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Risk of Miscarriage in Relation to Seasonal Influenza Vaccination Before or During Pregnancy

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OBJECTIVE: To evaluate the association between seasonal influenza vaccination and miscarriage using data from an ongoing, prospective cohort study.

METHODS: We analyzed 2013–2022 data from PRESTO (Pregnancy Study Online), a prospective prepregnancy cohort study of female pregnancy planners and their male partners in the United States and Canada. Female participants completed a baseline questionnaire and then follow-up questionnaires every 8 weeks until pregnancy, during early and late pregnancy, and during the postpartum period. Vaccine information was self-reported on all questionnaires. Miscarriage was identified from self-reported information during follow-up. Male partners were invited to complete a baseline questionnaire only. We used Cox proportional hazard models to estimate the hazard ratio (HR) and 95% CI for the association between vaccination less than 3 months before pregnancy detection through the 19th week of pregnancy and miscarriage, with gestational weeks as the time scale. We modeled vaccination as a time-varying exposure and used propensity-score fine stratification to control for confounding from seasonal and female partner factors.

RESULTS: Of 6,946 pregnancies, 23.3% of female partners reported exposure to influenza vaccine before or during pregnancy: 3.2% during pregnancy (gestational age 4–19 weeks) and 20.1% during the 3 months before pregnancy detection. The miscarriage rate was 16.2% in unvaccinated and 17.0% among vaccinated participants. Compared with no vaccine exposure, influenza vaccination was not associated with increased rate of miscarriage when administered before (HR 0.99, 95% CI 0.81–1.20) or during (HR 0.83, 95% CI 0.47–1.47) pregnancy. Of the 1,135 couples with male partner vaccination data available, 10.8% reported vaccination less than 3 months before pregnancy. The HR for the association between male partner vaccination and miscarriage was 1.17 (95% CI 0.73–1.90).

CONCLUSION: Influenza vaccination before or during pregnancy was not associated with miscarriage.

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Pregnant individuals are up to five times more likely to be hospitalized with influenza than nonpregnant individuals.[1] The American College of Obstetricians

and Gynecologists recommends influenza vaccination as standard prenatal care, stating that all individuals who are or will become pregnant during influenza season should receive an influenza vaccine.[2] This recommendation is supported globally by the World Health Organization.[3] About 50–61% of pregnant individuals in the United States receive an influenza vaccine before or during pregnancy,[4,5] and vaccination rates are lower during early pregnancy.[6] Concerns about the safety of influenza vaccination on pregnancy-related outcomes are commonly cited as factors contributing to reduced vaccination uptake.[7]

Numerous studies have assessed the association of influenza vaccination with health outcomes at delivery; fewer studies have evaluated miscarriage,[8,9] and the results of existing studies have been conflicting. Although the majority of previous studies have reported no risk of miscarriage associated with influenza vaccination,[10] two studies have reported a protective effect of pandemic influenza vaccination on miscarriage,[11,12] and a 2017 Vaccine Safety Datalink study identified a twofold increase in the odds of miscarriage associated with vaccination during the current and previous influenza seasons.[9] Although the strength and validity of the Vaccine Safety Datalink study were questioned by scientists because of sparse data[13,14] and an updated analysis with a larger patient cohort indicated no association,[15] surveys of obstetricians show that media reports from this study increased their concerns about influenza vaccine safety.[16] One in five obstetricians surveyed changed the way that they recommend influenza vaccine, with many reporting that they do not recommend vaccination during the first trimester.[16] To address this, we analyzed prospectively collected data from a large North American prepregnancy cohort study.

METHODS

PRESTO (Pregnancy Study Online) is a web-based prospective cohort study of couples residing in the United States and Canada (2013–present).[17] We recruited participants using targeted banner advertisements on social media, pregnancy-related and health-related websites, and parenting blogs. Eligible participants include self-identified women 18–45 years of age who are trying to conceive with a male partner and not using contraception or fertility treatments. Female participants can also invite their male partners to enroll. This study was approved by the IRB at the Boston University Medical Campus, and all participants provided online informed consent.

Eligible female participants completed an online baseline questionnaire that collects sociodemographic, lifestyle, and health information and follow-up questionnaires every 8 weeks until self-reported pregnancy. Additional questionnaires were administered early in pregnancy (at first self-report of pregnancy), late in pregnancy (about 32 gestational weeks), and 6 months postpartum. Participants were offered 6–12 free home pregnancy tests and a premium subscription to a fertility tracking application.[18] The majority of participants used home pregnancy tests at around 4 weeks of gestation.[18] Participants were given the option to withdraw using a standard withdrawal form.

Miscarriage was defined as a spontaneous intrauterine pregnancy loss, including biochemical pregnancy and blighted ovum, before 20 weeks of completed gestation. We identified miscarriage on the basis of self-reported information obtained from all available follow-up information (Appendix 1, available online at http://links.lww.com/AOG/D246). Participants could also report the occurrence of an ectopic or tubal pregnancy or an induced abortion. For participants lost to follow-up, we attempted to determine pregnancy outcome by emailing and phoning participants, searching social media, using information from fertility-tracking applications, searching online for baby registries, or linking to birth registries in selected states (California, Florida, Massachusetts, Michigan, Ohio, Pennsylvania, Texas, and New York).[19] Participants reporting miscarriage also recorded gestational weeks at loss and date the pregnancy ended. Among participants who did not provide their gestational weeks but gave their pregnancy due date (11%), we estimated gestational weeks at loss as follows: [pregnancy end date−(pregnancy due date−280 days)]/7. When gestational weeks at miscarriage and pregnancy due date were missing (21%), we estimated gestational weeks at loss as follows: (pregnancy end date−last menstrual period date)/7. Previous validation data from PRESTO have demonstrated high accuracy of these methods in estimating gestational age relative to birth record data.[19]

