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Original Article

Early pregnancy

A prospective cohort study of preconception COVID-19 vaccination and miscarriage

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ABSTRACT

STUDY QUESTION: To what extent is preconception maternal or paternal coronavirus disease 2019 (COVID-19) vaccination associated with miscarriage incidence?

SUMMARY ANSWER: COVID-19 vaccination in either partner at any time before conception is not associated with an increased rate of miscarriage.

WHAT IS KNOWN ALREADY: Several observational studies have evaluated the safety of COVID-19 vaccination during pregnancy and found no association with miscarriage, though no study prospectively evaluated the risk of early miscarriage (gestational weeks [GW] <8) in relation to COVID-19 vaccination. Moreover, no study has evaluated the role of preconception vaccination in both male and female partners.

STUDY DESIGN, SIZE, DURATION: An Internet-based, prospective preconception cohort study of couples residing in the USA and Canada. We analyzed data from 1815 female participants who conceived during December 2020–November 2022, including 1570 couples with data on male partner vaccination.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Eligible female participants were aged 21–45 years and were trying to conceive without use of fertility treatment at enrollment. Female participants completed questionnaires at baseline, every 8 weeks until pregnancy, and during early and late pregnancy; they could also invite their male partners to complete a baseline questionnaire. We collected data on COVID-19 vaccination (brand and date of doses), history of SARS-CoV-2 infection (yes/no and date of positive test), potential confounders (demographic, reproductive, and lifestyle characteristics), and pregnancy status on all questionnaires. Vaccination status was categorized as never (0 doses before conception), ever (≥1 dose before conception), having a full primary sequence before conception, and completing the full primary sequence ≤3 months before conception. These categories were not mutually exclusive. Participants were followed up from their first positive pregnancy test until miscarriage or a censoring event (induced abortion, ectopic pregnancy, loss to follow-up, 20 weeks' gestation), whichever occurred first. We estimated incidence rate ratios (IRRs) for miscarriage and corresponding 95% CIs using Cox proportional hazards models with GW as the time scale. We used propensity score fine stratification weights to adjust for confounding.

MAIN RESULTS AND THE ROLE OF CHANCE: Among 1815 eligible female participants, 75% had received at least one dose of a COVID-19 vaccine by the time of conception. Almost one-quarter of pregnancies resulted in miscarriage, and 75% of miscarriages occurred <8 weeks' gestation. The propensity score-weighted IRR comparing female participants who received at least one dose any time before conception versus those who had not been vaccinated was 0.85 (95% CI: 0.63, 1.14). COVID-19 vaccination was not associated with increased risk of either early miscarriage (GW: <8) or late miscarriage (GW: 8–19). There was no indication of an increased risk of miscarriage associated with male partner vaccination (IRR = 0.90; 95% CI: 0.56, 1.44).

LIMITATIONS, REASONS FOR CAUTION: The present study relied on self-reported vaccination status and infection history. Thus, there may be some non-differential misclassification of exposure status. While misclassification of miscarriage is also possible, the preconception cohort design and high prevalence of home pregnancy testing in this cohort reduced the potential for under-ascertainment of miscarriage. As in all observational studies, residual or unmeasured confounding is possible.

WIDER IMPLICATIONS OF THE FINDINGS: This is the first study to evaluate prospectively the relation between preconception COVID-19 vaccination in both partners and miscarriage, with more complete ascertainment of early miscarriages than earlier studies of vaccination. The findings are informative for individuals planning a pregnancy and their healthcare providers.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic is of particular concern for individuals who are pregnant or may become pregnant, as pregnant individuals are at greater risk of severe COVID-19 and its complications, which include adverse perinatal and pediatric outcomes (Allotey *et al.*, 2020). COVID-19 vaccination has high effectiveness in reducing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and hospitalization (Polack *et al.*, 2020; Baden *et al.*, 2021; Sadoff *et al.*, 2021; Collie *et al.*, 2022). Despite this, many individuals are concerned about the potential effects of COVID-19 vaccination on pregnancy outcomes, particularly miscarriage (i.e. pregnancy loss <20 gestational weeks [GW]) (Male, 2021). However, there is no clear biologic mechanism by which COVID-19 vaccines would cause miscarriage.

Although pregnant individuals were excluded from pre-authorization trials, several observational studies have been conducted to evaluate the relation of miscarriage to receipt of mRNA or viral vector COVID-19 vaccines early in pregnancy. Eight observational studies (Kharbanda *et al.*, 2021; Magnus *et al.*, 2021; Shimabukuro *et al.*, 2021; Trostle *et al.*, 2021; Zauche *et al.*, 2021; Aharon *et al.*, 2022; Citu *et al.*, 2022; Favre *et al.*, 2022), including three passive surveillance studies (Kharbanda *et al.*, 2021; Shimabukuro *et al.*, 2021; Zauche *et al.*, 2021), a descriptive study using electronic medical record data (Trostle *et al.*, 2021), two retrospective cohort studies (Aharon *et al.*, 2022; Citu *et al.*, 2022), and a case-control study using health registry data (Magnus *et al.*, 2021) indicate no increased risk of miscarriage following COVID-19 vaccination. None of these studies used a preconception cohort design, which can reduce bias associated with recall (due to retrospective data collection) and left truncation (due to participation being conditional on not experiencing the outcome until enrollment). Preconception designs also improve identification of early miscarriages (<8 GW). No study has evaluated the effects of male partner vaccination on miscarriage, though studies have investigated the potential effect of male vaccination on semen quality (Gonzalez *et al.*, 2021) and fecundability (Wesselink *et al.*, 2022). Although there is relatively little research on the importance of male factors in the etiology of miscarriage, several studies have suggested that semen quality or health status may play an important role (Bellver *et al.*, 2010; Gil-Villa *et al.*, 2010; Ruixue *et al.*, 2013; Kasman *et al.*, 2021).

In the present study, we used data from a North American preconception cohort study to evaluate preconception COVID-19 vaccination in relation to miscarriage incidence.

