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Assessing the reactogenicity of Tdap vaccine administered during pregnancy and antibodies to *Bordetella pertussis* antigens in maternal and cord sera of Thai women

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ABSTRACT

Introduction: Pregnant Thai women have low antibody titers against *B. pertussis* antigens, which coincide with an increasing incidence of pertussis among Thai infants. Thus, there exists a potential benefit of a booster dose of tetanus- diphtheria-acellular pertussis (Tdap) vaccine administered during pregnancy. Here, we report the vaccine reactogenicity profile and birth outcomes in Tdap-vaccinated pregnant women who have or have not had prior immunization with tetanus vaccine, and the IgG levels to *B. pertussis* antigens in maternal and cord sera at delivery.

Materials and methods: Pregnant women (N = 370) aged 18–40 years were administered the Tdap vaccine (Boostrix®, GlaxoSmithKline, Rixensart, Belgium) at 26–36 weeks gestation. Adverse events following vaccination were identified by follow-up telephone call and medical record review. IgG against pertussis toxin (anti-PT), filamentous hemagglutinin (anti-FHA) and pertactin (anti-PRN) in both maternal and umbilical cord blood obtained at delivery were quantitatively evaluated using enzyme-linked immunosorbent assay (EUROIMMUN®, Lübeck, Germany).

Results: There was no reported increase in the severity or duration of adverse events associated with the administration of an extra tetanus-containing vaccine within the previous five years (N = 181) or multiple doses of tetanus-containing vaccines during the current pregnancy (N = 98). Vaccination at least eight weeks prior to delivery resulted in high antibody titers to all *B. pertussis* antigens studied.

Conclusions: The reactogenicity of Tdap vaccine administered during pregnancy was not affected by prior tetanus toxoid immunization. High transplacental antibody against *B. pertussis* antigens in the cord blood provides evidence of antibody transfer and should thus help to protect newborns from pertussis during early life.

1. Introduction

Pertussis is a respiratory disease caused by the gram-negative bacteria *Bordetella pertussis*. Although pertussis is vaccine preventable, new infection readily occurs in both developed and developing countries despite the implementation of vaccination efforts worldwide. Severe morbidity and mortality associated with

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pertussis often occurs in infants and young children [1]. Current pertussis immunization strategies fail to protect infants who are too young to have received their primary series of pertussis vaccination. These infants are susceptible to severe pertussis-related complications and even death due to the lack of protective immunity.

Passively acquired maternal *B. pertussis*-specific antibodies are relatively low and transient in newborns despite an active transplacental transport [2]. Infants born to Tdap-vaccinated mothers had significantly higher titers of *B. pertussis* antibodies than those born to unvaccinated mothers [3]. Consequently, many countries including the UK, USA, Spain, Italy, Belgium and Argentina have implemented the Tdap vaccination during pregnancy in their national immunization programs in order to increase the maternal *B. pertussis* antibody levels which will be transplacentally transferred to protect the newborn during the first months of life [4–6]. High titers of naturally-acquired maternal-derived *B. pertussis* antibodies have been shown to interfere with the infant humoral immune response induced by the whole cell pertussis (wP) but not to acellular pertussis (aP) vaccine [7]. In contrast, an interference has been observed in maternal-derived Tdap-induced anti-*B. pertussis* antibody in aP-vaccinated infants in clinical studies from the US, Belgium and Vietnam [8–12].

At the April 2014 World Health Organization meeting by the Strategic Advisory Group of Experts on immunization to prevent early mortality, researchers concluded that data required for the implementation of maternal Tdap immunization in countries where wP vaccine is used in infant vaccination programs could not be derived from the extrapolated aP vaccine data. Tdap-induced maternal antibodies may interfere with infant immune response induced by wP vaccine. Moreover, additional information on the safety and reactogenicity of repeated tetanus vaccination are vital to the effective implementation of pertussis immunization in countries with an existing tetanus vaccination during pregnancy such as Thailand.

