COVID-19 Vaccination During Pregnancy and Major Structural Birth Defects

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abstract

BACKGROUND AND OBJECTIVES: COVID-19 vaccination is recommended during pregnancy; however, evidence on the prevalence of major structural birth defects born to people vaccinated early in pregnancy (≤20 weeks of gestation) is limited. We compared the prevalence of major structural birth defects by COVID-19 vaccination status and key strata: insurance provider, clinically diagnosed SARS-CoV-2 infection during pregnancy, and concomitant administration of other maternal vaccines. We also compared, head-to-head, the prevalence of birth defects by brand (Moderna mRNA-1273 vs Pfizer-BioNTech BNT162b2).

METHODS: A claims-based cohort study captured pregnancies ending in a live birth among people with an estimated last menstrual period between August 15, 2021, and December 24, 2021. Prevalence ratios comparing birth defects by exposure to COVID-19 vaccines were estimated using binomial regression with inverse probability treatment weights.

RESULTS: Among 78 052 pregnancies, we identified 1248 major structural birth defects (1049 [160.6 per 10 000 live births] among unvaccinated people and 199 [156.4 per 10 000 live births] among vaccinated people). No differences in the prevalence of major structural birth defects were observed given COVID-19 vaccination (adjusted prevalence ratio [aPR], 0.96; 95% CI, 0.81–1.13). Findings were unchanged by insurance provider, SARS-CoV-2 infection during pregnancy, and concomitant of other maternal vaccines. No differences in the prevalence of birth defects were observed among vaccinated people by brand (aPR, 1.02; 95% CI, 0.77–1.37).

CONCLUSIONS: COVID-19 vaccination during early pregnancy is not associated with an increased prevalence of major structural birth defects in infants. These results support the safety of COVID-19 vaccination in early pregnancy.

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Dr Regan conceptualized the study, secured funding for the research, extracted the data to define the study cohort, and provided critical input during study design and execution. Dr Rowe codesigned the study methodology, conducted all data analyses and interpretation of results, and prepared the initial and all subsequent manuscript versions. (Continued)

WHAT'S KNOWN ON THIS SUBJECT: COVID-19 vaccination is recommended during pregnancy, with several studies demonstrating its safety, including no elevated risk of adverse maternal and perinatal outcomes. Evidence relating to major structural birth defects among infants born to people vaccinated early in pregnancy is limited.

WHAT THIS STUDY ADDS: Major structural birth defects are not elevated among infants born to people vaccinated in the first 20 weeks of pregnancy. Moreover, the prevalence of birth defects is not modified by maternal SARS-CoV-2 infection nor concomitant administration of other maternal vaccines.

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INTRODUCTION

COVID-19—caused by SARS-CoV-2—during pregnancy has been associated with an increased risk of poor maternal and perinatal outcomes, including intensive care unit admission, neonatal intensive care unit admission, invasive ventilation, preterm birth, and stillbirth.[1,2] To support prevention efforts—and since August 1, 2021—COVID-19 vaccines were explicitly recommended for pregnant people in the US.[3] Although pregnant individuals were excluded from early randomized controlled trials for COVID-19 vaccines, subsequent observational studies have shown that COVID-19 vaccination during pregnancy is highly effective in providing protection to both the pregnant person and infant.[4] Studies have not found an increased risk of adverse maternal and perinatal outcomes following a COVID-19 vaccination in pregnancy[5,6,]; however, gaps in the literature remain.

During fetal development, exposure to teratogens poses the greatest risk for major structural birth defects,[7] yet there are limited data on the safety of COVID-19 vaccination administered in early pregnancy. A 2022 systematic review found no positive association between maternal COVID-19 vaccination and birth defects.[8] Similarly, recent retrospective cohort studies have observed no association between first-trimester COVID-19 vaccination and major structural birth defects, including neural-tube, otologic, ophthalmologic, cardiac, orofacial/respiratory, gastrointestinal, genitourinary/kidney, and musculoskeletal defects.[9–12] However, pharmacovigilance monitoring can be challenging because of the rarity of certain birth defects,[13] with small sample sizes further limiting analyses by important subgroups such as vaccine platform or concomitant administration of other maternal vaccines. As the number of people receiving COVID-19 vaccines during pregnancy and data availability increase, ongoing research is needed to monitor vaccine safety outcomes. Here, we compare the prevalence of major structural birth defects by COVID-19 vaccination status during pregnancy, overall and by insurance provider, clinically diagnosed SARS-CoV-2 infection during pregnancy, and concomitant of other maternal vaccines. Secondarily, we compare the prevalence of major structural birth defects by COVID-19 vaccine platform and brand.