Materials and methods

Study population

Pregnancy Study Online (PRESTO) is a prospective preconception cohort study of couples residing in the USA and Canada (2013–present) (Wise *et al.*, 2015). Eligible participants identify as female, are aged 21–45 years, and are trying to conceive without use of fertility treatment at enrollment, though participants may initiate fertility treatment during follow-up. Participants complete a baseline questionnaire and follow-up questionnaires every 8 weeks for up to 12 months or until pregnancy, cessation of pregnancy attempt, loss to follow-up, or study withdrawal. Participants who conceive, complete additional early and late pregnancy questionnaires at medians of 9 and 32 GW, respectively. All female participants are given the opportunity to invite their male partner to participate by completing a baseline questionnaire. Six Clearblue home pregnancy tests are mailed to US participants immediately after enrollment, and the majority of participants report using home pregnancy tests starting at 4 GW (Wise *et al.*, 2020).

This analysis was conducted among 1815 female participants who conceived between 20 December 2020 and 23 November 2022, including 1570 couples from whom we collected data on male partner vaccination. The Boston University Medical Campus Institutional Review Board approved the study protocol. All participants provided online informed consent.

Assessment of miscarriage

Female participants reported data on pregnancy outcomes on follow-up questionnaires, the early pregnancy questionnaire, the late pregnancy questionnaire, or at study withdrawal. On each follow-up questionnaire, participants reported the date of their last menstrual period, whether they were currently pregnant, and whether they had experienced any of the following events: miscarriage (including chemical pregnancy and blighted ovum), induced abortion, ectopic/tubal pregnancy. Participants were asked when and how often they tested for pregnancy and the results of each pregnancy test. Those who were currently pregnant completed the early pregnancy questionnaire, on which they reported any pregnancy losses since their previous questionnaire, the due date of their current pregnancy, the date of their first positive pregnancy test, and the type of test used to confirm their pregnancy (e.g. home pregnancy test, urine test in a doctor's office, blood test, ultrasound). Almost all participants reported using a home pregnancy test to confirm their pregnancy. Miscarriages occurring after the early pregnancy questionnaire were identified on the late pregnancy questionnaire.

Among participants who reported miscarriage, we ascertained how many weeks the pregnancy lasted and on what date the pregnancy ended (participant provided month, day, and year). We relied upon the participant's reported GW at loss. Among participants who did not report their GW at loss but who reported a due date (11%), we estimated gestational age as follows: (pregnancy end date – (pregnancy due date – 280 days))/7 ('ACOG Committee Opinion No 579: definition of term pregnancy', 2013).

Among participants who reported neither their GW at miscarriage nor their pregnancy due date (21%), we estimated GW at loss as: (pregnancy end date – last menstrual period date)/7. Based on the GW at loss recorded via this procedure, we categorized miscarriages as early (occurring <8 GW) or late (occurring ≥8 GW). For participants who were lost to follow-up, we attempted to collect pregnancy outcome data by contacting them via email or phone, by linking to birth registries in selected states (CA, FL, MA, MI, OH, PA, TX, NY), and by searching for baby registries and birth announcements online. Date of conception was estimated as 14 days after the LMP date.

Assessment of COVID-19 vaccination and SARS-CoV-2 infection

On baseline, follow-up, and pregnancy questionnaires, female participants indicated whether they had ever received a COVID-19 vaccine ('Have you ever received a COVID-19 vaccination?'), and if yes, the brand ('Moderna', 'Pfizer', 'Johnson & Johnson', 'Don't Know', or 'Other' with a text box to enter the brand) and calendar dates of each dose. Participants also reported whether they had ever tested positive for COVID-19 and the date they first tested positive. Female participants were asked to report on their male partner's vaccination and infection status. Male participants also reported their own vaccination and infection data on the male baseline questionnaire. For male exposures, we prioritized self-report where available (n = 484), and we used female partner reports where male self-report was unavailable (n = 1086).

The primary objective of this study was to quantify the association between preconception vaccination against COVID-19 and miscarriage. Therefore, we did not include vaccines received during pregnancy in the exposure definition. In other words, individuals who received their first dose during pregnancy (i.e. after conception) were included in the 'never vaccinated before conception' group.

Individuals who received one dose of J&J/Janssen or two doses of Moderna or Pfizer-BioNTech were considered to have received a full primary sequence. We categorized vaccine exposure as having never received a COVID-19 vaccine before conception, having received at least one dose of a COVID-19 vaccine at any time before conception, having completed a primary vaccine series at any time before conception, or having completed the primary sequence ≤3 months before conception. The categories were not mutually exclusive: individuals who completed the primary sequence ≤3 months before conception were nested within the group who completed the primary sequence any time before conception, which was nested within the group who received at least one dose at any time before conception. We used these categories to implement various comparisons, described below ('Statistical Analysis' section).

We also collected data on vaccine doses beyond the primary sequence. However, we did not have a sufficient number of participants who received a booster dose during the study period to examine the relation between additional vaccine doses and miscarriage.

Assessment of covariate data

We collected covariate data on baseline and follow-up questionnaires. Covariates included age (years); BMI (kg/m^2); race/ethnicity (non-Hispanic white, non-Hispanic Black, non-Hispanic Asian, non-Hispanic other race, Hispanic); geographic region of residence (Northeastern USA, Southern USA, Midwestern USA, Western USA, Canada); current smoking (yes/no); educational attainment (≤high school, some college, college degree, graduate school); private health insurance (yes/no); number of primary care visits in the past year (0, 1, 2–3, ≥4); annual household income (<50 000, 50 000–99 999, 100 000–149 999, ≥150 000 USD); employment status (yes/no); hours per week of work; diabetes (yes/no); hypertension (yes/no); asthma (yes/no); daily use of multivitamins and folate supplements (yes/no); the 10-item Perceived Stress Scale (PSS) score (Cohen *et al.*, 1983); Major Depression Inventory score (Bech, 1997); sleep duration (<6, 6–8, ≥9 h/night); number of cycles of pregnancy attempt for the current pregnancy; parity (yes/no); history of miscarriage (yes/no); use of fertility treatment for the current pregnancy (yes/no); history of sub- or infertility (yes/no; defined as previously trying 6 or more months to conceive); history of SARS-CoV-2 infection (yes/no); and calendar month/year at conception.

