OPEN

Original Research

Coronavirus Disease 2019 (COVID-19) Vaccination and Spontaneous Abortion

Sangini S. Sheth, MD, MPH, Gabriela Vazquez-Benitez, PhD, Malini B. DeSilva, MD, MPH, Jingyi Zhu, PhD, Elisabeth M. Seburg, MPH, Anna E. Denoble, MD, MSc, Matthew F. Daley, MD, Darios Getahun, MD, PhD, MPH, Nicola P. Klein, MD, PhD, Kimberly K. Vesco, MD, MPH, Stephanie A. Irving, MHS, Jennifer C. Nelson, PhD, Joshua T. B. Williams, MD, Simon J. Hambidge, MD, PhD, James G. Donahue, DVM, PhD, MPH, Heather S. Lipkind, MD, MS, and Elyse O. Kharbanda, MD, MPH

OBJECTIVE: To examine the association between coronavirus disease 2019 (COVID-19) vaccination and spontaneous abortion.

METHODS: We conducted a case–control study of clinically adjudicated spontaneous abortions (case group) occurring between January 19, 2021, and October 27, 2021, and live births (control group). Patients aged 16–49 years at eight Vaccine Safety Datalink sites who had singleton pregnancies, one or more prenatal visits, continuous health plan enrollment, and spontaneous abortion (fetal loss between 6 and less than 20 weeks of gestation) or live birth were eligible. A random sample of eligible patients with spontaneous abortions was adjudicated to confirm pregnancy outcome, outcome date, and gestational age at fetal death; patients in the adjudicated spontaneous abortion case group were matched 1:2 on Vaccine Safety Datalink site, maternal age, and pregnancy start date with eligible patients with live births. Vaccine exposure was considered from pregnancy start to spontaneous abortion date or equivalent gestational age for the matched live births (index date). Conditional logistic regression was used to evaluate the association between COVID-19 vaccination in pregnancy and spontaneous abortion; secondary analyses explored associations by dose number, vaccine manufacturer, and vaccination within 6 weeks of the spontaneous abortion.

RESULTS: Matched analyses included 296 patients in the spontaneous abortion case group and 592 in the live birth control group. There was no association between spontaneous abortion and COVID-19 vaccination (adjusted odds ratio [aOR] 0.85, 95% CI, 0.56–1.30). There was also no association between spontaneous abortion and dose number compared with no vaccine (one dose: aOR 0.81, 95% CI, 0.39–1.70; two doses: aOR 0.84, 95% CI, 0.51–1.38; vaccine manufacturer: Moderna aOR 0.59, 95% CI, 0.29–1.19 and Pfizer-BioNTech aOR 0.97, 95% CI, 0.57–1.66; or vaccine exposure window of 6 weeks before spontaneous abortion or index date: aOR 0.87, 95% CI, 0.53–1.44).

From the Yale School of Medicine, New Haven, Connecticut; HealthPartners Institute, Bloomington, Minnesota; the Institute for Health Research, Kaiser Permanente Colorado, and Ambulatory Care Services, Denver Health, Denver, Colorado; Kaiser Permanente Southern California, Pasadena, and Kaiser Permanente Vaccine Study Center, Oakland, California; Kaiser Permanente Center for Health Research, Portland, Oregon; Kaiser Permanente Washington Health Research Institute, Seattle, Washington; Marshfield Clinic Research Institute, Marshfield, Wisconsin; the Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, Georgia; and Weill-Cornell School of Medicine, New York, New York.

This publication was made possible by contract 200-2012-53526 from the Centers for Disease Control and Prevention (CDC). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC.

Each author has confirmed compliance with the journal's requirements for authorship.

Corresponding author: Sangini S. Sheth, MD, MPH, Yale School of Medicine, New Haven, CT; sangini.sheth@yale.edu.

Financial Disclosure

Gabriela Vazquez-Benitez receives research support from AbbVie and Sanofi for unrelated related studies. Malini B. DeSilva and Stephanie A. Irving's institutions received funding from Westat, Inc. Elisabeth M. Seburg receives research support from Sanofi for an unrelated study. Darios Getahun receives research support from Garfield Memorial Fund, Johnson & Johnson, and HOLOGIC Inc for unrelated studies. Nicola P. Klein has received research support from Pfizer for COVID-19 vaccine clinical trials, and from Pfizer, Sanofi, GlaxoSmithKline, Merck, Seqirus, Moderna, and AstraZeneca for unrelated studies. Jennifer C. Nelson has served as a statistical consultant on vaccine safety methods for Acumen LLC and Harvard Pilgrim Health Care for unrelated studies. Joshua T.B. Williams received payments from Immunize Colorado and the Colorado Department of Public Health and Environment. Heather S. Lipkind has previously served on the DSMB for the Pfizer COVID-19 vaccine. The other authors did not report any potential conflicts of interest.