METHODS

We used the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) Statement to guide the reporting of this study.[14] This research was conducted using previously collected, deidentified data and was deemed by the National Institute of Allergy and Infectious Diseases to be an activity on nonhuman subjects. Institutional review board approval exemption was also provided by a university-based institutional review board in the US.

Study Design, Data Sources, Setting, and Participants

A national claims-based cohort study was assembled using administrative health data from private and public health insurance providers. Two data sources were used to assemble the cohort. First, the Merative Marketscan Commercial Database was used to identify privately insured pregnant people and their medical encounters. This database captures nationwide, deidentified, patient-level data from privately insured employees and their dependents. Second, the Merative Marketscan Multi-state Medicaid claims database was used to identify publicly insured pregnant people and their medical encounters. This database captures deidentified, patient-level data for more than 47 million Medicaid enrollees across multiple states.[15] Collectively, these databases draw from all billed inpatient and outpatient medical encounters, including pregnancy-related procedures and tests, laboratory and prescription drug claims, and information on vaccines recorded by physicians, employers, insurance companies, mail-order prescriptions, and specialty pharmacies (see Supplementary Material).

The study period was August 1, 2021, to September 30, 2022. This timeframe was selected to coincide with the Centers for Disease Control and Prevention (CDC) and American College of Obstetrics and Gynaecology recommendation for COVID-19 vaccination for all pregnant people (~August 1, 2021)[16,17] and the end of data availability (September 30, 2022). Pregnancies and pregnancy outcomes were identified using a previously validated algorithm, which estimated the last menstrual period (LMP) and pregnancy end dates based on gestational age.[18] LMP was derived by subtracting gestational age at pregnancy end (in completed weeks) from the infant's date of birth. Pregnancies were eligible for inclusion in the cohort if they (1) ended in a live birth; (2) had an estimated LMP between August 15, 2021 (ie, 2 weeks after the CDC recommendation) and December 24, 2021 (ie, 40 weeks before the end of data availability to avoid oversampling preterm pregnancies); (3) had prescription benefits coverage; and (4) were continuously enrolled in their health plan 14 days before the estimated LMP through to 28 days after birth (Supplementary Material).

Study participants were pregnant people—including women and transgender people with the ability to become pregnant—aged 18 to 49 years. Throughout this manuscript, we use the term "maternal" to indicate exposures during pregnancy or attributes of a pregnant person, and, respectively, acknowledge this may encompass pregnant non-cisgendered individuals.

Exposure

The primary exposure of interest was the first dose of any COVID-19 vaccine administered between 14 days before the LMP and 20 weeks of gestation. A wider exposure window was chosen—contrasting with the traditional window of

0 to 13 weeks for teratogenic exposures—to align with recommendations from DeSilva et al.[19] They assert that a wider window of teratogenic exposure accounts for potential errors in the assignment of pregnancy start and end dates (a problematic factor in claims-based cohort studies) while retaining focus on exposures "during the most plausible period for development of congenital anomalies."[19] Sensitivity analyses were conducted to limit the exposure window to between 14 days prior to LMP and 13 weeks of gestation to align with the first trimester.

COVID-19 vaccines administered during pregnancy were identified from outpatient and inpatient claims and outpatient drug records using National Drug codes (Table 1s, Supplementary Material). Information on the date of vaccination and the COVID-19 vaccine brand were extracted from the medical encounter. The gestational age at vaccination was determined based on the date of vaccination and estimated LMP.

Two secondary analyses were conducted to compare, head-to-head, the prevalence of major structural birth defects by (1) COVID-19 vaccine platform and (2) COVID-19 vaccine brand. For our analysis examining COVID-19 vaccine platform, the main exposure of interest was the first dose of any mRNA COVID-19 vaccine administered between 14 days before the LMP and 20 weeks of gestation. The referent group was exposure to the first dose of a viral vector vaccine during the same exposure period. For our analysis examining COVID-19 vaccine brand, the main exposure of interest was the first dose of Moderna mRNA-1273 (Spikevax) COVID-19 vaccine administered between 14 days before the LMP and 20 weeks of gestation. The referent group was the first dose of Pfizer-BioNTech BNT162b2 (Comirnaty) during the same exposure period. Unvaccinated people were excluded from these head-to-head analyses.

Outcomes

Several major structural birth defects were examined. The outcomes examined in our study reflect the Brighton Collaboration case definitions for major external and internal structural defects that are commonly—although not consistently—reflected in several international and national birth defect registries.[19] These were: central nervous system anomalies (neural-tube defects, holoprosencephaly, and microcephaly), eye anomalies (anophthalmos, microphthalmos, and congenital cataract), ear anomalies (anotia and microtia), respiratory system anomalies (choanal atresia), genitourinary system anomalies (bladder exstrophy, renal dysplasia, posterior urethral valves, and hypospadias), musculoskeletal anomalies (gastroschisis, omphalocele, limb deficiency), digestive system anomalies (biliary atresia, esophageal atresia, intestinal atresia, pyloric stenosis, other malformation of intestine, congenital hernia, and cleft lip and palate), and congenital cardiac defects.