Statistical analysis

We performed all analyses using SAS statistical software (version 9.4, SAS Institute) and R (R Core Team, 2021). We defined time zero as the week of a participant's first positive pregnancy test. Participants were followed from time zero until miscarriage, induced abortion, ectopic pregnancy, loss to follow-up, or 20 GW, whichever came first. We estimated incidence rate ratios (IRRs) for miscarriage and corresponding 95% CIs using Cox proportional hazards models with GW as the time scale. We used the Andersen–Gill data structure to account for potential bias due to left truncation, which could arise since participants enter the risk set at their first positive pregnancy test (e.g. 4 or 5 weeks after LMP) (Howards *et al.*, 2007; Schisterman *et al.*, 2013), and there is variability in when participants first test for pregnancy (median = 2 days before first missed period). We estimated IRRs for miscarriage by comparing female participants who had received at least one dose of a COVID-19 vaccine any time before conception with those who had never received a COVID-19 vaccine before conception. We also compared female participants who had completed a full primary vaccine series at any time before conception, and ≤3 months before conception, versus those who had never received a COVID-19 vaccine. As a sensitivity analysis, we compared female participants who had completed a primary vaccine series ≤3 months before conception versus >3 months before conception, because these individuals were all vaccinated, and the groups may therefore be similar in terms of health-seeking behaviors.

For male partner vaccination, we compared couples where the male partner had received at least one dose of a COVID-19 vaccine at any time before conception versus couples where the male partner had never received a COVID-19 vaccine before conception and couples where the male partner had received a full primary sequence versus couples where the male partner had never received a COVID-19 vaccine before conception.

We fit models adjusted for female age (years) first and then for a wide range of potential confounders. For the fully adjusted models, we used propensity score fine stratification weights (Desai *et al.*, 2017; Desai and Franklin, 2019; Wesselink *et al.*, 2022). Use of propensity scores may improve validity over traditional methods by excluding individuals who are outside the overlapping range of propensity scores for exposed and unexposed participants (Stürmer *et al.*, 2006). We fit logistic regression models to calculate propensity scores as the predicted probability of COVID-19 vaccination conditional on the covariates described above. We then trimmed the non-overlapping range of the propensity score distribution for vaccinated (≥1 dose before conception) and unvaccinated (0 doses before conception) individuals. Within the trimmed dataset, we created 50 strata based on the distribution of propensity scores in vaccinated individuals. We fit weighted regression models to estimate the adjusted effect

of vaccination, such that vaccinated individuals were assigned a weight of 1 and unvaccinated individuals were weighted proportional to the distribution of vaccinated individuals in their stratum. To reduce the influence of extreme weights, we truncated the weight distribution at the 99th percentile. To assess the performance of the propensity score models, we compared the distribution of propensity scores and the balance of covariates across vaccination groups in the trimmed and weighted dataset. We adjusted for the same set of covariates in models assessing female and male partner exposures, though we additionally adjusted for female partner vaccination in analyses of male partner exposure.

Stratified analyses

We conducted several stratified analyses comparing individuals with at least one dose of a vaccine with those who were never vaccinated, for both female and male partner vaccination. We stratified by country of residence (USA versus Canada) due to differences in the timing and pace of vaccine rollout between countries. We restricted to couples who conceived without the use of fertility treatment due to the potential impact of fertility treatment on pregnancy outcomes, and to female participants without a history of miscarriage, as prior loss is a strong risk factor for incident miscarriage and may also impact an individual's attitude toward vaccination. We then stratified by vaccine brand (Moderna versus Pfizer-BioNTech [numbers were insufficient to evaluate J&J/Janssen alone]), timing of gestation (<8 versus ≥8 GW), and calendar month at conception. For analyses stratified by timing of gestation, individuals who first tested positive for pregnancy at <8 GW contributed person time to the <8 GW stratum from their first positive pregnancy test until miscarriage, a censoring event, or 7 GW, whichever occurred first. If they remained uncensored at 7 GW, they contributed person time to the ≥8-GW stratum from 8 GW until miscarriage, a censoring event, or 20 GW, whichever occurred first. Individuals who first tested positive for pregnancy at ≥8 GW did not contribute person time to the <8-GW stratum; they contributed time to the ≥8-GW stratum from 8 GW until miscarriage, a censoring event, or 20 GW, whichever occurred first. For analyses stratified by month, we restricted to US residents and divided the study period into four intervals: 20 December 2020–31 May 2021; 1 June 2021–31 October 2021; 1 November 2021–31 March 2022; and 1 April 2022–23 November 2022 (approximately corresponding with trends in US cases (CDC, 2023)). Stratified and subgroup analyses were adjusted for the same set of covariates as the primary analyses, with the following exceptions: we did not adjust for the stratification or restriction variable, and we did not adjust analyses of male exposure for female partner vaccination due to convergence issues.

Analysis of preconception SARS-CoV-2 infection

In a secondary analysis, we described the history of SARS-CoV-2 infection in the study population (defined as a positive test). Among individuals who tested positive for SARS-CoV-2 before conception, we fit a restricted cubic spline model to assess the possibly non-linear relationship between recency of infection and risk of miscarriage (Durrleman and Simon, 1989; Ruifeng *et al.*, 2011). We conducted this analysis for both female and male partner infection.

Post hoc analyses

We hypothesized that vaccine-related reductions in the occurrence and severity of COVID-19 infection, as well as symptoms of stress, could be plausible mechanisms by which vaccinations reduce the risk of miscarriage. We conducted two post hoc descriptive analyses to explore these relationships. First, we compared early pregnancy PSS-10 scores between vaccinated and unvaccinated female participants among those who completed the early pregnancy questionnaire (completed at a median of 9 GW). There is some evidence that psychological stress may increase the risk of miscarriage (Meaney *et al.*, 2014; Qu *et al.*, 2017), and it is plausible that individuals who were vaccinated would experience different levels of perceived stress in the context of the pandemic. Second, we compared the risk of first-trimester SARS-CoV-2 infection (defined as a positive test) between vaccinated and unvaccinated female participants. While there is no plausible biologic mechanism by which COVID-19 vaccination would directly affect miscarriage, vaccination reduces the risk of severe infection (Polack *et al.*, 2020; Baden *et al.*, 2021; Sadoff *et al.*, 2021; Collie *et al.*, 2022), which may affect pregnancy outcomes (Allotey *et al.*, 2020).