ISSN: 0029-7844/25

CONCLUSION: There was no observed association between COVID-19 vaccination in pregnancy and spontaneous abortion. Findings support the safety of COVID-19 vaccination in early pregnancy.
(Obstet Gynecol 2025;146:129–37)
DOI: 10.1097/AOG.0000000000005904

Recommendations for coronavirus disease 2019 (COVID-19) vaccination have been inclusive of pregnant women since first issued by the Advisory Committee on Immunization Practices on December 12, 2020.[1] Although pregnant women were excluded from initial COVID-19 vaccine trials,[2] the recommendation to not withhold COVID-19 vaccine from an otherwise eligible pregnant woman was based on existing safety data and the risks of COVID-19 to pregnant women and the fetus. Several studies have demonstrated worse clinical outcomes for pregnant women with COVID-19 compared with nonpregnant women.[3–6] The risks of hospitalization, intensive care unit (ICU) admission, and invasive ventilation increase with COVID-19 disease in pregnant women compared with nonpregnant women.[3,5,6] Adverse outcomes such as preterm birth, maternal death, and adult and neonatal ICU admission are increased in pregnant women with COVID-19 disease compared with pregnant women without COVID-19.[3] Studies have shown improved maternal and neonatal outcomes among pregnant women receiving a COVID-19 vaccine, including lower rates of preterm birth, stillbirth, or very low birth weight, as well as lower risk of severe neonatal morbidity, neonatal death, and neonatal ICU admission, compared with unvaccinated pregnant women.[7–9]

Despite the recommendation for COVID-19 vaccination in pregnant women, vaccination rates have remained suboptimal. Data from the National Immunization Survey Adult Covid Module and other national and global studies have shown that women who are pregnant, those trying to conceive, and those who are breastfeeding have lower rates of COVID-19 vaccination compared with nonpregnant women.[10–12] During the 2023–2024 season, the COVID-19 vaccine was received by less than 15% of pregnant women according to Vaccine Safety Datalink surveillance data.[13] Common reasons for hesitancy to receive a COVID-19 vaccine during pregnancy include concerns about side effects and lack of data on vaccine safety.[14–16]

Postlicensure studies of the available COVID-19 vaccines have provided critical data on their safety. Several large, population-based observational studies have shown no increased risk of stillbirth, preterm birth, or other birth and obstetric outcomes after COVID-19 vaccination.[17–20] Fewer studies have evaluated associations between first-trimester COVID-19 vaccinations and spontaneous abortion[21–26]; still, none have detected an increased risk with COVID-19 vaccination.[21–26] However, cases of spontaneous abortion included in these studies were based only on automated diagnostic codes from the electronic health record (EHR) or registry data and were not clinically reviewed or adjudicated or were not compared with an unvaccinated comparison group. Thus, there was the potential for misclassification of both the outcome and the timing of vaccine exposures in relation to spontaneous abortion.[27] The primary objective of this Vaccine Safety Datalink study was to assess the potential association between COVID-19 vaccination in pregnancy and spontaneous abortion.

METHODS

We performed a case–control study, individually matching women with pregnancies ending in spontaneous abortion (case group) and those with pregnancies ending in live birth (control group) by Vaccine Safety Datalink site, maternal age, and pregnancy start date, with a 1:2 match ratio. We compared the odds of vaccination from pregnancy start (last menstrual period [LMP]) up to the index date in a clinically adjudicated sample of spontaneous abortions and matched live births.

The Vaccine Safety Datalink was established in 1990 as a collaboration between the Centers for Disease Control and Prevention (CDC) and several integrated health care organizations. The Vaccine Safety Datalink studies vaccine safety and monitors for possible adverse outcomes after vaccination using population-based electronic health data from participating sites.[28] Eight Vaccine Safety Datalink sites contributed data to this study: Kaiser Permanente (Colorado, Northern California, Southern California, Northwest, Washington), HealthPartners, Marshfield Clinic, and Denver Health. This study was approved by the IRBs of all participating sites and the CDC with a waiver of informed consent because this was a minimal-risk, observational study conducted consistent with federal law and CDC policy (45 C.F.R. part 46.114; 21 C.F.R. part 56.114).

Pregnancies ending in live birth or spontaneous abortion were identified with a validated dynamic pregnancy algorithm. The dynamic pregnancy algorithm identifies pregnancies weekly by applying a hierarchical approach using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis and procedure

codes. Additional data, including estimated due date (EDD), LMP, gestational age diagnoses, and trimester-specific care diagnoses, are used to assign gestational age for completed or ongoing pregnancies.[29]

Spontaneous abortions that, according to automated data, occurred between February 1, 2021, and October 31, 2021, were identified. *Spontaneous abortion* was defined as fetal loss between 6 and less than 20 weeks of gestation. Spontaneous abortions before 6 weeks were excluded, because many pregnancies and spontaneous abortions at such an early gestational age go undiagnosed; even when brought to medical attention, information needed for spontaneous abortion confirmation and dating is often not available. Eligible patients were between age 16 and 49 years and had singleton pregnancies and a history of at least one prenatal visit in the Vaccine Safety Datalink care system, continuous health plan enrollment during pregnancy, and a pregnancy outcome of spontaneous abortion or live birth. Pregnancies resulting from assisted reproduction; those identified by diagnostic codes or medical record review; and those in patients with use of abortifacient medications given before the spontaneous abortion date, identified through medication-dispensing pharmacy data, were excluded. Spontaneous abortions with other conflicting diagnoses for non–live-birth outcomes (stillbirth, ectopic pregnancy, gestational trophoblastic disease, or therapeutic abortion) were also excluded.

Confirmation of spontaneous abortion required clinical adjudication for diagnosis and to establish date and gestational age of spontaneous abortion. Because this was not feasible for all the potential cases of spontaneous abortion, a sampling strategy was used. To reach the sample size goal, 714 potentially eligible spontaneous abortions were selected using a stratified random sampling, with site as the strata for medical record review and adjudication. Trained medical record abstractors at sites conducted manual retrieval of EHR data, including LMP, EDD, and ultrasound and pathology reports. Pregnancy outcome, date of spontaneous abortion, and gestational age at spontaneous abortion were adjudicated by a team of three trained adjudicators (E.O.K., M.B.D., E.S.), with complex cases reviewed by three obstetricians (H.S.L., S.S., A.D.). Previously established criteria for spontaneous abortion were used to confirm the diagnosis.[30,31] The date and gestational age of spontaneous abortion were determined from available medical records, ultrasound reports focusing on first-trimester ultrasonography, pathology reports, and health care encounter notes. Pregnancy dating was confirmed with a predetermined hierarchy: 1) ultrasound reporting of crown–rump length, 2) EDD as reported closest to the time of the spontaneous abortion, and 3) LMP date in cases in which the first two were not available.[32,33] Spontaneous abortions determined to be at less than 6 weeks of gestation, with a crown–rump length measure of the fetal pole less than 4 mm, or with no fetal pole present on ultrasonography were excluded. All medical record reviews and adjudications were recorded in structured REDCap forms.[34] Adjudicators were blinded to patients' vaccine status.