Birth defects were identified using *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*), *ICD-10* Procedure Coding System and Current Procedural Terminology as captured in infant outpatient and inpatient records from the infant date of birth to 28 days (Table 2s, Supplementary Material).

Covariates

Several maternal and sociodemographic covariates were identified as potentially confounding the relationship between COVID-19 vaccination and major structural birth defects. These were: maternal age; tobacco, drug, and alcohol use complicating pregnancy, childbirth, or the puerperium; whether the pregnancy was a singleton or multiple; whether the pregnancy was the outcome of assisted reproductive technology; maternal history of preterm birth; administration of other recommended maternal vaccines (influenza or pertussis at any time during pregnancy); and other infectious or parasitic diseases complicating pregnancy. The following 6 high-risk medical conditions in the 12 months prior to pregnancy were also considered potential confounders: renal disease (diabetes or chronic kidney disease), cardiovascular disease (acute myocardial infarction, heart failure, conditions affecting the heart valve[s], hypertension, cardiomyopathy, or sickle cell disease), immunocompromizing conditions (organ transplant or other immunocompromizing conditions), liver disease, cancer, and obesity (Table 3s, Supplementary Material).

To examine associations between COVID-19 vaccination and major structural birth defects within strata of interest, we extracted or derived 3 additional indicator (binary) variables: (1) insurance provider, (2) SARS-CoV-2 infection during pregnancy, and (3) concomitant administration of other maternal vaccines. Insurance provider type was identified through examination of the primary data source from which pregnancy records were sourced (ie, Medicaid or commercial). Insurance provider was examined as an important proxy for socioeconomic disadvantage and differential access to health care. Reduced access to health care—including reduced access to early screening—can impact diagnosis of birth defects. Examples include neural-tube defects, orafacial clefts, and conotruncal heart defects.[20,21] Furthermore, previous studies[22] have demonstrated that uptake of maternal vaccines is differential by insurance provider. Insurance provider may therefore represent an important effect modifier of the association between COVID-19 vaccination and birth defects.

SARS-CoV-2 infection during pregnancy was identified by reviewing maternal outpatient and inpatient medical claims. A person was considered infected if a medical claim with *ICD-10-CM* codes U07.1, U07.2, or J12.81 occurred within the main exposure window of interest (ie, 14 days prior to LMP through to 20 weeks of gestation).

Concomitant administration of other maternal vaccines was identified by examining exposure to 1 or more influenza and/or pertussis vaccines during the main exposure window of interest (ie, 14 days before LMP through to 20 weeks of gestation).

Statistical Analyses

We used descriptive statistics (counts, medians, minimum, maximum, and IQRs) to describe study participants and their characteristics. We estimated prevalence ratios (PRs) comparing rates of each major structural birth defect by COVID-19 vaccination status using unadjusted and adjusted binomial regression with robust SEs, overall and stratified by insurance provider, SARS-CoV-2 infection during pregnancy, concomitant administration of other maternal vaccines, and vaccine platform and brand. Stabilized inverse probability treatment (vaccination) weights (IPTWs) were used in the adjusted models to standardize each estimate to the distribution of all the measured covariates used in creating the IPTWs. For our main analyses, all 16 covariates were considered when building these models (see Covariates section above). Covariate balance after weighting was assessed using standardized mean differences (SMDs), with SMDs less than 0.10 considered adequate balance. Unadjusted and aPRs and their 95% CI were calculated to quantify the standardized relative prevalences of birth defects between the COVID-19 vaccinated and unvaccinated, accounting for all other measured factors. Data preparation and analyses were performed in Stata 18.0 (StataCorp LLC, College Station, TX).

RESULTS

There were 135 248 pregnancies in the study period. After excluding 57 196 (42.3%) pregnancies not meeting eligibility criteria, the final analytical cohort comprised 78 052 pregnancies (53.5% privately insured and 46.5% publicly insured) (Figure 1). Characteristics of the cohort are shown in Table 1. Proportionally, more vaccinated people were older (35–44 years), had a pregnancy that was the result of assisted reproductive technology, and had received other maternal vaccines. In contrast, proportionally more unvaccinated people had medical records indicating tobacco, drug, or alcohol use complicating pregnancy; had other infectious or parasitic diseases complicating pregnancy; were pregnant with multiples; or had past pregnancies ending in preterm birth. The median gestational age at pregnancy end was 38 weeks for both vaccinated and unvaccinated people. Applying the standardized IPTWs balanced the measured characteristics between the vaccinated and unvaccinated (Table 4s and Figure 1s, Supplementary Material).