Missing data

We used multiple imputation with the fully conditional specification method to impute missing values for covariates and gestational age at miscarriage. Most covariates had no missingness; however, for those with missing data, missingness ranged from 1 record (<1%; smoking status) to 41 records (2%; use of fertility treatment). We imputed gestational age at miscarriage for 16 participants (<1%). Date of first positive pregnancy test was missing for 54 participants (3%). For this variable, we used simple imputation and set missing values to 4 GW (median gestational age at first positive pregnancy test among all women with available data).

Results

Female partner vaccination

There were 1815 female participants eligible for this analysis. The median week at the first positive pregnancy test was 4 GW (range: 3–9 weeks). Among participants with a censoring event, 12 reported induced abortion, 20 reported ectopic pregnancy, 168 were lost to follow-up, and 1169 had an ongoing pregnancy at 20 GW. A total of 455 (25%) participants were unvaccinated at the time of conception, 1360 (75%) had received at least one dose of a COVID-19 vaccine any time before conception, 1186 (65%) had received a full primary sequence any time before conception, and 339 (19%) had completed the sequence ≤3 months before conception (Table 1). Most vaccinated participants (95%) received their first dose before 1 June 2021, although male partners were vaccinated slightly later than their female partners on average (Supplementary Fig. S1). Less than 1% of participants received the J&J/Janssen vaccine, while 35.8% received Moderna and 58.2% received Pfizer-BioNTech (Fig. 1). Loss to follow-up after pregnancy recognition occurred in 11% of unvaccinated participants and 9% of participants who had received at least one dose.

On average, participants reported a first positive pregnancy test at 4 GW, regardless of vaccination status (Table 1). The average age and BMI of participants at conception were 31 years and 26 kg/m^2, respectively. Compared with unvaccinated individuals, vaccinated individuals had greater educational attainment and household income; were more likely to have private health insurance, to be nulliparous, and to have conceived using fertility treatment; and were less likely to have a history of miscarriage.

Overall, 446 (24.6%) participants experienced a miscarriage. The distribution of GW at pregnancy loss, overall and stratified by COVID-19 vaccination status, is presented in Fig. 2. Approximately three-quarters of miscarriages occurred <8 GW,

Table 1. Baseline characteristics of female PRESTO participants according to preconception COVID-19 vaccination status (December 2020–November 2022; N = 1815).

	Female vaccination status			
			Full primary sequence completed:	
	Never vaccinated before conception	Ever vaccinated before conception	Any time before conception	≤3 months before conception
Number of participants, N	**n = 455**	**n = 1360**	**n = 1186**	**n = 339**
Gestational age at pregnancy recognition (weeks), mean	4.0	4.1	4.1	4.1
Age (years), mean	30.6	31.3	31.3	31.2
BMI (kg/m^2), mean	26.5	26.3	26.4	26.2
Race/ethnicity, %				
White, non-Hispanic	84.6	85.9	86.0	87.0
Hispanic	7.0	6.7	6.3	5.5
Black, non-Hispanic	1.9	0.9	0.9	0.8
Asian, non-Hispanic	1.6	2.3	2.5	2.6
Multiracial/other race	4.9	4.2	4.4	4.2
Region of residence, %				
Northeast	15.0	20.1	20.4	18.6
South	21.8	22.0	21.4	22.6
Midwest	16.5	20.9	21.4	20.8
West	17.6	20.2	21.0	22.4
Canada	29.2	16.8	15.8	15.6
Smoking status, %				
Current smoker	3.4	2.2	2.2	2.9
Past smoker	9.8	7.6	7.7	7.2
Never smoker	86.8	90.2	90.1	89.9
Educational attainment, %				
≤High school	3.6	0.9	0.9	0.8
Some college	16.7	6.7	6.9	7.4
College degree	33.5	31.3	31.2	31.8
Graduate school	46.3	61.1	61.1	60.0
Annual household income (USD), %				
<50 000	12.5	6.3	6.3	8.2
50 000–99 999	36.7	24.1	23.6	25.2
100 000–149 999	27.4	32.8	32.8	30.9
≥150 000	23.4	36.8	37.4	35.8
Currently employed, %	82.5	92.0	92.1	92.3
Hours per week of work (mean)	31.3	35.6	35.8	35.1
Occupation in healthcare industry, %	18.5	33.2	35.3	26.2
Private health insurance (among US residents only), %	64.4	81.4	82.5	82.1
Number of primary care visits in the past year, %				
0	15.8	14.0	13.8	12.1
1	33.5	39.1	39.9	38.3
2–3	37.1	36.7	36.6	38.6
≥4	13.7	10.2	9.8	11.0
Diabetes mellitus, %	0.9	1.1	1.2	0.9
Hypertension, %	0.9	1.2	1.3	1.2
Asthma, %	15.7	15.9	15.7	14.5
Daily use of multivitamins/folic acid, %	88.6	92.1	91.6	90.7
Perceived Stress Scale score, %				
<10	13.0	14.7	15.0	14.2
10–14	23.8	27.7	28.2	27.1
15–19	30.4	30.2	29.8	31.9
20–24	22.3	19.0	18.4	17.6
≥25	10.6	8.4	8.6	9.2
Major Depression Inventory score, %				
<10	52.0	57.1	57.6	53.6
10–19	31.8	30.2	29.8	33.5
20–29	12.1	9.8	9.6	10.8
≥30	4.1	3.0	3.0	2.2
Hours per night of sleep, %				
<6	4.4	2.3	2.4	3.4
6–8	88.7	89.2	89.1	86.7
≥9	7.0	8.5	8.5	10.0
Total number of menstrual cycles tried to conceive, mean	5.6	6.1	6.2	5.3
Parous, %	45.2	33.4	33.1	38.1
Menstrual cycle length (days), mean	29.5	29.6	29.5	29.2
Regular menstrual cycle, %	82.2	84.7	84.6	84.6
History of sexually transmitted infection, %	15.2	10.3	10.7	10.1
Ever diagnosed with endometriosis, %	4.2	2.4	2.0	1.7
Ever diagnosed with polycystic ovarian syndrome, %	6.4	7.0	7.0	6.2

(continued)

Table 1. Continued

	Female vaccination status			
			Full primary sequence completed:	
	Never vaccinated before conception	Ever vaccinated before conception	Any time before conception	≤3 months before conception
History of miscarriage, %	35.3	27.7	27.6	33.6
History of subfertility or infertility in previous attempts, %	18.4	14.1	14.2	15.1
Conceived study pregnancy through fertility treatment, %	4.0	8.8	9.5	4.3

USD, United States Dollar.
All characteristics except for age were age-standardized.

