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Opinion Editorial

Lack of Compelling Safety data for mRNA COVID Vaccines in Pregnant Women

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Response to the Shimabukuro *et al.* (2021) NEJM Publication

The article by Shimabukuro *et al*. (2021) presents preliminary safety results of coronavirus 2019 (COVID-19) mRNA vaccines given to pregnant women from the V-Safe Registry.[1] These findings are of particular importance, as pregnant women were excluded from the phase III trials assessing mRNA vaccines.

In Table 4, the authors report a rate of spontaneous abortion (Sab) in early pregnancy (<20 weeks) of 12.6% (104 Sabs/827 completed pregnancies). This number is misleading, however, as this subset represents only 20.9% of women enrolled in the registry, and 84.6% (n=700) of women received their first vaccine dose in the third trimester. For all other pregnancy outcomes, the authors calculated event proportions by dividing the number of events by the number of participants eligible for that event. However, for Sab they divide the number of events by the entire cohort of completed pregnancies, rendering the statistic meaningless.

Moreover, although authors fail to report the median follow-up at the time of the analysis, they do state that limited follow-up calls were placed every 10 to 12 weeks, and pregnancies were ongoing in the vast majority of women who were vaccinated in their first and second trimesters. Therefore, the effect of the vaccines on early pregnancy losses (<20 weeks) is concerning and remains to be determined. Presumably, the Sab rate will be higher than 12.6% when more of the data on women vaccinated in early pregnancy is fully disclosed. Additionally, the authors indicate that the rate of Sabs in the published literature is between 10% and 26%.[2-4] However, this range includes clinically-unrecognized pregnancies[2,5,6] so the upper limit should be closer to 10% because the study relied on self-reporting that would only detect clinically recognized pregnancies.[2,5,7] Reporting a Sab rate of 12.6% in Table 4 may lead some to conclude that there is no increased vaccine-associated risk of Sab in early pregnancy by comparing it to the background rate of 10% to 26%, whereas in reality the analysis cannot address this question in a meaningful fashion.

Finally, the authors conclude that “no obvious safety signals were detected among pregnant persons who received mRNA COVID-19 vaccines”. However, this does not seem to account for the >12.6% of reported grade 3 adverse events or 8% of women who reported a temperature ≥38 °C among those receiving 2 doses where it is known fever itself can induce miscarriage or premature labor.[8-10] Additionally, administration of mRNA COVID-19 vaccines results in the production of the

spike protein, which has been implicated in pathogenic mechanisms that affect the uterus, placenta, and possibly the fetus.[11-21] To our knowledge these biologically active agents lack studies of teratogenicity, oncogenicity, and genotoxicity that assure their safety.[22-24] As mentioned previously, these agents have not been proven safe in phase III trials of pregnant women nor have they been studied long-enough to ensure their continued safety through the nine-month development trajectory of the unborn infants and into their early years.

We therefore suggest that it would be more appropriate for the authors to exercise the precautionary principle and conclude that the "mRNA COVID-19 vaccines may be associated with severe adverse events; their effect on pregnancy outcomes, especially when administered in early pregnancy, have yet to be determined and their use should be limited to clinical trials". Given that the V-safe registry is the best source of vaccine safety data in pregnant women, we request that the authors make the data available for public scrutiny, conduct a temporal association analysis to explore vaccine-related events in pregnant women, and calculate Sab rates based on cohorts at risk of the event, especially when the vaccines are given in early pregnancy. Thus, according to the Requirements for Pregnancy and Lactation Labeling by the US DHHS and the FDA,[25,26] the vaccines should contain a narrative summary equivalent to a "Category X" labeling in pregnancy, indicating that the potential risks involved in use of the COVID-19 vaccine in pregnant women clearly outweigh any future benefits since COVID-19 is mild[27] and treatable[28] for the majority of pregnant women.

Table 4. Pregnancy Loss and Neonatal Outcomes in Published Studies and V-safe Pregnancy Registry Participants.

Participant-Reported Outcome	Published Incidence*	V-safe Pregnancy Registry†
	%	*no./total no. (%)*
Pregnancy loss among participants with a completed pregnancy		
Spontaneous abortion: <20 wk[15-17]	10~~–26~~	~~104/827 (12.6)~~ N/E‡
Stillbirth: ≥20 wk[18-20]	<1	1/725 (0.1)§
Neonatal outcome among live-born infants		
Preterm birth: <37 wk[21,22]	8–15	60/636 (9.4)¶
Small size for gestational age[23,24]‖	3.5	23/724 (3.2)
Congenital anomalies[25]**	3	16/724 (2.2)
Neonatal death[26]††	<1	0/724

N/E, not estimable

* The populations from which these rates are derived are not matched to the current study population for age, race and ethnic group, or other demographic and clinical factors.
† Data on pregnancy loss are based on 827 participants in the v-safe pregnancy registry who received an mRNA COVID-19 vaccine (BNT162b2 [Pfizer–BioNTech] or mRNA-1273 [Moderna]) from December 14, 2020, to February 28, 2021, and who reported a completed pregnancy. **A total of 700 participants (84.6%) received their first eligible dose in the third trimester. Data on neonatal outcomes are based on 724 live-born infants, including 12 sets of multiples.**
‡ A total of 96 of 104 spontaneous abortions (92.3%) occurred before 13 weeks of gestation.
§ The denominator includes live-born infants and stillbirths.
¶ The denominator includes only participants vaccinated before 37 weeks of gestation.
‖ Small size for gestational age indicates a birthweight below the 10th percentile for gestational age and infant sex according to INTERGROWTH-21st growth standards (http://intergrowth21.ndog.ox.ac.uk). These standards draw from an international sample including both low-income and high-income countries but exclude children with coexisting conditions and malnutrition. They can be used as a standard for healthy children growing under optimal conditions.
** Values include only major congenital anomalies in accordance with the Metropolitan Atlanta Congenital Defects Program 6-Digit Code Defect List (www.cdc.gov/ncbddd/birthdefects/macdp.html); all pregnancies with major congenital anomalies were exposed to Covid-19 vaccines only in the third trimester of pregnancy (i.e., well after the period of organogenesis).
†† Neonatal death indicates death within the first 28 days after delivery.

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