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ORIGINAL ARTICLE

Prevalence of Pertussis Antibodies in Maternal Blood, Cord Serum, and Infants From Mothers With and Those Without Tdap Booster Vaccination During Pregnancy in Argentina

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Background. Morbidity and mortality rates for pertussis in infants are high because disease often occurs before the onset of routine immunization or in those who do not complete a primary immunization series. Pertussis immunization is recommended during pregnancy to achieve antibody levels sufficient to protect young infants. To our knowledge, no previous reports of maternal pertussis immunization results in Latin America exist in the literature.

Methods. This study compared pertussis antibody levels in newborns from mothers who received or did not receive a tetanus-diphtheria-acellular pertussis vaccination (TdapV) during pregnancy. Each mother's level of immunoglobulin G antibodies against pertussis toxin (IgG-PT) was measured with a validated, specific enzyme-linked immunosorbent assay (ELISA).

Results. Paired mother and cord serum samples were compared in 105 mothers with and 99 mothers without a TdapV. At birth, the mothers with and those without a TdapV had serum IgG-PT geometric mean concentrations (GMCs) of 35.1 and 9.8 ELISA units (EU)/mL, respectively ($P < .0001$); cord blood GMCs were 51.3 and 11.6 EU/mL, respectively ($P < .0003$); and cord blood IgG-PT levels were <5 EU/mL in 2.9% and 16.1% of the cord blood samples, respectively ($P < .001$). The mothers received their TdapV at a mean (± standard deviation [SD]) of 24.7 ± 4.8 weeks' gestation. Vaccination timing did not affect the IgG-PT GMC at birth. Placental antibody transference efficiencies (measured as the ratio of the cord blood GMC to the maternal GMC) were 1.46 and 1.18 for mothers with and those without a TdapV, respectively. The IgG-PT GMCs were 17.7 EU/mL in 36 infants in their first month of life and 11.6 EU/mL in 32 infants in their second month of life.

Conclusions. Women who received a TdapV during pregnancy had significantly a higher serum/cord IgG-PT concentration at birth than mothers who did not receive a TdapV. Timing of the immunization was not correlated with antibody concentrations. Infants born to immunized mothers had significantly higher antibody levels during their first 2 months of life.

Keywords. maternal immunization; pertussis; placental transfer of antibodies; pregnancy vaccines; Tdap immunization.

Pertussis (whooping cough) is a highly contagious and potentially fatal disease that is preventable by vaccination. In fact, widespread introduction of the pertussis vaccination in the 1950s dramatically reduced morbidity and mortality rates associated with the disease. However, in the past few years, the incidence rates of whooping cough have increased in many countries, including countries with high vaccination coverage [1]. In Argentina, epidemiological monitoring of whooping cough has revealed a growing trend in the numbers of case reports since 2002 in children, adolescents, and adults. In 2011, 76 pertussis-related infant deaths occurred. Of these infants, 89.5% were younger than 4 months [2]. Because of this epidemiological situation, the Argentinian Ministry of Health proposed a pertussis vaccination strategy for pregnant women. It recommended a tetanus-diphtheria-acellular pertussis (Tdap) vaccine for mothers during pregnancy, which would be delivered by placental transfer to their fetus; this strategy can confer protection to infants who are too young to undergo vaccination. In 2012, Argentina became the first country in Latin America to implement this vaccination strategy for pregnant women [3].

Data on immune response among pregnant Latin American women who received only the whole-cell pertussis vaccine in childhood are not currently available. Therefore, we compared

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the levels of pertussis antibodies in newborns from mothers who received the Tdap vaccine (5 components) during pregnancy with mothers who did not receive the vaccine.

MATERIALS AND METHODS

Study Design

A prospective observational study was conducted in 2 consecutive periods in Buenos Aires, Argentina. The first period, from 2011 to 2012, included healthy pregnant women who delivered their child at a public hospital, D. F. Santojanni, and did not receive a Tdap vaccine. The control group included healthy women who had donated blood at the Hospital de Niños "Ricardo Gutiérrez" Blood Center. In 2012, the Tdap vaccine was recommended for pregnant women in Argentina. Therefore, the second study period was conducted from 2013 to 2014; healthy pregnant women who delivered their child at the same center but received a Tdap vaccination were recruited. Both study groups of pregnant mothers included similar populations who attended the same public hospital (D. F. Santojanni). The group of Tdap immunized pregnant women was offered follow-up for their newborn, and study visits were planned for when the infants reached the ages of 1 and 2 months. These follow-ups were performed before initiating the combined diphtheria, tetanus toxoid, and whole-cell pertussis (DTwP) vaccination scheme recommended for all infants.