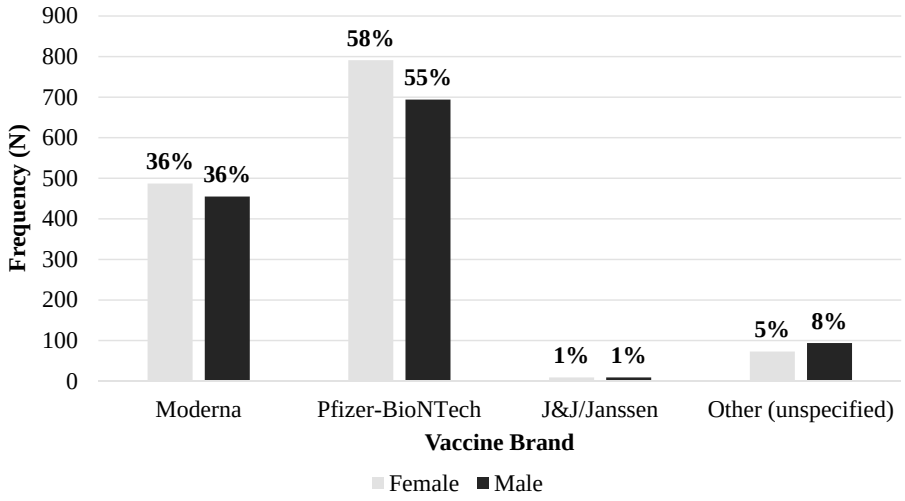

Figure 1. Distribution of the type of COVID-19 vaccine received, among 1360 female and 1252 male participants who were vaccinated before conception (PRESTO December 2020–November 2022). Participants in the 'Other (unspecified)' category did not indicate which brand of vaccine they received.

and the weekly distribution of miscarriage was similar across exposure groups. Risk of miscarriage was 26.6% among unvaccinated female participants, 23.9% among female participants who had received ≥1 dose before conception, 24.5% among those who completed a full primary sequence before conception, 22.1% among those who completed the sequence ≤3 months before conception (Table 2), and 20.1% among those who received only one dose of a two-dose vaccine before conception. Results were similar between age-adjusted models and propensity score-weighted models. The distributions of the propensity scores were similar between vaccinated (≥1 dose before conception) and unvaccinated (0 doses before conception) individuals after truncation: the distributions of the propensity scores are presented before and after weighting in Supplementary Figs S2 and S3, respectively. The propensity score weights ranged from 0.14 to 135.67 before truncation and 0.14 to 3.93 after truncation among unvaccinated participants (Supplementary Table S1). In the main analysis of female vaccination (ever versus never vaccinated before conception), 0.1% of unvaccinated participants and 7.5% of vaccinated participants were trimmed. The propensity score-weighted IRR comparing individuals who received at least one dose any time before conception versus those who were never vaccinated before conception was 0.85 (95% CI: 0.63, 1.14) (Table 2). The propensity score-weighted IRR comparing individuals who completed a full primary sequence within 3 months before conception versus those who were never vaccinated before conception was 0.72 (95% CI: 0.51, 1.01). The IRR comparing individuals who were fully vaccinated ≤3 months before conception with those who were fully vaccinated >3 months before conception was 0.58 (0.38, 0.89), suggesting that vaccination nearer to conception may be protective.

Stratified analyses

Figure 3 presents propensity score-weighted IRRs and 95% CIs for subgroup and stratified analyses comparing female participants who had received ≥1 dose of a vaccine with those who were unvaccinated before conception. Among US residents, the IRR was somewhat attenuated compared with the primary analysis (IRR = 0.94; 95% CI: 0.68, 1.28). The IRRs for all subgroups indicated a moderate inverse association between vaccination and miscarriage, but all CIs were consistent with no effect. There were no substantial variations in IRRs among those without fertility treatment (IRR = 0.87; 95% CI: 0.64, 1.19), among those with no history of miscarriage (IRR = 0.83; 95% CI: 0.57, 1.23), or by vaccine brand (Moderna IRR = 0.80; 95% CI: 0.55, 1.17; Pfizer-BioNTech IRR = 0.90; 95% CI: 0.66, 1.22). There was a slightly stronger inverse association for early miscarriage (GW <8; IRR = 0.77; 95% CI: 0.54, 1.11) compared with late miscarriages (GW ≥8; IRR = 0.92; 95% CI: 0.51, 1.66). IRRs were similar for conceptions during 20 December 2020–31 May 2021 (IRR = 0.72; 95% CI: 0.47, 1.08) and 1 June 2021–31 October 2021 (IRR = 0.70; 95% CI: 0.39, 1.25). There was a substantially stronger inverse association for conceptions during 1 November 2021–23 November 2022, but the CI was wide (IRR = 0.53; 95% CI: 0.22, 1.30).