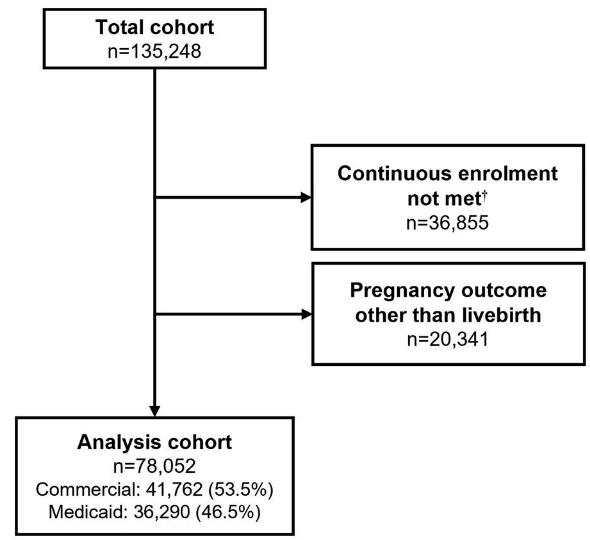

FIGURE 1.
Study flowchart.
†Continuous enrolment was defined as people enrolled in their insurance plan on or before 14 days prior to their estimate last menstrual period, through to 28 days following the end of pregnancy event.

We identified 12 725 (16.3%) people vaccinated between 14 days before LMP and 20 weeks of gestation. Of these exposures, 71.1% occurred in the first 13 weeks of gestation. Vaccine coverage differed by insurance provider (25.3% and 6.0% of privately and publicly insured people, respectively), SARS-CoV-2 infection during pregnancy (16.8% and 11.3% of people without and with SARS-CoV-2 during pregnancy, respectively), and administration of other maternal vaccines (13.6% and 34.2% of people not receiving or receiving other maternal vaccines, respectively) (Table 5s, Supplementary Material).

There were 1248 major structural birth defects identified, equating to a prevalence of 159.9 per 10 000 live births. The most commonly occurring defect was hypospadias (292 cases; 37.4 per 10 000 live births), followed by congenital cardiac defects (212 cases; 27.2 per 10 000 live births). There were 1049 major structural birth defects (160.6 per 10 000 live births) among unvaccinated people compared with 199 (156.4 per 10 000 live births) among vaccinated people (Table 2). We observed no demonstrable differences in the prevalence of birth defects by COVID-19 vaccination (any major structural birth defect [composite] aPR, 0.97; 95% CI, 0.84–1.13). Prevalence of genitourinary system anomalies (composite) was 24% lower among vaccinated people, although this estimate did not reach statistical significance (aPR, 0.76; 95% CI, 0.52–1.12). Fewer cases of hypospadias were observed among vaccinated people (aPR, 0.82; 95% CI, 0.58–1.23). No cases of bladder exstrophy and posterior urethral valves were identified among vaccinated people, precluding the calculation of PRs (Table 2, Figure 2).

TABLE 1. Characteristics of Cohort, by COVID-19 Vaccination Status (Vaccinated Between 14 d Before LMP to 20 wk of Gestation), Among People With an Estimated Last Menstrual Period from August 15, 2021, Through December 24, 2021, US		
	Not Vaccinated, N (%)	**Vaccinated, N (%)**
	65 327 (83.7)	12 725 (16.3)
Gestational age at pregnancy end[a]	38.0 (36.0–38.0)	38.0 (37.0–39.0)
Maternal age, y		
18–34	53 426 (81.8)	8574 (67.4)
35–44	11 799 (18.1)	4116 (32.3)
45–49	102 (0.2)	35 (0.3)
Tobacco use complicating pregnancy		
No	59 634 (91.3)	12 338 (97.0)
Yes	5693 (8.7)	387 (3.0)
Alcohol use complicating pregnancy		
No	65 154 (99.7)	12 697 (99.8)
Yes	173 (0.3)	28 (0.2)
Drug use complicating pregnancy		
No	61 049 (93.5)	12 433 (97.7)
Yes	4278 (6.5)	292 (2.3)
Current pregnancy a result of assisted reproduction		
No	64 440 (98.6)	12 172 (95.7)
Yes	887 (1.4)	553 (4.3)
Past history of pregnancy ending with preterm birth		
No	62 149 (95.1)	12 239 (96.2)
Yes	3178 (4.9)	486 (3.8)
Multiple pregnancy/birth		
No	63 017 (96.5)	12 353 (97.1)
Yes	2310 (3.5)	372 (2.9)
Maternal pertussis vaccination		
No	36 057 (55.2)	3573 (28.1)
Yes	29 270 (44.8)	9152 (71.9)
Maternal influenza vaccination		
No	58 332 (89.3)	9084 (71.4)
Yes	6995 (10.7)	3641 (28.6)
Other infectious/parasitic disease		
No	51 032 (78.1)	10 455 (82.2)
Yes	14 295 (21.9)	2270 (17.8)
Renal complications prior to pregnancy		
No	63 831 (97.7)	12 427 (97.7)
Yes	1496 (2.3)	298 (2.3)
Obesity prior to pregnancy		
No	57 001 (87.3)	11 276 (88.6)
Yes	8326 (12.7)	1449 (11.4)
Cardiovascular complications prior to pregnancy		
No	60 695 (92.9)	11 879 (93.4)
Yes	4632 (7.1)	846 (6.6)
Immunocompromizing conditions prior to pregnancy		
No	64 512 (98.8)	12 585 (98.9)
Yes	815 (1.2)	140 (1.1)
Liver disease prior to pregnancy		
No	63 948 (97.9)	12 488 (98.1)
Yes	1379 (2.1)	237 (1.9)
Cancer prior to pregnancy		
No	64 937 (99.4)	12 600 (99.0)
Yes	390 (0.6)	125 (1.0)

