

VIEWPOINT

Optimizing the Timing of Vaccine Administration During Pregnancy

Bahaa Abu-Raya, MD
Experimental Medicine Program, University of British Columbia, Vancouver, British Columbia, Canada; and British Columbia Children's Hospital Research Institute, University of British Columbia, Vancouver, British Columbia, Canada.

Kathryn M. Edwards, MD
Vanderbilt Vaccine Research Program, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee.

Vaccination during pregnancy is an important strategy to protect infants from life-threatening infections during the first months of life. It increases the transplacental transfer of maternal vaccine-specific antibodies to newborns with the potential to protect infants from vaccine-preventable diseases until they are no longer at increased risk for infection or are protected by their own active immunization. Pertussis and influenza vaccinations are recommended for pregnant women by the Advisory Committee on Immunization Practices of the US Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists. The tetanus, diphtheria, and acellular pertussis (Tdap) vaccine is routinely administered during each pregnancy at 27 to 36 weeks' gestation and provides pertussis-specific antibodies to the infant during the time window in infancy with heightened susceptibility to severe pertussis disease.¹ Inactivated influenza vaccine is recommended for all pregnant women or those who might be pregnant during the influenza season anytime in pregnancy.^{2,3} Recent US data indicated that an estimated 54% of women received Tdap vaccine during pregnancy and an estimated 49% of women received inactivated influenza vaccine before or during pregnancy.³

In addition, new vaccines against group B streptococcus and respiratory syncytial virus, which could be beneficial if given in pregnancy, are being developed. Determining the optimal timing of maternal vaccination in pregnancy to maximize protection from infections of the mother and the infant is critical. In this Viewpoint, variables to consider for optimal timing of maternal vaccination are discussed.

What Is the Safest Time for Vaccine Administration?

Pregnancy is associated with specific time-sensitive developmental changes in the embryo and the fetus. The first trimester and early in the second trimester are periods of embryogenesis and fetal organogenesis, and maternal infection during these stages can be associated with fetal infection leading to abortion, embryopathy, or congenital malformations. Vaccination in early pregnancy has the potential to protect the mother from contracting infections early in pregnancy, mitigating the risk of in utero infection and severe adverse birth outcomes.⁴ However, due to theoretical safety concerns, clinicians have been hesitant to administer vaccines during this time. Yet, accumulating evidence supports the safety of pertussis and influenza vaccines when administered in the first trimester of pregnancy.^{5,6} For example, first-trimester

pertussis vaccination was not significantly associated with birth defects.⁵

Maternal infection late in the second trimester or in the third trimester usually does not produce major structural abnormalities, and vaccination during this time is also not associated with adverse birth outcomes. Therefore, the safest time for vaccine administration in pregnancy needs to balance these factors.

What Is the Time Associated With the Highest Disease Susceptibility?

Ideal maternal vaccination programs need to provide the greatest clinical protection during the window of highest susceptibility to infection. Consequently, it is essential to define who is the main target of vaccination: mother, infant, or both. Vaccines administered in pregnancy target infections that are relevant for mothers and infants to different degrees. For example, influenza vaccine is administered to protect mothers during pregnancy and infants after birth, while vaccines protecting against pertussis, group B streptococcus, and respiratory syncytial virus mainly target infants.

In addition, the period in pregnancy or infancy associated with the highest window of susceptibility to the infection targeted by vaccination is dependent on the targeted pathogen. Influenza disease is most severe in the third trimester of pregnancy, while pertussis disease is most severe in infancy during the first few weeks of life.

What Is the Time Associated With the Most Robust Vaccine-Induced Immune Response?

The time of vaccination associated with the most robust vaccine-induced immune response in the pregnant woman, which would produce optimal transplacental antibody transfer to the infant and maintenance of vaccine-induced antibodies during the time of highest susceptibility to disease, needs to be defined for each vaccine.

Studies have focused on vaccine-induced antibody levels achieved at delivery to determine the optimal timing of vaccination. For example, pertussis vaccination early in the third trimester was associated with higher antipertussis antibodies at birth compared with vaccination late in the third trimester.⁷ Vaccine-induced antibody cutoffs that correlate with protection against infection and disease have not been defined for every pathogen (eg, no correlate is established for pertussis and variable correlates have been proposed for different group B streptococcus serotypes). The lack of correlates limits the translation of vaccine-specific antibody levels into clinically meaningful evidence-based recommendations.

Corresponding Author: Bahaa Abu-Raya, MD, British Columbia Children's Hospital Research Institute, University of British Columbia, 950 W 28th Ave, Room A5-174, Vancouver, British Columbia V5Z 4H4, Canada (baburaya@bcchr.ubc.ca).

What Is the Time Associated With the Least Interference With Infants' Active Immunization?

Elevated maternal antibody levels can interfere with active immunization in the infant, leading to lower postimmunization vaccine-specific antibody levels when compared with infants of unvaccinated mothers.¹ Infants born to Tdap-vaccinated mothers have lower antipertussis antibodies after pertussis vaccination in infancy, compared with infants whose mothers did not receive pertussis vaccine in pregnancy.¹

The mechanism of interference has not been fully elucidated, and the clinical significance of interference is unclear. Thus, the optimal timing of vaccination in pregnancy needs to balance the highest vaccine-induced immune response with the least immunological interference with the infant's active vaccination.

What Is the Time Associated With the Highest Vaccine Uptake?

The uptake of vaccines in pregnancy is affected by timing of other routine follow-up appointments and interventions during pregnancy, the timing of administration of other vaccines, and access to care. Coordination between the optimal timing of vaccination and timing of other routine contacts with health care professionals has the potential to increase the uptake of vaccines administered in pregnancy. Also, as an increasing number of vaccines are introduced, administering several vaccines during the same vaccination visit should increase vaccine uptake.

The access to vaccination services is influenced by location and economic factors. The need to pay for the vaccine and administration costs are barriers to vaccination. The rate of IIV uptake was lower among US women who had no medical insurance (~24%), compared with women who had public insurance (31%) or private or military insurance (40%).⁸

Research Needs to Optimize Timing of Vaccination in Pregnancy

More research is needed on the safety and effectiveness of vaccines administered at different times in pregnancy. This research can be facilitated through large observational studies and clinical trials in which vaccines are administered at different times during pregnancy. Determining effectiveness can be difficult since some vaccine-preventable diseases are not prevalent in the population. Although pertussis disease incidence is highest among infants younger than 3 months of age (reaching 247/100 000),⁹ it is challenging to determine differential time-dependent vaccine effectiveness in infants following maternal pertussis vaccination in pregnancy because this research would require large studies.

Researchers should strive to comprehensively characterize functional immune responses after vaccination in pregnancy and identify immunologic correlates of protection against infection and disease. The results of such functional assays could be combined with systems biology approaches to assess vaccination at different gestational ages in pregnancy and define the optimal timing of vaccination associated with optimal protection. The cost-effectiveness of maternal vaccination programs recommended in different time windows in pregnancy also should be studied.

Time-dependent safety, vaccine effectiveness, maternal and infant immune responses, and vaccine uptake should be considered by policy makers when making recommendations about the timing of vaccination in pregnancy. As the strategy of vaccination in pregnancy is gaining support and has the potential to be expanded to new vaccines, maximizing the strategy will ensure the highest benefit for pregnant women and their infants.

ARTICLE INFORMATION

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