The cohort from which the control group was matched included patients with live births occurring from March 1, 2021, to June 25, 2022, with gestational age of 22 or more weeks and 42 or fewer weeks and birth weight of 500 g or more identified with the dynamic pregnancy algorithm. Pregnancy dating for patients in the live-birth control group was based on a predetermined hierarchy using the physician-determined gestational age at delivery as the primary criteria, consistent with our prior studies.[19,35,36]

Adjudicated spontaneous abortions were matched 1:2 to eligible live births on maternal age (±3 years), pregnancy start date (±14 days), and Vaccine Safety Datalink site using greedy matching.[34] Live births were censored at the gestational age of the matched spontaneous abortion case, and that date was assigned as the index date. Women were retained in the final data set for only one pregnancy; one pregnancy was selected when sampling for spontaneous abortions, and women were excluded as potential live-birth control group matches if they were included in the spontaneous abortion case group.

All COVID-19 vaccines approved for use in the United States were included, and vaccine exposure was determined from EHRs, claims, and bidirectional communication with state or regional immunization registries to identify vaccines administered within and outside the health system.[37] Vaccine exposure was assigned as occurring from pregnancy start (LMP) and before spontaneous abortion according to the adjudicated date of spontaneous abortion or before the index date for matched live births. For secondary analyses, vaccines were classified by total number of doses received before the spontaneous abortion outcome or index date, with at least one occurring during pregnancy, and manufacturer (Pfizer-BioNTech or Moderna). *Vaccine exposure*, defined as receipt of vaccine within 6 weeks of the spontaneous abortion outcome (or the index date for a matched control), also was examined in the secondary analysis.

We a priori determined potential confounders associated with propensity to receive a COVID-19 vaccine during pregnancy and risk for spontaneous abortion. These included maternal age, Vaccine Safety Datalink site, race and ethnicity, socioeconomic status, mean number of prenatal visits before spontaneous abortion or index date, history of COVID-19, history of pregnancy complications, COVID-19 during pregnancy, alcohol use, substance use, tobacco use, and comorbidities, including cancer, preexisting cardiovascular disease, pregestational diabetes mellitus, chronic hypertension, prepregnancy obesity, pulmonary disease, and systemic lupus erythematosus. Socioeconomic status was categorized according to neighborhood poverty level, determined from American Community Survey 5-year data (2016–2020) at the Census tract level.[38] History of complications of pregnancy was based on ICD-10-CM diagnosis codes and included recurrent pregnancy loss and spontaneous abortion (pregnancy-related conditions in Appendix 1, available online at http://links.lww.com/AOG/E103). Medically attended COVID-19 during pregnancy was identified with ICD-10-CM diagnosis codes. Alcohol use and tobacco use were determined from 3 months before the spontaneous abortion or index date according to ICD-10-CM diagnosis codes. *Presence of comorbidities* was defined as having one or more inpatient or two or more outpatient diagnoses in the 3 years leading up to the pregnancy through the spontaneous abortion or index date. Prepregnancy obesity was determined from ICD-10-CM diagnosis codes from 6 months before pregnancy through the spontaneous abortion or index date. The ICD-10-CM diagnosis codes used in the study are available in Appendix 1 (http://links.lww.com/AOG/E103).

Baseline characteristics were described with means and SDs or frequency distribution by spontaneous abortion or live birth and by COVID-19 vaccination status. Differences in baseline characteristics of patients in the spontaneous abortion case group compared with those in the live-birth control group and for COVID-19 vaccination status were evaluated as standardized mean differences (SMDs). We defined a nonnegligible difference to be an SMD greater than 0.20.[39]

Associations of COVID-19 vaccine and spontaneous abortion, odds ratios (ORs) and adjusted odds ratios (aORs), and 95% CIs were evaluated with conditional logistic regression with the reference being unvaccinated women during pregnancy up to the date of spontaneous abortion or index date. Models included covariates with nonnegligible differences. Age and study week at LMP were included in the model as cubic splines, and race and ethnicity and neighborhood poverty level were included as main effects. The primary outcome was the adjusted odds of vaccination in patients in the spontaneous abortion case group compared with those in the live-birth control group. Secondary analyses evaluated outcomes by dose number during pregnancy, by mRNA vaccine manufacturer, and when applying a 6-week exposure window. The unexposed case and control groups consisted of patients with no vaccine exposure during pregnancy up to the spontaneous abortion or index date. Statistical significance was set at a $P<.05$.

Using a sample of 500 expected adjudicated confirmed spontaneous abortions, a 1:2 match ratio to the live-birth control group, an α of 0.05, and assuming an exposure of COVID-19 vaccine of 10%[23,27] and a 0.1 correlation of COVID-19 vaccine with other covariates, we anticipated that the study would have 80% power to detect an OR of 1.6 of getting vaccinated among patients with spontaneous abortion compared with those with live birth. However, fewer than anticipated spontaneous abortions were confirmed, and vaccine uptake was higher than anticipated at 17%. A post hoc power analysis based on the final number of confirmed spontaneous abortions and the observed proportion of patients with COVID-19 vaccine in the live-birth control group of 17% before the index date demonstrated that the study was able to detect an OR of 1.75 with 80% power. Analysis was performed with SAS/STAT 9.4.