Recommended Pertussis Immunization Schedule for Infants and Children in Argentina

The first 3 doses of the DTwP vaccine is recommended at 2, 4, and 6 months of age, the fourth dose at 15 to 18 months, and the fifth dose at 5 to 6 years. Since 2011, the diphtheria, tetanus, and pertussis (DTaP) vaccine has been recommended at 11 years of age.

We included 3 study groups (not enrolled concurrently) (Figure 1): pregnant nonimmunized women (2011–2012) (G1), nonpregnant nonimmunized female controls (2011–2012) (G2), and pregnant immunized women and their offspring (2013–2014) (G3).

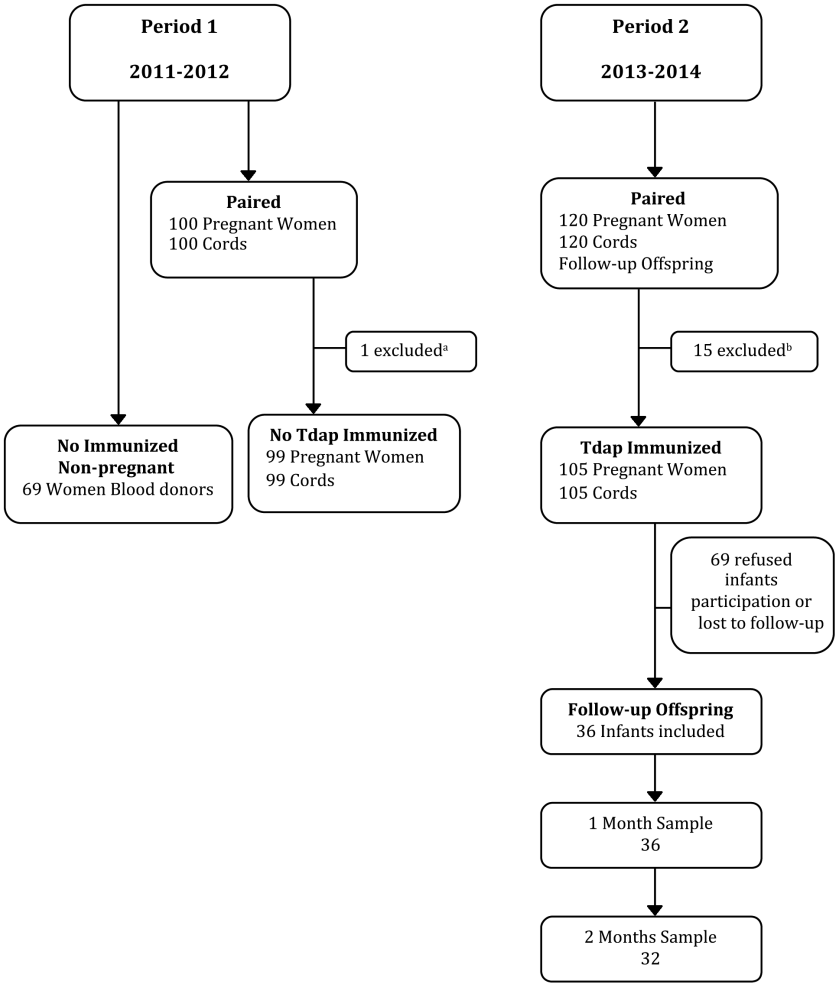

Figure 1. Flowchart of study participants. [a]One mother met diagnostic criteria for recent pertussis infection (level of immunoglobulin G antibodies against pertussis toxin, >94 EU/mL). [b]Fifteen mothers met exclusion criteria or did not met inclusion criteria.

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The study protocol was approved by the institutional review board and ethics committee at each study site. Written informed consent was obtained from each participant.

Study Population

A questionnaire (which requested information on past vaccinations and all clinical events, including cough lasting more than 2 weeks and exposure or other symptoms related to whooping cough) was completed by the women at recruitment and for the infants at each visit. Demographic and clinical data were derived from medical records.

Paired maternal blood and umbilical cord blood samples were collected at the time of delivery. Women were eligible for inclusion if they were ≥18 years old, gave birth at ≥37 weeks' gestation, had a singleton pregnancy, and had no underlying chronic medical conditions. The control group of blood donors comprised healthy women aged 18–44 years.

Excluded were mothers who had obstetric complications, a cough that lasted >2 weeks, and/or received immunoglobulins, immunosuppressive drugs (including high-dose steroids), or blood products in the previous year. Newborns were excluded if their birth weight was <2000 g.

