12. Chan KCA, Lam WKJ, King A, et al. Plasma Epstein-Barr virus DNA and risk of future nasopharyngeal cancer. NEJM Evid 2023;2(7).

DOI: 10.1056/NEJMe2311101

Maternal RSV Vaccine — Weighing Benefits and Risks

Sonja A. Rasmussen, M.D., and Denise J. Jamieson, M.D., M.P.H.

Respiratory syncytial virus (RSV) poses a substantial burden to the health of infants. An estimated 1.4 million RSV-associated hospitalizations and 45,700 RSV-attributable deaths occur worldwide each year in infants younger than 6 months of age.[1] In the United States, RSV is the leading cause of hospitalization among infants, with 2 to 3% of infants younger than 6 months of age hospitalized for RSV infection annually.[2] Recently, two agents to protect young infants from severe RSV disease have become available. In July 2023, the Food and Drug Administration (FDA) approved nirsevimab, a long-acting monoclonal antibody,[3] for use in infants; 1 month later, the FDA approved the first RSV vaccine, which is based on the RSV prefusion F protein (RSVPreF; Abrysvo, Pfizer), for use in pregnancy.[2]

This issue of the *Journal* includes a report of a phase 3 trial by Dieussaert et al.,[4] who evaluated the effects of a candidate maternal RSV vaccine (RSVPreF3-Mat) on severe RSV-associated disease in young infants. Data suggest that the vaccine was efficacious; however, the trial was halted early because of a higher incidence of preterm birth in the vaccine group than in the placebo group (6.8% [237 of 3494 infants] vs. 4.9% [86 of 1739 infants]; relative risk, 1.37; 95% confidence interval [CI], 1.08 to 1.74; P=0.01). An imbalance in the risk of neonatal death in the two trial groups was also seen — a finding that was probably attributable to a higher incidence of preterm birth in the vaccine group than in the placebo group — but the imbalance was not significant (relative risk, 2.16; 95% CI, 0.62 to 7.56; P=0.23). The development of RSVPreF3-Mat was subsequently discontinued.

The difference in the incidence of preterm birth between the vaccine and placebo groups was primarily seen in low- and middle-income countries (relative risk, 1.56; 95% CI, 1.17 to 2.09) as compared with high-income countries (relative risk, 1.04; 95% CI, 0.68 to 1.58). The difference was observed only during a particular period, with the greatest difference having occurred during the wave of infections due to the B.1.617.2 (delta) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); however, no relationship was identified between preterm birth and the report of coronavirus disease 2019 (Covid-19) by the maternal participants or evidence of SARS-CoV-2 infection during pregnancy. The difference between the vaccine and placebo groups was seen for all three pathways to preterm birth in pregnant persons (premature preterm rupture of membranes, preterm labor, and provider-induced preterm birth), and the time between vaccination and preterm birth varied from weeks to months, which made it difficult to identify a potential mechanism for preterm birth.

Ultrasonography during the first trimester pregnancy — the most accurate method to establish or confirm gestational age[5,6] — was not performed in 45% of the pregnancies (146 of 323) that resulted in preterm birth (see the Supplementary Results section in the Supplementary Appendix, available with the full text of the article by Dieussaert et al. at NEJM.org). However, misclassification of gestational age would be expected to occur similarly in the vaccine and placebo groups owing to randomization and thus would not explain the between-group difference in the risk of preterm birth. The detection of fetal growth restriction and being small for gestational age also relies on the accurate assessment of gestational age; in the current trial, both events were less frequent in the vaccine group than in the placebo group (relative risk, 0.57 [95% CI, 0.34 to 0.97] and 0.78 [95% CI, 0.65 to 0.95], respectively).

