The influence of maternal antibodies on the immune responses of term and preterm born infants

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Abstract

Vaccination during pregnancy is effective in providing protection against vaccine-preventable diseases in young infants. Here, timely (second rather than third trimester) pertussis vaccination during pregnancy is recommended, conveying protection against Bordetella pertussis in both term and preterm born infants. Additionally, breastfeeding during the first months of life can be advised to achieve additional mucosal protection. One must note that after infant vaccination, humoral and limited cellular interference by maternal antibodies was observed. However, clinical relevance of maternal interference has yet to be determined, as evidence of good serological and cellular immunogenicity against DTaP-IPV-HB-PRP~T vaccine after primary and booster vaccination was provided.

Introduction

The immune system of the young infant, although uniquely adapted to cope with various early life changes, relies on maternal help to overcome first encounters with pathogens (1). The transfer of maternal antibodies (Mabs) and other immune components in utero and later via the breast milk, is essential to protect the newborn against infectious diseases during the first months of life. The strategy of vaccinating pregnant women augments the disease-specific Mab concentrations in the newborn and offers protection against the targeted pathogen until the start of the infant's own primary immunization schedule or until the period of vulnerability is over (e.g. around 6 months for RSV) (2). The successes of this public health intervention have become more apparent over the last decades, as routine vaccination of pregnant women with tetanus toxoid, acellular pertussis (whooping cough), and inactivated influenza (flu) vaccines have led to a global reduction of neonatal tetanus, decreased pertussis outbreaks and have lowered the burden of seasonal influenza in pregnant women (3-5). The reassuring safety and efficacy data of vaccinating pregnant women with inactivated (non-live) vaccines has inspired many new targets for maternal immunization to improve global maternal and neonatal health against infectious diseases like e.g. RSV, CMV, GBS, and Zika (6). Yet, several questions regarding the strategy of in-pregnancy vaccination remain, for example: the optimal timing to vaccinate pregnant women or the effect of the strategy on preterm born infants. In addition, the observation that Mabs interfere with (or modulate) the infants' antibody responses at the time of the infants' vaccination, often resulting in significantly lower antibody concentrations amongst infants born to vaccinated mothers, has raised some concerns to the strategy (7, 8). Here, we explored the benefit of maternal pertussis vaccination (per example of a recommended maternal vaccine) in a preterm cohort and provide evidence on the impact of high Mabs on both humoral and cellular immune responses after infants' primary and booster vaccination.