Antibody Assays

Paired mother and cord blood samples were transported to the Hospital de Niños "Ricardo Gutiérrez" laboratory, where they were processed and frozen at −20°C for storage until testing. Aliquots of each sample were blinded with codes and shipped to the Instituto Nacional de Microbiología Dr. C. Malbran (National Reference Center) for processing. The samples were tested for immunoglobulin G antibodies against pertussis toxin (IgG-PT) with a Centers for Disease Control and Prevention–validated specific pertussis IgG enzyme-linked immunosorbent assay (ELISA). Purified pertussis toxin (Protein Express, Inc, Cincinnati, OH) was used as the positive control [4]. The assay was calibrated to World Health Organization international reference standard 06/140 [5].

The lower limit of quantification was 1 ELISA unit (EU)/mL. In each assay, values lower than 1 EU/mL were assigned a value of 0.5 EU/mL.

Mothers who did not receive a Tdap vaccine were excluded from further analysis when they met the diagnostic criteria for recent pertussis infection (IgG-PT > 94 EU/mL) [6].

Statistical Analysis

Serum IgG-PT values are expressed here as geometric mean concentrations (GMCs) with 95% confidence intervals (CIs). The efficiency of placental transfer of IgG-PT was measured as the ratio of the cord blood GMC to the maternal GMC. IgG-PT concentrations in infants after birth were compared to a protective benchmark, which we defined as ≥5 EU/mL. At this time, no concentration has been approved as an acceptable level of protection; however, the use of an IgG-PT level of ≥5 EU/mL is supported by the results of previous studies [7–9].

It is unknown how much antibody is required at birth for seroprotection that persists in infants for up to 2 months of age. We assumed that IgG-PT concentrations of >20 EU/mL at birth were associated with seropositivity, considering the waning of antibodies during the first months of life and on the basis of results from other similar studies [9–11].

We measured IgG-PT levels in infants at birth (cord blood) and at approximately 1 and 2 months of age (before the first dose of DTwP vaccine). These measurements were compared with the expected levels, as estimated on the basis of the published half-life of passively acquired maternal IgG-PT [12].

The association between the timing of vaccination and the base-10 logarithm-transformed cord IgG-PT levels was assessed using linear regression. The correlation was determined using the Pearson correlation coefficient.

Statistical significance for dichotomous outcomes was determined with the χ^2 and Fisher exact tests. Normally distributed demographic data were assessed by comparing mean values. When data were skewed positively or negatively, medians were compared, and statistical significance was assessed with the Mann Whitney U test. Statistical significance was established at a P value of $< .05$.

Statistical analyses were performed with SPSS 11.0 and Epi Info 7.1.5.

RESULTS

This study included serological data from 205 healthy pregnant women (100 without and 105 with Tdap vaccination). We collected circulating blood and cord blood samples from each woman (paired mother/cord serum samples). Serum samples from 1 pregnant woman without the Tdap vaccination was excluded because her IgG-PT level was >94 EU/mL. The control group comprised 69 blood donors who were healthy nonpregnant women (Figure 1). Except for the Tdap vaccine received during the current pregnancy, no participant of this study had been immunized against pertussis since the age of 6 years.

Demographic and clinical characteristics of the study participants are presented in Table 1. No significant differences were found among the 3 groups of subjects. No participant reported exposure to pertussis or cough consistent with pertussis during the pregnancy.

As shown in Table 2, the 69 nonpregnant women had significantly higher concentrations of IgG-PT than the 99 pregnant women who were not vaccinated ($P = .03$); the IgG-PT GMCs were 14.4 EU/mL (95% CI, 10.2–20.1 EU/mL; range, 2.7–85.5 EU/mL) and 9.8 EU/mL (95% CI, 8–12.1 EU/mL; range, 0.5–68.1 EU/mL), respectively. We found that 16 (16.1%) of the pregnant women had an IgG-PT level of <5 EU/mL, but only 2 (2.9%) of the nonpregnant women had a value that low ($P = .004$).

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Table 1. Characteristics of Women Who Did and Those Who Did Not Receive Tdap Vaccine

Characteristic	Tdap-Immunized Mothers (n = 105)	Nonimmunized Mothers (n = 99)	Female Blood Donors[a] (n = 69)
Mean age ± SD (y)	26.5 ± 6.3	26.7 ± 6.5	28 ± 6
Age range (y)	18–43	18–44	18–44
Mean parity ± SD	1.2 ± 1.4	1.6 ± 2.1	1.5 ± 1.7
Household contacts with children/ adolescents (% [n])	80.9 (85)	75.7 (75)	71 (49)
Age at last DTwP vaccine (y)	6	6	6
Previous Tdap booster	None	None	None

Abbreviations: DTwP, diphtheria, tetanus toxoid, and whole-cell pertussis; SD, standard deviation; Tdap, tetanus, diphtheria, and acellular pertussis.
[a]Not immunized against Tdap and not pregnant (controls).

