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Immunology of pregnancy and vaccination: importance, recommended vaccines, and appropriate timing of administration

Inmunología de la gestación y vacunas: Importancia, qué vacunas y cuándo administrar

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ABSTRACT

During pregnancy, the maternal immune system dynamically adapts, balancing tolerance to paternal-fetal antigens with active protection against pathogens. Maternal immunization is a fundamental public health strategy that provides protection to pregnant women, fetuses, and newborns. During pregnancy, the risk of morbidity and mortality associated with vaccine-preventable diseases increases. Maternal immunization takes advantage of the mother's natural ability to generate antibodies that cross the placenta (immunoglobulin A (IgG), which is secreted in breast milk). Inactivated vaccines, such as those recommended for pertussis (Tdap), influenza, and COVID-19, have been shown to be safe and effective during pregnancy. However, vaccine coverage is low in many regions, driven primarily by vaccine hesitancy and concerns about safety for the infant. Healthcare professionals play a key role in improving uptake through clear and proactive communication.

Keywords: Vaccine, pregnat, influenza, pertussis

RESUMEN

Durante el embarazo, el sistema inmunitario materno se adapta de manera dinámica, equilibrando la tolerancia a los antígenos paternos fetales con la protección activa contra patógenos. La inmunización materna es una estrategia fundamental de salud pública que brinda protección a la mujer embarazada, al feto y al neonato, Durante la gestación se incrementa el riesgo de morbilidad y mortalidad asociada a enfermedades prevenibles por vacunación. La inmunización materna aprovecha la capacidad natural de la madre para generar anticuerpos que atraviesan la placenta (la inmunoglobulina g IgG) y en la leche materna hay Inmunoglobulina A (IgA) secretora. Las vacunas inactivadas, como las recomendadas contra la tos ferina (Tdap), influenza y COVID-19, han demostrado ser seguras y eficaces durante el embarazo. Sin embargo, la cobertura vacunal es baja en muchas regiones, impulsada principalmente por la reticencia vacunal y las dudas sobre la seguridad para el bebé. El profesional de la salud desempeña un papel clave en mejorar la aceptación mediante la comunicación clara y proactiva.

Palabras clave: Vacunas, gestante, influenza, tos ferina

Introducción

The maternal immune system undergoes complex adaptation (immunomodulation) during pregnancy to ensure tolerance to the fetus (considered a semi-allograft)[1]. At the same time, physiological changes in the cardiopulmonary and immune systems make pregnant women more susceptible to serious infectious diseases, including an increased risk of hospitalization and adverse obstetric outcomes, such as premature birth[2].

Vaccination during pregnancy offers a triple benefit: protection for the mother, protection for the fetus (by preventing infection in utero), and passive protection for the newborn and infant during the first months of life[3].

Immunology of pregnancy

During pregnancy, the fetus is a "semi-allograft" that evades maternal rejection. The maternal immune system adapts dynamically, balancing tolerance to paternal fetal antigens and maintaining active protection against pathogens[2].

The delicate immunological balance during pregnancy is maintained through specific and dynamic mechanisms:

- **Specific tolerance mechanisms:** There are specific mechanisms of tolerance to paternal antigens that are not associated with systemic immune suppression. The process of tolerance during pregnancy is more similar to tumor-induced tolerance than to graft-induced tolerance[3].

- **Immune cells at the maternal-fetal interface:** The human decidua contains a large number of immune cells, most of which are innate immune cells such as macrophages, dendritic cells (DCs), and natural killer (NK) cells, as well as adaptive immune cells such as CD4+, CD8+, and regulatory T (Treg) cells. These cells maintain the balance between tolerance to paternal antigens, support for the fetal growth process, and protection against pathogens[4].

- **Dynamic immune environment:** Each stage of development requires a unique immune environment:

    - Implantation and early placentation require an inflammatory environment. Dendritic cells are essential for preparing the endometrium for implantation by creating this inflammatory environment. Human chorionic gonadotropin (hCG) derived from the embryo is one of the first immunomodulatory factors that change the phenotype of signals present in the uterus[1].

    - Fetal growth is associated with improved tolerance, which requires anti-inflammatory signals.

    - Childbirth (the "expulsion of an aged organ" such as the placenta) again requires an inflammatory environment.

- **Communication between the placenta and the maternal immune system:** The transition from a pro-inflammatory to an anti-inflammatory state is essential for a successful pregnancy and is the result of communication between the placenta and maternal immune cells[1].

    - The placenta acts as an immunoregulatory organ. Through cytokines and hormones secreted by trophoblast cells, the placenta "educates" maternal uterine immune cells and determines the immune environment at the maternal-fetal interface, as well as in the maternal systemic immune system[3].