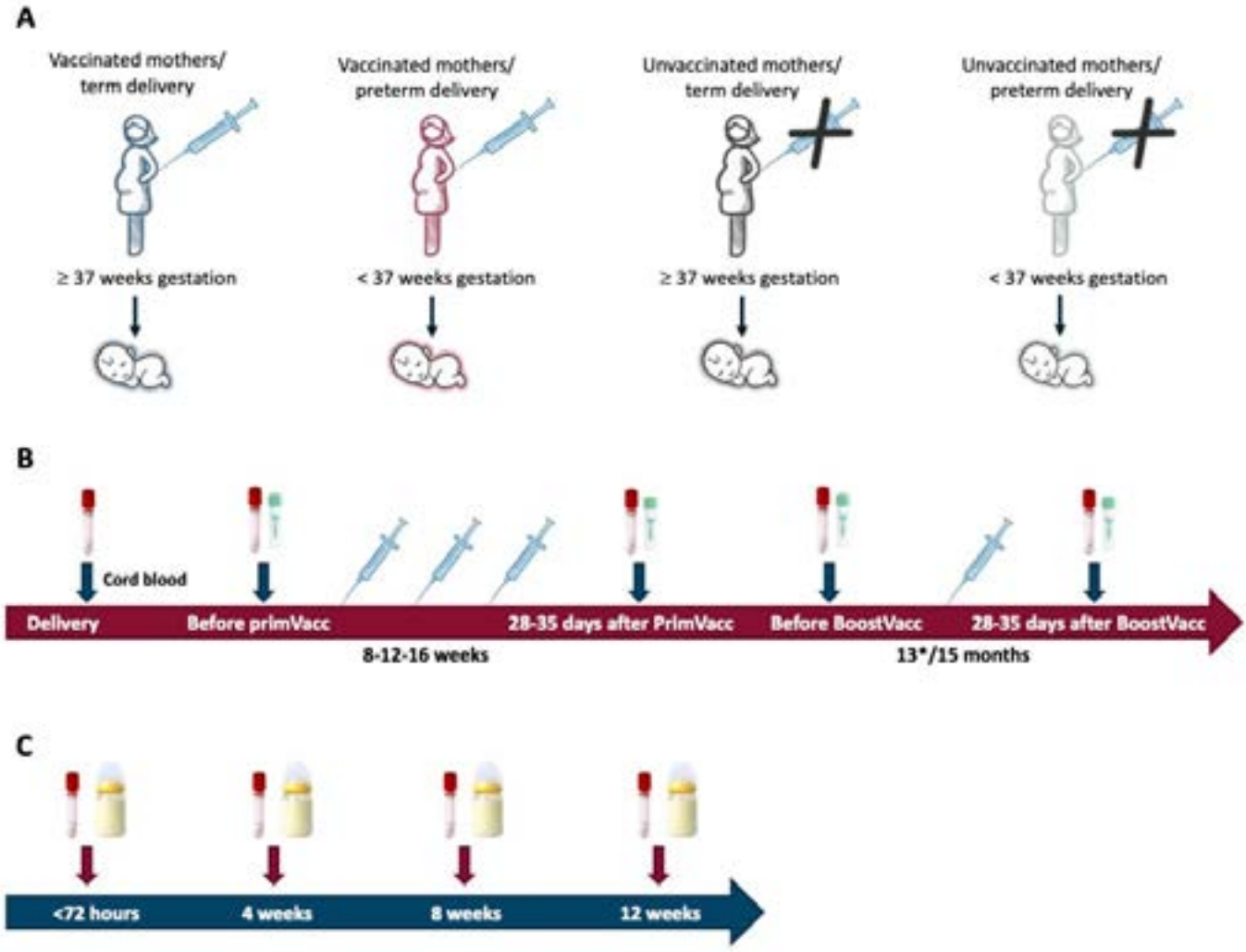
Results

A prospective observational study (NCT02511327) conducted in Belgium, included mother-infant pairs who were either vaccinated or not vaccinated with a pertussis-containing vaccine (Tdap, Boostrix®, GSK Biologicals) during pregnancy and did or did not deliver prematurely (Figure 1). Infants were vaccinated with DTaP-IPV-HB-PRP~T vaccine (HexyonÆ, Sanofi Pasteur) at 8-12-16 weeks (primary vaccination) and at 13 or 15 months of age (booster vaccination for preterm and term born infants, respectively), according to the recommended Belgian vaccination schedule.

This study confirmed that premature delivery is linked to a reduced transplacental transport, resulting in lower maternal-fetal transplacental transport ratios in preterm infants born to in-pregnancy vaccinated and unvaccinated women (9). Additionally, no influence of the maternal vaccination status on these transplacental transport ratios was detected. Nevertheless, at birth and before primary vaccination significantly higher Tdap antibody levels were observed in preterm infants from vaccinated women compared with term and preterm infants from unvaccinated women. Moreover, longer in-pregnancy vaccination to delivery intervals were significantly correlated with higher transplacental transport ratios in both term and preterm infants. These findings illustrate that preterm infants can profit from Tdap vaccination during pregnancy, even more so when the vaccination-delivery interval is increased by vaccinating earlier in pregnancy (e.g. second trimester rather than third trimester) (9).

Additional advantages of maternal pertussis vaccination might be attained when preterm infants are being breastfed, as we demonstrated comparable pertussis specific antibody levels in breast milk between in-pregnancy vaccinated mothers who delivered term or preterm babies that remained detectable up until 12 weeks after delivery (10). This strengthened the hypothesis that antibodies in breast milk could help bridge the vulnerability gap induced by a shortened period of transplacental transport of antibodies linked to prematurity, and potentially offer additional mucosal and clinical protection.

Figure 1: Schematic representation of the study design (A), serum and heparin sample collection in infants (B), serum and breast milk sample collection in women (C). * vaccination timepoint for preterm born infants.