We evaluated paired serum/cord samples from 105 mothers immunized with the Tdap vaccine and 99 mothers not immunized (Table 2). The concentrations of IgG-PT in these mothers at delivery were 35.1 EU/mL (95% CI, 28.5–43.1 EU/mL) and 9.8 EU/mL (95% CI, 8–12.1 EU/mL) for women with and those without Tdap immunization, respectively ($P < .0001$). The IgG-PT GMCs in the cord samples were 51.3 EU/mL (95% CI, 41.3–63.8 EU/mL) and 11.6 EU/mL (95% CI, 9.7–14 EU/mL), respectively ($P < .0003$). The IgG-PT level was <5 EU/mL in 3 (2.9%) of the 105 mothers immunized with the Tdap vaccine and 16 (16.1%) of the 99 mothers not immunized ($P < .001$). No correlation was found between cord IgG-PT concentrations and maternal age or infant birth weight.

In both groups (immunized and nonimmunized), the cord blood concentrations of IgG-PT were higher than the IgG-PT concentrations in maternal serum at delivery. These concentrations were linearly correlated. The placental antibody transference efficiencies were 1.46 for mothers immunized with the Tdap vaccine and 1.18 for mothers not immunized.

All maternal and cord samples had detectable levels of IgG-PT in mothers immunized with Tdap vaccine. Mothers received their Tdap vaccine at a mean (±SD) of 24.7 ± 4.8 weeks' gestation (range, 13.2–36.6 weeks). All the mothers received their vaccine more than 15 days before delivery. At delivery, only 2.9% (3 of 105) of the maternal samples had an IgG-PT level of <5 EU/mL, and 31.4% (33 of 105) had a level of <20 EU/mL. Only 1.9% (2 of 105) of the cord samples had an IgG-PT level of <5 EU/mL, and 19% (20 of 105) had a level of <20 EU/mL. We observed a tendency toward lower antibody levels at delivery in mothers vaccinated before 20 weeks' gestation, but there were no significant differences between maternal or cord serum levels and weeks of gestation at Tdap vaccination (Table 3). No significant linear correlation was observed between cord serum antibody concentrations and the time of immunization during pregnancy (Pearson correlation coefficient, 0.51) (Figure 2).

After birth, we analyzed the evolution of IgG-PT in newborns from mothers immunized with the Tdap vaccine. We evaluated antibody levels in 36 infants in their first month of life (mean ± SD, 31.9 ± 5.4 days) and in 32 of those 36 in their second month of life (mean ± SD, 61.8 ± 8 days, before initiating the recommended immunization schedule). In the 36 infants in their first month of life, the IgG-PT GMC detected was 17.7 EU/mL, which represented a 63.4% decrease from the levels measured in cord blood samples. In the 32 infants in their second month of life, the IgG-PT GMC was 11.6 EU/mL, which represented a 76% decrease from the levels measured in the cord samples (Table 2). Each infant with a IgG-PT GMC higher than 20 EU/mL at birth (cord sample) had a level of >5 EU/mL at 2 months of age. Four (10%) infants experienced at least 1 coughing episode, but none of them had signs or symptoms of

Table 2. GMCs of IgG-PT in Mothers, Cords, Infants, and Nonpregnant Female Blood Donors

Sample Type	Pregnant Tdap-Immunized Women (N = 105)			Pregnant Nonimmunized Women (N = 99)			Nonimmunized Female Blood Donors (N = 69)		
	N	GMC (95% CI), Range (EU/mL)	IgG-PT < 5 EU/mL (n [%])	N	GMC (95% CI), Range (EU/mL)	IgG-PT < 5 EU/mL (n [%])	N	GMC (95% CI), Range (EU/mL)	IgG-PT < 5 EU/mL (n [%])
Maternal blood	105	35.1[a] (28.5–43.1), 3.9–386.1	3 (2.9)[b]	99	9.8[a] (8–12.1),[c] 0.5–68.1	16[b] (16.1)[d]	69	14.4 (10.2–20.1),[e] 2.7–87.5	2 (2.9)[d]
Cord blood	105	51.3[a] (41.3–63.8), 3–542.1	2[e] (1.9)	99	11.6[a] (9.7–14), 0.5–89.4	16[e] (16.1)			
Infant blood	36								
Cord[f] (at birth)	36	48.4 (28.4–62.2), 8–414.7	1 (2.7)						
1 mo of age (31.9 ± 5.4 days)[g]	36	17.7 (11.5–25.1), 2.8–216.9	6 (16.6)						
2 mo of age (61.8 ± 8 days)[g]	32	11.6 (8.1–20.1), 3.1–95.9	4 (12.5)						