As part of the baseline questionnaire, female participants reported whether they had received an influenza vaccine in the past 12 months and the date of vaccination. During each subsequent questionnaire, participants were asked whether they had received an influenza vaccine in the past 2 months and the date of vaccination (Appendix 1, http://links.lww.com/AOG/D246). We used the date of the vaccination in relation to the last menstrual period and date of pregnancy detection (measured by first positive pregnancy test) to determine whether immunization occurred 1) during pregnancy (4–19 weeks of gestation), 2) during

the 3 months before pregnancy detection (less than 3 months before last menstrual period or 0–3 weeks of gestation), or 3) 3–12 months before the last menstrual period.

We defined an individual as *vaccinated* if they reported receipt of an influenza vaccine 3 months before pregnancy detection or during the first 19 weeks of pregnancy. For our primary analysis, we defined an individual as *unvaccinated* if they reported no receipt of influenza vaccine during the 3 months before pregnancy detection through the 19th week of pregnancy. For participants who completed the baseline questionnaire within the preceding 12 months overlapping the vaccine availability period of the previous influenza season (ie, September–January), we examined exposure to influenza vaccine during the previous season. We used this information to classify participants as vaccinated in the previous year only, in the current year only, in both the previous and current years, or in neither the previous nor current year.

Male partners reported information on receipt of influenza vaccine during the 12 months preceding their baseline questionnaire. To ensure complete exposure information, we included only male partners who completed the baseline survey within 3 months of the couples' last menstrual period. We classified male partners as vaccinated if they reported vaccination during the 3 months before the last menstrual period. Using male and female partner vaccination status, we classified couples as female partner only vaccinated (either 3 months before or during pregnancy), male partner only vaccinated, both partners vaccinated, or neither partner vaccinated.

We restricted analyses to participants with an intrauterine pregnancy, who had the opportunity to receive seasonal influenza vaccination during either the 3 months before pregnancy detection or during the first 19 weeks of pregnancy (ie, if these periods overlapped September–January), and who had complete information on influenza vaccination. We compared rates of miscarriage among vaccinated and unvaccinated participants using a Cox proportional hazard model with gestational weeks as the time scale. Participants contributed observation time from the date of first pregnancy detection to the date of miscarriage, induced abortion, withdrawal or loss to follow-up, or 20 weeks of gestation. We treated influenza vaccination at any time during the 3 months before pregnancy detection as a fixed exposure. To account for time-varying influenza vaccination during pregnancy and to avoid immortal time bias,[20,21] we treated vaccination during pregnancy as a time-varying exposure by partitioning observation time by exposure status.[22] Participants who were vaccinated during pregnancy contributed unvaccinated person-time until the date of vaccination, after which time they contributed vaccinated person-time. Participants who were vaccinated before pregnancy contributed only vaccinated person-time, and participants who remained unvaccinated contributed unvaccinated person-time throughout the observation period. Because the composition of influenza vaccines can change annually, we estimated rates of miscarriage overall and by year, when numbers sufficed.

Models incorporated inverse probability of censoring weights to account for bias attributable to differential loss to follow-up.[23] We used propensity-score fine stratification to adjust for confounding.[24] Briefly, we fit a logistic regression model to estimate the probability of vaccination conditional on potential confounders that were identified from bivariate analyses and prior literature,[25,26] including the female partner's age, race and ethnicity, education, household income, region of residence, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), asthma diagnosis, thyroid disease, cigarette smoking status, marijuana use, history of miscarriage, parity, and frequency of primary care visits. Race and ethnicity were self-identified by respondents and were included as confounding variables according to documented differences in vaccination rates[27] and miscarriage rates.[28] Month and year of the last menstrual period were included as an interaction term. Propensity scores in the 5th and 95th percentiles were trimmed.

We performed several sensitivity analyses to test the consistency of our findings. First, we considered alternative definitions to our unvaccinated comparator. To avoid possible influence from earlier exposure to influenza vaccines, we excluded those who were vaccinated 3–12 months before pregnancy from analysis. In another model, we considered those vaccinated 3–12 months before pregnancy as the unvaccinated comparator because these individuals could be more like those vaccinated before or during pregnancy in terms of health-seeking behavior.

To evaluate the influence of induced abortion, which could share pathogenetic pathways with miscarriage (especially in a cohort of pregnancy planners in whom elective terminations are unlikely), we compared the risk of any reported intrauterine fetal loss during the first 20 weeks of pregnancy by vaccination status. To further avoid potential time-varying confounding by seasonality,[29] we restricted the analytic sample to those with a last menstrual period during the time period when most influenza

vaccines are administered before or during early pregnancy (July–December). Finally, to evaluate the influence of inaccurate reporting, we restricted the analysis to include only miscarriages reported during the first 28 weeks after the last menstrual period, thereby excluding retrospectively reported miscarriages that may be more prone to reporting error.

