling matched analysis

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ABSTRACT

OBJECTIVE To examine the association between maternal mRNA covid-19 vaccination during the first trimester of pregnancy and the prevalence of major congenital anomalies in offspring.

DESIGN Population based cohort study with sibling matched analysis.

SETTING Multiple health administrative databases, linked and analysed at ICES, an independent, non-profit research institute that collects and analyses healthcare and demographic data, Ontario, Canada, from 16 October 2021 to 1 May 2023.

POPULATION 174 296 singleton live births >20 weeks' gestation with an expected birth date between 16 October 2021 and 1 May 2023: 34 181 (20%) born to mothers who received one or two doses of an mRNA covid-19 vaccine in the first trimester and 34 951 (20%) born to mothers who did not receive a vaccine before or during pregnancy. The sibling matched analysis included 13 312 infants exposed to a covid-19 vaccine in the first trimester and 15 089 matched older siblings with the same mother, with an expected birth date after 16 October 2016 and no reported in utero exposure to a covid-19 vaccine.

MAIN OUTCOME MEASURES Major congenital anomalies, overall and grouped by specific organ systems, diagnosed within 28 days of birth.

RESULTS Major congenital anomalies were present in 832 (24.3 per 1000 live births) infants exposed to an mRNA covid-19 vaccine in the first trimester compared with 927 (26.5 per 1000 live births) infants not exposed to a vaccine, resulting in an adjusted prevalence ratio of 0.89 (95% confidence interval (CI) 0.79 to 1.01). Major congenital anomalies were present in 283 (21.3 per 1000 live births) and 343 (22.7 per 1000 live births) infants exposed to an mRNA covid-19 vaccine in the first trimester and their older siblings not exposed to a vaccine, respectively (adjusted prevalence ratio 0.91, 95% CI 0.77 to 1.07). First trimester vaccination was not associated with an increase in major congenital anomalies grouped by specific organ system in the primary or sibling matched analyses. Results were similar across a range of subgroup and sensitivity analyses.

CONCLUSIONS In this large population based cohort study and sibling matched analysis, mRNA covid-19 vaccination during the first trimester of pregnancy was not associated with an increase in major congenital anomalies in offspring, overall or grouped by organ system.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Evidence on the prevalence of congenital anomalies after maternal covid-19 vaccination during pregnancy is limited and most studies have important methodological limitations

WHAT THIS STUDY ADDS

⇒ No increase was found in the prevalence of major congenital anomalies in infants exposed to an mRNA covid-19 vaccine in the first trimester compared with infants not exposed to the vaccine or with matched siblings

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ The findings of the study can inform evidenced based decision making on the benefits and risks of maternal covid-19 vaccination during pregnancy

⇒ Continued monitoring to provide more precise estimates for rare organ system anomalies is needed

Introduction

Physiological and immunological changes during pregnancy increase the risk of severe covid-19 disease compared with non-pregnant women of reproductive age, particularly when infection is acquired in the later stages of pregnancy.[1–5] Covid-19 disease during pregnancy has also been associated with increased rates of fetal and neonatal morbidity and mortality.[4–6] Maternal covid-19 vaccination during pregnancy has been shown to protect mothers[2 7] and their newborn infants[8 9] from severe infection. Hence covid-19 vaccination is recommended at any stage of pregnancy in Canada[10–12] and in many countries worldwide.[13–16]

Multiple population based epidemiological studies have found no increase in adverse perinatal or newborn outcomes after maternal covid-19 vaccination during pregnancy, such as spontaneous abortion,[17–19] stillbirth,[20–22] preterm birth,[20–23] and neonatal morbidity and mortality.[22–25] Evidence on the prevalence of congenital anomalies after maternal covid-19 vaccination during pregnancy is more limited and most studies have important

methodological limitations.[23 26–34] For example, most studies were not large enough to detect a clinically important increase in the prevalence of major congenital anomalies,[23 26–33] which generally affect only 2-3% of newborn infants.[35] Definitions of congenital anomaly outcomes have varied across studies,[23 26–34] and only two studies[23 34] so far have examined congenital anomalies in specific organs. Several studies did not restrict the exposure period to early pregnancy,[26 27 31] when fetal organogenesis occurs. Although some studies adjusted for confounders, such as maternal age, ethnic group, comorbidity, and income,[23 31–34] none has considered confounding by familial factors (ie, shared genetic, environmental, and behavioural factors).

In this study, we examined the association between maternal vaccination with an mRNA covid-19 vaccine during early pregnancy and major congenital anomalies in offspring. This large population based cohort included >34 000 infants exposed to an mRNA covid-19 vaccine in the first trimester. To minimise the effect of intrafamilial confounding, we used matched siblings not exposed to the vaccine as an additional comparator group.

Methods

We followed guidance for conducting studies on congenital anomalies in offspring of mothers who receive a vaccine during pregnancy[36] and reporting observational studies based on routinely collected health data.[37]

Study design, setting, and population

We performed a population based retrospective cohort study and sibling matched analysis in Ontario, Canada's most populous province with about 15.1 million residents[38] and 140 000 live births[39] each year. The primary cohort included singleton live births >20 weeks' gestation with an expected birth date between 16 October 2021 and 1 May 2023. We used the expected birth date rather than the actual birth date to prevent overselection of preterm births, and thus congenital anomalies, near the end of the study period. For the sibling matched analysis, we included older siblings with the same mother who were not exposed to the covid-19 vaccine in utero and who had an expected birth date after 16 October 2016. We excluded infants with incomplete birth records or records that could not be linked to databases, infants of mothers who were not continuously eligible for Ontario health insurance during pregnancy, infants of mothers aged <12 or >50 years, infants with chromosomal anomalies, congenital toxoplasmosis, other infections (syphilis, varicella zoster, or parvovirus B19), rubella, cytomegalovirus, and herpes infections, and infants with missing covariates (0.5%). We also excluded infants of mothers who received a non-mRNA covid-19 vaccine before or during pregnancy.