RESULTS

A total of 8,476 potential spontaneous abortions were identified to have occurred between February 1, 2021, and October 31, 2021, with the automated dynamic pregnancy algorithm. A sample of 714 potentially eligible women with spontaneous abortions were reviewed and adjudicated. After medical record review and adjudication, 297 cases (41.6%) were confirmed as spontaneous abortions between 6 and less than 20 weeks of gestation (Appendix 2, available online at http://links.lww.com/AOG/E103), with spontaneous abortions occurring from January 19, 2021, to October 27, 2021, according to adjudicated outcome dates. Patients in the spontaneous abortion case group (296) were matched to patients in the live-birth control group (592), with all patients having an LMP between October 1, 2020, and September 7, 2021. One spontaneous abortion case was excluded from analyses because of not having a matched live-birth control. The mean±SD gestational age at spontaneous abortion was 68±17 days. The baseline

characteristics of pregnant women with spontaneous abortions were similar to those with matched live births (Table 1). Comparing pregnant women who received the COVID-19 vaccine with those unvaccinated in pregnancy, we found that vaccinated women were older (34.6±4.9 years vs 33.5±5.6 years, SMD 0.20), were less likely to identify as Hispanic (20.4% vs 31.0%, SMD −0.24), and came from Census tracts with lower levels of neighborhood poverty (6.2% vs 7.9%, SMD −0.25).

Among 888 pregnant women included in the study, 152 (17.1%) were exposed to at least one dose of COVID-19 vaccine, with 15.9% of patients in the spontaneous abortion case group and 17.7% of those in the live-birth control group exposed before the spontaneous abortion or index date, respectively (Appendix 3, available online at http://links.lww.com/AOG/E103, gives characteristics of COVID-19 vaccines received in the study population). According to the aOR, there was no significant association between spontaneous abortion and COVID-19 vaccination (aOR 0.85, 95% CI, 0.56–1.30) (Table 2). Similarly, there was no significant association between spontaneous abortion and number of vaccine doses during pregnancy compared with no vaccine (first dose: aOR 0.81, 95% CI, 0.39–1.70; second dose: aOR 0.84, 95% CI, 0.51–1.38). Similarly, there was no association with spontaneous abortion by vaccine manufacturer (Moderna: aOR 0.59, 95% CI, 0.29–1.19; Pfizer-BioNTech: aOR 0.97, 95% CI, 0.57–1.66). There was also no significant association between COVID-19 vaccination receipt within the 6 weeks before spontaneous abortion and index date compared with unvaccinated during pregnancy (aOR 0.87, 95% CI, 0.53–1.44).

DISCUSSION

Using a case–control study design, this Vaccine Safety Datalink study demonstrated no significant association between spontaneous abortion and exposure to COVID-19 vaccine during pregnancy (ie, before the spontaneous abortion). There was also no association between spontaneous abortion and the number of COVID-19 vaccine doses received during pregnancy, vaccine manufacturer, or vaccine receipt within the 6 weeks before spontaneous abortion. This study reinforces findings from prior studies demonstrating that COVID-19 vaccines have a high degree of safety during pregnancy, including during early pregnancy.[18,21,23,25,26] Many previous studies have focused on later-pregnancy outcomes such as stillbirth or preterm birth.[17,19,20,35,36] This study focuses on early-pregnancy vaccine exposure and a single early-pregnancy outcome, with spontaneous abortion cases clinically adjudicated.

Findings from this study are important for pregnant women, women attempting to become pregnant, and their clinicians because the COVID-19 vaccine exposure window included the time frame when fertilization, implantation, and early cell division for embryo development occur. One recent cohort study of couples in the United States and Canada enrolled before pregnancy found that COVID-19 vaccination was not associated with an increased risk of early miscarriage (before 8 weeks of gestation).[40] Strengthening the evidence to support safety of COVID-19 vaccination can help address vaccine hesitancy and improve the effectiveness of vaccine recommendations delivered to patients. Extensive prior research on vaccine uptake has demonstrated that the strength of a clinician's recommendation can have a positive effect on receipt of vaccines.[41–43]

The current study has several strengths, including that it was conducted in the Vaccine Safety Datalink, which includes data for about 4% of the U.S. population. Unlike prior studies in which spontaneous abortion outcomes were identified solely through automated diagnostic codes from EHR or registry data, in this study, spontaneous abortion and gestational age at spontaneous abortion were confirmed through clinical review and adjudication, with the most complex cases adjudicated by obstetricians. As shown in Appendix 2 (http://links.lww.com/AOG/E103), one-third of spontaneous abortions initially identified through the dynamic pregnancy algorithm were subsequently excluded after adjudication. The rigorous approach to spontaneous abortion case identification minimized both outcome misclassification and exposure misclassification as a result of more precise dating. In addition, we evaluated the association between spontaneous abortion and vaccine manufacturer and vaccine dose administered during pregnancy. The potential for bias in this case–control study was mitigated by the application of inclusion and exclusion criteria for case and control selection before matching to minimize systematic differences between the case and control populations.