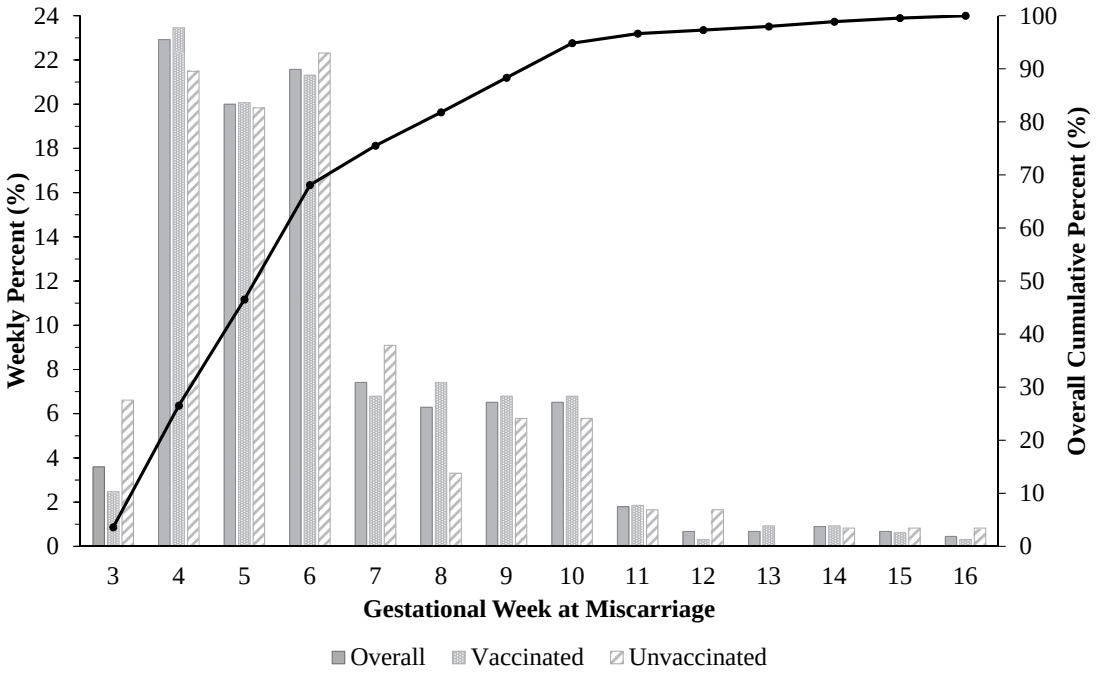

Figure 2. Distribution of timing of miscarriage in PRESTO, overall and according to COVID-19 vaccination status, December 2020–November 2022. Vaccinated individuals received at least one dose of a COVID-19 vaccine before pregnancy, while unvaccinated individuals received zero doses before pregnancy. The shaded bars represent the percentage of miscarriages that occurred in each gestational week (e.g. about 4% of all miscarriages occurred during GW 3), overall and by vaccination status. The connected black points represent the weekly cumulative percentage of miscarriages, regardless of vaccination status (e.g. 75% of miscarriages occurred by 8 GW).

Table 2. Associations between vaccination status at the estimated date of conception and rate of miscarriage in PRESTO (December 2020–November 2022).

Vaccination status at date of conception	N	# GW	# miscarriages (%)	Age-adjusted IRR (95% CI)	PS-weighted IRR (95% CI)
Female partner vaccination (N = 1815)					
Never vaccinated	455	5290	121 (26.6%)	Reference	Reference
Ever vaccinated	1360	15 366	325 (23.9%)	0.88 (0.71, 1.08)	0.85 (0.63, 1.14)
Full primary sequence completed	1186	13 088	290 (24.5%)	0.91 (0.73, 1.12)	0.89 (0.64, 1.23)
≤3 months before conception	339	4363	75 (22.1%)	0.77 (0.58, 1.03)	0.72 (0.51, 1.01)
Male partner vaccination (N = 1570)					
Never vaccinated	427	5303	90 (21.1%)	Reference	Reference
Ever vaccinated	1143	13 227	263 (23.0%)	1.06 (0.84, 1.35)	0.90 (0.56, 1.44)
Full primary sequence completed	953	10 717	225 (23.6%)	1.11 (0.86, 1.41)	0.86 (0.53, 1.40)

GW, gestational weeks; IRR, incidence rate ratio; PS, propensity score.
PS-weighted models adjusted for: age (years); BMI (kg/m^2); race/ethnicity (non-Hispanic white, non-Hispanic Black, non-Hispanic Asian, non-Hispanic other race, Hispanic); geographic region of residence (Northeastern USA, Southern USA, Midwestern USA, Western USA, Canada); current smoking (yes/no); educational attainment (≤high school, some college, college degree, graduate school); private health insurance (yes/no); number of primary care visits in the past year (0, 1, 2-3, ≥4); household income (<50 000, 50 000–99 999, 100 000–149 999, ≥150 000 USD); employment status (yes/no); hours per week of work; diabetes (yes/no); hypertension (yes/no); asthma (yes/no); daily use of multivitamins and folate supplements (yes/no); 10-item Perceived Stress Scale score; Major Depression Inventory score; sleep duration (<6, 6–8, ≥9 h/night); number of cycles of pregnancy attempt for the current pregnancy; parity (yes/no); history of miscarriage (yes/no); use of fertility treatment for the current pregnancy (yes/no); history of sub- or infertility (yes/no); history of SARS-CoV-2 infection (yes/no); and calendar month at conception. Analyses of male partner vaccination were additionally adjusted for female partner vaccination status.

Analysis of female SARS-CoV-2 infection

There were 72 (24.5%) miscarriages among 294 female individuals who tested positive for SARS-CoV-2 any time before conception. Among female participants with a history of infection, 83 tested positive during the 90 days before conception; there were 26 (31.3%) miscarriages in this group. The restricted cubic spline indicated little association between recency of preconception infection and miscarriage (Supplementary Fig. S4).

Post hoc analyses

In a subset of female participants with data available on perceived stress levels during early pregnancy (n = 1519), the mean PSS score of individuals who had received at least one dose of a vaccine was 14.4 (standard deviation = 6) compared with 15.8 among individuals who received 0 doses before conception (standard deviation = 6), indicating no substantial difference in stress levels between exposure groups.

The risk of first-trimester SARS-CoV-2 infection was also similar between individuals who had received ≥1 dose of a COVID-19 vaccine before conception (3.1%), those who completed their full primary sequence before conception (3.4%), and those who were never vaccinated before conception (2.6%). These findings are not indicative of a strong mediating role of prenatal stress or SARS-CoV-2 infection in the association between preconception vaccination and miscarriage, though we were unable to evaluate the severity of infection.