Sources of data

We used multiple health administrative databases that were linked with unique coded identifiers and analysed at ICES, an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyse healthcare and demographic data, without consent, for health system evaluation and improvement. Online supplemental table 1 provides details on the databases.

We identified maternal-newborn pairs from the MOMBABY database. The MOMBABY database has deterministically linked hospital delivery records of mothers and newborns from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD).[40] Hospital births represent >98% of births in Ontario,[41] and >99% of hospital live birth records are successfully linked in the MOMBABY.[40]

Exposure

Ontario's covid-19 vaccine programme began in December 2020 and pregnant women were designated as a priority group for the primary vaccine series in April 2021. Owing to constraints in the supply of vaccine, some people received a heterologous mRNA vaccine series, and the recommended interval between the first and second doses of the primary series varied from three to 16 weeks. In August 2021, people with immunosuppression became eligible for a third vaccine dose as part of an extended primary series, and eligibility for a third dose (first booster dose) expanded over the autumn of 2021 to include all adults by December 2021. A fourth dose (second booster dose) was available to adults at high risk in April 2022, and for all adults in July 2022. Complete information on all covid-19 vaccinations in Ontario is entered into the centralised vaccine registry, COVaxON (online supplemental table 1).

The primary exposure in this study was receipt of an mRNA covid-19 vaccine (Pfizer-BioNTech or Moderna) between 14 days after the date of the last menstrual period and 14 weeks' gestation (referred to here as the first trimester of pregnancy). The date of the last menstrual period was calculated by subtracting gestational age from the birth date. Gestational age is determined with early ultrasound for >95% of births in Ontario.[42] Infants were considered exposed if their mother received any mRNA vaccine dose (first, second, third, or fourth) and any number of vaccinations (one or two) during the first trimester; mothers of infants in the primary exposure group could also have received a vaccine before conception and during the second and third trimesters of pregnancy. Infants of mothers with no reported covid-19 vaccination before conception or at any

point during pregnancy were the unexposed comparison group in the primary analysis. Older siblings of infants exposed to an mRNA covid-19 vaccine in the first trimester who had no reported in utero exposure to a covid-19 vaccine was the comparison group in the sibling matched analysis.

Outcomes

We identified major congenital anomalies (ie, those that are medically, surgically, or cosmetically significant),[43] diagnosed during the birth admission or ≤28 days after birth, based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision, Canada (ICD-10-CA) codes in the CIHI-DAD and Same Day Surgery Database, which contain diagnostic codes for all hospital discharges and day surgeries in Canada, respectively. We classified major congenital anomalies overall as a composite outcome and grouped by specific organ systems with the algorithm from the Metropolitan Atlanta Congenital Defects Programme. The Metropolitan Atlanta Congenital Defects Programme is a population based surveillance system established by the US Centers for Disease Control and Prevention (details provided in online supplemental tables 2 and 3).[43–45] Infants with more than one major congenital anomaly contributed to the composite outcome only once, whereas infants with major congenital anomalies in multiple organ systems contributed to the prevalence for each relevant organ system.

Statistical analysis

We used inverse probability of treatment weighting to control for confounding.[46] We derived weights from a propensity score representing the predicted probability of receiving at least one covid-19 vaccine dose during the first trimester of pregnancy, estimated with logistic regression.[46] Covariates included: month and year of conception; maternal age; parity; use of assisted reproductive technology; pre-existing maternal medical conditions (asthma, hypertension, heart disease, diabetes mellitus, epilepsy, autoimmune disease, and immunosuppression); maternal influenza vaccination during the 2019-20 or 2020-21 influenza seasons (as a proxy for health behaviour); maternal outpatient opioid prescription during the first trimester of pregnancy[44]; neighbourhood level income, divided by quintiles (groups 1-5, with group 1 being the lowest income); neighbourhood level proportion of the population who self-identify as a visible minority, divided by quintiles (groups 1-5); Public Health Unit region; and rural residence. We computed stabilised weights to reduce variability induced by extreme weights.[46] We assessed the balance of covariate distributions with standardised differences, with values ≥0.10 indicating potentially clinically important imbalance.[46]

In the primary analysis, we estimated crude and inverse probability of treatment weighted prevalence ratios and corresponding 95% confidence intervals (CIs) for congenital anomalies in infants of mothers who received at least one dose of a covid-19 vaccine during the first trimester of pregnancy compared with infants of mothers who did not receive a covid-19 vaccine before conception or at any time during pregnancy. We fitted weighted log binomial generalised linear models and used 200 bootstrapped iterations to estimate the standard errors, and used these to calculate 95% CIs.[47]

In the sibling matched analysis, we calculated crude and adjusted prevalence ratios and 95% CIs with modified Poisson regression, estimated with generalised estimating equation methods that accounted for clustering within the same mother. We included maternal age as a covariate in the adjusted analyses.

