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RESEARCH PAPER

Randomized clinical trial of the safety and immunogenicity of the Tdap vaccine in pregnant Mexican women

Jesús Zacarías Villarreal Pérez[a,b], José Manuel Ramírez Aranda[a,b], Manuel de la O Cavazos[a,b], Michelle de J. Zamudio Osuna[b], José Perales Dávila[b], María Romelia Ballesteros Elizondo[b], Marco Vinicio Gómez Meza[a,b], Francisco Javier García Elizondo[b], and Azucena M. Rodríguez González[b]

[a]Universidad Autónoma de Nuevo León, Monterrey, Mexico; [b]Servicios de Salud de Nuevo León, Monterrey, Mexico

ABSTRACT

Immunization with the tetanus, diphtheria, and pertussis (Tdap) vaccine raises controversies on immunogenicity and possible antibody interference. We performed an experimental, double-blind, parallel group controlled clinical trial to evaluate the safety and immunogenicity of the Tdap vaccine in 204 pregnant women and their children and to determine its interference in antibody production. Pregnant women 18 to 38 y of age with 12 to 24 weeks gestation, a low obstetric risk, and without serious disease were randomly selected. The experimental group received 0.5 mL IM of Tdap and the control group normal saline. Six blood samples were drawn before and after solution application, and from the umbilical cord of the infants and at 2, 4, and 6 months of age. Pertactin and Pertussis toxin antibodies and possible interference of maternal antibodies with the vaccine were determined.

In the experimental group, antibodies against Bordetella pertussis pertactin (anti-PRN) (112 E/mL 95% CI 89.9–139.9) and antibodies against pertussis toxin (anti-PT) (24.0 E/mL, 95% CI 18.3–31.4) were elevated in the mother before vaccination. These were higher in the umbilical cord and descended in the infant at 2 months (71.4 (95% CI 56.8–89.7 and 10.9; 95% CI 8.7–13.7, respectively). Anti-PT showed a delay in production. Tdap safety was confirmed with only mild local pain at 24 and 48 hours.

Anti-PRN and anti-PT antibodies in the infant descend at 2 months of age. There is a delay in anti-PT in children of immunized mothers. Further studies are needed to elucidate its clinical significance.

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anti-PRN; anti-PT; bordetella pertussis; DPT vaccine; pertussis vaccine; tdap; vaccination in pregnancy

Introduction

Pertussis is a significant cause of infant mortality worldwide, despite high vaccine coverage.[1] In Mexico, the pentavalent acellular vaccine (DPaT/VIP+Hib) is administered at 2, 4, 6 and 18 months of age, and a diphtheria, pertussis and tetanus (DPT) booster is administered at 4 y.[2] Very good coverage has been achieved–up to 90.2% nationally and up to 91.8% in the state of Nuevo León.[3] Despite this, in September 2015, 113 cases of whooping cough were reported in Nuevo León.[4]

Pertussis related incidence and mortality occurs more frequently in children under 3 months, as during an epidemic in California in 2010.[5]

An explanation for this may be transplacental loss of antibodies because of a decreased titer of maternal antibodies over time[6] and the rapid decomposition of antibodies in the infant after approximately 2 months of age.[7]

In a study of blood samples from pregnant women and umbilical cords performed in Nuevo León, no protective titers were obtained.[8] In another study—part of phase I of this project—immunoglobulin G (IgG) was found in only 4.3% of umbilical cord blood samples, 1.4% from the mother and 0% from the child.[6]

The epidemiology of the disease has changed with adolescents and adults acting as reservoirs. In Mexico City, 32.8% of adolescents who had a cough for more than 14 d tested positive for pertussis, with the potential to transmit the disease.[9]

In the face of this global epidemiological panorama, several strategies have been implemented, including administering a 6th dose of the tetanus, diphtheria, and pertussis acellular (Tdap) vaccine in adolescence[10] and immunizing adolescents and adults that live with newborns,[11] although this latter strategy is considered impractical and costly.[12,13]

Administering Tdap to pregnant women with the aim of intensifying the transfer of antibodies to the child[14,15] seems appropriate ; however, there are reservations about its safety.[16]

In the United States, the Vaccine Adverse Event Reporting System stated that no adverse events occurred in 42% (55) of individuals who received Tdap immunization. The most common adverse event was reaction at the application site in 4.5% (6).[17] Similar findings were obtained in children born to women who received this vaccine in the study by Shakib, et al.[18]

In Mexico, studies on the efficacy and safety of acellular vaccines in pregnant women are nonexistent; therefore, the objective of this study is to evaluate the safety and immunogenicity of the Tdap vaccine in pregnant women and their newborns up to 6 months of age and assess the interference of the Tdap vaccine in pregnant women with the DPaT in their children.

CONTACT Dr. med. José Manuel Ramírez Aranda sersabe2010@gmail.com Servicios de Salud de Nuevo León, Matamoros 520 Ote., Colonia Centro, Monterrey N.L., CP 64000, Mexico.
Trial Registration: ClinicalTrials.gov Identifier: NCT01445743; URL: https://clinicaltrials.gov/ct2/show/NCT01445743?term=Tdap+AND+pregnancy&rank=2

Materials and methods

Study design

This was randomized, double-blind, parallel group controlled clinical trial.

Participants

The participants were pregnant women who sought prenatal care from September 2011 to August 2014 at 12 outpatient health centers of the Nuevo León Health Services. The centers were within a specific geographical area to ensure follow-up. The women were 18 to 38 y of age, had a low obstetric risk, a normal anatomical ultrasound in the second trimester of pregnancy, volunteered to participate, and signed informed consent prior to inclusion (Table 1).