    - The trophoblast and the maternal immune system have coevolved and established a cooperative state, helping each other for the success of pregnancy. In addition, the trophoblast secretes multiple factors that modulate the differentiation of maternal immune cells, such as macrophages, from a pro-inflammatory to an anti-inflammatory phenotype[1].

- General immune response: The immunology of pregnancy is the result of a combination of signals and responses originating in both the maternal immune system and the fetal-placental immune system. Signals originating in the placenta modulate the behavior of the maternal immune system in the presence of potentially dangerous signals[5].

Immunological bases of product protection

Neonatal protection is based on the transfer of antibodies and immune cells from the mother to the newborn.

1. Passive Transfer of Antibodies

    Passive immunity is achieved primarily through the transport of immunoglobulin G (IgG) across the placenta (5).

    - Mechanism: Active transport is mediated by the neonatal Fc receptor (FcRn), which is expressed in the syncytiotrophoblast of the placenta.

    - Timeline: IgG transfer begins between weeks 13 and 17 of gestation and increases sig-

nificantly in the third trimester. IgG titers in the baby at birth may equal or even exceed maternal titers.

- Subtypes: Protein-based vaccines (such as tetanus toxoid) predominantly induce the IgG1 subtype, which is more easily transported across the placenta.

- Duration: Transferred antibodies provide protection to the infant during the first 4 to 6 months of life, a period of vulnerability until the infant can mount an efficient immune response to active immunization.

2. Inmune Education and Microchimerism

The transfer process is described as "immune education" that begins in utero[3].

- Breastfeeding provides an additional protective mechanism through the transfer of secretory IgA, IgG, and IgM. These immunoglobulins protect against pathogens in the gastrointestinal and respiratory tracts[3].

- The presence of maternal immune cells in fetal blood, a phenomenon known as microchimerism, has also been demonstrated. These cells may play a key role in training the neonatal immune system[3].

3. Optimal Timing and Specific Vaccines

The timing of vaccination is critical and depends on whether the goal is maternal protection, prevention of fetal infection, or passive neonatal immunity[2].

A. Pertussis (Tetanus, diphtheria, and acellular pertussis Tdap)

Whooping cough can be life-threatening in newborns, especially before 3 months of age, when they have not yet completed their primary vaccination schedule (6, 8-10).

- Recommendation: A Tdap vaccine is needed in every pregnancy, regardless of the mother's previous vaccination history[6, 11-12].

- Ideal timing: The best time is between 27 and 36 weeks of gestation, preferably during the first part of this period (weeks 27-28). This ensures maximum transfer of protective antibodies to the baby before delivery[4,6, 13-19].

- Neonatal Protection: Maternal vaccination with Tdap prevents 91% of pertussis cases in infants, and its effectiveness has remained very high (around 92%) against infant death from Bordetella pertussis[6,8-14].

- Risk of Premature Birth: Tdap can be administered from week 20 in cases of risk of premature birth. Safety studies have found no significant association with chorioamnionitis, premature birth, or other adverse events[7, 17, 19].

B. Influenza

Pregnancy increases the likelihood of the mother becoming seriously ill if she contracts influenza, due to changes in the immune system, heart, and lungs[2,20].

- Recommendation: All pregnant women are recommended to receive the inactivated vaccine in any trimester during the flu season[19-22].

- Optimal timing: Ideally, vaccination should occur before influenza activity increases. While vaccinating in the third trimester benefits the fetus more due to increased antibody transfer, vaccination should be administered as early as possible during the season to maximize maternal protection[6,19,23].

- Benefits: Vaccination reduces the risk of severe illness and hospitalization in the mother and protects the infant during the first few months. Vaccination during pregnancy has been associated with a reduced risk of prematurity and low birth weight[6,22-24].

C. Respiratory Syncytial Virus (RSV)

RSV is a common cause of severe respiratory illness and hospitalization in newborns and infants[25-26].

- Recommendation: Maternal vaccination (RSVPreF) is recommended to protect the newborn. In the US (Centers for Disease Control and Prevention [CDC]/ Food and Drug Administration [FDA]), it is recommended between 32 and 36 weeks of gestation. In Europe (European Medicines Agency [EMA]), it is authorized between 24 and 36 weeks[2,27].

- Objective: The vaccine induces antibodies against the F protein of RSV. These pass through the placenta, offering protection to the newborn until 6 months of age[7,19].

- Safety: Although some studies found a slight, non-significant increase in premature births when administered between weeks 24 and 36, the FDA limited its recommendation to between weeks 32 and 36, when the risk appears to be lower[3,24-28].

D. COVID-19 (SARS-CoV-2)

Pregnancy increases the mother's risk of severe illness and complications if she contracts COVID-19, including ICU admission, mechanical ventilation, premature delivery, and fetal/maternal death[5,30].

