Clinical Clues / *Klinik İpuçları*

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Which Vaccines Are Routinely Recommended During Pregnancy? What is the Optimal Timing of Maternal Vaccination to Protect the Infant?

Gebelere Rutin Olarak Hangi Aşılar Önerilir? Bebeği Korumak İçin Gebeye En Uygun Aşı Zamanı Ne Olmalıdır?

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Question: *Which vaccines are routinely recommended during pregnancy? What is the optimal timing of vaccination during pregnancy to provide protection for the infant?* **Int. Dr. Oğulcan Toplutepe**

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Answer (Havva Kaya, MD; Mustafa Kemal Hacımustafaoğlu, MD)

Introduction and general information: To answer this question, it is first useful to briefly discuss the general principles of vaccination during pregnancy, the development of antibody responses following primary and booster immunization, and the kinetics of transplacental antibody transfer.

Prior to pregnancy, completion of all routinely recommended adult vaccinations is strongly advised if any doses are missing, including live vaccines such as measles-mumps-rubella and varicella vaccines. In addition to protecting the mother, these vaccinations may confer passive protection to the infant through transplacental transfer of maternal antibodies.

As a general principle, live vaccines are contraindicated during pregnancy. Furthermore, because of insufficient safety and efficacy data, certain inactivated vaccines, including human papillomavirus, meningococcal B, pentavalent meningococcal conjugate vaccines (MenABCWY), and recombinant zoster vaccines, are generally not recommended during pregnancy. However, other inactivated vaccines, such as *Haemophilus influenzae* type b (Hib), hepatitis A, hepatitis B, MenACWY, and pneumococcal polysaccharide vaccines, may be administered when medically indicated. In situations involving specific medical indications, such as animal bites, injuries, or other high-risk exposures, inactivated vaccines including rabies and tetanus-containing vaccines (T, Td, or Tdap) should be administered promptly.

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Apart from these circumstances, the vaccines routinely recommended during pregnancy include seasonal inactivated influenza vaccine (IIV), tetanus-diphtheria-acellular pertussis vaccine (Tdap), tetanus-diphtheria vaccine (Td), tetanus vaccine (T), respiratory syncytial virus (RSV) vaccine, and coronavirus disease-2019 (COVID-19; SARS-CoV-2) vaccines (1).

In Türkiye, Tdap vaccination is currently recommended during every pregnancy and is provided free of charge through family health centers between 18 and 24 weeks of gestation. Seasonal influenza vaccination may also be administered free of charge to all pregnant women through the national health insurance system after obtaining a physician's prescription or medical report (2,3). Maternal RSV vaccination (non-adjuvanted RSV vaccine) is also recommended. Although licensed for use during pregnancy in Türkiye, it is not reimbursed by the Social Security Institution and is not included in the national immunization schedule. At present, no updated COVID-19 vaccine is licensed or available in Türkiye.

In primary immunization (i.e., first-time vaccination), vaccine-induced IgG antibody concentrations generally begin to rise within 1-2 weeks and reach peak levels within approximately 2-4 weeks, depending on the vaccine administered. Consequently, maternal serum antibody concentrations usually reach their maximum levels approximately 14-28 days after primary vaccination. Following booster doses (secondary immune responses), antibody production occurs more rapidly, with measurable increases typically observed within 3-7 days and peak concentrations reached within 7-14 days. Following both primary and booster immunizations, antibody levels gradually decline over subsequent months. Immunological responses to vaccination during pregnancy are generally comparable to those observed in healthy non-pregnant individuals and exhibit similar antibody kinetics.

The purpose of maternal vaccination may be primarily to protect the mother, the infant, or both. Pertussis, tetanus, and RSV vaccines are administered principally to protect the infant, particularly during the first months after birth, while simultaneously providing protection to the mother. In contrast, influenza and COVID-19 vaccines are intended to protect both mother and infant, with maternal protection being the primary objective.

For vaccines intended to protect the infant, the goal is to achieve sufficient concentrations of vaccine-induced maternal antibodies that can be transferred transplacentally and provide protection against infection or severe disease during the infant's first months of life, generally up to six months of age. Therefore, unless urgent maternal protection is required, vaccination is ideally administered during a period when maternal antibody concentrations are expected to be high (e.g., 14-28 days after vaccination) and when transplacental antibody transfer is maximal, preferably after 32-36 weeks of gestation. However, for vaccines in which maternal protection is the primary objective, such as influenza and COVID-19 vaccines, administration should not be delayed and should occur during the recommended seasonal vaccination period regardless of gestational age (4).

The antibodies responsible for protecting the infant following maternal vaccination are predominantly of the IgG class. Although maternal vaccination may induce IgM, IgA, and IgE antibodies, these immunoglobulins do not cross the placenta and therefore do not contribute to neonatal protection. Among IgG subclasses, transplacental transfer occurs most efficiently for IgG1, followed by IgG4, IgG3, and IgG2. IgG1 is also the subclass with the greatest neutralizing capacity (5).