Subgroup and sensitivity analyses

To test the robustness of the results, we conducted a range of subgroup and sensitivity analyses with the primary analysis cohort: we assessed whether the prevalence of major congenital anomalies differed by the type of vaccine (Pfizer-BioNTech or Moderna); we performed a dose-response analysis (one or two doses of vaccine during the first trimester of pregnancy); to reduce the potential for misclassification of exposure because of inaccurate estimates of gestational age, we extended the exposure window to 30 days before conception to 20 weeks' gestation;[36] because infants with congenital anomalies are more likely to be born preterm and anomalies might be discovered in preterm infants that would not have been diagnosed in term infants (ie, because of longer hospital admissions or more thorough examinations),[48] we repeated the primary analysis restricting the cohort to term infants; to test for effect modification by infant sex, we repeated the analysis separately for female and male infants; although covid-19 is not known to be teratogenic, data are limited[34 49] and therefore we excluded infants of mothers with a reported SARS-CoV-2 infection during the first trimester of pregnancy; to increase reporting of comorbidities before pregnancy, we excluded infants of mothers who were not continuously eligible for Ontario health insurance during the year preceding the estimated date of the last menstrual period; we performed an analysis with infants of mothers who received their first dose of covid-19 vaccine during the second or third trimester of pregnancy as the unexposed comparator group, predicated on an assumption that women who received a vaccine later in pregnancy would share many of the unmeasured confounders related to health behaviour with those who received the vaccine during the first trimester, but the exposure would be outside the sensitive window of organogenesis and thus not causally related to congenital anomalies; we evaluated the relation between maternal covid-19 vaccination

Table 1 | Unweighted distribution of baseline characteristics of primary cohort by maternal covid-19 vaccination status: ≥1 covid-19 vaccine dose during the first trimester of pregnancy (maternal covid-19 vaccination) or no covid-19 vaccination before or during pregnancy (no maternal covid-19 vaccination)

Variables	Maternal covid-19 vaccination (n=34 181)	No maternal covid-19 vaccination (n=34 951)	Absolute standardised difference*
Mother's age (years):			
<25	1744 (5.1)	4853 (13.9)	0.30
25-29	6793 (19.9)	10 056 (28.8)	0.21
30-34	14 622 (42.8)	11 874 (34.0)	0.18
35-39	9241 (27.0)	6516 (18.6)	0.20
≥40	1781 (5.2)	1652 (4.7)	0.02
Mean±SD (years)	32.35±4.60	30.48±5.39	0.37
Caesarean delivery	11 296 (33.0)	10 577 (30.3)	0.06
Nulliparous	15 990 (46.8)	14 123 (40.4)	0.13
Use of assisted reproductive technology	1496 (4.4)	850 (2.4)	0.11
Maternal comorbidities before pregnancy:			
Diabetes mellitus	890 (2.6)	707 (2.0)	0.04
Hypertension	795 (2.3)	617 (1.8)	0.04
Heart disease	220 (0.6)	173 (0.5)	0.02
Asthma	5995 (17.5)	5832 (16.7)	0.02
Epilepsy	1007 (2.9)	1223 (3.5)	0.03
Autoimmune disease	879 (2.6)	654 (1.9)	0.05
Maternal immunosuppression†	393 (1.1)	472 (1.4)	0.02
Maternal opioid prescription during first trimester‡	339 (1.0)	658 (1.9)	0.07
Pregnancy complications:			
Gestational diabetes	3622 (10.6)	3064 (8.8)	0.06
Gestational hypertension	1761 (5.2)	1466 (4.2)	0.05
Pre-eclampsia	799 (2.3)	627 (1.8)	0.04
Eclampsia	12 (0.0)	20 (0.1)	0.01
Prenatal care index:§			
No care¶	2984 (8.7)	4220 (12.1)	0.11
Inadequate	7162 (21.0)	9540 (27.3)	0.15
Intermediate	18 476 (54.1)	16 783 (48.0)	0.12
Adequate	5302 (15.5)	4176 (11.9)	0.1
Intensive	257 (0.8)	232 (0.7)	0.01
Maternal influenza vaccination**	11 712 (34.3)	2767 (7.9)	0.68
Positive maternal SARS-CoV-2 polymerase chain reaction test result during first trimester	494 (1.4)	591 (1.7)	0.02
Neighbourhood income (divided into groups by quintiles):††‡‡			
1 (lowest)	5724 (16.7)	9128 (26.1)	0.23
2	6615 (19.4)	7763 (22.2)	0.07
3	7543 (22.1)	7411 (21.2)	0.02
4	7600 (22.2)	6235 (17.8)	0.11
5 (highest)	6699 (19.6)	4414 (12.6)	0.19
Visible minority (divided into groups by quintiles):††§§			
1 (lowest)	4377 (12.8)	6366 (18.2)	0.15
2	5487 (16.1)	5697 (16.3)	0.01
3	6349 (18.6)	5291 (15.1)	0.09
4	8331 (24.4)	7147 (20.4)	0.09
5 (highest)	9637 (28.2)	10 450 (29.9)	0.04
Public Health Unit region:			
Central East	1972 (5.8)	2479 (7.1)	0.05
Central West	6985 (20.4)	7443 (21.3)	0.02
Durham	2053 (6.0)	1922 (5.5)	0.02
Eastern	2156 (6.3)	2151 (6.2)	0.01

Continued

Table 1 Continued

Variables	Maternal covid-19 vaccination (n=34 181)	No maternal covid-19 vaccination (n=34 951)	Absolute standardised difference*
Northern	1600 (4.7)	1954 (5.6)	0.04
Ottawa	3028 (8.9)	1657 (4.7)	0.16
Peel	3265 (9.6)	4181 (12.0)	0.08
South West	3799 (11.1)	5468 (15.6)	0.13
Toronto	6871 (20.1)	5683 (16.3)	0.10
York	2452 (7.2)	2013 (5.8)	0.06
Rural residence¶¶	2939 (8.6)	4684 (13.4)	0.15

Data are number (%) unless indicated otherwise.

*Values ≥0.10 indicate a potentially clinically important difference in the distribution between groups.