- Recommendation: Vaccination is recommended for everyone aged 6 months and older, including pregnant women, breastfeeding women, and women planning to conceive. mRNA vaccines have been shown to be safe and effective[4,31].

- Timing: The vaccine can be administered from 12 weeks of gestation. Vaccination in advanced stages of gestation (late second and early third trimester) may result in higher antibody titers in the umbilical cord, offering better neonatal protection against hospitalization[4,30-32].

E. The Blunting Effect

The blunting effect is the concern that high levels of transferred maternal antibodies (particularly for pertussis) may interfere with or diminish the baby's response to their own childhood vaccines administered from 2 months of age (3).

- Clinical Relevance: Although a diminished antibody response (blunting) has been observed, there is no evidence to suggest that this translates into an increased clinical risk of pertussis in older children[4].

- Priority: Protecting the most vulnerable infants (those younger than 3 months) through maternal vaccination remains the critical priority[3].

- Co-administration: Inactivated vaccines, such as influenza, Tdap, and COVID-19, can be administered on the same day or at any interval between them[6].

Preconception vaccination and contraindications

It is important to ensure that all women of childbearing age have completed their vaccination schedule.

- Live attenuated vaccines: These are contraindicated during pregnancy due to the theoretical risk of transmission of the attenuated virus to the fetus and possible embryopathy/ fetopathy. These include the rubella vaccine (part of the MMR vaccine) and the chickenpox vaccine[22,30,33].

- Waiting Period: If a woman receives a live attenuated vaccine before conception, it is recommended to wait at least one month (28 days) before attempting to conceive[2,30].

- Unintentional Exposure: Unintentional administration of live attenuated vaccines during pregnancy does not justify termination of the pregnancy[2,30].

Vaccine coverage and strategies to increase acceptance

Despite strong evidence that maternal vaccination is safe and effective, vaccine coverage is generally low and could be improved[33-34].

1. Barriers and Vaccine Hesitancy

The three most common reasons for vaccine hesitancy include:

- Fear of side effects or adverse events. In the context of COVID-19, concerns about vaccine safety were the most commonly cited reason for not accepting the vaccine (90.1%) [33].
- Lack of confidence in safety, including concern that it has not been tested in pregnant women. This mistrust is fueled by the historical exclusion of pregnant women from clinical trials, which limits the available information[34-35].
- Low perception of personal risk of infection or the importance of the disease[2].

2. The Crucial Role of Healthcare Providers

The most important factor driving vaccine acceptance is a clear and firm recommendation from a healthcare provider[36-37].

- Access to Information: Studies show that women are more willing to be vaccinated during pregnancy when they have been adequately informed by a healthcare professional about the benefits and safety of vaccines[37-38].
- Improvement Strategies: It is essential to implement a multidisciplinary strategy involving midwives, obstetricians, nurses, and pediatricians[37]. Strategies to increase coverage include:
  - Point-of-Care Vaccination: The availability of the vaccine and immediate administration at the point of prenatal care (clinic or office) can increase vaccination coverage[38].
  - Proactive Counseling: Health professionals should be proactive in their advice. Healthcare professionals involved in the care of pregnant women are the professionals whom pregnant women trust most and are able to counter misinformation[38].
  - Communication Skills: While most resources focus on knowledge about vaccines, there is a need for resources that develop communication skills to address vaccine hesitancy in a culturally safe and effective manner[37-38].
  - Cocooning strategy: It is recommended that everyone around the pregnant woman and the infant be up to date with their vaccinations (especially Tdap) at least two weeks before meeting the baby, as the newborn's immune system is immature and vulnerable[30, 8].

Vaccines in the research phase

Active research focuses on developing new maternal vaccines that provide passive neonatal protection against pathogens with high morbidity:

- Group B Streptococcus: This is a major global cause of neonatal sepsis and meningitis. Candidate vaccines, such as polysaccharide-protein conjugates, are currently in Phase 2 trials in pregnant women.
- Cytomegalovirus: This is the most common congenital infection and a leading cause of hearing loss. mRNA platforms are in advanced stages of development, with a Phase 3 trial underway, with the ultimate goal of vaccinating pregnant women to prevent infection in their babies.
- Other vaccines under investigation include Zika, Ebola, and Malaria.

Conclusions

The immunology of pregnancy is the result of a combination of signals and responses originating in both the maternal immune system and the fetal-placental immune system. Signals originating in the placenta modulate the behavior of the maternal immune system.

Maternal immunization is a powerful, effective, and safe tool for protecting the most vulnerable populations: pregnant women and newborns. The transplacental transfer of IgG antibodies, together with the benefits of environmental protection, represents an essential public health strategy. Despite notable achievements, current low coverage rates, particularly for influenza and

COVID-19, highlight the urgent need for effective communication strategies and training for healthcare professionals to dispel fears about safety and encourage acceptance..

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