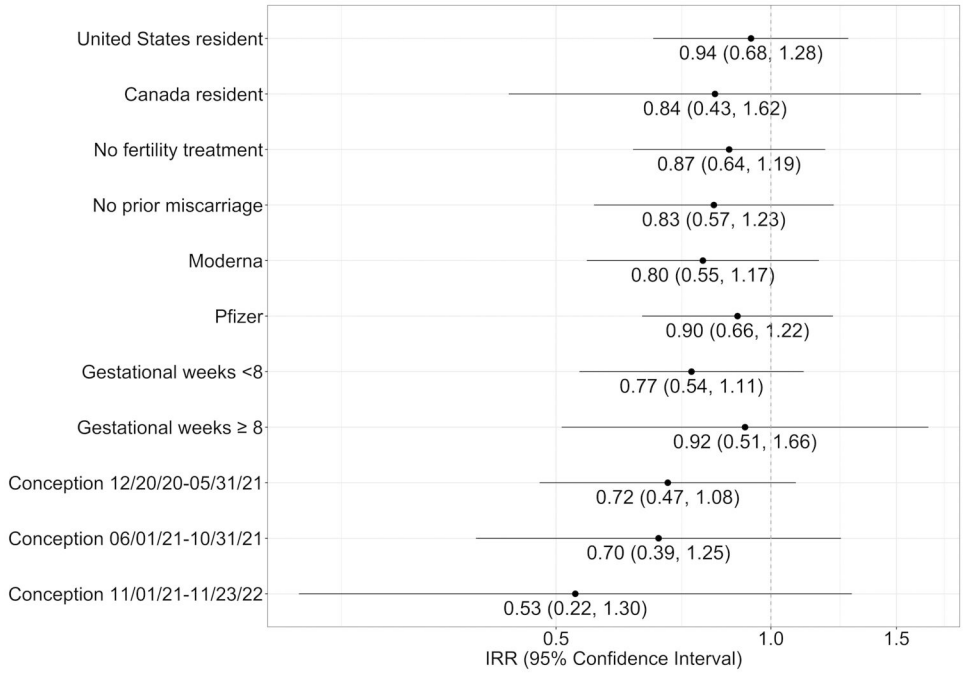

Figure 3. Subgroup and stratified analyses comparing female participants who had received at least one dose of a COVID-19 vaccine with those who were unvaccinated, PRESTO (December 2020–November 2022).

Male partner vaccination and infection

Selected baseline characteristics of study participants by male partner vaccination status are presented in Supplementary Table S2. Among couples with data on male partner vaccination (N = 1570), 353 pregnancies (22.5%) resulted in miscarriage (Table 2). After adjusting for maternal age, the IRR comparing couples where the male partner had ever been vaccinated before conception versus couples where the male partner had never been vaccinated was 1.06 (95% CI: 0.84, 1.35). The propensity score-weighted IRR was 0.90 (95% CI: 0.56, 1.44). The IRR for completing a full primary sequence was 1.11 (95% CI: 0.86, 1.41) in age-adjusted models and 0.86 (95% CI: 0.53, 1.40) in propensity score-adjusted models. The results from all stratified analyses were consistent with no effect of male partner vaccination on miscarriage (Fig. 4).

When we assessed male partner infection, the restricted cubic spline indicated a slight U-shaped association between recency of preconception paternal infection and miscarriage (Supplementary Fig. S5). Couples with male partner infection ~6 months before conception had the lowest rate of miscarriage.

Discussion

In this prospective preconception cohort study of 1815 pregnancies conceived since December 2020, we evaluated the association between COVID-19 vaccination and miscarriage. Approximately three-quarters of participants (both male and female) had received at least one dose of a COVID-19 vaccine at any time before conception. Nearly 25% of participants experienced miscarriage, with 75% of miscarriages occurring before 8 GW. Our findings indicate a slightly lower rate of miscarriage among individuals who were vaccinated against COVID-19 before pregnancy compared with unvaccinated individuals, though the CIs were largely consistent with no effect of vaccination on miscarriage. Results were similar for female and male partner vaccination, and there was no substantial variation in results across clinical and demographic subgroups. Importantly, COVID-19 vaccination was not associated with an increased risk of either early miscarriage (GW <8) or late miscarriage (GW ≥8).

Our findings are consistent with previous studies, which indicate no harmful effect of COVID-19 vaccination on miscarriage (Kharbanda *et al.*, 2021; Shimabukuro *et al.*, 2021; Trostle *et al.*, 2021; Zauche *et al.*, 2021; Calvert *et al.*, 2022; Citu *et al.*, 2022; Favre *et al.*, 2022; Hagrass *et al.*, 2022; Kalafat *et al.*, 2022; Prasad *et al.*, 2022). Several comparative studies have been conducted. Calvert *et al.* (2022) analyzed data from 18 780 pregnant individuals who were vaccinated during 6–19 GW, 56 340 historical controls (pre-pandemic), and 18 780 contemporary controls (during pandemic vaccination period). The authors reported similar rates of miscarriage across the three groups. A prospective cohort study evaluated pregnancy outcomes among 1012 Swiss individuals who received at least one dose of an mRNA vaccine between 1 week before LMP and 20 GW (Favre *et al.*, 2022). However, there were only two miscarriages reported in this study. A retrospective study of 3094 pregnancies in Romania evaluated the odds of miscarriage comparing individuals who received an mRNA COVID-19 vaccination with unvaccinated individuals in analogous 4-week periods during the first trimester. The authors reported no meaningful association between vaccination and miscarriage (Citu *et al.*, 2022). Kharbanda *et al.* (2021) analyzed data from 105 446 pregnancies in the Vaccine Safety Datalink during 15 December 2020 through 28 June 2021; miscarriage was not associated with COVID-19 vaccination (odds ratio = 1.02; 95% CI: 0.96, 1.08).

Three studies evaluated the risk of miscarriage among vaccinated individuals without a comparison group. Zauche *et al.* (2021) analyzed data from the CDC v-safe COVID-19 vaccine pregnancy registry. Among 2465 pregnant participants who were vaccinated before 20 GW, the cumulative risk of miscarriage after 6 GW was 14.1%. Shimabukuro *et al.* (2021) utilized data from three US vaccine safety monitoring systems and reported that the risk of miscarriage among vaccinated pregnant individuals