Abbreviation: LMP, last menstrual period.
[a] Results presented as median (interquartile range).

TABLE 2. Prevalence of Major Structural Birth Defects per 10 000 Live Births Among Infants Born to Pregnant People in the US (August 15, 2021, to December 24, 2021), Total and by Maternal COVID-19 Vaccination Status, With aPRs (Reference, Not Vaccinated) and 95% CI				
	Number (Prevalence per 10 000 Live Births)			
Defect	Total	Not Vaccinated	Vaccinated	
	N = 78 052	N = 41 762	N = 36 290	aPR (95% CI)
Structural birth defect (any)[a]	1248 (159.9)	1049 (160.6)	199 (156.4)	0.96 (0.81–1.13)
Central nervous system anomalies (composite)	207 (26.5)	177 (27.1)	30 (8.3)	1.00 (0.63–1.58)
Neural-tube defect	24 (3.1)	21 (3.2)	3 (0.8)	1.14 (0.27–4.84)
Microcephaly	181 (23.2)	156 (23.9)	25 (6.9)	0.89 (0.54–1.47)
Holoprosencephaly	6 (0.8)	4 (0.6)	2 (0.6)	3.56 (0.64–19.99)
Eye anomalies (composite)	27 (3.5)	21 (3.2)	6 (1.7)	1.59 (0.60–4.19)
Cataracts	18 (2.3)	15 (2.3)	3 (0.8)	0.78 (0.21–2.91)
Anophthalmos or microphthalmos	10 (1.3)	7 (1.1)	3 (0.8)	3.15 (0.78–12.69)
Chonal atresia	15 (1.9)	13 (2.0)	2 (0.6)	0.62 (0.13–2.89)
Genitourinary system anomalies (composite)	331 (42.4)	288 (44.1)	43 (11.8)	0.76 (0.52–1.12)
Hypospadias	292 (37.4)	252 (38.6)	40 (11.0)	0.82 (0.55–1.23)
Bladder exstrophy	4 (0.5)	4 (0.6)	0 (0.0)	nc
Renal dysplasia	34 (4.4)	31 (4.7)	3 (0.8)	0.38 (0.11–1.28)
Posterior urethral valves	4 (0.5)	4 (0.6)	0 (0.0)	nc
Musculoskeletal system anomalies (composite)	40 (5.1)	33 (5.1)	7 (1.9)	0.96 (0.41–2.24)
Gastroschisis	13 (1.7)	11 (1.7)	2 (0.6)	1.17 (0.26–5.30)
Omphalocele	11 (1.4)	9 (1.4)	2 (0.6)	0.62 (0.13–2.90)
Limb deficiency	18 (2.3)	15 (2.3)	3 (0.8)	0.89 (0.25–3.15)
Digestive system defects (composite)	279 (35.7)	231 (35.4)	48 (13.2)	0.96 (0.69–1.33)
Biliary atresia	9 (1.2)	8 (1.2)	1 (0.3)	0.41 (0.05–3.30)
Esophageal atresia	19 (2.4)	15 (2.3)	4 (1.1)	1.02 (0.31–3.39)
Intestinal atresia	71 (9.1)	61 (9.3)	10 (2.8)	0.90 (0.45–1.77)
Pyloric stenosis	44 (5.6)	37 (5.7)	7 (1.9)	0.93 (0.40–2.13)
Other malformation of intestine	47 (6.0)	37 (5.7)	10 (2.8)	1.36 (0.62–2.98)
Congenital hernia	23 (2.9)	20 (3.1)	3 (0.8)	0.56 (0.15–2.10)
Cleft palate/lip	82 (10.5)	65 (9.9)	17 (4.7)	1.10 (0.63–1.91)
Congenital cardiac defects (composite)	212 (27.2)	177 (27.1)	35 (9.6)	0.93 (0.63–1.37)

Abbreviations: aPR, adjusted prevalence ratio; nc, not calculable.
[a] Structural birth defect (any) is a composite of all outcomes of interest. Cases could be diagnosed with multiple defects. No cases of anotia/microtia were identified.