We considered the possible influence of exposure misclassification in quantitative bias analyses using the episensr package in R.[30] Inputs for the sensitivity and specificity values for self-reported influenza vaccination status were informed by published validation studies of self-reported influenza vaccination status among reproductive-aged adults between 18 and 49 years of age (lower bound for estimated sensitivity 98%, lower bound for estimated specificity 95%).[30] In addition, we considered a wider range of sensitivity values using a probabilistic sensitivity analysis to correct for exposure misclassification (range in values 70–100%, replications 100,000).[31]

Missing covariate information and gestational age were multiply imputed with fully conditional specification methods with 20 data sets. Missing data ranged from 0% (eg, age, race and ethnicity) to 2.7% (income). We pooled effect estimates and standard errors in SAS using the MIANALYZE command.

RESULTS

We identified a total of 7,748 pregnancies between June 2013 and February 2022: 56 were ectopic, 35 ended in an induced abortion, 1,476 ended in miscarriage (26 of which were identified as blighted ovum), and the remaining 6,181 were ongoing to 20 gestational weeks. Of the 7,692 intrauterine pregnancies, we excluded 18 pregnancies with no opportunity to receive influenza vaccination during the exposure period and 728 pregnancies with missing exposure information. The final analytic sample included 6,946 pregnancies, of which 1,135 had information on male partner vaccine exposure and 2,165 had information on vaccine exposure during the previous influenza season (Appendix 2, available online at http://links.lww.com/AOG/D246).

More than one-half of female participants (54.2%) reported any exposure to influenza vaccination: 221 (3.2%) were vaccinated between 4 and 19 weeks of pregnancy, 1,398 (20.1%) were vaccinated during the 3 months preceding pregnancy detection, and 2,146 (30.9%) were vaccinated during the 3–12 months preceding the last menstrual period. Between the 2012–2013 influenza season and the 2020–2021 influenza season, the percentage of pregnancies with no reported influenza vaccination during the 12 months preceding the last menstrual period declined from 44.4% to 32.3% (Appendix 3, available online at http://links.lww.com/AOG/D246). Median follow-up time was 14 weeks for female partners vaccinated between 4 and 19 weeks of gestation and 16 weeks for female partners vaccinated during the 3 months preceding pregnancy detection. Vaccination was more commonly reported by White, non-Hispanic participants residing in the United States, participants with higher education, nulliparous participants, participants reporting prenatal supplement use, and participants conceiving between July and December (Table 1). Vaccination was less commonly reported by those with a history of miscarriage. Examination of the standardized mean differences in covariates between vaccinated and unvaccinated participants (Fig. 1) and comparison of the probability of vaccination by exposure group before and after propensity score weighting indicated good balance (Appendix 4, available online at http://links.lww.com/AOG/D246).

Among the 1,135 participants with information on male partner vaccination, 123 male partners (10.8%) reported vaccination during the 3 months preceding the last menstrual period. For 23.6% (29/123) of these couples, only the male partner was vaccinated (Appendix 5, available online at http://links.lww.com/AOG/D246). Median follow-up time for male and female partner vaccination was 16 weeks. For the 2,165 female participants with information on the previous influenza season, 38 (1.7%) were vaccinated during the current season only, 867 (40.0%) during the previous season only, and 408 (18.8%) during the current and previous seasons (Appendix 6, available online at http://links.lww.com/AOG/D246). Median follow-up time was 16 weeks for female partners vaccinated during the previous season, vaccinated during the current and previous seasons, and never vaccinated. Median follow-up time was 12 weeks for female partners vaccinated in the current season only.

We identified 905 miscarriages in the final data set, of which 519 (57.3%) were identified around the time of the event (follow-up questionnaire n=480, early pregnancy questionnaire n=39), and 386 (42.7%) were identified later (withdrawal form n=28, late pregnancy questionnaire n=332, postpartum questionnaire n=20, fertility tracker or contact log n=6); 97.4% of miscarriages occurred before 13 weeks of gestation. The miscarriage rate was 16.2% in unvaccinated and 17.0% among vaccinated participants. After accounting for time at risk and controlling for confounders, the weighted hazard ratio (HR) was 0.98 (95% CI 0.81–1.18) (Table 2 and Fig. 2). There was no indication of an increased rate of miscarriage associated with influenza vaccination during the 3

Table 1. Baseline Characteristics of Participating Pregnant Individuals, by Exposure to Inactivated Influenza Vaccine Before or During Pregnancy (N=6,946)

