Vaccine 32 (2014) 5787–5793

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels – A prospective study

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ARTICLE INFO

Article history:
Received 11 June 2014
Received in revised form 2 August 2014
Accepted 15 August 2014
Available online 28 August 2014

Keywords:
Immunoglobulin G transfer
Tetanus-diphtheria-acellular pertussis
Maternal immunization
Pertussis

ABSTRACT

Background: The Centers for Disease Control and Prevention recommend Tdap immunization during pregnancy, preferably at 27–36 weeks.
Aim: To ascertain whether there is a preferential period of maternal Tdap immunization during pregnancy that provides the highest concentration of pertussis-specific antibodies to the newborn.
Methods: This prospective study measured pertussis-specific antibodies in paired maternal-cord sera of women immunized with Tdap after the 20th week of their pregnancy ($n = 61$).
Results: The geometric mean concentrations (GMCs) of Immunoglobulin G (IgG) to pertussis toxin (PT) were higher in the newborns' cord sera when women were immunized at 27–30^{+6} weeks ($n = 21$) compared with 31–36 weeks ($n = 30$) and >36 weeks ($n = 7$), 46.04 international units/milliliter (IU/mL) (95% CI, 24.29–87.30) vs. 8.69 IU/mL (95% CI, 3.66–20.63) and 21.12 IU/mL (95% CI, 7.93–56.22), $p < 0.02$, respectively. The umbilical cord GMCs of IgG to filamentous hemagglutinin (FHA) were higher in the newborns' cord sera when women were immunized at 27–30^{+6} weeks compared with 31–36 weeks and >36 weeks, 225.86 IU/mL (95% CI, 182.34–279.76) vs. 178.31 IU/mL (95% CI, 134.59–237.03) and 138.03 IU/mL (95% CI, 97.61–195.16), $p < 0.02$, respectively.
Conclusions: Immunization of pregnant women with Tdap between 27–30^{+6} weeks was associated with the highest umbilical cord GMCs of IgG to PT and FHA compared with immunization beyond 31 weeks gestation. Further research should be conducted to reaffirm these finding in order to promote an optimal pertussis controlling policy.

1. Introduction

Despite widespread vaccination, there have been worldwide reports of high *Bordetella pertussis* morbidity and mortality [1–3]. Infants during the first months of life have the highest rates of confirmed cases and ≥90% of fatalities occur in neonates and infants <3 months of age [4,5].

In 2011, the U.S. Centers for Disease Control and Prevention (CDC) issued a recommendation for use of tetanus, diphtheria and acellular pertussis (Tdap) vaccine in unimmunized pregnant women, preferably during the third or late second trimester (after 20 weeks gestation) [6]. In 2012, this recommendation was broadened to include all pregnant women, irrespective of their immunization status, preferably at 27–36 weeks of each pregnancy [7]. Similarly, Israel's Ministry of Health initially recommended immunization of unimmunized pregnant women with Tdap after the 20th week, but later expanded the policy to target all pregnant women at 27–36 weeks gestation, regardless of their vaccination history [8,9].

These recommendations were based primarily on studies in which Tdap was administered to women prior to their pregnancy

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http://dx.doi.org/10.1016/j.vaccine.2014.08.038
0264-410X/

or cases in which the timing of administration to the pregnant women could not be ascertained [10–12]. In another study, only 3 of the 19 women who had been Tdap-immunized during their pregnancy were immunized after 20 weeks gestation [13]. Most recently, Munoz et al. [14] found that maternal immunization of 33 women at 30–32^{+6} weeks gestation with Tdap resulted in high concentrations of pertussis-specific antibodies at 2 months and did not interfere with subsequent diphtheria, tetanus toxoids and acellular pertussis immunization. Still, to date, no study has examined whether there is an optimal period to immunize pregnant women with Tdap within the CDC's 27–36 week recommendation that maximizes the newborn's pertussis antibody concentrations at delivery.

The purpose of the current study is to reaffirm in a larger cohort of pregnant women that immunization with Tdap at variable gestational ages during the late second and third trimester of pregnancy provides trans-placental passive pertussis-specific antibody transfer to the newborn. Moreover, we sought to ascertain whether there exists a preferential period of maternal immunization with Tdap that results in the highest concentrations of pertussis-specific antibodies to the newborn at delivery.

