CORRESPONDENCE

Covid-19 Vaccination during Pregnancy and First-Trimester Miscarriage

TO THE EDITOR: Pregnant women with coronavirus disease 2019 (Covid-19) are at increased risk for adverse outcomes, and Covid-19 vaccination is recommended during pregnancy.[1,2] However, safety data on Covid-19 vaccination during pregnancy remain limited.[3,4]

We performed a case–control study with data from Norwegian registries on first-trimester pregnancies, Covid-19 vaccination, background characteristics, and underlying health conditions (Supplementary Methods and Tables S1 through S3 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). We identified all women who were registered between February 15 and August 15, 2021, as having had a miscarriage before 14 weeks of gestation (case patients) and those with a primary care–based confirmation of ongoing pregnancy in the first trimester (controls). In Norway, although vaccination during the first trimester is not recommended except in women with underlying risk conditions, women not yet aware that they were pregnant may still be vaccinated in the first trimester. We estimated odds ratios with 95% confidence intervals for Covid-19 vaccination within 5-week and 3-week windows before a miscarriage or ongoing pregnancy, adjusting for women's age, country of birth, marital status, educational level, household income, number of children, employment in a health care profession, underlying risk conditions for Covid-19, previous test positive for severe acute respiratory syndrome coronavirus 2, and calendar month.

Among 13,956 women with ongoing pregnancies (of whom 5.5% were vaccinated) and 4521 women with miscarriages (of whom 5.1% were vaccinated), the median number of days between vaccination and miscarriage or confirmation of ongoing pregnancy was 19 (Fig. S2). Among women with miscarriages, the adjusted odds ratios for Covid-19 vaccination were 0.91 (95% confidence interval [CI], 0.75 to 1.10) for vaccination in the previous 3 weeks and 0.81 (95% CI, 0.69 to 0.95) for vaccination in the previous 5 weeks (Table 1). The results were similar in an analysis that included all available vaccine types (Table S5), in an analysis stratified according to the number of doses received (one or two) (Table S6), and in sensitivity analyses limited to health care personnel (for whom vaccination was routinely recommended other than in the first trimester) or women with at least 8 weeks of follow-up after confirmed pregnancy (to exclude subsequent pregnancy loss) (Table S7).

A limitation of our report is that the registry lacks information on gestational age at the time of early pregnancy registration, and thus we

Table 1. Odds Ratios for Covid-19 Vaccination in a 5-Week or 3-Week Window before Miscarriage or Confirmation of an Ongoing Pregnancy.

Vaccination Status	5-Week Exposure Window				3-Week Exposure Window			
	Ongoing Pregnancies	Miscarriages	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*	Ongoing Pregnancies	Miscarriages	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
	number				*number*			
Among all women								
Unvaccinated	13,184	4,290	Reference	Reference	13,507	4,375	Reference	Reference
Vaccinated	772	231	0.92 (0.79–1.07)	0.81 (0.69–0.95)	449	146	1.00 (0.83–1.21)	0.91 (0.75–1.10)
Among health care personnel								
Unvaccinated	2,419	756	Reference	Reference	2,533	788	Reference	Reference
Vaccinated	261	75	0.92 (0.70–1.20)	0.93 (0.70–1.22)	147	43	0.94 (0.66–1.33)	0.92 (0.64–1.32)

* The odds ratios among all women were adjusted for age, country of birth, marital status, educational level, household income, number of children, employment in a health care profession, underlying risk conditions for coronavirus disease 2019 (Covid-19), and previous test positive for severe acute respiratory syndrome coronavirus 2. The odds ratios among health care personnel were adjusted for the same variables as among all women except for employment in a health care profession.

could not match case patients and controls according to gestational age. However, most recognized miscarriages are known to occur between pregnancy weeks 6 and 10,[5] a period that is similar to the gestational ages at which women in Norway consult a physician to confirm pregnancy (Fig. S1). Also, only approximately 40% of women in Norway have a primary care appointment to confirm pregnancy, but the characteristics of these women appear to be similar to those of women who do not have a registered pregnancy confirmation (Table S4). We cannot address associations between vaccination and miscarriages that were not clinically recognized. Although adjustment for potential confounders had minimal effect on our results, the registry does not include information on lifestyle and other factors that might confound our findings (see Supplementary Appendix).