Female Partner Characteristic	Total	Unvaccinated 12 mo or Longer Before LMP (n=3,181)	Vaccinated 3–12 mo Before LMP (n=2,146)		Vaccinated Less Than 3 mo Before Pregnancy Detection (n=1,398)		Vaccinated at 4–19 wk of Pregnancy (n=221)	
			Value	Std diff*	Value	Std diff*	Value	Std diff*
Age (y)	30.1±3.8	29.5±3.9	30.5±3.7	0.22	30.7±3.6	0.26	29.9±3.5	0.09
Race and ethnicity								
Asian or Pacific Islander	127 (1.8)	42 (1.3)	49 (2.3)	0.06	32 (2.3)	0.06	4 (1.8)	0.03
Black, non-Hispanic	123 (1.8)	74 (2.3)	35 (1.6)	−0.04	11 (0.8)	−0.11	3 (1.4)	−0.06
Hispanic or Latinx	430 (6.2)	211 (6.6)	122 (5.7)	−0.03	83 (5.9)	−0.02	14 (6.3)	−0.01
Multiple and races not listed†	277 (4.0)	132 (4.1)	85 (4.0)	0.00	53 (3.8)	−0.01	7 (3.2)	−0.04
White, non-Hispanic	5,989 (86.2)	2,722 (85.6)	1,855 (86.4)	0.02	1,219 (87.2)	0.04	193 (87.3)	0.04
Educational attainment (y)								
12 or less	204 (2.9)	156 (4.9)	22 (1.0)	−0.21	20 (1.4)	−0.18	6 (2.7)	−0.10
13–15	1,143 (16.5)	771 (24.2)	211 (9.8)	−0.34	145 (10.4)	−0.32	16 (7.2)	−0.43
16	2,427 (34.9)	1,165 (36.6)	708 (33.0)	−0.06	468 (33.5)	−0.05	86 (38.9)	0.04
17 or more	3,172 (45.7)	1,089 (34.2)	1,205 (56.1)	0.37	765 (54.7)	0.34	113 (51.1)	0.28
Household income ($)								
Less than 25,000	273 (3.9)	206 (6.5)	36 (1.7)	−0.22	29 (2.1)	−0.19	2 (0.9)	−0.28
25,000–49,999	686 (9.9)	449 (14.1)	142 (6.6)	−0.21	79 (5.7)	−0.25	16 (7.2)	−0.19
50,000–74,999	1,141 (16.4)	639 (20.1)	284 (13.2)	−0.16	189 (13.5)	−0.15	29 (13.1)	−0.16
75,000–99,999	1,353 (19.5)	656 (20.6)	389 (18.1)	−0.05	260 (18.6)	−0.04	48 (21.7)	0.02
100,000–124,999	1,191 (17.1)	469 (14.7)	422 (19.7)	0.11	250 (17.9)	0.07	50 (22.6)	0.16
125,000 or more	2,302 (33.1)	762 (23.9)	873 (40.7)	0.29	591 (42.3)	0.32	76 (34.4)	0.19
Region								
Northeast	1,547 (22.3)	626 (19.7)	448 (22.7)	0.06	369 (26.4)	0.13	64 (29.0)	0.17
South	1,566 (22.5)	734 (23.1)	508 (23.7)	0.01	278 (19.9)	−0.06	46 (20.8)	−0.05
Midwest	1,544 (22.2)	618 (19.4)	519 (24.2)	0.09	352 (25.2)	0.11	55 (24.9)	0.11
West	1,123 (16.2)	512 (16.1)	353 (16.5)	0.01	220 (15.7)	−0.01	38 (17.2)	0.02
Canada	1,166 (16.8)	691 (21.7)	278 (12.9)	−0.20	179 (12.8)	−0.20	18 (8.1)	−0.34
Mean BMI (kg/m^2)	26.7±6.5	27.2±6.7	26.3±6.2	−0.11	26.3±6.2	−0.11	26.7±6.9	−0.06
Medical diagnoses								
Asthma	1,133 (16.3)	498 (15.7)	379 (17.7)	0.04	224 (16.0)	0.01	32 (14.5)	−0.03
Depression	1,668 (24.0)	732 (23.0)	549 (25.6)	0.05	340 (24.3)	0.02	47 (21.3)	−0.03
Hypertension	96 (1.4)	35 (1.1)	35 (1.6)	0.03	22 (1.6)	0.03	4 (1.8)	0.05
Diabetes mellitus	70 (1.0)	30 (0.9)	23 (1.1)	0.02	13 (0.9)	0.00	4 (1.8)	0.06
Endometriosis	195 (2.8)	99 (3.1)	51 (2.4)	−0.04	42 (3.0)	0.00	3 (1.4)	−0.10
Uterine fibroids	159 (2.3)	73 (2.3)	57 (2.7)	0.02	26 (1.9)	−0.02	3 (1.4)	−0.06
GERD	363 (5.2)	117 (3.7)	132 (6.1)	0.09	98 (7.0)	0.11	16 (7.2)	0.04
Hay fever	665 (9.6)	251 (7.9)	232 (10.8)	0.08	157 (11.2)	0.09	25 (11.3)	0.09
Migraine	1,426 (20.5)	599 (18.8)	493 (23.0)	0.08	292 (20.9)	0.04	42 (19.0)	0.00
PCOS	420 (6.1)	208 (6.5)	118 (5.5)	−0.03	83 (5.9)	−0.02	11 (5.0)	−0.05
PTSD	118 (1.7)	51 (1.6)	37 (1.7)	0.01	28 (2.0)	0.02	2 (0.9)	−0.05
Thyroid disease	497 (7.2)	208 (6.5)	152 (7.1)	0.02	123 (8.8)	0.07	14 (6.3)	−0.01
Substance use								
Current marijuana use	941 (13.5)	480 (15.1)	262 (12.2)	−0.07	175 (12.5)	−0.06	24 (10.9)	−0.10
Current cigarette smoker	433 (6.2)	294 (9.2)	72 (3.4)	−0.21	63 (4.5)	−0.16	4 (1.8)	−0.30
Mean caffeine use (mg/d)	129.8±113.3	126.8±116.9	132.6±111.4	0.04	133.8±109.8	0.05	119.7±97.8	−0.05
Mean alcohol use (drinks/wk)	3.2±4.2	3.2±4.6	3.1±3.8	−0.02	3.1±4.0	−0.02	3.3±4.0	0.02
History of miscarriage	1,808 (26.0)	871 (27.4)	553 (25.8)	−0.03	333 (23.8)	−0.07	51 (23.1)	−0.08
Received fertility treatment	519 (7.5)	241 (7.6)	155 (7.2)	−0.01	108 (7.7)	0.00	15 (6.8)	−0.03