†Defined as solid organ or stem cell transplant, active cancer, sickle cell anaemia, HIV infection, immunosuppressing treatments, and other immune system disorders, derived from the Johns Hopkins ACG System, version 10.0.1 second quarter release expanded diagnostic cluster for disorders of the immune system.

‡Includes outpatient prescriptions for buprenorphine, codeine, fentanyl, hydromorphone, pethidine, methadone, morphine, oxycodone, and tramadol.

§Adequacy of prenatal care characterised with the Revised-Graduated Prenatal Care Utilisation Index (R-GINDEX).[62]

¶Includes prenatal care under a midwife.

**During the 2019-20 or 2020-21 influenza seasons, or both.

††Dissemination area (400-700 residents) level variable.

‡‡Household income group has variable cut-off values in different cities and census areas to account for cost of living. A dissemination area in group 1 means the area is among the lowest 20% of dissemination areas in its city by income.

§§Percentage of people in the area who self-identified as a visible minority. Census counts for people are randomly rounded up or down to the nearest number divisible by 5, which causes some minor imprecision.

¶¶<10 000 residents.

during the first trimester of pregnancy and chromosomal anomalies as a negative tracer outcome (ie, no association expected); because some congenital anomalies might not be evident during the first month of life,[50 51] we extended the determination period to six months for infants who had reached six months of age by the end of the study; because a case definition based on one diagnostic code might have imperfect specificity, we redefined cases as infants with two or more unique major congenital anomaly diagnostic codes recorded during the birth admission or in the first 28 days of life; we used overlap weights based on the propensity score because this approach creates exact covariate balance between groups and makes inference about the population whose propensity score is close to 0.5[52]; and lastly, because the cohort was restricted to live births, we performed a quantitative bias analysis to examine the potential effect of missing pregnancies ending in stillbirth and spontaneous or therapeutic abortion[53 54] (online supplemental methods).

We interpreted results based on an evaluation of: the direction and magnitude of adjusted prevalence ratios, regardless of whether the 95% CIs included one; the precision of estimates together with the extent to which the upper limit of the 95% CIs suggested low compatibility with a moderate to strong increased prevalence of major congenital anomalies in infants exposed to a vaccine; and the consistency of results across subgroup and sensitivity analyses.[55–57] We performed all analyses with SAS, version 9.4.

Patient and public involvement

We did not involve patients or the public in the design, conduct, reporting, or dissemination plans of our study due to time limitations. It was not possible to inform study participants of the results because we used de-identified data. Results will be disseminated through this publication and legacy and social media.

Results

Primary analysis

Study population

The source population was 205 481 live births >20 weeks' gestation in Ontario with an expected birth date between 16 October 2021 and 1 May 2023. After applying our exclusion criteria, 174 296 infants remained: 34 181 (20%) infants born to mothers who received a vaccine in the first trimester and 34 951 (20%) infants born to mothers who did not receive any covid-19 vaccine before or during pregnancy (online supplemental figure 1).

Compared with mothers who were not vaccinated before or during pregnancy, we found that those who received an mRNA covid-19 vaccine during the first trimester were more likely to be aged >30 years, nulliparous, users of assisted reproductive technology, recipients of the influenza vaccine during either of the two previous influenza seasons, and residents of urban areas and areas with higher incomes (table 1). Figure 1 shows the unweighted distributions of estimated conception dates and birth dates in infants exposed to a covid-19 vaccine in the first trimester compared with infants not exposed to a vaccine. After propensity score weighting, measured baseline covariates were well balanced between groups, with all standardised differences <0.10 and with adequate overlap in weighted propensity score distributions (online supplemental figures 2 and 3).

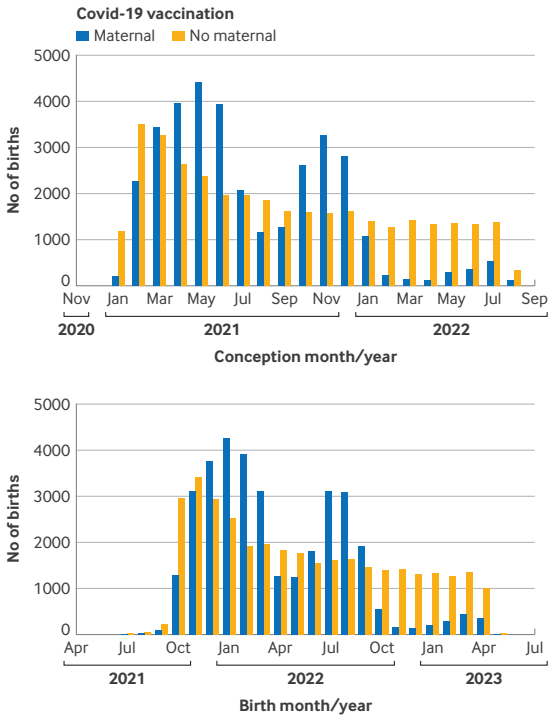

Figure 1 | Maternal covid-19 vaccination during the first trimester of pregnancy compared with no maternal covid-19 vaccination before conception or during pregnancy. Bottom panel=birth month and year by maternal vaccination status. Top panel=conception month and year by maternal vaccination status

Vaccination characteristics

Among 34 181 mothers who received at least one dose of a covid-19 vaccine during the first trimester of pregnancy, 29 831 (87%) received one dose and 4350 (13%) received two doses during the first trimester (table 2). The initial vaccine dose during the first trimester was the first dose, second dose, and third (or higher) dose for 14 020 (41%), 9698 (28%), and 10 460 (31%) mothers, respectively. Most mothers (23 345; 68%) received a Pfizer-BioNTech vaccine for all vaccine doses during the first trimester.

