CORRESPONDENCE

Evaluation of Acute Adverse Events after Covid-19 Vaccination during Pregnancy

TO THE EDITOR: Pregnant women with symptomatic coronavirus disease 2019 (Covid-19) have a higher risk of adverse outcomes than do women who are not pregnant.[1,2] In part because of these findings, Covid-19 vaccination has been recommended for pregnant women. However, uptake has been lower in pregnant women than among women who are not pregnant.[3,4] The concern of many women regarding safety remains a barrier to maternal vaccination.

We performed a retrospective, observational, matched-cohort study involving pregnant women between the ages of 16 and 49 years at eight Vaccine Safety Datalink sites from December 15, 2020, through July 1, 2021. We matched each dose of a Food and Drug Administration–authorized Covid-19 vaccine received by a pregnant woman to an unvaccinated pregnant woman, according to study site and pregnancy start date. Included in the pregnancy cohort were women who were subsequently found to be pregnant within 28 days after receiving the vaccine. Vaccinations were captured through electronic health records, claims data, and bidirectional linkages with state and local immunization registries.[5]

We evaluated the incidences of 25 medically attended acute adverse events (known reactogenic adverse events and clinically serious outcomes) among the vaccinated women as compared with the unvaccinated matched controls. For the primary analyses, we focused on events occurring within 21 days after any vaccination. In secondary analyses, we included events that had occurred within 42 days after the second dose of a messenger RNA (mRNA) vaccine (either the BNT162b2 [Pfizer–BioNTech] or mRNA-1273 [Moderna] vaccine) (Table S4 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). We estimated adjusted rate ratios using Poisson regression after applying stabilized inverse probability weighting for propensity to receive a vaccination. Additional details regarding the statistical methods are provided in the Supplementary Appendix.

We identified 45,232 pregnant women who had received one or two doses of a Covid-19 vaccine immediately preceding or during pregnancy (78,026 vaccine doses) (Fig. S1). Of these women, 32,794 (72.5%) had received two doses of an mRNA vaccine, 5652 (12.5%) had received only the first dose of an mRNA vaccine, 4912 (10.9%) had received only the second dose of an mRNA vaccine, and 1874 (4.1%) had received a single dose of the Ad26.COV2.S vaccine (Johnson & Johnson–Janssen). (The women who received only a second dose of vaccine had received the first dose >28 days before becoming pregnant.) A higher percentage of vaccinated women were between the ages of 30 and 49 years and were non-Hispanic White or non-Hispanic Asian as compared with unvaccinated women (Table S4).

Frequencies of all medically attended acute adverse events were less than 1%. Among vaccinees, the most common events were fever (adjusted rate ratio as compared with unvaccinated controls, 2.85; 95% confidence interval [CI], 1.76 to 4.61), malaise or fatigue (adjusted rate ratio, 2.24; 95% CI, 1.71 to 2.93), local reactions (adjusted rate ratio, 1.89; 95% CI, 1.33 to 2.68), and lymphadenopathy or lymphadenitis (adjusted rate ratio, 2.16; 95% CI, 1.42 to 3.28) (Fig. 1). No serious acute adverse events that were evaluated (e.g., cerebral venous sinus thrombosis, encephalitis or myelitis, Guillain–Barré syndrome, myocarditis or pericarditis, or pulmonary embolism) occurred more frequently in vaccinated women after each dose than among matched unvaccinated controls. Overall associations were similar in subgroup analyses comparing the incidence of outcomes in the two groups, as stratified ac-