A few limitations of the study should be noted. Fewer than anticipated spontaneous abortion cases were confirmed after adjudication; therefore, the study was not adequately powered to detect smaller effects. Spontaneous abortions occurring before 6 weeks of gestation were not included because they can occur without clinical recognition and are difficult

Table 1. Baseline Characteristics of Patients by Pregnancy Outcome and Vaccination Status in the Vaccine Safety Datalink for Clinically Adjudicated Spontaneous Abortion Cases Between January 19, 2021, and October 27, 2021

Characteristic	SAB (n=296)	Live Birth (n=592)	SMD*	Vaccinated (n=152)	Unvaccinated (n=736)	SMD*
Age at SAB or delivery (y)	33.8±5.7	33.7±5.4	0.02	34.6±4.9	33.5±5.6	0.20
Race and ethnicity						
Hispanic	81 (27.4)	178 (30.1)	−0.06	31 (20.4)	228 (31.0)	−0.24
Non-Hispanic Asian	38 (12.8)	74 (12.5)	0.01	23 (15.1)	89 (12.1)	0.09
Non-Hispanic Black	23 (7.8)	51 (8.6)	−0.03	8 (5.3)	66 (9.0)	−0.14
Non-Hispanic multiracial	15 (5.1)	20 (3.4)	0.08	10 (6.6)	25 (3.4)	0.15
Non-Hispanic White	125 (42.2)	253 (42.7)	−0.01	76 (50.0)	302 (41.0)	0.18
Another race[†]	4 (1.4)	6 (1.1)	0.03	1 (0.7)	9 (1.2)	−0.06
Unknown	10 (3.4)	10 (1.7)	—	3 (2.0)	17 (2.3)	—
Percent neighborhood poverty	5.9 (2.5–9.7) 7.4±6.7	5.9 (2.7–10.4) 7.7±7.2	−0.05	4.4 (1.7–8.5) 6.2±6.5	6.1 (3.0–10.3) 7.9±7.1	−0.25
Pregnancy start date period[‡]			−0.01			−0.37
October 1–November 28, 2020	11 (3.7)	23 (3.9)		1 (0.7)	33 (4.5)	
November 29, 2020–January 16, 2021	55 (18.6)	109 (18.4)		26 (17.1)	138 (18.8)	
January 17–March 13, 2021	66 (22.3)	132 (22.3)		60 (39.5)	138 (18.8)	
March 14–May 8, 2021	57 (19.3)	115 (19.4)		43 (28.3)	129 (17.5)	
May 9–June 29, 2021	58 (19.6)	115 (19.4)		14 (9.2)	159 (21.6)	
June 30–September 7, 2021	49 (16.6)	98 (16.6)		8 (5.3)	139 (18.9)	
Prenatal care visits up to SAB or index date	2.0 (1.0–3.0) 2.0±1.6	1.0 (0.5–2.0) 1.7±1.6	0.25	1.0 (1.0–2.0) 1.8±1.7	2.0 (1.0–3.0) 1.8±1.5	0.00
Maternal comorbidities[§]						
Cancer	0	4 (0.7)	−0.12	1 (0.7)	3 (0.4)	0.03
Cardiovascular disease	4 (1.4)	4 (0.7)	0.07	0	8 (1.1)	−0.15
Tobacco use[‖]	11 (3.7)	17 (2.9)	0.04	3 (2.0)	25 (3.4)	−0.09
COVID-19 in pregnancy[¶]	0	3 (0.5)	−0.10	0	3 (0.4)	−0.09
Any history of COVID-19	17 (5.7)	43 (7.3)	−0.06	8 (5.3)	52 (7.1)	−0.07
Pregestational diabetes (type 1 or 2)	4 (1.4)	17 (2.9)	−0.10	8 (5.3)	13 (1.8)	0.19
Hypertension	16 (5.4)	30 (5.1)	0.02	7 (4.6)	39 (5.3)	−0.03
Pulmonary disease	24 (8.1)	54 (9.1)	–0.04	13 (8.6)	65 (8.8)	−0.01
Obesity[#]	46 (15.5)	77 (13)	0.07	17 (11.2)	106 (14.4)	−0.10
Substance use	2 (0.7)	8 (1.4)	−0.07	0	10 (1.4)	−0.17
Alcohol use[‖]	2 (0.7)	5 (0.8)	−0.02	1 (0.7)	6 (0.8)	−0.02
History of complication of pregnancy	21 (7.1)	25 (4.2)	0.12	9 (5.9)	37 (5.0)	0.04

SAB, spontaneous abortion; SMD, standardized mean difference; COVID-19, coronavirus disease 2019.
Data are mean±SD, n (%), or median (interquartile range) unless otherwise specified.
* An absolute SMD greater than 0.20 indicates a nonnegligible difference in variable distributions between SAB and live birth or between unvaccinated and vaccinated.
† Includes non-Hispanic American Indian or Alaska Native, non-Hispanic Native Hawaiian, or other Pacific Islander.
‡ The SMD calculation used study week as numeric.
§ *Presence of comorbidities* was defined as having one or more inpatient or two or more outpatient diagnoses in the 3 years leading up to the pregnancy through the SAB or index date. Other coagulation defects and systemic lupus erythematosus were included among comorbidities given their association with SAB; however, these are not shown here because of low counts.
‖ Alcohol use and tobacco use were determined from 3 months before the SAB or index date according to International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes.
¶ Diagnosed in pregnancy on the basis of the ICD-10-CM diagnosis code.
# Prepregnancy obesity was determined from ICD-10-CM diagnosis code from 6 months before pregnancy through the SAB or index date.

to date. It is also possible that some early pregnancy episodes may not have been detected, the outcome could not be determined after adjudication, or potential cases were erroneously misclassified by the automated dynamic pregnancy algorithm. As a retrospective observational study, there were limitations in