Table 2 | Vaccination characteristics among mothers who received ≥1 dose of covid-19 vaccine during the first trimester of pregnancy

Characteristics	No of mothers (n=34 181)
No of doses of vaccine:	
1	29 831 (87.3)
2	4350 (12.7)
Dose number of first vaccination:	
1	14 020 (41.0)
2	9698 (28.4)
3	9369 (27.4)
4	1094 (3.2)
Type of vaccine received:	
Pfizer-BioNTech only	23 345 (68.3)
Moderna only	10 102 (29.6)
Heterologous mRNA covid-19 vaccine doses	734 (2.2)

Data are number (%).

Congenital anomalies

In infants exposed to a covid-19 vaccine in the first trimester, 832 (24.3 per 1000 live births) had major congenital anomalies compared with 927 (26.5 per 1000 live births) in infants not exposed to a vaccine, resulting in a crude prevalence ratio of 0.92 (95% CI 0.84 to 1.01). Results were similar after propensity score weighting (adjusted prevalence ratio 0.89, 0.79 to 1.01). Covid-19 vaccination in the first trimester was not associated with increases in the prevalence of major congenital anomalies grouped by organ system, although the small number of cases and resulting wide 95% CIs for some organ system groups (eg, oral clefts and respiratory) limits the certainty of estimates (table 3).

Sibling analysis

The sibling matched cohort included 13 312 infants exposed to a covid-19 vaccine in the first trimester and 15 089 siblings not exposed to a vaccine (online supplemental figure 4). Table 4 shows the baseline characteristics. We found no increase in the prevalence of major congenital anomalies overall in infants exposed to a covid-19 vaccine in the first trimester compared with their siblings who were not exposed to a vaccine (adjusted prevalence ratio 0.91, 95% CI 0.77 to 1.07), or when grouped by organ system, although group estimates for several organ systems lacked precision because of the small number of infants (table 5).

Subgroup and sensitivity analyses

Results of subgroup and sensitivity analyses were, in general, consistent with the primary analysis (table 6). The adjusted prevalence ratios of major congenital anomalies were similar in separate analyses of infants of mothers who received only Pfizer-BioNTech or only Moderna during the first trimester of pregnancy (adjusted prevalence ratio 0.91, 95% CI 0.80 to 1.04 *v* 0.88, 0.65 to 1.21, respectively). We found no evidence of a dose-response relation (one dose: adjusted prevalence ratio 0.88, 95% CI 0.78 to 0.99; two doses: adjusted prevalence ratio 1.04, 0.67 to 1.62). Results were mostly unchanged when the primary exposure window was extended to 30 days before conception to 20 weeks' gestation (adjusted prevalence ratio 0.88, 0.80 to 0.97). The prevalence of congenital anomalies was lower when the cohort was restricted to term infants (19.5 and 21.0 per 1000 live births for infants exposed and not exposed, respectively), but the adjusted prevalence ratio was consistent with that of the full cohort (adjusted prevalence ratio 0.90, 95% CI 0.79 to 1.03).

Table 3 | Prevalence ratios for major congenital anomalies in infants exposed to maternal covid-19 vaccination during the first trimester of pregnancy compared with infants not exposed to a vaccine

Congenital anomaly	No of infants (prevalence per 1000 live births) exposed to covid-19 vaccine (n=34 181)*	No of infants (prevalence per 1000 live births) not exposed to covid-19 vaccine (n=34 951)*	Unadjusted prevalence ratio (95% CI)	Adjusted prevalence ratio (95% CI)†
Major	832 (24.3)	927 (26.5)	0.92 (0.84 to 1.01)	0.89 (0.79 to 1.01)
Organ system:				
Cardiovascular	295 (8.6)	331 (9.5)	0.91 (0.78 to 1.07)	0.95 (0.80 to 1.13)
Digestive system	65 (1.9)	80 (2.3)	0.83 (0.60 to 1.15)	0.71 (0.44 to 1.13)
Musculoskeletal	104 (3.0)	164 (4.7)	0.65 (0.51 to 0.83)	0.69 (0.52 to 0.93)
Genital	92 (2.7)	77 (2.2)	1.22 (0.90 to 1.65)	1.19 (0.85 to 1.66)
Urinary	254 (7.4)	235 (6.7)	1.11 (0.93 to 1.32)	1.03 (0.83 to 1.28)
Central nervous system	57 (1.7)	87 (2.5)	0.67 (0.48 to 0.94)	0.56 (0.37 to 0.87)
Oral clefts	28 (0.8)	48 (1.4)	0.60 (0.37 to 0.95)	0.99 (0.45 to 2.16)
Respiratory	23 (0.7)	19 (0.5)	1.23 (0.67 to 2.27)	1.07 (0.50 to 2.28)

*Infants exposed to ≥1 dose of covid-19 vaccine during the first trimester of pregnancy or not exposed to any dose of covid-19 vaccine.

†Adjusted with stabilised inverse probability of treatment weights. Probability weights from a propensity score represented the predicted probability of receiving ≥1 doses of covid-19 vaccine during the first trimester of pregnancy compared with no maternal covid-19 vaccination before conception or at any time during pregnancy.

CI, confidence interval.

We found no evidence of effect modification by the sex of the infant (female infants: adjusted prevalence ratio 0.85, 95% CI 0.68 to 1.06; male infants: adjusted prevalence ratio 0.92, 0.80 to 1.06). Results were unchanged when we excluded infants of mothers with a reported SARS-CoV-2 infection during the first trimester of pregnancy or infants of mothers who were not continuously eligible for Ontario health insurance during the year preceding pregnancy (adjusted prevalence ratio 0.89, 95% CI 0.79 to 1.01 and 0.89, 0.79 to 1.00, respectively). Comparison of infants exposed to a vaccine in the first trimester with infants of mothers who were vaccinated in the second or third trimester gave generally similar results (adjusted prevalence ratio 0.95, 0.73 to 1.25). Maternal vaccination in the first trimester of pregnancy was not associated with chromosomal anomalies (ie, negative tracer outcome, adjusted prevalence ratio 0.65, 0.38 to 1.10).