Our study found no evidence of an increased risk for early pregnancy loss after Covid-19 vaccination and adds to the findings from other reports supporting Covid-19 vaccination during pregnancy.[3,4]

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Differential Kinetics of Immune Responses Elicited by Covid-19 Vaccines

TO THE EDITOR: Previous studies have shown that the BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna), and Ad26.COV2.S (Johnson & Johnson–Janssen) vaccines provide robust protective efficacy against coronavirus disease 2019 (Covid-19). Here, we report comparative kinetics of humoral and cellular immune responses elicited by the two-dose BNT162b2 vaccine (in 31 participants), the two-dose mRNA-1273 vaccine (in 22 participants), and the one-dose Ad26.COV2.S vaccine (in 8 participants). We evaluated antibody and T-cell responses from peak immunity at 2 to 4 weeks after the second immunization in recipients of the messenger RNA (mRNA) vaccines or after the first immunization in recipients of the Ad26.COV2.S vaccine to 8 months (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

At peak immunity, the BNT162b2 vaccine induced a high median live-virus neutralizing antibody titer (1789), a high median pseudovirus neutralizing antibody titer (700), and a high median binding antibody titer against the receptor-binding domain (RBD) (21,564). However, these titers declined sharply by 6 months after vaccination, as previously reported,[1,2] and they declined further by 8 months (Figs. 1A through 1C, S1, and S2). By 8 months after BNT162b2 vaccination, the median live-virus neutralizing antibody titer (53), pseudovirus neutralizing antibody titer (160), and RBD-specific binding antibody titer (755) elicited by the vaccine were lower than the peak titers by a factor of 34, 4, and 29, respectively.

At peak immunity, the mRNA-1273 vaccine also elicited a high median live-virus neutralizing antibody titer (5848), pseudovirus neutralizing antibody titer (1569), and RBD-specific binding antibody titer (25,677). By 8 months after mRNA-1273 vaccination, the median live-virus neutralizing antibody titer was 133, the pseudovirus neutralizing antibody titer was 273, and the median RBD-specific binding antibody titer was 1546; these titers were lower than the peak titers by a factor of 44, 6, and 17, respectively.

The Ad26.COV2.S vaccine induced substantial-

Figure 1 (facing page). Kinetics of Humoral and Cellular Immune Responses Elicited by the BNT162b2, mRNA-1273, and Ad26.COV2.S Vaccines.

Shown are immune responses after vaccination with BNT162b2, mRNA-1273, and Ad26.COV2.S at peak immunity (2 to 4 weeks after the second dose in recipients of the messenger RNA vaccines or 4 weeks after one dose in recipients of the Ad26.COV2.S vaccine) and at 6 months, 8 months, or both after the first dose. Panel A shows the serum 50% inhibitory dilution (ID_{50}) titers in the live-virus neutralizing antibody assay. Red bars indicate medians, dashed lines the limit of detection for each assay, and each dot a single participant. Panel B shows the serum dilution for 50% reduction (NT_{50}) expressed in relative light units in the pseudovirus neutralizing antibody assay. Panel C shows the binding IgG antibody titers against the receptor-binding domain (RBD) in the serum enzyme-linked immunosorbent assay. Intracellular cytokine-staining assays were performed to measure the percentage of interferon-γ production in T cells; Panel D shows this percentage in CD4+ T cells, and Panel E shows this percentage in CD8+ T cells. Flow cytometric gating was performed to identify T cells (which are CD3+) rather than other CD4+- or CD8+-expressing immune cells. All assays were performed with the use of the SARS-CoV-2 WA1/2020 strain. The Ad26.COV2.S vaccine data in Panels B through E were published previously[3] and are included here for comparative purposes.