Results were unchanged in our sensitivity analyses using a more restrictive window for COVID-19 vaccine exposures (between 14 days prior to LMP and 13 weeks of gestation, data not shown).

Subgroup analyses did not show demonstrable differences in PRs by insurance provider, SARS-CoV-2 infection during pregnancy, or concomitant with other maternal vaccines (Table 6s, Figure 2s, Table 7s, Figure 3s, Table 8s, Figure 4s; Supplementary Material). In our analyses examining differences by insurance provider, we observed an elevated PR of anophthalmos/microphthalmos among infants born to privately insured people (aPR, 6.53; 95% CI, 1.06–40.33). However, numbers were small, with 3 cases occurring among vaccinated, privately insured people and 2 cases among unvaccinated people. No cases were observed among vaccinated, publicly insured people. Prevalence of genitourinary system anomalies was lower in COVID-19 vaccinated people across all subgroup analyses, although estimates did not reach statistical significance (Supplementary Material).

For our secondary analyses, most vaccines administered were Pfizer-BioNTech BNT162b2 (Comirnaty) (n = 8247, 65.0%), followed by Moderna mRNA-1273 (Spikevax) (n = 4444, 35.0%). Only 34 (0.3%) Janssen Ad26.COV2.S vaccine exposures were identified in our cohort. There were insufficient numbers to compare differences in prevalence of birth defects by vaccine platform because no birth defects were identified among people vaccinated with the Janssen Ad26.COV2.S vaccine. In our analyses comparing COVID-19 vaccine brands, we observed no differences in the prevalence of birth defects (any major structural birth defect [composite] aPR, 1.02; 95% CI, 0.77–1.37). (Table 9s, Figure 5s Supplementary Material).

DISCUSSION

In this large, national cohort study, we found no evidence that exposure to COVID-19 vaccines in the first 20 weeks of gestation increases the prevalence of major structural birth defects in infants. Notably, our study captured a