Although the FDA-approved maternal RSV vaccine is bivalent and RSVPreF3-Mat is monovalent, the vaccines are otherwise similar. The bivalent maternal RSV vaccine was studied in a phase 3 randomized clinical trial, in which pregnant persons received the vaccine or placebo

between 24 and 36 weeks of gestation.[7] Through month 6 after birth, the efficacy of the bivalent vaccine was 69.4% (97.58% CI, 44.3 to 84.1) against severe medically attended RSV-associated lower respiratory tract infection and 51.3% (97.58% CI, 29.4 to 66.8) against any medically attended RSV-associated lower respiratory tract infection. Preterm birth occurred in 5.7% of the infants (95% CI, 4.9 to 6.5) in the bivalent-vaccine group and in 4.7% of those (95% CI, 4.1 to 5.5) in the placebo group, a difference that was not significant.[8] Most preterm births were late preterm (gestational age, 34 to <37 weeks) and occurred more than 30 days after vaccination. The apparent difference in the incidence of preterm birth between the bivalent-vaccine and placebo groups was largely explained by results from a single country.[8] Given the concern about a possible association between receipt of the bivalent vaccine and preterm birth, FDA approval was limited to administration of the vaccine between 32 weeks 0 days and 36 weeks 6 days of gestation to eliminate the vaccine-associated risk of extremely preterm birth (at <28 weeks of gestation) and very preterm birth (at 28 to <32 weeks of gestation). The manufacturer and the Centers for Disease Control and Prevention have initiated postmarketing studies to assess the risk of preterm birth associated with use of the bivalent vaccine.[2]

Whether the safety signal in the RSVPreF3-Mat trial is real or occurred by chance is unknown. Despite many post hoc analyses, the authors were unable to identify a mechanism by which the receipt of RSVPreF3-Mat might have increased the risk of preterm birth. However, given the findings of the present trial and the modest imbalance in the incidence of preterm birth in the phase 3 trial of the bivalent vaccine, postmarketing surveillance of the bivalent vaccine is warranted.

Even if there is a true association between the receipt of the bivalent vaccine and preterm birth, it is essential to weigh this small risk against the proven benefits of maternal RSV vaccination. Moreover, any potential risk of preterm birth associated with the receipt of the bivalent vaccine is reduced by the administration of the vaccine at 32 weeks or more of gestation.

Highly effective, safe vaccines are available for the protection of infants from influenza, pertussis, Covid-19,[9] and now RSV, and more maternal vaccines are on the horizon.[10] Continued focus on balancing the benefits with the potential risks of maternal vaccination will be essential as we move forward to protect infants from the severe effects of infectious diseases.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Johns Hopkins University School of Medicine, Baltimore (S.A.R.); and the University of Iowa Carver College of Medicine, Iowa City (D.J.J.).

1. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet 2022;399:2047-64.
2. Fleming-Dutra KE, Jones JM, Roper LE, et al. Use of the Pfizer respiratory syncytial virus vaccine during pregnancy for the prevention of respiratory syncytial virus-associated lower respiratory tract disease in infants: recommendations of the Advisory Committee on Immunization Practices — United States, 2023. MMWR Morb Mortal Wkly Rep 2023;72:1115-22.
3. Drysdale SB, Cathie K, Flamein F, et al. Nirsevimab for prevention of hospitalizations due to RSV in infants. N Engl J Med 2023;389:2425-35.
4. Dieussaert I, Kim JH, Luik S, et al. RSV prefusion F protein–based maternal vaccine — preterm birth and other outcomes. N Engl J Med 2024;390:1009-21.
5. Committee opinion no 700: methods for estimating the due date. Obstet Gynecol 2017;129(5):e150-e154.
6. Quinn J-A, Munoz FM, Gonik B, et al. Preterm birth: case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. Vaccine 2016;34:6047-56.
7. Kampmann B, Radley D, Munjal I. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. N Engl J Med 2023;389:1053-5.
8. Food and Drug Administration. Vaccines and related biological products advisory committee meeting, May 18, 2023. Respiratory syncytial virus vaccine (proposed trade name: Abrysvo): applicant: Pfizer. 2023 (https://www.fda.gov/media/168185/download).
9. Etti M, Calvert A, Galiza E, et al. Maternal vaccination: a review of current evidence and recommendations. Am J Obstet Gynecol 2022;226:459-74.
10. Madhi SA, Anderson AS, Absalon J, et al. Potential for maternally administered vaccine for infant group B streptococcus. N Engl J Med 2023;389:215-27.

DOI: 10.1056/NEJMe2401072