At the end of the study, 32 736 (96%) infants exposed to a covid-19 vaccine in the first trimester and 28 571 (83%) infants not exposed were aged at least six months. In this subgroup, 89% of major congenital anomalies overall and 64-98% of congenital anomalies grouped by organ system were diagnosed within the first 28 days of life (online supplemental table 4). Adjusted prevalence ratios for major congenital anomalies were almost identical at 28 days and six months in this subgroup (adjusted prevalence ratio 0.90, 95% CI 0.81 to 0.99 and 0.89, 0.81 to 0.99, respectively). Multiple congenital anomalies were present in 199 (5.9 per 1000 live births) and 266 (7.8 per 1000 live births) infants exposed and not exposed to the vaccine, respectively. First trimester vaccination was not associated with an increased prevalence of infants with multiple congenital anomalies (adjusted prevalence ratio 0.78, 95% CI 0.63 to 0.98). The use of overlap weights produced estimates that were consistent with the primary analysis (adjusted prevalence ratio 0.89, 95% CI 0.80 to 0.99).

Online supplemental figure 5 shows the analysis of the potential effect of missing non-live births. Under the most extreme scenario modelled (ie, a probability of live birth among pregnancies not exposed to a vaccine with and without a congenital anomaly of 55% and 80%, respectively, and a 20% decrease in the probability of a live birth in pregnancies exposed to a vaccine in the first trimester), the point estimate for major congenital anomalies would shift from 0.89 to 1.05.

Discussion

Principal findings

In this large population based study of 34 181 infants born to mothers who received one or two doses of an mRNA covid-19 vaccine in the first trimester of pregnancy, we found no association between vaccination during early pregnancy and the birth prevalence of major congenital anomalies, overall or when grouped by specific organ systems, in the primary analysis. The results were similar in the sibling matched analysis and across multiple subgroup and sensitivity analyses.

Comparison with other studies

Our results support previous findings of no association between covid-19 vaccination during pregnancy and major congenital anomalies. At least four studies have included >1000 infants exposed to covid-19 vaccines during early pregnancy.[23 32–34] An Israeli population based cohort study of 2021 live births exposed to BNT162b2 in the first trimester of pregnancy reported no association between maternal vaccination and any congenital anomaly

Table 4 | Distribution of baseline characteristics of sibling matched cohort

Variable	Maternal covid-19 vaccination group (n=13 312)*	Matched siblings (n=15 089)*	Absolute standardised difference†
Mother's age (years):			
<25	473 (3.6)	1504 (10.0)	0.26
25-29	2026 (15.2)	4800 (31.8)	0.40
30-34	5822 (43.7)	6790 (45.0)	0.03
35-39	4344 (32.6)	1873 (12.4)	0.50
≥40	647 (4.9)	122 (0.8)	0.25
Mean±SD (years)	33.00±4.23	30.04±4.21	0.70
Estimated year of conception:			
2016	0 (0.0)	1691 (11.2)	0.50
2017	0 (0.0)	2682 (17.8)	0.66
2018	0 (0.0)	3970 (26.3)	0.85
2019	0 (0.0)	5098 (33.8)	1.01
2020	0 (0.0)	1639 (10.9)	0.49
2021	12 270 (92.2)	9 (0.1)	4.83
2022	1042 (7.8)	0 (0.0)	0.41
Caesarean delivery	3925 (29.5)	3994 (26.5)	0.07
Use of reproductive technology	384 (2.9)	580 (3.8)	0.05
Maternal opioid prescription during first trimester‡	136 (1.0)	167 (1.1)	0.01
Pregnancy complications:			
Gestational diabetes	1347 (10.1)	1243 (8.2)	0.07
Gestational hypertension	540 (4.1)	718 (4.8)	0.03
Pre-eclampsia	201 (1.5)	344 (2.3)	0.06
Eclampsia	≤5 (0.0)**	≤5 (0.0)**	0
Prenatal care index:§			
No care¶	1367 (10.3)	987 (6.5)	0.13
Inadequate	2813 (21.1)	2749 (18.2)	0.07
Intermediate	7080 (53.2)	6857 (45.4)	0.16
Adequate	1960 (14.7)	4218 (28.0)	0.33
Intensive	92 (0.7)	278 (1.8)	0.10

Data are number (%) unless indicated otherwise.

*Infants exposed to ≥1 dose of covid-19 vaccine during the first trimester of pregnancy or matched older siblings with the same mother not exposed to any dose of covid-19 vaccine.

†Values ≥0.10 indicate a potentially clinically important difference in the distribution between groups.

‡Includes outpatient prescriptions for buprenorphine, codeine, fentanyl, hydromorphone, pethidine, methadone, morphine, oxycodone, and tramadol.

§Adequacy of prenatal care was characterised with the Revised-Graduated Prenatal Care Utilisation Index (R-GINDEX).[62]

¶Includes prenatal care under a midwife.

**In accordance with Ontario's privacy legislation, ICES data privacy policy prohibits reporting of non-zero cells with fewer than six observations.