(*continued*)

Table 1. Baseline Characteristics of Participating Pregnant Individuals, by Exposure to Inactivated Influenza Vaccine Before or During Pregnancy (N=6,946) (*continued*)

Female Partner Characteristic	Total	Unvaccinated 12 mo or Longer Before LMP (n=3,181)	Vaccinated 3–12 mo Before LMP (n=2,146)		Vaccinated Less Than 3 mo Before Pregnancy Detection (n=1,398)		Vaccinated at 4–19 wk of Pregnancy (n=221)	
			Value	Std diff*	Value	Std diff*	Value	Std diff*
Parity								
Nulliparous	3,420 (49.2)	1,529 (48.1)	1,050 (48.9)	0.01	721 (51.6)	0.06	120 (54.3)	0.11
Primiparous	1,845 (26.6)	798 (25.1)	616 (28.7)	0.07	377 (27.0)	0.04	54 (24.4)	−0.01
Multiparous	1,681 (24.2)	854 (26.9)	480 (22.4)	−0.09	300 (21.5)	−0.10	47 (21.3)	−0.11
Frequency of contact with PCP in previous year								
None	876 (12.6)	474 (14.9)	244 (10.4)	−0.11	145 (10.4)	−0.11	33 (14.9)	0.00
Once	2,300 (33.1)	1,011 (31.8)	714 (33.3)	0.03	500 (35.8)	0.07	75 (33.9)	0.04
2–3 times	2,809 (40.4)	1,224 (38.5)	922 (43.0)	0.07	573 (41.0)	0.04	90 (40.7)	0.04
4–5 times	609 (8.8)	295 (9.3)	191 (8.9)	−0.01	108 (7.7)	−0.05	15 (6.8)	−0.08
6 or more times	352 (5.1)	177 (5.6)	95 (4.4)	−0.05	72 (5.1)	−0.02	8 (3.6)	−0.08
Prenatal supplement use	5,990 (86.2)	2,585 (81.3)	1,944 (90.6)	0.23	1,266 (90.6)	0.23	195 (88.2)	0.16
Month of pregnancy start								
January–March	1,697 (24.4)	823 (25.9)	450 (21.0)	−0.10	417 (29.8)	0.07	7 (3.2)	−0.64
April–June	1,693 (24.4)	788 (24.8)	856 (39.9)	0.26	37 (2.7)	−0.64	12 (5.4)	−0.51
July–September	1,771 (25.5)	729 (22.9)	748 (34.9)	0.21	146 (10.4)	−0.29	148 (67.0)	0.79
October–December	1,785 (25.7)	841 (26.4)	92 (4.3)	−0.59	798 (57.1)	0.52	54 (24.4)	−0.04

LMP, last menstrual period; Std diff, standardized difference; BMI, body mass index; GERD, gastroesophageal reflux disease; PCOS, polycystic ovarian syndrome; PTSD, posttraumatic stress disorder; PCP, primary care physician.
Data are mean±SD or n (%) unless otherwise specified.
* Reflects the standardized difference comparing vaccinated individuals with those unvaccinated 12 months or more before LMP.
† Races not listed include American Indian and Alaskan Native individuals.

months before pregnancy detection (weighted HR 0.99, 95% CI 0.81–1.20) or during pregnancy (weighted HR 0.83, 95% CI 0.47–1.47).

Compared with couples in whom the male partner was unvaccinated, the weighted HR for vaccination of male partners during the 3 months preceding the last menstrual period was 1.17 (95% CI 0.73–1.90). Compared with pregnancies in which neither partner was vaccinated, pregnancies in which both the female and male partner were vaccinated had similar rates of miscarriage (weighted HR 0.97, 95% CI 0.54–1.74) (Table 2). Compared with unvaccinated participants, we observed little variation in the rate of miscarriage associated with vaccination during the current and preceding years (weighted HR 1.07, 95% CI 0.74–1.56), current year only (weighted HR 0.96, 95% CI 0.23–3.89), or prior year only (weighted HR 0.96, 95% CI 0.74–1.24).

Hazard ratios comparing rates of miscarriage by vaccination status were consistent across study years (Appendix 7, available online at http://links.lww.com/AOG/D246) and were similar for early miscarriages occurring before 13 weeks of gestation (weighted HR 0.98, 95% CI 0.80–1.18) and miscarriage occurring at 13–20 weeks of gestation (weighted HR 1.05, 95% CI 0.41–2.71). Our findings were robust to sensitivity analyses that 1) included induced abortions in the outcome measure (Appendix 8, available online at http://links.lww.com/AOG/D246), 2) restricted to pregnancies with the last menstrual period between July and December (Appendix 9, available online at http://links.lww.com/AOG/D246), and 3) restricted to miscarriages reported during the first 28 weeks of pregnancy (Appendix 10, available online at http://links.lww.com/AOG/D246). Compared with those vaccinated 3–12 months before the last menstrual period, vaccination before or during pregnancy was not associated with the rate of miscarriage (weighted HR 0.93, 95% CI 0.71–1.21). Similarly, when we excluded those who were vaccinated between 3 and 12 months before pregnancy, vaccination was not associated with the rate of miscarriage (weighted HR 0.99, 95% CI 0.81–1.21).