Table 2. Coronavirus Disease 2019 (COVID-19) Vaccine Received During Pregnancy by Pregnancy Outcome and Odds Ratio in Matched Case–Control Patients in the Vaccine Safety Datalink for Clinically Adjudicated Spontaneous Abortion Cases That Occurred Between January 19, 2021, and October 27, 2021

Exposure During Pregnancy	SAB (n=296)	Live Birth (n=592)	Crude OR (95% CI)*	aOR (95% CI)*,†
Primary				
Any COVID-19 vaccination in pregnancy up to SAB or index date	47 (15.9)	105 (17.7)‡	0.86 (0.57–1.28)	0.85 (0.56–1.30)
Secondary				
COVID-19 vaccine dose received during pregnancy up to SAB or index date				
1st dose§	15/264 (5.7)	30/517 (5.8)‡	0.94 (0.46–1.92)	0.81 (0.39–1.70)
2nd dose‖	32/281 (11.4)	74/561 (13.2)‡	0.83 (0.52–1.32)	0.84 (0.51–1.38)
Vaccine manufacturer in pregnancy up to SAB or index date				
mRNA-1273, Moderna¶	18/267 (6.7)	40/527 (7.6)	0.69 (0.37–1.31)	0.59 (0.29–1.19)
BNT162b2, Pfizer-BioNTech#	26/275 (9.5)	59/546 (10.8)	0.93 (0.55, 1.57)	0.97 (0.57–1.66)
Vaccine dose within 6 wk of outcome or index date**	32/281 (11.4)	69/556 (12.4)	0.90 (0.56–1.45)	0.87 (0.53–1.44)

SAB, spontaneous abortion; OR, odds ratio; aOR, adjusted odds ratio; COVID-19, coronavirus disease 2019.
Data are n (%) or n/N (%) unless otherwise specified.
* Associations of COVID-19 vaccine and SAB were estimated with conditional logistic regression.
† The model for the aOR included study week and maternal age as cubic splines and race and ethnicity and neighborhood poverty as main effects.
‡ Total number of COVID-19 vaccinations in pregnancy up to the SAB or index date includes a third booster dose in one patient. This dose was excluded from first- and second-dose analysis.
§ Numerator reflects first dose given during pregnancy up to the SAB or index date; denominator reflects unvaccinated during pregnancy or first dose given during pregnancy up to SAB or index date.
‖ Numerator reflects second dose given during pregnancy up to the SAB or index date; denominator reflects unvaccinated during pregnancy or second dose given during pregnancy up to SAB or index date.
¶ Numerator reflects receipt of mRNA-1273 (Moderna) during pregnancy up to SAB or index date; denominator reflects unvaccinated during pregnancy or received mRNA-1273 (Moderna) during pregnancy up to SAB or index date.
# Numerator reflects receipt of BNT162b2 (Pfizer-BioNTech) during pregnancy up to SAB or index date; denominator reflects unvaccinated during pregnancy or received BNT162b2, Pfizer-BioNTech during pregnancy up to SAB or index date.
** Numerator reflects receipt of COVID-19 vaccine within 6 weeks of outcome or index date; denominator reflects those unvaccinated during pregnancy or received COVID-19 vaccine within 6 weeks of outcome or index date.

the identification of possible confounders, and because of feasibility limitations in conducting medical record reviews for all patients in the live-birth control group, only covariates identified from automated data files were included. Although patients in the case group were matched to patients in the control group, it is possible that the patients in the case group differed from those in the control group in important ways that could have biased the results. The findings may not be generalizable to the general public because the population in the Vaccine Safety Datalink population is primarily insured. In addition, the Vaccine Safety Datalink is not representative of all geographic regions of the United States. In addition, increased use of home COVID-19 antigen testing limited our ability to reliably identify severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; however, COVID-19 diagnosis during pregnancy was included as a comorbidity when ascertained.

Future studies examining the safety of COVID-19 vaccination in pregnancy should examine populations representative of the U.S. population and include a larger sample size. In addition, further refinement of spontaneous abortion case identification could be considered, as well as more specific examination of COVID-19 vaccine safety in women attempting pregnancy and early in pregnancy.

The findings from this study strengthen the evidence that COVID-19 vaccines are not associated with an increased risk of spontaneous abortion. Through a robust case–control study design and use of medical record review and case adjudication, the study provides further evidence for the safety of receipt of COVID-19 vaccine for women attempting to become pregnant or pregnant in the first trimester.

Health care professionals can incorporate this evidence into their vaccine counseling.