Abbreviations: CI, confidence interval; EU, ELISA units; GMC, geometric mean concentration; IgG-PT, immunoglobulin G antibodies against pertussis toxin; Tdap, tetanus, diphtheria, and acellular pertussis.
[a]$P < .0001$ (Mann-Whitney U test) for IgG-PT GMC in Tdap-immunized versus nonimmunized pregnant women and their respective cords.
[b]$P < .001$ (Fisher exact test) for IgG-PT level of < 5 EU/mL in Tdap-immunized versus nonimmunized pregnant women.
[c]$P = .03$ (Mann-Whitney U test) for IgG-PT GMC in nonimmunized pregnant women versus blood donors.
[d]$P = .004$ (Fisher exact test) for nonimmunized pregnant women versus blood donors.
[e]$P < .0003$ (Fisher exact test) for cords from Tdap-immunized mothers versus cords from nonimmunized mothers (proportion of cords with an IgG-PT level of < 5 EU/mL).
[f]Only results of cords from infants with available first- and second-month samples were analyzed.
[g]Sample time (mean ± standard deviation).

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Table 3. GMCs of IgG-PT for Tdap-Immunized Mothers and Their Cords Stratified According to Timing of Gestational Tdap Administration[a]

Gestational Age (wk) (N = 101)[b]		Maternal Delivery				Cords			
	N	GMC (EU/mL)	95% CI	Range	*P*[c]	GMC (EU/mL)	95% CI	Range	*P*[c]
13 to <20	12	26.2	16–47.6	6.1–75.5	NS[d]	41.5	24.5–71.4	7.4–137.4	NS[d]
20 to <24	37	38.6	27.3–54.6	4.6–268.8		56.3	40.3–80.8	3.6–542.1	
24 to <28	25	35.7	21.8–58.2	6.4–386.1		52.2	33.4–81.4	7.5–400.3	
28 to <32	17	32.1	17.9–57.7	6.5–191.1		45.4	21.8–94.8	3.8–414.7	
32 to 36	10	39.7	18.7–84.7	4.4–231.2		61.8	27.7–137.7	8–428.6	
13 to 26	71	36.4	29.6–47.7	4.6–386.1	.5[e]	53.1	41.8–72.6	7.4–542.1	.9[e]
27 to 36	30	32.4	21.7–48.3	4.4–231.2		49.1	30.8–78.2	3.84–28.6	

Abbreviations: CI, confidence interval; EU, ELISA units; GMC, geometric mean concentration; IgG-PT, immunoglobulin G antibodies against pertussis toxin; NS, not significant; Tdap, tetanus, diphtheria, and acellular pertussis.

[a]The mean time of Tdap immunization ± standard deviation was 24.7 ± 4.8 weeks.

[b]In 4 cases, the date of vaccination was not available in the official vaccination card, so it was excluded.

[c]Mann-Whitney U test.

[d]No significant differences between each group with the rest were found.

[e]No significant differences for antibody levels between Tdap vaccination at the second or third trimester.

whooping cough. Figure 3 shows the decay of IgG-PT in infants during their first 1 and 2 months of life. The decay was slightly rapid compared to expected levels, estimated by applying the half-life (~36 days) for maternally acquired IgG-PT published by Van Savage et al [12].

DISCUSSION

To our knowledge, this is the first study to have evaluated a maternal pertussis immunization strategy in Latin America. We analyzed data obtained before and after the implementation of pertussis vaccination in pregnancy. It is interesting to note that the group of pregnant women who were not vaccinated had very low levels of IgG-PT. These levels were significantly lower than those in the nonpregnant women (blood donor control group, $P < .03$). This difference was not unexpected, because altered immune function in women during pregnancy was reported previously from some studies that tested other vaccines, such as that against influenza [13–15].

In pregnant women, mothers immunized with the Tdap vaccine had a significantly higher concentration of IgG-PT than mothers who were not immunized ($P < .0001$). Furthermore, consistent with results from other studies, we detected a linear correlation in IgG-PT levels between paired mother and cord serum samples [16–18].

