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Combined tetanus-diphtheria and pertussis vaccine during pregnancy: Transfer of maternal pertussis antibodies to the newborn

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ABSTRACT

Background and objectives: Pertussis is currently an emerging public health concern in some countries with high vaccination coverage. It is expected that maternal pertussis immunization could provide newborn protection. We compared pertussis toxin antibody (anti-PT) levels in women during pregnancy (pre- and post-vaccination) with respect to levels in the newborn at delivery in women vaccinated during pregnancy. We also estimated anti-PT titers at primary infant vaccination.
Methods: Observational study of pregnant women vaccinated with Tdap (≥20 weeks gestation) and their newborns between May 2012 and August 2013. Anti-PT levels were determined by ELISA in maternal (pre- and post-vaccination) and newborn blood.
Results: Pre-vaccination, post-vaccination maternal and newborn samples were available in 132 subjects. Mean maternal age was 34.2 (SD 4.3) years. Median weeks of gestation at vaccination were 27.2 (Q1–Q3 21.7–30.8). Anti-PT (≥10 IU/ml) levels were found in 37.1% of maternal pre-vaccination samples (geometric mean titer (GMT) 7.9 IU/ml (95% CI 6.8–9.2)), 90.2% of post-vaccination samples (GMT 31.1 IU/ml (95% CI 26.6–36.3)) and 94.7% of newborns (GMT 37.8 IU/ml (95% CI 32.3–44.1)). The Lin concordance index between post-vaccination maternal and newborn samples was 0.8 (95% CI 0.8–0.9). Transplacental transfer ratio was 146.6%. At two months of age, 66% of newborns had estimated anti-PT levels ≥10 IU/ml.
Conclusions: There was a high correlation between anti-PT levels in mothers and newborns, with higher levels in newborns, which should be sufficient to provide protection against pertussis during the first months of life. Vaccination of pregnant women seems to be an immunogenic strategy to protect newborns until primary infant immunization.

1. Introduction

Pertussis is a major cause of infant morbidity and mortality worldwide and is currently an emerging public health concern. Recent years have seen an increase in cases in developed countries, even those with high vaccination coverage such as Spain [1], the United States [2] and the United Kingdom [3]. In an outbreak in California in 2010, more than 9000 cases were reported, with the highest incidence rates being recorded in children aged <2 months [2].

Pertussis is caused by the bacterium *Bordetella pertussis* [4]. In infants aged <6 months pertussis presents the greatest morbidity and mortality [5]. In adolescents and adults, pertussis almost always presents as a persistent cough, often of undiagnosed cause, and these cases are the main sources of infection to susceptible children [6].

The incidence of pertussis is cyclical, with a peak every 2–5 years [7]. Vaccination is the only effective way to combat epidemics [8]. In Spain, the last dose of acellular pertussis containing vaccine is

Abbreviations: CDC, centers for disease control and prevention; CI, confidence interval; DTaP, diphtheria, tetanus and high antigenic load of acellular pertussis vaccine; DTwP, diphtheria, tetanus and whole-cell pertussis vaccine; EU, ELISA units; GMT, geometric mean titers; HCB, hospital clinic of Barcelona; IgG, immunoglobulin G; LLOD, lower limit of detection; anti-PT, Pertussis toxin antibody; Tdap, diphtheria, tetanus and low antigenic load of acellular pertussis vaccine.

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administered at 4–6 years of age [1]. The length of vaccine and natural immunity is limited [7,9–11].

The current situation requires consideration of other vaccination strategies to protect newborns [12,13]. Vaccination of pregnant women is a mixed form of protection: direct through the transplacental transmission of antibodies and indirect as part of the cocooning strategy (consisting in vaccinating those in close contact with infants).

In studies carried out in women vaccinated in childhood, low levels of pertussis antibodies have been found in both mothers and newborns [14–17]. Leuridan et al. [18] found higher levels of specific antibodies in infants whose mothers had received a booster dose of Tdap in the two years pre-pregnancy compared with infants of unvaccinated mothers. However, Healy et al. [19] suggested that vaccination before conception or during early pregnancy (inadvertent vaccination) does not appear sufficient to achieve and maintain high levels of pertussis antibodies capable of protecting the infant.

In October 2011, the centers for disease control and prevention (CDC) recommended to implement a Tdap (combined tetanus, diphtheria and low antigenic load of acellular pertussis vaccine) vaccination program for pregnant women who previously have not received Tdap [20]. Various countries, agencies and scientific societies have incorporated this strategy. The United Kingdom recommended, in October 2012, pertussis vaccination of all pregnant women between 28 and 38 weeks of gestation, achieving coverage of 50% [21]. In December 2012, the CDC issued interim recommendations indicating that women should be revaccinated during each pregnancy, being optimal timing for Tdap administration between 27 and 36 weeks of gestation to maximize the maternal antibody response and passive antibody transfer to the infant [22,23]. The available evidence suggests that the incorporation of the pertussis component does not increase the risk of harm to the mother and fetus [24–26].