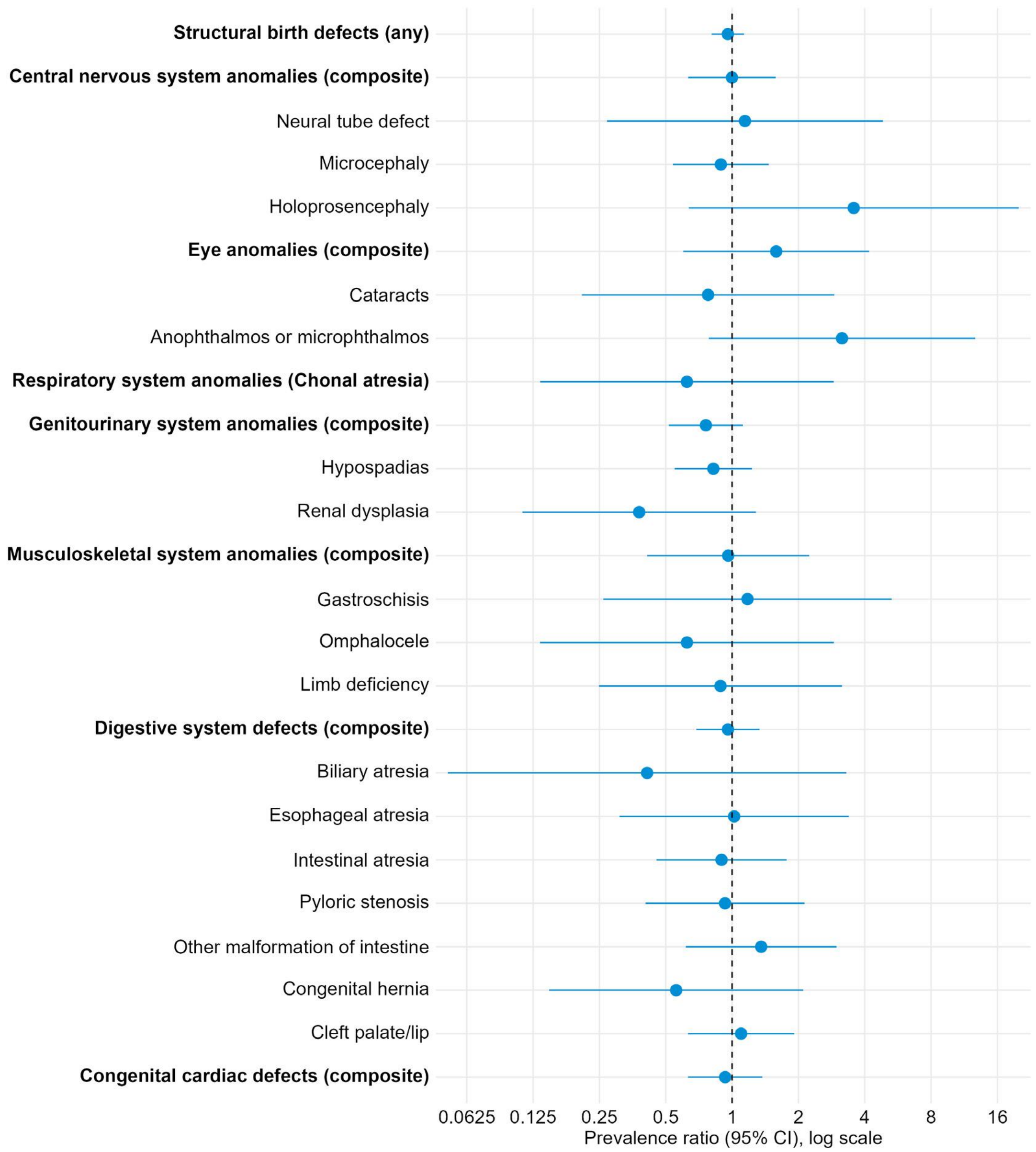

FIGURE 2.
Adjusted prevalence ratios (and 95% CI) of infants diagnosed with major structural birth defects comparing maternal COVID-19 vaccination status among people with an estimated last menstrual period from August 15, 2021, through December 24, 2021, US.

diverse population across the US, including Medicaid enrollees comprising low-income individuals and other traditionally underserved populations. We observed no demonstrable differences in the prevalence of major structural birth defects in infants by maternal insurance provider, SARS-CoV-2 infection during pregnancy, or concomitant administration of other maternal vaccines. Furthermore, our head-to-head comparison of the prevalence of major structural birth defects in infants born to people vaccinated with Moderna mRNA-1273 (Spikevax) and Pfizer-BioNTech BNT162b2 (Comirnaty) COVID-19 vaccines also showed no differences in these outcomes.

The study's findings are consistent with a growing body of literature supporting the safety of COVID-19 vaccines and their use in pregnancy, including in early periods of gestation. Recent studies from Israel,[9] Scotland,[10] the US,[11] and Scandinavia[12] have found no elevated risk of birth defect among infants born to people vaccinated during pregnancy. While comparability between studies is challenged because of variations in exposure definitions (vaccination at any time during pregnancy—per the Israeli[9] study—or vaccination in the first trimester—per the US[11] and Scandanavian[12] studies), collective conclusions all support the safety of COVID-19 vaccination during pregnancy at any stage. Distinct from previously published literature, our findings demonstrate that the prevalence of major structural birth defects is not modified by maternal insurance provider, SARS-CoV-2 infection during pregnancy, or concomitant administration of other maternal vaccines.

We observed considerably fewer diagnoses of genitourinary system anomalies among infants born to people vaccinated against COVID-19 during pregnancy (aPR, 0.76; 95% CI, 0.52–1.12). While our results did not reach statistical significance, the point estimate was low overall and across all other strata examined. This finding was consistent with a previous US study, which showed an aPR of 0.55 (95% CI, 0.33–0.91).[11] The pathophysiological mechanism to explain these findings is unclear and requires further investigation. Additionally, we cannot exclude the possibility of a type I error that may have led to this spurious observation.

Vaccine safety is a common concern for patients considering vaccination.[23] Provider recommendations are the most important predictors of person's decision to vaccinate during pregnancy,[24] even for those who have previously declined.[23] Our findings can strengthen provider-to-patient discussions relating to the safety of COVID-19 vaccines during pregnancy. Providers across all clinical and public health settings should recommend COVID-19 vaccination for their pregnant patients at any period of gestation. This includes patients with SARS-CoV-2 infection during pregnancy or recent administration of other vaccines during, such as influenza and pertussis.