Results of quantitative bias analysis showed that when estimates of sensitivity and specificity consistent with prior validation studies of influenza vaccine in adults were applied,[30] our findings did not substantially

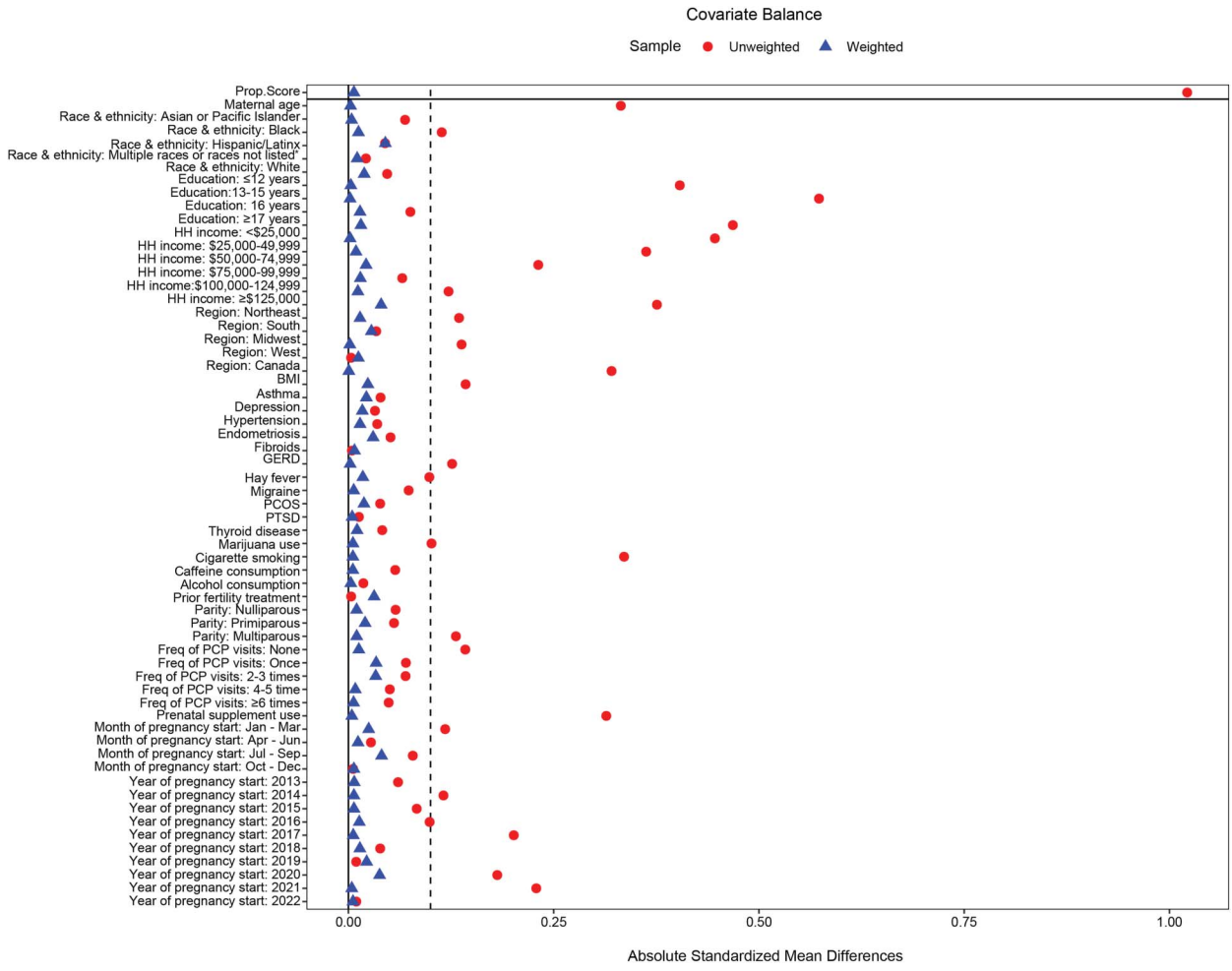

Fig. 1. Absolute standardized mean differences in observed covariates between vaccinated and unvaccinated participants before and after propensity score weighting. Inverse probability of treatment weights was derived from the estimated probability of influenza vaccination using multivariable logistic regression with female partner's age, race and ethnicity, education, household income, region of residence, body mass index (BMI), asthma diagnosis, thyroid disease, cigarette smoking status, marijuana use, history of miscarriage, parity, and frequency of contact with primary care, as well as month and year of pregnancy start (included as interaction terms), as independent variables. All weights were trimmed at the 5th and 95th percentiles. HH, household; GERD, gastroesophageal reflux disease; PCOS, polycystic ovary syndrome; PTSD, posttraumatic stress disorder; PCP, primary care physician. *Races not listed include American Indian and Alaskan Native individuals.

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change (risk ratio 1.05, 95% CI 0.80–1.36). Consideration of a wider range of sensitivity and specificity values indicated that estimated risk ratios clustered around the null, with 95% of risk ratio values estimated to be between 0.87 and 1.23 (Appendix 11, available online at http://links.lww.com/AOG/D246).

DISCUSSION

Results from this North American prospective cohort study indicate that receipt of seasonal inactivated influenza vaccines around the start of pregnancy among female partners was not associated with an increased rate of miscarriage. Our results show an inverse or near-null association between female partner influenza vaccination and miscarriage when the vaccine is administered before or during pregnancy. This information may assist vaccine decision making among pregnancy planners and alleviate concerns of health care professionals about administering influenza vaccines during first trimester.