2. Materials and methods

This prospective study evaluated maternal and newborn pertussis-specific antibody levels following gestational Tdap immunization. Periparturient women at Bnai Zion Medical Center who delivered between November 2013 and May 2014 were assessed for participation in the study. Inclusion criteria were women with singleton births at gestational age ≥36 weeks who had received Tdap after the 20th week of the current pregnancy. Periparturient women unimmunized for pertussis during the current pregnancy served as controls. Exclusion criteria were one or more of the following: having a newborn with a birth weight <2000 g; having an immunologic disorder; receipt of immunoglobulins in the previous year; receipt of immunosuppressive drugs during the current pregnancy, including high-dose steroids; receipt of blood products 3 months prior to delivery; documented (culture, polymerase chain reaction, immunoglobulin G [IgG] to pertussis toxin [PT] ≥94 international unit/milliliter [IU/mL] [15]) or suspected pertussis infection (cough >2 weeks) within the previous 5 years; receipt of a pertussis-containing vaccine within 5 years of the current pregnancy; and receipt of any vaccine besides Tdap within 2 weeks of delivery. Paired maternal and cord blood were available for analysis from 61 Tdap-immunized women and 20 unimmunized women.

At recruitment, demographic data were derived from the women's medical records. The study investigator recruited all of the participants and questioned each woman about her clinical history, inquiring specifically about exposure, infection, and past vaccination against pertussis. Gestational age at delivery was derived from the date of the woman's last menstrual period as recorded in her Obstetrics and Gynecology medical records. The study was approved by the Medical Center's Internal Review Board and all participants gave informed consent.

2.1. Vaccine

Participants had been immunized with Tdap (Boostrix) containing tetanus toxoid (≥20 IU), diphtheria toxoid (≥20 IU), PT (8 mcg), filamentous hemagglutinin (FHA) (8 mcg), and Pertactin (PRN) (2.5 mcg).

2.2. Laboratory specimens

A routine maternal peripartum blood sample and a venous umbilical cord sample (both routinely discarded) were utilized for analysis after receipt of informed consent. The blood samples were processed at Bnai Zion Medical Center's Clinical Microbiology laboratory and stored at −20 °C prior to analysis.

2.3. Serology

Pertussis-specific IgG and immunoglobulin A (IgA) were measured by a validated IgG and IgA-specific enzyme-linked immunosorbent assay (ELISA) in maternal and umbilical cord sera (EUROIMMUN Medizinische Labordiagnostika, Lübeck, Germany). Results were reported in IU/mL as per the EU Perstrain group recommendations [16]. The anti-*Bordetella pertussis* controls of the anti-Bordetella PT ELISA were calibrated using the first International WHO standard (WHO International Standard Pertussis Antiserum, human, 1st IS NIBSC Code 06/140).

The lower limits of detection for IgG to PT and IgA to PT were 0.2 IU/mL and 0.7 IU/mL, respectively. The lower limits of detection for IgG to FHA and IgA to FHA were 1 IU/mL and 0.2 IU/mL, respectively. The lower limit of detection for IgG to PRN was 0.6 IU/mL. Utilizing the half-life of IgG to PT of 36 days, we interpolated postpartum antibody concentrations from the cord blood titers [17].

2.4. Statistics

To test for differences in the demographic data between the immunized and unimmunized groups, χ^2 and Fisher exact tests were performed for the categorical data, and Student's *t*-test or the Mann–Whitney *U* test, where appropriate, for the continuous data. Antibody concentrations below the limit of detection were assigned the lower limit of detection value for that antigen. Geometric mean concentration (GMC) and 95% confidence intervals (CI) for maternal sera and cord blood concentrations were calculated. In order to rule out the effect of pertussis exposure history on maternal and cord sera antibody levels, an analysis of patients with and without exposure was performed via the Mann–Whitney *U* test. The Kruskal–Wallis test was used to assess differences in antibody concentrations in different immunization time groups. This was followed by post hoc analysis of the significant differences between matched pairs using Mann–Whitney *U* tests with Bonferroni-type correction to take into account multiple testing. A similar analysis was performed for time between immunization and delivery. The analyses were performed using SPSS software version 19.0 (SPSS, Chicago, IL). Significance was set at $p < 0.05$.

3. Results

A total of 61 women were immunized with Tdap between 23 and 38 weeks gestation (3 at 23–26^{+6}, 51 at 27–36 and 7 at >36 weeks gestation), and 20 unimmunized women served as controls (Fig. 1). The Tdap vaccine was administered to the pregnant women between 6 and 115 days before delivery (mean: 50 days, median: 46 days).

The demographic and clinical characteristics of the study population are presented in Table 1. Notably, there were no statistical differences between the Tdap-immunized and unimmunized women and their newborns in maternal and pregnancy morbidity, gestational age, delivery mode and birth weight. However, the women with Tdap gestational immunization had a statistically significant higher percentage of influenza vaccine uptake than those women unimmunized with gestational Tdap.

3.1. Pertussis exposure history

With the aim of capturing the vast potential of natural pertussis boosting, all participants were questioned regarding pertussis infection and/or known potential exposure. Regardless of the