The effectiveness and optimal concentration of maternal IgG-PT in newborns remain to be determined. High levels of these antibodies at birth are likely to confer protection and might prevent the development of pertussis disease. The antibodies theoretically should reach a peak 15 days after the vaccination. Thus, immunizations delivered at approximately 32 weeks' gestation hypothetically should produce the best

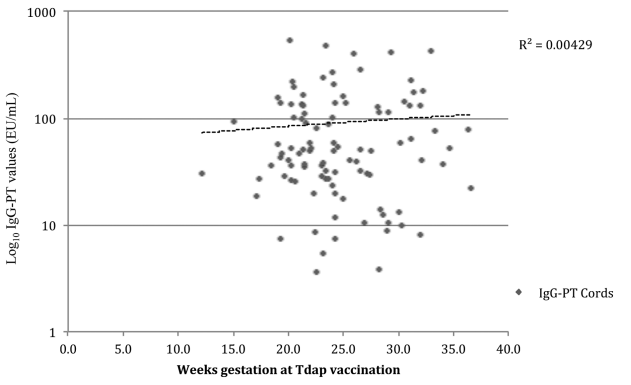

Figure 2. Timing of vaccination and cord blood levels of immunoglobulin G antibodies against pertussis toxin (IgG-PT); $\log_{10}$-transformed cord blood IgG-PT levels are shown in enzyme-linked immunoassay units (EU)/mL (R^2, 0.004 [95% confidence interval, –0.006 to 0.011]; Pearson correlation coefficient, 0.51).

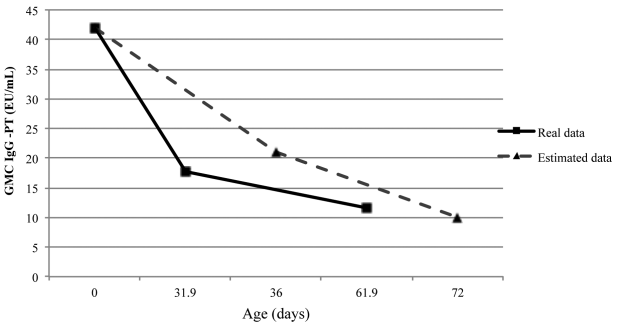

Figure 3. Geometric mean concentrations (GMCs) of IgG-PT decay in infants born to Tdap-immunized mothers. Squares and triangles represent GMCs of immunoglobulin G antibodies against pertussis toxin (IgG-PT) at birth and the first and second months of life from infants born to Tdap-immunized mothers; the solid line with square represents the values measured in our study infant population; and the dashed line with triangles represents the estimated waning of antibodies (starting with the IgG-PT GMC of cord blood in the study population) based on the published half-life of antibodies [11]. Abbreviation: EU, enzyme-linked immunosorbent assay units.

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antibody levels for transference to the neonate. Most guidelines recommend Tdap immunization in the third trimester of pregnancy, but the optimal time for pertussis vaccination remains controversial.

In 2012, the Advisory Committee on Immunization Practices (Centers for Disease Control and Prevention) recommended Tdap vaccination for all pregnant women during their third trimester irrespective of their immunization status (optimal timing, between 27 and 36 weeks' gestation) for every pregnancy [19]. In Argentina, the actual recommendation is a Tdap vaccination for all pregnant women after 20 weeks' gestation (preferably during the third trimester) for every pregnancy [20].

Few studies have evaluated the optimal time for immunizing pregnant women. In a study by Healy et al [21], only 3 women were immunized after 20 weeks' gestation. In a randomized study by Munoz et al [17], immunization at 30 to 32 weeks' gestation resulted in a high concentration of pertussis antibodies that persisted in infants until 2 months of age. In an Abu Raya et al [18] study, an analysis of Tdap receipt according to gestational age included women vaccinated in their third trimester (between 27 and 36 weeks' gestation); the authors found that immunization at 27 to 30 weeks' gestation might protect infants best. In a recent study by Naidu et al [22], 115 women vaccinated in their third trimester were included, and the authors concluded that vaccination early in the third trimester seems more effective than vaccination later in pregnancy. In these last 3 studies, only vaccination during the third trimester was evaluated.

Vilajeliu et al [16] found that antibody levels in infants were not significantly different when mothers were immunized during their second or third trimester; these authors did not include mothers immunized before 20 weeks' gestation. A recent study by Eberhardt et al [11] found that IgG-PT GMCs were significantly higher after immunization in the early second trimester (13–25 weeks' gestation) than after immunization in the third trimester; as a consequence, they proposed to extend the immunization window to start in the early second trimester.

In our cohort, we found no relationship between the time of immunization during pregnancy and the concentration of IgG-PT in maternal serum or cord samples at delivery; no significant differences in cord levels of antibodies were found between mothers immunized in their second and those immunized in their third trimester of gestation.