REFERENCES

1. Oliver SE, Gargano JW, Marin M, Wallace M, Curran KG, Chamberland M, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Pfizer-BioNTech COVID-19 vaccine–United States, December 2020. MMWR Morb Mortal Wkly Rep 2020;69:1922–4. doi: 10.15585/mmwr.mm6950e2
2. Beigi RH, Krubiner C, Jamieson DJ, Lyerly AD, Hughes B, Riley L, et al. The need for inclusion of pregnant women in COVID-19 vaccine trials. Vaccine 2021;39:868–70. doi: 10.1016/j.vaccine.2020.12.074
3. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 2020;370:m3320. doi: 10.1136/bmj.m3320
4. Rasmussen SA, Jamieson DJ. COVID-19 vaccination during pregnancy–two for the price of one. N Engl J Med 2022;387:178–9. doi: 10.1056/NEJMe2206730
5. Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status–United States, January 22–June 7, 2020. MMWR Morb Mortal Wkly Rep 2020;69:769–75. doi: 10.15585/mmwr.mm6925a1
6. Khan DSA, Pirzada AN, Ali A, Salam RA, Das JK, Lassi ZS. The differences in clinical presentation, management, and prognosis of laboratory-confirmed COVID-19 between pregnant and non-pregnant women: a systematic review and meta-analysis. Int J Environ Res Public Health 2021;18:5613. doi: 10.3390/ijerph18115613
7. Piekos SN, Hwang YM, Roper RT, Sorensen T, Price ND, Hood L, et al. Effect of COVID-19 vaccination and booster on maternal-fetal outcomes: a retrospective cohort study. Lancet Digit Health 2023;5:e594–606. doi: 10.1016/s2589-7500(23)00093-6
8. Hui L, Marzan MB, Rolnik DL, Potenza S, Pritchard N, Said JM, et al. Reductions in stillbirths and preterm birth in COVID-19-vaccinated women: a multicenter cohort study of vaccination uptake and perinatal outcomes. Am J Obstet Gynecol 2023;228:585.e1–16. doi: 10.1016/j.ajog.2022.10.040
9. Jorgensen SCJ, Drover SSM, Fell DB, Austin PC, D'Souza R, Guttmann A, et al. Newborn and early infant outcomes following maternal COVID-19 vaccination during pregnancy. JAMA Pediatr 2023;177:1314–23. doi: 10.1001/jamapediatrics.2023.4499
10. Razzaghi H, Yankey D, Vashist K, Lu PJ, Kriss JL, Nguyen KH, et al. COVID-19 vaccination coverage and intent among women aged 18-49 years by pregnancy status, United States, April-November 2021. Vaccine 2022;40:4554–63. doi: 10.1016/j.vaccine.2022.06.029
11. Skjefte M, Ngirbabul M, Akeju O, Escudero D, Hernandez-Diaz S, Wyszynski DF, et al. COVID-19 vaccine acceptance among pregnant women and mothers of young children: results of a survey in 16 countries. Eur J Epidemiol 2021;36:197–211. doi: 10.1007/s10654-021-00728-6
12. Sutton D, D'Alton M, Zhang Y, Kahe K, Cepin A, Goffman D, et al. COVID-19 vaccine acceptance among pregnant, breastfeeding, and nonpregnant reproductive-aged women. Am J Obstet Gynecol MFM 2021;3:100403. doi: 10.1016/j.ajogmf.2021.100403
13. Centers for Disease Control and Prevention. 2023-24 - COVID-19 pregnant person vaccination coverage. Accessed July 22, 2024. https://cdc.gov/covidvaxview/weekly-dashboard/2023-24-pregnant-persons-vaccination.html
14. Regan AK, Kaur R, Nosek M, Swathi PA, Gu NY. COVID-19 vaccine acceptance and coverage among pregnant persons in the United States. Prev Med Rep 2022;29:101977. doi: 10.1016/j.pmedr.2022.101977
15. Mhereeg M, Jones H, Kennedy J, Seaborne M, Parker M, Kennedy N, et al. COVID-19 vaccination in pregnancy: views and vaccination uptake rates in pregnancy, a mixed methods analysis from SAIL and the Born-in-Wales Birth Cohort. BMC Infect Dis 2022;22:932. doi: 10.1186/s12879-022-07856-8
16. Williams JTB, Kurlandsky K, Breslin K, Durfee MJ, Stein A, Hurley L, et al. Attitudes toward COVID-19 vaccines among pregnant and recently pregnant individuals. JAMA Netw Open 2024;7:e245479. doi: 10.1001/jamanetworkopen.2024.5479
17. Fell DB, Dhinsa T, Alton GD, Török E, Dimanlig-Cruz S, Regan AK, et al. Association of COVID-19 vaccination in pregnancy with adverse peripartum outcomes. JAMA 2022;327:1478–87. doi: 10.1001/jama.2022.4255
18. Magnus MC, Örtqvist AK, Dahlqwist E, Ljung R, Skår F, Oakley L, et al. Association of SARS-CoV-2 vaccination during pregnancy with pregnancy outcomes. JAMA 2022;327:1469–77. doi: 10.1001/jama.2022.3271
19. Lipkind HS, Vazquez-Benitez G, DeSilva M, Vesco KK, Ackerman-Banks C, Zhu J, et al. Receipt of COVID-19 vaccine during pregnancy and preterm or small-for-gestational-age at birth–eight integrated health care organizations, United States, December 15, 2020-July 22, 2021. MMWR Morb Mortal Wkly Rep 2022;71:26–30. doi: 10.15585/mmwr.mm7101e1
20. Goldshtein I, Steinberg DM, Kuint J, Chodick G, Segal Y, Shapiro Ben David S, et al. Association of BNT162b2 COVID-19 vaccination during pregnancy with neonatal and early infant outcomes. JAMA Pediatr 2022;176:470–7. doi: 10.1001/jamapediatrics.2022.0001
21. Magnus MC, Gjessing HK, Eide HN, Wilcox AJ, Fell DB, Håberg SE. COVID-19 vaccination during pregnancy and first-trimester miscarriage. N Engl J Med 2021;385:2008–10. doi: 10.1056/NEJMc2114466
22. Kharbanda EO, Haapala J, DeSilva M, Vazquez-Benitez G, Vesco KK, Naleway AL, et al. Spontaneous abortion following COVID-19 vaccination during pregnancy. JAMA 2021;326:1629–31. doi: 10.1001/jama.2021.15494
23. Kharbanda EO, Haapala J, Lipkind HS, DeSilva MB, Zhu J, Vesco KK, et al. COVID-19 booster vaccination in early pregnancy and surveillance for spontaneous abortion. JAMA Netw Open 2023;6:e2314350. doi: 10.1001/jamanetworkopen.2023.14350
24. Velez MP, Fell DB, Shellenberger JP, Kwong JC, Ray JG. Miscarriage after SARS-CoV-2 vaccination: a population-based cohort study. BJOG 2024;131:415–22. doi: 10.1111/1471-0528.17721
25. Calvert C, Carruthers J, Denny C, Donaghy J, Hillman S, Hopcroft LEM, et al. A population-based matched cohort study of early pregnancy outcomes following COVID-19 vaccination and SARS-CoV-2 infection. Nat Commun 2022;13:6124. doi: 10.1038/s41467-022-33937-y
26. Mansour O, Hernandez-Diaz S, Wyszynski DF. mRNA COVID-19 vaccination early in pregnancy and the risk of spontaneous abortion in an international pregnancy registry. Pharmacoepidemiol Drug Saf 2023;32:685–93. doi: 10.1002/pds.5600