Strengths and Limitations

Major strengths of this study include the use of national data capturing medical encounters for large cohorts of publicly and privately insured people with sufficient study size to compare the prevalence of major structural birth defects by COVID-19 vaccination within several strata of interest (eg, maternal insurance provider, SARS-CoV-2 infection during pregnancy, and concomitant administration of maternal vaccines) seldom reported in other cohort studies. Nonetheless, several limitations should be noted. First, misclassification (underascertainment) of major structural birth defects may have occurred because of our use of medical claims data. While prospective, standardized screening and medical record review would offer the most complete documentation of major structural birth defects, these procedures are not possible with a cohort of this size and because of our use of a retrospective study design. For this reason, we restricted our analyses to major structural birth defects, which may be less prone to detection bias. Furthermore, there is no evidence that outcome misclassification in our study would be differential by COVID-19 vaccination status. Second, our study excluded pregnancies ending early (due to spontaneous or medical abortion, ectopic and trophoblastic implantation, and stillbirth) and thus may be affected by live-birth bias: a form of selection bias that occurs when an exposure affects both diagnosis of the outcome and fetal survival.[25] Birth defects[26] and respiratory tract infections during pregnancy[27–29] can cause or increase the risk of preterm birth or stillbirth, and exclusion of these pregnancies may lead to an underestimation of identified outcomes. The quantification of this bias is challenging because birth defects are not routinely recorded in pregnancies ending prior to 20 weeks, and capture of birth defects among stillborn infants is often incomplete. Furthermore, the effect of live-birth bias on studies examining major structural birth defects is considered to be small.[25] Third, we relied on an estimated date of LMP to define our exposure window of interest, which may have led to misclassification of exposures (COVID-19 vaccines). We used a validated algorithm to estimate LMP, which has high agreement against physician-adjudicated electronic health records and is widely used in postmarketing maternal vaccine safety surveillance.[18] Nevertheless, the sensitivity and specificity of these types of algorithms are imperfect and may have resulted in error in gestational age estimation[30]; however, taking a wider period to assess vaccine exposures accounts for these potential errors while still allowing focus on the most plausible period for development of congenital anomalies.[19] Fourth, although we used IPTWs to standardize model estimates to the distribution of other important covariates that potentially confound the relationship between vaccination and birth defects, our study's findings may still be influenced by unmeasured or residual confounding.

CONCLUSION

In this large, national cohort study, we found that administration of COVID-19 vaccines early in pregnancy (from 14 days before LMP to 20 weeks of gestation) was not associated with increased prevalence of major structural birth defects. No demonstrable differences in the prevalence of major structural birth defects were observed with maternal insurance provider, SARS-CoV-2 infection during pregnancy, or concomitant of other recommended maternal vaccines. Furthermore, among people vaccinated during pregnancy, there were no differences in the prevalence of major structural birth defects when vaccinated with Moderna mRNA-1273 (Spikevax) compared with Pfizer-BioNTech BNT162b2 (Comirnaty) vaccines. Our findings align with other comparable studies[9–12] and provide reassurance to potential vaccinees and vaccine providers considering COVID-19 vaccination early in pregnancy.

ABBREVIATIONS

aPR: adjusted prevalence ratio
CDC: Centers for Disease Control and Prevention
ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification
IPTW: inverse probability treatment weight
LMP: last menstrual period
PR: prevalence ratio
SMD: standardized mean difference

Dr Arah provided critical feedback to the study design, statistical analyses, and manuscript content. Dr Sullivan provided critical feedback to the study design, statistical analyses, and manuscript content and additionally supported the preparation of figures. Dr Muñoz, Mr Coates, and Ms Agnew provided critical feedback and/or contributed to the manuscript content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. The data that support the findings of this study are available from Merative Marketscan; however, restrictions apply to the availability of these data. These data were used under license for the current study. Deidentified individual participant data will not be made available. The underlying code for this study is not publicly available but may be made available to qualified researchers on reasonable request to the corresponding author.

CONFLICT OF INTEREST DISCLOSURES: Dr Sullivan reports paid consulting and/or advisory board participation from CSL Seqirus, Evo Health, Moderna, Novavax, and Pfizer but declares no nonfinancial competing interests. All other authors declare no financial or nonfinancial competing interests. Dr Muñoz is an investigator of pediatric studies of COVID-19 vaccines for Pfizer and Moderna and for a pediatric remdesivir study conducted by Gilead Sciences, Inc; serves as investigator on projects supported by a National Institutes of Health (NIH) contract for a Vaccine Treatment and Evaluation Unit (VTEU); serves as member of the Data and Safety Monitoring Board (DSMB) for clinical trials conducted by Pfizer, Moderna, Meissa Vaccines, Virometix, and the NIH; and is a member of the American Academy of Pediatrics Committee of Infectious Diseases (COID), the Immunization Expert Group of the American College of Obstetrics and Gynecology (ACOG), and Co-Chair of the COVAX Maternal Immunization Working Group. Dr Regan is supported by the National Institute of Allergy and Infectious Diseases of the NIH under award number R01AI169239 and serves on a Data and Safety Monitoring Board for Moderna. The remaining authors have indicated they have no conflicts of interest relevant to this article to disclose.

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