Medically Attended Acute Adverse Event	Covid-19 Vaccination during Pregnancy	No Covid-19 Vaccination during Pregnancy	Adjusted Rate Ratio (95% CI)
	no. of events/rate per 10,000		
1 to 7 days after vaccination			
Fever	60/7.7	26/3.3	2.85 (1.76–4.61)
Malaise or fatigue	183/23.5	89/11.4	2.24 (1.71–2.93)
Skin and soft-tissue or local allergic reaction	94/12	55/7	1.89 (1.33–2.68)
1 to 21 days after vaccination			
Lymphadenopathy or lymphadenitis	74/9.5	36/4.6	2.16 (1.42–3.28)
Acute myocardial infarction	1/0.1	2/0.3	0.41 (0.04–4.59)
Appendicitis	5/0.6	5/0.6	0.93 (0.26–3.29)
Bell's palsy	3/0.4	6/0.8	0.54 (0.13–2.20)
Cerebral venous sinus thrombosis	0/0	1/0.1	1.00 (0.00–18.92)
Disseminated intravascular coagulation	0/0	2/0.3	0.41 (0.00–3.46)
Stroke, hemorrhagic	0/0	3/0.4	0.26 (0.00–1.71)
Stroke, ischemic	0/0	3/0.4	0.26 (0.00–1.71)
Immune thrombocytopenic purpura	57/7.3	59/7.6	1.01 (0.68–1.51)
Trigeminal neuralgia and related disorders	1/0.1	1/0.1	0.94 (0.06–15.09)
Pulmonary embolism	0/0	1/0.1	1.00 (0.00–18.92)
Seizure	2/0.3	6/0.8	0.36 (0.07–1.89)
Venous thromboembolism	3/0.4	3/0.4	0.92 (0.18–4.63)

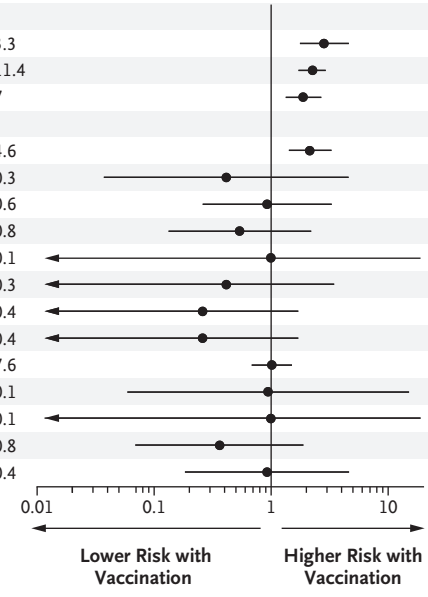

Figure 1. Medically Attended Acute Adverse Events during Pregnancy, According to Receipt or Nonreceipt of a Covid-19 Vaccine (December 15, 2020–July 1, 2021).

Shown is the incidence of medically attended acute adverse events in 45,232 pregnant women who had received one or two doses of a Covid-19 vaccine immediately preceding or during pregnancy (78,026 vaccine doses) and unvaccinated matched controls. The rate of adverse events per 10,000 vaccine doses was calculated for the vaccinated women and was matched with the rate in an unvaccinated control. Data were evaluated within 21 days after vaccination at eight Vaccine Safety Datalink sites. There were no reports of a prespecified list of adverse events that included acute disseminated encephalomyelitis, cerebral venous sinus thrombosis, disseminated intravascular coagulation, encephalitis or myelitis, Guillain–Barré syndrome, myocarditis or pericarditis, hemorrhagic or ischemic stroke, Stevens–Johnson syndrome or toxic epidermal necrolysis, thrombosis with thrombocytopenia syndrome, transverse myelitis, thrombotic thrombocytopenic purpura, or pulmonary embolism. Anaphylaxis was evaluated only in the vaccinated group, and no confirmed cases were reported.

cording to vaccine dose and mRNA vaccine manufacturer (Tables S4 and S5 and Figs. S3 and S4). Limitations of the study included potential underestimation of outcome incidence if the actual risk interval differed from the 21-day or 42-day interval that we used, the presence of wide confidence intervals around some rate ratios, and potential misclassification or incomplete capture of Covid-19 vaccine exposure or other covariates.

Medically attended acute adverse events after Covid-19 vaccination immediately preceding or during pregnancy were uncommon. Covid-19 vaccines were not associated with an increased risk of the clinically serious acute adverse events that were evaluated. The present data add to the growing literature supporting the safety of Covid-19 vaccination during pregnancy.

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