Maternal IgG antibodies are actively transported across the placenta to the fetus. This process is mediated by neonatal Fc receptors expressed on placental syncytiotrophoblast cells, which bind maternal IgG and facilitate its active transfer into the fetal circulation. The efficiency of transplacental antibody transfer—and consequently fetal IgG concentrations—is closely associated with gestational age. During the first half of pregnancy, transfer is minimal. It increases progressively thereafter, reaching approximately 50% of maternal antibody concentrations between 28 and 32 weeks of gestation, approaching maternal levels around 36 weeks, and frequently exceeding maternal concentrations at term delivery (1,6).

For this reason, inactivated vaccines administered during pregnancy are generally recommended during the second trimester or later, provided there is no urgent indication for immediate vaccination and postponement does not pose a clinical risk. This strategy maximizes the transfer of protective antibodies from mother to infant. With respect to transplacental antibody transfer, fetal-to-maternal antibody ratios at term may vary according to the infectious agent involved. Although differences have been reported among studies, approximate fetal/maternal antibody ratios have been described as 1.0 for pertussis, 0.7 for influenza, 0.8 for COVID-19, and 1.6 for RSV (4). Likewise, the level of infant protection achieved following maternal immunization varies according to the vaccine administered and the gestational age at vaccination.

For Tdap vaccination administered between 27 and 36 weeks of gestation, protection against pertussis during the first months of life has been reported to range between 77% and 90%. For seasonal inactivated influenza vaccination administered at any stage of pregnancy, protection during the first six months of life has been reported to range between 17% and 63%, with higher effectiveness generally observed when vaccination is administered during the third trimester.

For COVID-19 vaccination administered during pregnancy, effectiveness against hospitalization in infants has been reported as 54% during the first three months of life and 35% during the first six months of life. Maternal RSV vaccination administered between 32 and 36 weeks of gestation has been shown to reduce severe RSV infection in infants younger than three months of age by 82% and any RSV-associated lower respiratory tract infection by 57% (4,7).

It should be recognized that conditions affecting maternal antibody production, such as immunodeficiency disorders associated with hypogammaglobulinemia, diseases resulting in excessive antibody loss (e.g., nephrotic syndrome, protein-losing enteropathy, massive blood loss, or massive transfusion), or infections such as HIV, may result in lower maternal antibody concentrations. Consequently, lower quantities of protective antibodies may be transferred to the fetus, potentially reducing the effectiveness of passive neonatal protection.

The protective effect of maternal vaccination on the infant is mediated primarily through transplacentally transferred IgG antibodies. Vaccines administered during pregnancy may also contribute, to a lesser extent, to neonatal protection through antibodies present in breast milk. This phenomenon has been demonstrated for Tdap, influenza, and COVID-19 vaccines (7-13).

Following administration of Tdap vaccine at 20 weeks of gestation, significantly higher concentrations of anti-pertussis secretory IgA (sIgA) have been detected in breast milk compared with unvaccinated pregnant women (7-11). Similarly, a study conducted in Japan demonstrated that anti-pertussis toxin IgG positivity (≥10 EU/mL) was present in 94% of cord blood samples from infants born to mothers vaccinated with DTaP during pregnancy, compared with only 14% among infants born to unvaccinated mothers ($p< 0.0001$) (14).

Following administration of SARS-CoV-2 mRNA vaccines during pregnancy, significantly higher concentrations of SARS-CoV-2-specific IgG and IgA antibodies have been detected in the breast milk of vaccinated mothers compared with unvaccinated mothers (15). Likewise, after maternal seasonal influenza vaccination, breast milk has been shown to contain significantly elevated levels of anti-influenza antibodies for up to six months, predominantly anti-influenza IgA, together with lower concentrations of anti-influenza IgG and IgM (8,12,13).

sIgA present in breast milk is not derived from maternal serum. Rather, it is produced locally by plasma cells originating from B cells that migrate from other mucosal tissues to the mammary glands (16). Although the precise role and magnitude of protection conferred by breast milk immunoglobulins remain incompletely understood, these antibodies may contribute to protection against mucosal pathogens such as influenza virus, Bordetella pertussis, SARS-CoV-2, and RSV by interfering with the early stages of infection.

In summary, maternal immunization with Tdap, seasonal IIV, RSV vaccine, and SARS-CoV-2 vaccines is recommended to protect both the mother and the infant. When infant protection is the primary objective of maternal vaccination, administration should ideally occur at a time when maternal antibody concentrations are highest and transplacental transfer is maximal, thereby maximizing protective antibody concentrations in the infant's circulation.

These vaccines are both effective and safe. Seasonal influenza vaccination should be administered before or during the influenza season regardless of gestational age, primarily to protect the mother while also providing protection to the infant during the first six months of life. In Türkiye, influenza vaccination is reimbursed through the national health insurance system upon presentation of a physician's prescription and/or medical report.

Tdap vaccination is administered as a single dose during every pregnancy, free of charge through family health centers, primarily to protect the infant while also conferring maternal protection. Additional Td doses may be administered during pregnancy if previous vaccination is incomplete.

The non-adjuvanted RSV vaccine is recommended primarily to protect infants during the first months of life. In Türkiye, it is licensed for administration as a single dose between 24 and 36 weeks of gestation, whereas the current CDC recommendation in the United States is administration between 32 and 36 weeks of gestation. Although licensed in Türkiye, the vaccine is not currently reimbursed by the Social Security Institution.

At present, updated COVID-19 vaccines are not available in Türkiye.

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