The main objective of this study was to compare pertussis toxin (anti-PT) antibody levels in pregnant women during pregnancy (pre- and post-vaccination) with respect to levels in the newborn at delivery in women vaccinated with Tdap during pregnancy. Secondary objectives were to analyze factors associated with the vaccine response and transplacental transfer and estimate the titers of anti-PT antibodies in the infants at two months of age.

2. Materials and methods

2.1. Study characteristics

Prospective observational study of women attended by the Maternal-Fetal Unit of the Hospital Clinic of Barcelona (HCB) (who attend around 3000 births annually) vaccinated with Tdap during pregnancy between May 2012 and August 2013 (PERTU Study).

Inclusion criteria were maternal age ≥18 years old, Tdap vaccine administered between 20 and 36 weeks of gestation, and the signature of written informed consent. A retrospective blood sample from the first trimester of pregnancy was obtained from the Hospital Clínic-IDIBAPS Biobank. A sample of maternal blood was obtained at least 15 days after Tdap vaccination during routine blood sample collection in the second or third trimester. At delivery, a blood sample was taken from the umbilical cord or, alternatively from the heel of the newborn during routine neonatal screening for metabolic disorders at 48 h after the birth. In the case of twin pregnancies, only one sample was collected, from the first newborn. We recruited a convenience sample, including only cases in which the results of pre-vaccination, post-vaccination maternal and neonatal determinations were available.

2.2. Hospital Clínic of Barcelona Tdap vaccination protocol

Vaccination with one dose of Tdap was recommended to all pregnant women from 20 weeks of gestation. The vaccine was administered intramuscularly into the deltoid muscle during a routine pregnancy check-up. The vaccine used was Triaxis (Sanofi Pasteur MSD, France), in some countries licensed as Adacel, which contains five antigens purified from *B. pertussis* (2.5 μg PT, 5 μg HFA, 3 μg PER, 5 μg FIM2 and 5 μg FIM3), ≥20 IU tetanus toxoid and ≥20 IU diphtheria toxoid [27].

2.3. Laboratory methods

Levels of immunoglobulin G (IgG) against pertussis toxin (PT) were determined using the Pertussis Toxin ELISA Testkit IgG/IgA TESTKIT, Sekisui Virotech GmbH, Germany, and expressed as international units (IU/ml). Absorbance readings were measured and quantified against an international reference serum with known amounts of the respective antibodies (in 2008, preparation No. 6/140 was established as the First International Standard for Pertussis Antiserum (Human), expressed in IU/ml, using, as a reference, a pattern drawn up by the FDA: U.S. Human anti-pertussis reference sera lot 3 and lot 4 for IgG antibodies. IU were taken to be equivalent to ELISA units (EU) referring to the widely used pattern of the FDA in studies carried out before 2008) [28–30]. The lower limit of detection (LLOD) of IgG anti-PT was 5 IU/ml. Titers of ≥10 IU/ml were considered as an elevated cut-off [31–33]. A vaccine response was defined as an antibody level multiplied by four for baseline determinations of <20 IU/ml and duplication of titers when baseline determinations were ≥ 20 IU/ml [34]. All samples were analyzed by the HCB microbiology service.

2.4. Collection of variables

The following variables were collected from medical records: maternal date of birth, country of origin, parity, history of immune system disorders (autoimmune disease or HIV infection), date of last menstruation, date of administration of Tdap, date of pre-and post-vaccination blood samples, and date of birth, sex and birth weight of the newborn. Anti-PT antibody levels in the mother (pre- and post-vaccination) and the newborn were established as dependent variables.

2.5. Statistical analysis

In the univariate analysis absolute frequencies and percentages were used to describe categorical variables and means and standard deviation (SD) or 95% confidence intervals (CI) for quantitative variables with a normal distribution and medians and interquartile range otherwise. IgG anti-PT levels were described as geometric mean titers (GMT) and 95% CI. Values below the LLOD were considered to be half of the value of detection [19,35]. For quantitative comparisons of antibody levels in maternal blood (baseline versus post-vaccination) and versus levels in the newborn, the Wilcoxon test for paired data was used. The Lin concordance index was used to measure the concordance between two samples: maternal post-vaccination and newborn. The ratio of transplacental transmission of antibodies to the fetus was calculated by dividing the titers in the newborn by those of the mother. A bivariate analysis was done to evaluate the influence of variables in the vaccine response and elevated cut-off (≥10 IU/ml) of antibodies transferred. Antibody titers at two months of age were estimated by a linear interpolation using the GMT of newborn samples, considering the half-life of IgG anti-PT at 43 days [25]. The statistical analysis was performed using the STATA® statistical package v12.1. Statistical significance was established as $p < 0.05$.

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