Next to the benefits of maternal Tdap vaccination in preterm infants, our research also provides a first report on the antibody responses to Hexyon® in preterm infants (Figure 2) (9). We hereby show that primary vaccination induces comparable antibody levels for all pertussis antigens in term and preterm infants, yet booster vaccination promoted significantly lower antibody levels for some pertussis antigens in preterm infants born to Tdap-vaccinated women when compared to their term counterparts. Nevertheless, their antibody levels for all Tdap vaccine antigens remained comparable to those of term and preterm infants from unvaccinated women after booster vaccination, supporting immunogenicity of Hexyon® vaccine after primary and booster vaccination in preterm infants.

Despite this good serological immunogenicity in both term and preterm infants, the presence of high Mab concentrations at the time of primary vaccination significantly reduced the infant's humoral immune responses to some of the Tdap antigens (Diphtheria Toxoid [DT] and Filamentous Hemagglutinin [FHA]) (9). After booster vaccination, this interference by Mabs was only observed for the DT antigen in term infants of vaccinated mothers. Still, all infants achieved antibody levels above the correlate of protection for DT, suggesting that interference by Mabs did not increase the infant's susceptibility to Diphtheria. Unfortunately, it remains difficult to predict the clinical significance of this interference, especially for pertussis where no serological correlate of protection has been defined.

So far research has focused on the effect of Mabs on the infant's humoral immune response, however knowledge regarding the influence on the infant's cell-mediated immune (CMI) responses are lacking (11). Previous data demonstrated that the infants' T cell compartment remains largely unaffected after vaccination in the presence of Mabs, with some studies observing differences in cytokine secretions (12). Overall, it remains challenging to confirm the hypothesis that Mabs do or do not modulate the CMI responses of the infant, as most data originate from animal studies and no information on maternal vaccines like pertussis and influenza vaccination are available (11). Within our research the cellular responses of term and preterm infants born to in-pregnancy vaccinated women was evaluated. We demonstrated that both term and preterm born infants are capable of mounting a CMI response after primary and booster vaccination with Hexyon® vaccine, providing evidence on the immune competence of young infants (13). With regards to the hypothesis of cellular interference by Mabs, no significant differences in the specific T lymphocyte responses of infants born to vaccinated or unvaccinated mothers were recognized after primary vaccination. However, infants who were cellular non-responders for IL-13 one month after booster vaccination were observed to have significantly higher Mab concentrations at birth, implicating that Mabs might modulate the infant's CMI responses later in life. In addition, a positive correlation between the infants' serum antibodies and their lymphoblast proliferation and cytokine secretions after primary and booster vaccination was observed, adding weight to this hypothesis. Still, more research on the impact of high Mabs on the immune development of the infant and their possible long-term effects are needed.

In general, our research provides confidence towards the strategy of in-pregnancy vaccination for term and preterm infants, as both transplacental and antibodies provided by breast milk can offer additional protection during the first months of life. However, vaccinating term and preterm infants in the presence of high Mab concentrations resulted in lower antibody levels to some of the Tdap antigens. Moreover, modulation of the infant's CMI response by Mabs after booster vaccination was also observed. Yet, good serological and cellular immunogenicity against Hexyon® was established in both term and preterm infants, raising questions on the possible long-term effects of maternal immunization and its clinical significance.

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Figure 2: Antibody concentrations (with anti-pertussis toxin [PT] as an example [A]) and PT-specific cellular immune responses (CD3+CD4+ response as an example [B]) in term infants from vaccinated women (VT cohort), preterm infants from vaccinated women (VP cohort), term infants from unvaccinated women (UnVT cohort) and preterm infants from unvaccinated women (UnVP cohort) at the different study time points. Full depiction of the infants antibody responses against the DTaP-IPV-HB-PRP~T (Hexyon®) vaccine available in Maertens et al. (9) and full report of cellular responses available in Orije et al. (13). PT antibody concentrations are expressed in EU/mL and on a natural logarithmic scale. CD3+CD4+ lymphoblasts populations are presented in percentages (%CD4 blast; after correction with the unstimulated culture).