(adjusted relative risk 0.69, 95% CI 0.44 to 1.04) or heart anomalies (adjusted relative risk 0.75, 0.43 to 1.26).[23] Vaccination with an mRNA or adenovirus vector covid-19 vaccine between 30 days before conception and 14 weeks' gestation was not associated with major structural anomalies identified on ultrasonography in a single centre study in the US of 1149 pregnancies exposed to a vaccine (adjusted odds ratio 1.05, 95% CI 0.72 to 1.54).[32] A multicentre Australian cohort study of 2442 infants born to mothers who received an mRNA covid-19 vaccine before 20 weeks' gestation found no increase in major congenital anomalies (adjusted odds ratio 0.80, 0.57 to 1.13).[33] No association was found between covid-19 vaccination (mRNA or adenovirus vector) six weeks before conception to 20 weeks' gestation and major congenital anomalies in a Scottish population based matched cohort study of 6623 pregnancies reaching at least 12 weeks' gestation, exposed to a vaccine (adjusted odds ratio 1.01, 0.83 to 1.24).[34]

Strengths and limitations

Our study overcame many of the limitations of previous studies evaluating the association between covid-19 vaccination during pregnancy and congenital anomalies. We used deterministically linked population based databases in a universal healthcare system, which allowed us to identify all hospital births in Ontario during the study period, limiting potential selection bias. The large study cohort, including >34 000 infants exposed to an mRNA covid-19 vaccine in the first trimester, was of sufficient size to rule out moderate to large increases in the prevalence of major congenital anomalies overall and anomalies grouped by organ system for more

Table 5 | Prevalence ratios for congenital anomalies in infants exposed to maternal covid-19 vaccination during the first trimester of pregnancy compared with matched siblings with the same mother not exposed to the vaccine

Congenital anomaly	No of infants (prevalence per 1000 live births) exposed to covid-19 vaccine (n=13 312)	No of matched siblings (prevalence per 1000 live births) not exposed to covid-19 vaccine (n=15 089)	Unadjusted prevalence ratio (95% CI)	Adjusted prevalence ratio (95% CI)*
Major	283 (21.3)	343 (22.7)	0.93 (0.80 to 1.09)	0.91 (0.77 to 1.07)
Major organ system:				
Cardiovascular	98 (7.4)	115 (7.6)	0.97 (0.74 to 1.26)	0.93 (0.70 to 1.23)
Digestive system	16 (1.2)	26 (1.7)	0.70 (0.37 to 1.30)	0.74 (0.39 to 1.41)
Musculoskeletal	30 (2.3)	58 (3.8)	0.59 (0.38 to 0.91)	0.59 (0.37 to 0.95)
Genital	25 (1.9)	37 (2.5)	0.77 (0.46 to 1.27)	0.63 (0.35 to 1.14)
Urinary	97 (7.3)	93 (6.2)	1.18 (0.89 to 1.56)	1.12 (0.84 to 1.52)
Central nervous system	14 (1.1)	25 (1.7)	0.63 (0.33 to 1.22)	0.73 (0.36 to 1.47)
Oral clefts	10 (0.8)	19 (1.3)	0.61 (0.31 to 1.19)	0.71 (0.36 to 1.43)
Respiratory	15 (1.0)	9 (0.7)	0.68 (0.30 to 1.55)	0.76 (0.36 to 1.59)

*Adjusted for maternal age at birth.
CI, confidence interval.

common organ system groups. Detailed information on vaccinations through a centralised covid-19 vaccine registry minimised the potential for bias from misclassification of exposure. The use of early ultrasound for most births in Ontario assured accurate gestational timing of maternal vaccination and allowed us to restrict the exposure window to the sensitive period of organogenesis.

Our study had some limitations. Firstly, although we adjusted for many potential confounders with propensity score methods and used matched siblings to minimise confounding due to shared genetic and environmental factors within families, we cannot rule out the possibility of residual confounding by characteristics incompletely or not captured in our databases (eg, obesity, smoking, alcohol dependence, drug treatments (except for opioids), or exposure to other potential teratogens). Secondly, we used a period of 28 days for detection of major congenital anomalies, rather than the usual 12 months, to allow for timely analysis. This use of a shorter period for detection will likely have resulted in non-differential under detection of major congenital anomalies that are not evident at birth or shortly after. Our sensitivity analysis suggested that, among infants aged six months by the end of the study, nearly 90% of major congenital anomalies overall were diagnosed during the neonatal period, and we found no increase in the prevalence of congenital anomalies at 28 days or six months in this subgroup. Detection of major congenital anomalies grouped by organ system ranged from 64% (digestive system) to 98% (genital), however, and we could not compare prevalence ratios at two time points because of the small numbers of infants.

Thirdly, we defined the presence of congenital anomalies based on one diagnostic code recorded during the neonatal period, which might be less specific than case findings verified in medical records or approaches that identify congenital anomalies with algorithms that require multiple diagnostic codes, encounters, or data sources to meet the case definition (usually over 12 months). Previous studies, based on case definitions verified in medical records as the gold standard, have found that passive surveillance systems that rely on one diagnostic code capture the overall occurrence of major congenital anomalies well (positive predictive value >93%), but they often fail to identify specific congenital anomalies with high accuracy.[58 59] More restrictive case definition algorithms generally have greater accuracy for specific congenital anomalies but improvements in identifying major congenital anomalies overall are modest (positive predictive value 97.5-99.2% *v* 94.2% for one diagnostic code).[59] Moreover, minimising false positive results is at the expense of completeness of detection, because more restrictive algorithms generally select for infants with severe complications that require more frequent contact with the healthcare system than infants who received a diagnosis during one encounter.[59]

Fourthly, despite including more than twice as many infants exposed to a vaccine as previous studies combined, group estimates for rare organ system anomalies had low precision because of the small numbers of infants with congenital anomalies. Thus although our study rules out large increases in the risk of rare organ system anomalies, we cannot rule out smaller increases. Finally, our analyses were restricted to live births, which could miss associations between first trimester covid-19 vaccination and stillbirths and spontaneous or therapeutic abortions, if any, potentially resulting in live birth bias.[60] Therefore, we explored the effect of this potential bias on the adjusted prevalence ratio estimate for major congenital anomalies and found that changes to the estimate were modest under modelled scenarios. A National Birth Defects Prevention Network Study also that found that restricting to live births had a