Our findings are consistent with the majority of previous studies that have found little association between female partner influenza vaccination during pregnancy and miscarriage[10,13,32,33] and stand in

Table 2. Rate of Miscarriage by Female and Male Partner Exposure to Seasonal Inactivated Influenza Vaccines Before or During Pregnancy

Exposure	No. of Events	Miscarriage Rate (95% CI)	Unweighted HR (95% CI)	Weighted HR* (95% CI)
By period of exposure (female only)				
Before or during pregnancy	190	17.0 (14.8–19.2)	1.04 (0.89–1.22)	0.98 (0.81–1.18)
During 3 mo before pregnancy detection	178	17.1 (14.8–19.4)	1.05 (0.89–1.23)	0.99 (0.81–1.20)
During 4–19 wk of pregnancy	12	15.6 (6.4–23.9)	0.98 (0.56–1.70)	0.83 (0.47–1.47)
Unvaccinated	715	16.2 (15.1–17.3)	1.00	1.00
By male partner vaccination status				
Vaccinated	22	20.9 (12.7–28.4)	1.30 (0.84–2.03)	1.17 (0.73–1.90)
Unvaccinated	133	16.3 (13.8–18.8)	1.00	1.00
By female and male partner vaccination status				
Male and female partner vaccinated	16	20.3 (10.8–28.7)	1.19 (0.71–1.99)	0.97 (0.54–1.74)
Female partner only vaccinated	16	12.4 (6.5–18.0)	0.72 (0.43–1.21)	0.65 (0.34–1.22)
Male partner only vaccinated	6	22.9 (4.9–37.5)	1.39 (0.62–3.11)	1.26 (0.58–2.74)
Neither partner vaccinated	117	17.1 (14.2–19.9)	1.00	1.00
By immunization history (female only)				
Vaccinated current and previous year	54	19.7 (18.6–20.1)	1.28 (0.93–1.76)	1.07 (0.74–1.56)
Vaccinated current year only	2	12.4 (8.7–16.0)	0.94 (0.26–3.33)	0.96 (0.23–3.89)
Vaccinated previous year only	113	15.9 (15.3–16.5)	1.03 (0.79–1.33)	0.96 (0.74–1.24)
Unvaccinated	108	15.8 (15.2–16.4)	1.00	1.00

HR, hazard ratio.

* Hazard ratios were weighted to account for loss to follow-up with inverse probability weights and to account for confounding with propensity score–based fine stratification. Propensity scores were derived from the estimated probability of influenza vaccination with multivariable logistic regression with female partner's age, race and ethnicity, education, household income, region of residence, body mass index, asthma diagnosis, thyroid disease, cigarette smoking status, marijuana use, history of miscarriage, parity, and frequency of contact with primary care, as well as month and year of pregnancy detection (included as interaction terms), as independent variables. All weights were trimmed at the 5th and 95th percentiles.

contrast to previous studies reporting an increase[9] or decrease in miscarriage rates.[11] One common limitation to previously conducted observational studies of miscarriage after prenatal vaccination, and a potential source of variation in findings, is that recruitment began during pregnancy and only as early as the eighth week of pregnancy[11] or first medical visit.[12] Thus, these studies missed losses that occur early in pregnancy, resulting in left truncation.[34–36] In our cohort, this would have resulted in the exclusion of 68% of all reported miscarriages. Because our study recruited participants before pregnancy and followed them up prospectively in time, our study design minimizes selection bias, which could explain some discrepancy between study findings.

Our study had several strengths. First, this prospective cohort study is one of the first to examine miscarriage in relation to seasonal influenza vaccination shortly before pregnancy[10] and the first to evaluate the potential influence of male partner vaccination, although the evaluation was limited because the small sample of male partners. Although male partner exposures have biologically plausible links with reproductive and perinatal outcomes, including early pregnancy loss,[37] limited prior research has considered male partner exposure to influenza vaccines. One previous study by our team investigated the effect of male partner influenza vaccination on fecundability[38] and found no harmful association. Our study suggests that male partner vaccination does not appear to increase the risk of miscarriage appreciably, either when administered to only the male partner or when administered to both partners, but these results were based on smaller numbers. Although these results provide important, novel evidence on the association between male partner vaccination and miscarriage, they should be treated with caution, given the small percentage of male partners participating, the small number of events, and imprecise CIs–all of which limit the certainty of conclusions from these findings. Second, in addition to limiting left truncation bias, we attempted to reduce the influence of additional selection bias introduced through loss to follow-up by applying inverse probability of censoring weights. Furthermore, as a result of the comprehensive baseline and follow-up questionnaires, we were able to collect information on a wide range of covariates not typically included in previous studies, including history of miscarriage, fertility treatment, alcohol and