More prospective studies are necessary to estimate both the optimal timing for vaccinations and the persistence of antibodies, because a recommendation to start vaccinating pregnant women in their second trimester might be a useful strategy for avoiding missed immunization opportunities and providing mothers the benefit to transfer antibodies to potentially preterm infants.

We found that maternal immunization with the Tdap vaccine resulted in significantly higher antibody concentrations in infants from birth to the initiation of an immunization schedule at the age of 2 months. Few studies on maternal immunization results have reported the persistence of antibodies beyond the neonatal period, but all studies have revealed high concentrations of pertussis antibodies up to 2 months of age, which is consistent with our findings [9, 17, 23, 24].

It is important to note that the mechanisms that provide protection against pertussis are currently not well understood, and there is no generally accepted correlate of immunity or seroprotective antibody concentration after vaccination against pertussis [7, 9, 25]. If we consider an IgG-PT level of >5 EU/mL to be protective, then in anticipation of the waning of antibodies during the first 2 months of age, it is desirable to ensure a high level of antibodies at birth. To estimate that level, we must take into account that the half-life of the transferred IgG-PT is approximately 36 days, as suggested by Van Savage et al [12]. Therefore, a level higher than 20 EU/mL at birth might be considered desirable [11, 24]. In this study, our waning-antibody curve was similar to that observed by Van Savage et al, but the antibody levels seemed to decay slightly faster in our infant population. This difference in decay patterns might have been a result of the difference in the timing for collecting the serum specimens between studies or a difference in the patterns between infants born to mothers immunized or not immunized with the Tdap vaccine, because the Van Savage et al study included mothers who were not immunized. Nevertheless, we observed that all infants with an IgG-PT concentration of >20 EU/mL at birth had a level higher than 5 EU/mL at 2 months of age.

Previous immunogenicity studies in adults found immune responses to Tdap vaccine of 85% to 93% [26–28]. In our study, only 3 (2.9%) of the 105 immunized mothers had an antibody level lower than 5 EU/mL, but 31.4% had an IgG-PT of <20 EU/mL. It is important to consider that 19% (20 of 105) of the cord blood samples had a level of <20 EU/mL, which might have been insufficient to provide adequate protection in infants up to the age of 2 months.

CONCLUSIONS

We have confirmed that implementing Tdap vaccination for pregnant women was a good strategy for our population, because immunized mothers had significantly higher paired serum/cord concentrations of IgG-PT at delivery than the mothers who were not immunized. We also observed that infants born to immunized mothers had a high level of antibodies during their first 2 months of life. However, in this Tdap era, we propose that new studies are necessary to provide a better definition of the IgG-PT half-life in infants and to gain a better understanding of the decay of transferred maternal antibodies.

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One potential concern is that high maternal antibody levels can interfere with immunogenicity acquisition when the infant begins the pertussis immunization schedule. This concern might be particularly important in countries such as Argentina, where the DTwP is used in the initial vaccination scheme. Therefore, further investigations are necessary to evaluate the immune response to a whole-cell pertussis vaccine in infants born to mothers immunized with the Tdap vaccine.

This study has some potential limitations. First, only pertussis antibodies were measured, because other pertussis antigens were not available in Argentina when the study was done. Second, this study was prospective and observational rather than randomized, and Tdap-immunized pregnant women and nonimmunized women were not enrolled concurrently.