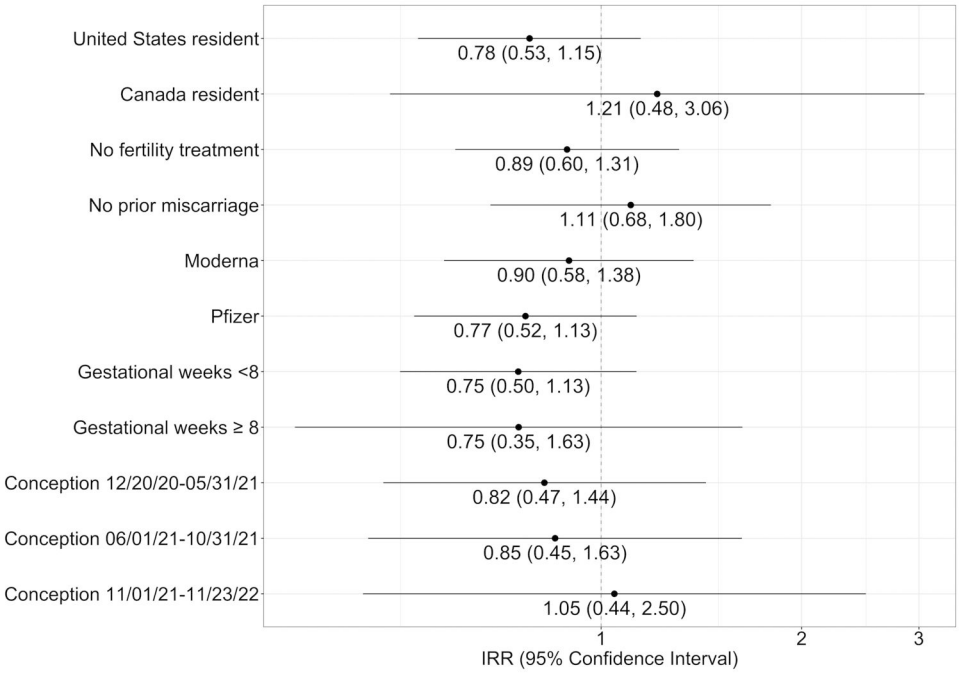

Figure 4. Subgroup and stratified analyses comparing participants whose male partner had received at least one dose of a COVID-19 vaccine with those whose partner was unvaccinated, PRESTO (December 2020–November 2022).

was within the range of expectation. Using electronic medical record data, Trostle *et al.* (2021) evaluated pregnancy outcomes among 424 pregnant individuals who received an mRNA vaccination and reported that 6.5% of pregnancies resulted in miscarriage.

Most studies on COVID-19 vaccination and miscarriage have relatively low ascertainment of early miscarriage (<8 GW) because follow-up begins several weeks after typical pregnancy recognition and inclusion depends on receipt of healthcare. Further, no previous study was able to evaluate gestational timing of miscarriage in relation to vaccination. Although miscarriages occurring earlier than 6 GW are often not detected in a healthcare clinic, a large proportion of these early losses are recognized by individuals who are actively trying to conceive and are regularly using home pregnancy tests (Wilcox *et al.*, 1988). In the present study, we identified pregnancies as early as 3 GW and almost all participants used at-home pregnancy tests. Approximately three-quarters of reported miscarriages occurred before 8 GW, highlighting the need for early assessment of pregnancy outcomes. In analyses stratified by gestational timing, there was little indication of an increased risk of early miscarriage (<8 GW) associated with vaccination.

Only one other study evaluated the association between preconception (rather than prenatal) COVID-19 vaccination and miscarriage. Aharon *et al.* (2022) conducted a retrospective cohort study of individuals undergoing *in vitro* fertilization during February through May 2021. The adjusted odds ratio for clinical pregnancy loss was 1.02 (95% CI: 0.51, 2.06), comparing individuals who had received two doses of an mRNA vaccine at least 14 days before cycle initiation with those who had received zero doses. To our knowledge, no prior studies have examined the relation between paternal COVID-19 vaccination and miscarriage, though studies have suggested no effect of male COVID-19 vaccination on semen quality (Gonzalez *et al.*, 2021) or fecundability (Wesselink *et al.*, 2022).

The present study relied on self-reported vaccination status and infection history. Thus, there may be some non-differential misclassification of vaccination status. However, validation studies of influenza vaccination in the past year found 97% agreement between self-reported vaccination status and medical records (King *et al.*, 2018). It is likely that reporting of COVID-19 vaccination would be similar and highly accurate. Although SARS-CoV-2 infection was not the primary exposure of interest, under-ascertainment of infection data may have impacted our results. Participants may have had an asymptomatic infection or lacked timely access to a COVID-19 test. Thus, while we expect that the date of a positive COVID-19 test would have been reported with reasonably high accuracy, our evaluation of early pregnancy infection (classified as yes/no) may be biased. Misclassification of male partner vaccination is also possible, given that we relied on female partner reports for ~70% of couples in the male vaccination analysis. Finally, residual confounding may have affected our results, though we adjusted for a wide range of sociodemographic, lifestyle, medical, and reproductive characteristics. We considered additionally adjusting for miscarriage risk factors such as STI history and endometriosis. However, adjusting for these factors did not appreciably change our findings.

Conclusion

This is the first prospective cohort study with preconception enrollment and regular bimonthly follow-up to evaluate the relationship between preconception female and male COVID-19 vaccination and miscarriage, representing a broad range of gestational ages at loss (4–19 GW) and a large percentage of early losses (<8 GW: 75%). Our findings indicate no harmful effect of vaccination on miscarriage. Further, the rate of miscarriage among vaccinated individuals was comparable with that of PRESTO participants who conceived before the COVID-19 pandemic. These findings are informative for individuals planning a pregnancy, their families, and their healthcare providers.

Data availability

The data underlying this article cannot be shared publicly, as PRESTO participants did not provide informed consent to share their data with external entities.

Authors' roles

J.J.Y. was responsible for formulation of the study hypotheses and study design, statistical analyses, results interpretation, manuscript writing, revision, and finalization. A.K.W., E.E.H., and L.A.W. were responsible for study design, development and implementation of the study cohorts, and manuscript revision. All authors were responsible for study design, analysis methods, results interpretation, and manuscript revision. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Conflict of interest

L.A.W. is a fibroid consultant for AbbVie, Inc. She also receives in-kind donations from Swiss Precision Diagnostics (Clearblue home pregnancy tests) and Kindara.com (fertility apps). Michael Eisenberg received consulting fees from Ro, Hannah, Dadi, VSeat, and Underdog, holds stock in Ro, Hannah, Dadi, and Underdog, is a past president of SSMR, and is a board member of SMRU. K.F.H. reports being an investigator on grants to her institution from UCB and Takeda, unrelated to this study. S.H.-D. reports being an investigator on grants to her institution from Takeda, unrelated to this study, and a methods consultant for UCB and Roche for unrelated drugs. The authors report no other relationships or activities that could appear to have influenced the submitted work.

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