The increasing incidence of pertussis in Thai infants [13], reportedly low antibody titers to *B. pertussis* antigens among Thai pregnant women [14] and the lack of data on potential blunting after wP vaccine administration in the presence of maternal antibodies, warrant the need to assess the effect of a booster dose of Tdap vaccination during pregnancy. Here, we report the reactogenicity profile of Tdap vaccine in a randomized controlled clinical trial involving Tdap-vaccinated Thai mothers, and describe the concentrations of *B. pertussis*-specific antibodies in paired maternal and umbilical cord sera. We also report on the adverse events and pregnancy outcomes when multiple tetanus-containing vaccines are administered. Further studies regarding the interference of maternal-derived antibodies in wP-vaccinated infants are ongoing for this cohort.

2. Materials and methods

2.1. Study design

This study was conducted according to the Declaration of Helsinki and Good Clinical Practice Guidelines (ICH-GCP). It was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB No. 604/57) and the ethical committee of the University of Antwerp, Belgium. Written informed consent was obtained from all pregnant women prior to enrollment.

This prospective randomized controlled study involved pregnant women of Thai citizenship who were offered vaccination with Tdap vaccine administered between 26 and 36 weeks of gestation according to the US Advisory Committee on Immunization Practices (ACIP) recommendation [15]. Healthy pregnant women aged 18–45 years with low obstetrical risks (inclusion and exclusion criteria in Appendix 1) were recruited during routine antenatal visits at King Chulalongkorn Memorial Hospital in Bangkok between April 2015 and September 2016. All healthy infants born after 36 weeks of gestation and weighed greater than 2500 g, were included for the follow-up study (ClinicalTrial.gov NCT02408926). Ten milliliters of blood were collected from pregnant women and the umbilical cord at delivery. Serum was separated from whole blood and stored at −20 °C prior to testing.

2.2. Study vaccine

Each 0.5 mL dose of the Tdap vaccine (Boostrix®, GlaxoSmithKline Biologicals, Rixensart, Belgium) contained 2.5 Lf of diphtheria toxoid (DT), 5 Lf of tetanus toxoid (TT), 8 μg of inactivated pertussis toxin (PT), 8 μg of formaldehyde-treated filamentous hemagglutinin (FHA) and 2.5 μg of formaldehyde-treated pertactin (PRN) adjuvanted with aluminium hydroxide. The vaccine was administered to pregnant women in the musculus deltoideus by the nurse or doctor.

2.3. Safety and reactogenicity

Acute adverse reaction was assessed in all women 30 min post-injection. Research nurses made follow-up telephone calls on day 2 and again on day 7 post-vaccination to record adverse events (AE) such as redness, pain, and induration at the site of injection, or fever. Participants were encouraged to report possible AE anytime thereafter. In instances where AE were reported, daily follow-up telephone calls were made to record the severity and duration of AE until symptom resolution. Serious adverse events (SAE) and pregnancy outcome were recorded for all participants. AEs and SAEs that occurred after vaccination were evaluated jointly by the investigators and the data safety monitoring board.

2.4. Laboratory testing

The anti-PT, anti-FHA and anti-PRN IgG titers were analyzed using commercial ELISA kits (EUROIMMUN, Lübeck, Germany) according to the manufacturer's instructions. The ELISA kits used were calibrated based on the World Health Organization international standards. The values were expressed in International Units (IU) per milliliter. Serum samples were initially diluted 1:101 and further dilutions were made as needed to yield results within the detection range. Values below the lower limit of detection (<5 IU/ml) observed in some samples were calculated as 50% of the cut-off values (2.5 IU/ml).

2.5. Statistical analysis

The number of pregnant women in this study was calculated based on the estimation of possible interference of maternal anti-PT in wP-vaccinated children [7] (significance level = 0.05, power = 0.90). The IgG levels were expressed as geometric mean concentrations (GMC) with 95% confidence interval. Data were analyzed using SPSS software version 24 (IBM Inc., Armonk, NY, USA) and R statistical software version 3.4.1. Pearson's correlation was used to show the relationship between maternal and cord antibody titers. The conventional *t*-test was performed on the antibody logarithmic scales to compare the GMC in pregnant women who received Tdap before and after 30 weeks gestation [16]. The *t*-test was also used to test the difference in cord/maternal ratios of antibody levels in these two groups. Since the sample sizes of the two groups were reasonable high, we could rely on the central limit theorem and hence a conventional *t*-test would be valid [17]. To