Table 6 | Subgroup and sensitivity analyses

Description of subgroup or sensitivity analysis	No/total No of infants (prevalence per 1000 live births) exposed to covid-19 vaccine	No/total No of infants (prevalence per 1000 live births) not exposed to covid-19 vaccine	Unadjusted prevalence ratios (95% CI)	Adjusted prevalence ratios (95% CI)*
Primary analysis†	832/34 181 (24.3)	927/34 951 (26.5)	0.92 (0.84 to 1.01)	0.89 (0.79 to 1.01)
Pfizer-BioNTech ‡	587/23 345 (25.1)	927/34 951 (26.5)	0.95 (0.86 to 1.05)	0.91 (0.80 to 1.04)
Moderna ‡	221/10 102 (21.8)	927/34 951 (26.5)	0.82 (0.71 to 0.95)	0.88 (0.65 to 1.21)
One dose of vaccine during first trimester	730/29 831 (24.5)	927/34 951 (26.5)	0.92 (0.84 to 1.02)	0.88 (0.78 to 0.99)
Two doses of vaccine during first trimester§	101/4332 (23.3)	777/29 361 (26.5)	0.90 (0.74 to 1.11)	1.04 (0.67 to 1.62)
Extended exposure period¶	1 499/62 159 (24.1)	927/34 951 (26.5)	0.91 (0.84 to 0.99)	0.88 (0.80 to 0.97)
Preterm infants excluded	626/32 041 (19.5)	684/32 622 (21.0)	0.93 (0.84 to 1.04)	0.90 (0.79 to 1.03)
Female infants only	299/16 566 (18.0)	360/17 060 (21.1)	0.86 (0.73 to 1.00)	0.85 (0.68 to 1.06)
Male infants only	533/17 615 (30.3)	567/17 891 (31.7)	0.95 (0.85 to 1.07)	0.92 (0.80 to 1.06)
Infants of mothers with a positive SARS-CoV-2 polymerase chain reaction test result in first trimester excluded	817/33 687 (24.3)	910/34 360 (26.5)	0.92 (0.83 to 1.01)	0.89 (0.79 to 1.01)
Infants of mothers not continuously eligible for Ontario health insurance in the year preceding pregnancy excluded	799/32 816 (24.3)	852/31 679 (26.9)	0.91 (0.82 to 1.00)	0.89 (0.79 to 1.00)
Infants of mothers who received first vaccine dose during the second or third trimester of pregnancy as not exposed comparator group	832/34 181 (24.3)	309/13 168 (23.5)	1.04 (0.91 to 1.18)	0.95 (0.73 to 1.25)
Negative tracer outcome**	35/34 230 (1.0)	63/35 022 (1.8)	0.57 (0.37 to 0.86)	0.65 (0.38 to 1.10)
Infants with 6 months of follow-up:				
Major congenital anomalies diagnosed within 28 days of birth	800/32 736 (24.4)	776/28 571 (26.9)	0.91 (0.82 to 1.00)	0.90 (0.81 to 0.99)
Major congenital anomalies diagnosed within 6 months of birth	892/32 736 (27.2)	861/28 571 (30.1)	0.90 (0.82 to 0.99)	0.89 (0.81 to 0.99)
Infants with multiple major congenital anomalies††	199/33 548 (5.9)	266/34 290 (7.8)	0.76 (0.64 to 0.92)	0.78 (0.63 to 0.98)

*Adjusted with stabilised inverse probability of treatment weights. Propensity scores were re-estimated for each subgroup and sensitivity analysis.

†Infants of mothers vaccinated in the first trimester of pregnancy compared with infants of mothers who received no vaccine doses before or during pregnancy.

‡For all doses during the first trimester of pregnancy.

§Infants with an estimated conception date in January 2021 or May-August 2022 were excluded because of insufficient overlap in conception dates between groups.

¶From 30 days before conception to 20 weeks' gestation.

**Chromosomal anomalies.

††Infants with isolated major congenital anomalies (n=1259) were not included in the denominator.

CI, confidence interval.

limited effect on results, except for congenital anomalies with high mortality risks, such as anencephaly, in the context of exposures strongly associated with live birth.[61]

Conclusions

This study adds substantially to the existing literature suggesting no increase in major congenital anomalies among infants of mothers who received an mRNA covid-19 vaccine during the first trimester of pregnancy. Although our study findings are reassuring and can inform evidenced based decision making on the benefits and risks of maternal covid-19 vaccination during pregnancy, continued monitoring to provide more

precise estimates for rare organ system anomalies is needed.

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Ethics approval ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorises ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation, or monitoring of, the allocation of resources to, or planning for all or part of the health system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from research ethics board review. The use of the data in this project is authorised under section 45 and approved by the privacy and legal office of ICES.

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Data availability statement Data may be obtained from a third party and are not publicly available. The dataset from this study is held securely in coded form at ICES. Although legal data sharing agreements between ICES and data providers (eg, healthcare organisations and government) prohibit ICES from making the dataset publicly available, access might be granted to those who meet prespecified criteria for confidential access, available at https://www.ices.on.ca/DAS (email das@ices.on.ca). SJ and JCK had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The full dataset creation plan and underlying analytic code are available from the authors on request, understanding that the computer programmes might rely on coding templates or macros that are unique to ICES and are therefore either inaccessible or might require modification. Correspondence and requests for materials should be addressed to JCK.

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