Last, the optimal timing of maternal Tdap immunization should be evaluated in randomized controlled trials to establish the best options for protecting infants, because to extend the timing of recommended vaccination might prevent missed opportunities to vaccinate and, perhaps, extend protection to preterm infants.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. World Health Organization. Pertussis vaccines: WHO position paper, September 2015. Wkly Epidemiol Rec. **2015**; 90:433–60.
2. Vizzotti C, Neyro S, Katz N, et al. Maternal immunization in Argentina: a storyline from the prospective of a middle income country. Vaccine **2015**; 33:6413–9.
3. Ministerio de Salud, Programa Nacional de Control de Enfermedades Inmunoprevenibles. Fundamentos de la vacunación de mujeres embarazadas con vacuna triple bacteriana acelular (dTpa), Argentina 2012. Available at: http://www.msal.gov.ar/images/stories/epidemiologia/inmunizaciones/lineamientos_vacuna_dTpa_%20en_embarazadas.pdf. Accessed September 4, 2014.
4. Kapasi A, Meade BD, Plikaytis B, et al. Comparative study of different sources of pertussis toxin (PT) as coating antigens in IgG anti-PT enzyme-linked immunosorbent assays. Clin Vaccine Immunol **2012**; 19:64–72.
5. Xing D, Wirsing von König CH, Newland P, et al. Characterization of reference materials for human antiserum to pertussis antigens by an international collaborative study. Clin Vaccine Immunol **2009**; 16:303–11.
6. Baughman AL, Bisgard KM, Edwards KM, et al. Establishment of diagnostic cutoff points for levels of serum antibodies to pertussis toxin, filamentous hemagglutinin, and fimbriae in adolescents and adults in the United States. Clin Diagn Lab Immunol **2004**; 11:1045–53.
7. Cherry JD, Gornbein J, Heininger U, Stehr K. Search for serologic correlates of immunity to *Bordetella pertussis* cough illnesses. Vaccine **1998**; 16:1901–6.
8. Storsaeter J, Hallander HO, Gustafsson L, Olin P. Levels of anti-pertussis antibodies related to protection after household exposure to *Bordetella pertussis*. Vaccine **1998**; 16:1907–16.
9. Hardy-Fairbanks AJ, Pan SJ, Decker MD, et al. Immune responses in infants whose mothers received Tdap vaccine during pregnancy. Pediatr Infect Dis J **2013**; 32:1257–60.
10. Leuridan N, Peeters N, de Witte L, et al. Effect of a prepregnancy pertussis booster dose on maternal antibody titers in young infants. Pediatr Infect Dis J **2011**; 30:608–10.
11. Eberhardt CS, Blanchard-Rohner G, Lemaître B, et al. Maternal immunization earlier in pregnancy maximizes antibody transfer and expected infant seropositivity against pertussis. Clin Infect Dis **2016**; 62:829–36.
12. Van Savage J, Decker MD, Edwards KM, et al. Natural history of pertussis antibody in the infant and effect on vaccine response. J Infect Dis **1990**; 161:487–92.
13. Bischoff AL, Følsgaard NV, Carson CG, et al. Altered response to A (H1N1) pnd09 vaccination in pregnant women: a single blinded randomized controlled trial. PLoS One **2013**; 8:1–10.
14. Schlaudecker EP, McNeal MM, Dodd CN, et al. Pregnancy modifies the antibody response to trivalent influenza immunization. J Infect Dis **2012**; 206:1670–3.
15. Jamieson DJ, Theile RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis **2006**; 12:1638–43.
16. Vilajeliu A, Goncé A, López M, et al. Combined tetanus-diphtheria and pertussis vaccine during pregnancy: transfer of maternal pertussis antibodies to the newborn. Vaccine **2015**; 33:1056–62.
17. Munoz FM, Bond NH, Maccato M, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. JAMA **2014**; 311:1760–9.
18. Abu Raya B, Srugo I, Kessel A, et al. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels—a prospective study. Vaccine **2014**; 32:5787–93.
19. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices (ACIP), 2012. MMWR Morb Mortal Wkly Rep **2013**; 62:131–5.
20. Ministerio de Salud, Programa Nacional de Control de Enfermedades Inmunoprevenibles. Memorandum—Vacunación de embarazadas con triple bacteriana acelular (dTpa)-Marzo 2016. Available at: http://www.ms.gba.gov.ar/sitios/tocoginecologia/files/2016/03/Memo-vacunacion-dTpa-embarazadas-2016.pdf. Accessed August 4, 2016.
21. Healy CM, Rench MA, Baker CJ. Importance of timing of maternal combined tetanus, diphtheria, and acellular pertussis (Tdap) immunization and protection of young infants. Clin Infect Dis **2013**; 56:539–44.
22. Naidu MA, Muljadi R, Davies-Tuck ML, et al. The optimal gestation for pertussis vaccination during pregnancy: a prospective cohort study. Am J Obstet Gynecol **2016**; 215:237.e1–6.
23. Maertens K, Caboré RN, Huygen K, et al. Pertussis vaccination during pregnancy in Belgium: results of a prospective controlled cohort study.Vaccine **2016**; 34:142–50.
24. Smallenburg LC, van Welie NA, Elvers LH, et al. Decline of IgG pertussis toxin measured in umbilical cord blood, and neonatal and early infant serum. Eur J Clin Microbiol Infect Dis **2014**; 33:1541–5.
25. Hewlett EL, Halperin SA. Serological correlates of immunity to *Bordetella pertussis*. Vaccine **1998**; 16:1899–900.
26. Centers for Disease Control and Prevention. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. MMWR Recomm Rep **2006**; 55:1–37.
27. Halperin B, Morris A, MacKinnon-Cameron A, et al. Kinetics of antibody response to tetanus-diphtheria-acellular pertussis vaccine. Clin Infect Dis **2011**; 53:885–92.
28. Mc Guirr A, Fisman DN. Duration of pertussis immunity after DTaP immunization: a meta-analysis. Pediatrics **2015**; 135:331–43.

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