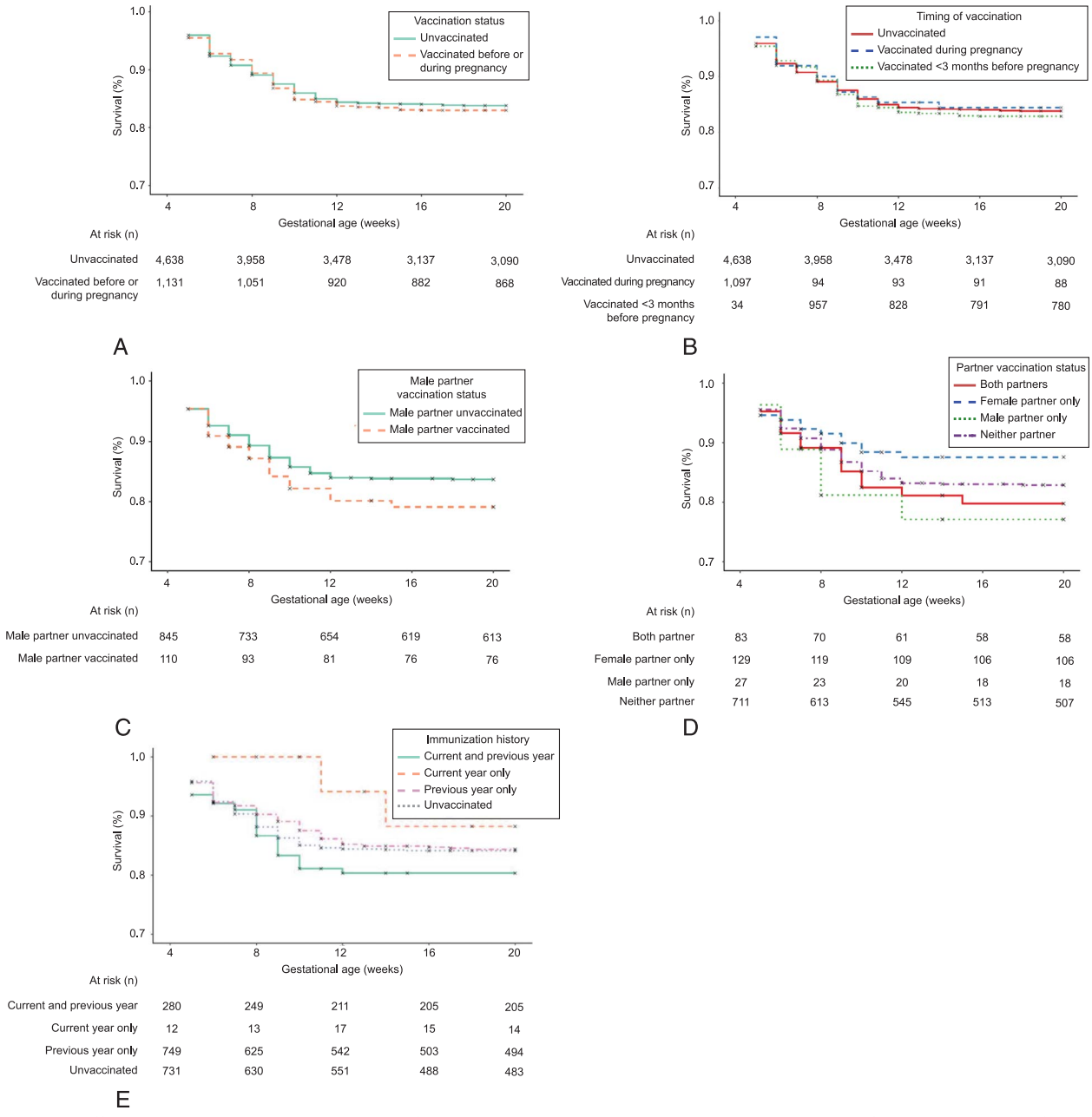

Fig. 2. Offspring survival probability by any female partner exposure to seasonal inactivated influenza vaccine before or during pregnancy (yes or no) (**A**); female partner exposure to seasonal inactivated influenza vaccine before pregnancy compared with during pregnancy and compared with neither before nor during pregnancy (**B**); exposure to seasonal influenza vaccine before pregnancy among male partner compared with no male partner vaccination (**C**); exposure to seasonal influenza vaccine before or during pregnancy among male partner compared with female partner, compared with both partners, and compared with neither partner (**D**); and female partner exposure to seasonal influenza vaccine before or during pregnancy in the current season only compared with prior season only, compared with both the current and prior seasons, and compared with neither season (**E**).

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marijuana use, and multiple medical conditions. Although we cannot exclude the possibility of residual confounding, the incorporation of a range of covariate information and the application of propensity score methods helped to minimize the influence of confounding.

Despite these strengths, our study had several limitations. For example, outcome and exposure and outcome information were self-reported, which could have resulted in misclassification. Previous validation studies from the PRESTO cohort have shown self-report to be a valid measurement of other pregnancy outcomes, including gestational age, preterm birth, and low birth weight,[19] and other studies have highlighted the reliability of self-reporting previous miscarriage.[39] The validity of self-reported vaccination status is likely to be high. Prior studies of self-reported influenza vaccination have documented the validity of self-reported influenza vaccination during the current and preceding influenza seasons.[30,40] We considered possible exposure misclassification in our quantitative bias analysis and found that, over a broad range of assumptions, our study conclusions were unlikely to change. We believe the influence of outcome misclassification was small. A previous validation study indicated that more than 97% of PRESTO participants reported their last menstrual period within 1 day of the last menstrual period recorded with a menstrual charting application,[17] and the prevalence of miscarriage in our cohort aligns with nationally representative data.[41] Second, male partner vaccination was collected only at baseline; therefore, we may have missed some vaccinations occurring between baseline and the couples' last menstrual period. Finally, analyses were performed on data from a cohort of pregnancy planners who were willing to take part in a web-based cohort study. This may influence the generalizability of our findings.

Pregnant people and those planning pregnancy are priority groups for annual influenza vaccination. Vaccination can prevent severe influenza and complications during pregnancy. Although limited and conflicting evidence evaluating influenza vaccination and miscarriage has negatively influenced health care professionals' confidence in administering influenza vaccines, our findings indicate no increase in the rate of miscarriage after influenza vaccination.

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