27. Vazquez-Benitez G, Haapala JL, Lipkind HS, DeSilva MB, Zhu J, Daley MF, et al. COVID-19 vaccine safety surveillance in early pregnancy in the United States: design factors affecting the association between vaccine and spontaneous abortion. Am J Epidemiol 2023;192:1386–95. doi: 10.1093/aje/kwad059

28. Baggs J, Gee J, Lewis E, Fowler G, Benson P, Lieu T, et al. The Vaccine Safety Datalink: a model for monitoring immunization safety. Pediatrics 2011;127(suppl 1):S45–53. doi: 10.1542/peds.2010-1722H

29. Naleway AL, Crane B, Irving SA, Bachman D, Vesco KK, Daley MF, et al. Vaccine Safety Datalink infrastructure enhancements for evaluating the safety of maternal vaccination. Ther Adv Drug Saf 2021;12:20420986211021233. doi: 10.1177/20420986211021233

30. Doubilet PM, Benson CB, Bourne T, Blaivas M, Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy, Barnhart KT, et al. Diagnostic criteria for nonviable pregnancy early in the first trimester. N Engl J Med 2013;369:1443–51. doi: 10.1056/NEJMra1302417

31. Early pregnancy loss. ACOG Practice Bulletin No. 200. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e197–207. doi: 10.1097/AOG.0000000000002899

32. Kharbanda EO, Vazquez-Benitez G, DeSilva MB, Naleway AL, Klein NP, Hechter RC, et al. Association of inadvertent 9-valent human papillomavirus vaccine in pregnancy with spontaneous abortion and adverse birth outcomes. JAMA Netw Open 2021;4:e214340. doi: 10.1001/jamanetworkopen.2021.4340

33. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, Sheth SS, Zhu J, Naleway AL, et al. Risk of spontaneous abortion after inadvertent human papillomavirus vaccination in pregnancy. Obstet Gynecol 2018;132:35–44. doi: 10.1097/aog.0000000000002694

34. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81. doi: 10.1016/j.jbi.2008.08.010

35. Vesco KK, Denoble AE, Lipkind HS, Kharbanda EO, DeSilva MB, Daley MF, et al. Obstetric complications and birth outcomes after antenatal coronavirus disease 2019 (COVID-19) vaccination. Obstet Gynecol 2024;143:794–802. doi: 10.1097/AOG.0000000000005583

36. Denoble AE, Vazquez-Benitez G, Sheth SS, Ackerman-Banks CM, DeSilva MB, Zhu J, et al. Coronavirus disease 2019 (COVID-19) vaccination and stillbirth in the Vaccine Safety Datalink. Obstet Gynecol 2024;144:215–22. doi: 10.1097/AOG.0000000000005632

37. Groom HC, Crane B, Naleway AL, Weintraub E, Daley MF, Wain K, et al. Monitoring vaccine safety using the Vaccine Safety Datalink: assessing capacity to integrate data from immunization information systems. Vaccine 2022;40:752–6. doi: 10.1016/j.vaccine.2021.12.048

38. U.S. Census Bureau. American Community Survey information guide. Accessed October 21, 2024. https://census.gov/programs-surveys/acs/about/information-guide.html

39. Ali MS, Groenwold RH, Belitser SV, Pestman WR, Hoes AW, Roes KCB, et al. Reporting of covariate selection and balance assessment in propensity score analysis is suboptimal: a systematic review. J Clin Epidemiol 2015;68:112–21. doi: 10.1016/j.jclinepi.2014.08.011

40. Yland JJ, Wesselink AK, Regan AK, Hatch EE, Rothman KJ, Savitz DA, et al. A prospective cohort study of preconception COVID-19 vaccination and miscarriage. Hum Reprod 2023;38:2362–72. doi: 10.1093/humrep/dead211

41. Nguyen KH, Yankey D, Lu PJ, Kriss JL, Brewer NT, Razzaghi H, et al. Report of health care provider recommendation for COVID-19 vaccination among adults, by recipient COVID-19 vaccination status and attitudes–United States, April-September 2021. MMWR Morb Mortal Wkly Rep 2021;70:1723–30. doi: 10.15585/mmwr.mm7050a1

42. Oh NL, Biddell CB, Rhodes BE, Brewer NT. Provider communication and HPV vaccine uptake: a meta-analysis and systematic review. Prev Med 2021;148:106554. doi: 10.1016/j.ypmed.2021.106554

43. Lu PJ, Srivastav A, Amaya A, Dever JA, Roycroft J, Kurtz MS, et al. Association of provider recommendation and offer and influenza vaccination among adults aged ≥18 years–United States. Vaccine 2018;36:890–8. doi: 10.1016/j.vaccine.2017.12.016

PEER REVIEW HISTORY

Received November 18, 2024. Received in revised form February 5, 2025. Accepted February 20, 2025. Peer reviews and author correspondence are available at http://links.lww.com/AOG/E104.