Women who did not meet the inclusion criteria (7), suffered a psychiatric disease (schizophrenia, psychosis, major depression) or a severe physical disease (diabetes mellitus, hypertension or degenerative diseases), consumed drugs or tobacco, had a history of severe reactions to any vaccine or had had a febrile illness in the 72 hours prior to vaccination were excluded. Some women who had been immunized against tetanus and/or pertussis in the 2 y prior to the study or who refused to participate were also excluded.

Additionally, women who developed any severe disease during pregnancy, who had an abortion and those who were lost to follow-up during pregnancy or whose child was lost to follow-up were excluded (Fig. 1).

Table 1. Demographic and obstetrical data.

	Experimental		Control		Total	
Variable	*f*	%	*f*	%	*f*	%
School level						
Primary	10	11.1	11	13.6	21	12.3
Secondary	51	56.7	59	72.8	110	64.3
Preparatory	23	25.6	9	11.1	32	18.7
University	3	3.3	2	2.5	5	2.9
Technical	3	3.3	0	0.0	3	1.8
Total	90	100.0	81	100.0	171	100.0
Marital status						
Single	10	11.1	7	8.6	17	9.9
Married	32	35.6	21	25.9	53	31.0
Common law	47	52.2	52	64.2	99	57.9
Widow	1	1.1	0	0.0	1	0.6
Separated/divorced	0	0.0	1	1.2	1	0.6
Total	90	100.0	81	100.0	171	100.0
Occupation						
Student	2	2.2	1	1.2	3	1.8
Worker	0	0.0	2	2.5	2	1.2
Employee	4	4.4	4	4.9	8	4.7
Housewife	83	92.2	74	91.4	157	91.7
Other	1	1.1	0	0.0	1	0.6
Total	90	100.0	81	100.0	171	100.0
	Mean	SD	Mean	SD		
Age (years)	23.8	4.8	23.7	5.0		
No. of pregnancies	2.2	1.2	2.3	1.1		
No. of births	0.7	1.0	0.8	1.0		
No. of cesarean sections	0.3	0.6	0.3	0.5		
No. of abortions	0.2	0.5	0.1	0.4		

No data were statistically significant.

Ethical aspects

The project was approved by the Ethics Committee and the Research Committee of a university hospital and registered at clinical trials.gov with registration no. NCT01445743; URL: https://clinicaltrials.gov/ct2/show/NCT01445743?term=Tdap+AND+pregnancy&rank=2. The study subjects' participation was voluntary and their anonymity was protected. They also received no compensation and signed a written informed consent.

Main outcomes and measures

The main results were immunogenicity and interference of maternal antibodies. Patients were recruited and interviewed by their doctors in the outpatient unit and then completed the corresponding sections of the instrument. They were sent to a hospital with obstetric care for 1) an abdominal ultrasound examination to detect abnormalities (weeks 24–26) prior to the extraction of the first 5-cc blood sample; 2) the administration of the Tdap vaccine or placebo between weeks 30 and 32 of gestation by a trained nurse who was blinded to the procedure; and 3) for delivery or Caesarian section and the collection of the second blood sample at least 4 weeks after vaccine administration and the third blood sample from the umbilical cord. Home visits were conducted when the children were 2, 4, and 6 months of age, at which point the 4th, 5th and 6th blood samples were taken prior to the administration of the vaccines indicated in the national vaccination schedule for Mexico, which includes the pentavalent vaccine with the DTaP component (Fig. 2).

Each blood sample tube was carefully labeled with the date, hour and participant code and was taken directly to the laboratory for preservation at −70° Celsius until the procedure was conducted.

To determine the level of antibodies against specific pertussis antigens, a quantitative *in vitro* assay of human IgG antibodies against Bordetella pertussis pertactin (PRN) and pertussis toxin (PT) in serum was conducted using the anti-Bordetella pertussis toxin ELISA (IgG) and the anti-Bordetella PRN ELISA (IgG) (EUROIMMUN Medizinische Labordiagnostika AG, Lubeck Germany) commercial kits according to the manufacturer's instructions. The IgG levels in serum were reported as optical densities, which were transformed to ELISA units (EU) per milliliter.

To evaluate the safety of the vaccine, a trained nurse at the hospital completed the record of adverse events at 30 minutes after vaccination. Subsequent evaluations were performed 24 and 48 hours and one month after vaccination. Additional information was recorded during postpartum and healthy child check-ups and when the infant was 2, 4, and 6 months old.

Sampling and sample size

The sample size was determined with a power of 90% for effect sizes of 0.50;[19] 86 observations per group were required. To account for a nonresponse rate of 15%, a final sample size of 204 with 102 in each group was obtained.

The selected pregnant women were randomly assigned to one of the groups, vaccine or placebo. Randomization occurred

Table 2. Adverse reactions.

	Experimental		Control		Total	
Variable	*f*	%	*f*	%	*F*	%
30 minutes						
None	90	100.0	81	100.0	171	100.0
TOTAL	90	100.0	81	100.0	171	100.0
24 hours						
Headache	0	0.0	2	2.5	2	1.2
Local erythema	2	2.2	1	1.2	3	1.8
Local heat	1	1.1	0	0.0	1	0.6
Mild local pain	20	22.2	17	21.0	37	21.6
Nausea and/or vomiting	1	1.1	2	2.5	3	1.8
Fatigue	2	2.4	0	0.0	2	1.2
More than one symptom	11	12.1	3	3.7	14	8.1
None	53	58.9	56	69.1	109	63.7
TOTAL	90	100.0	81	100.0	171	100.0
48 hours						
Mild local pain	7	7.8	5	6.2	12	7.0
Nausea and/or vomiting	0	0.0	1	1.2	1	0.6
Muscle pain	1	1.1	0	0.0	1	0.6
None	76	84.4	73	90.1	149	87.1
More than one symptom	6	6.7	2	2.5	8	4.7
TOTAL	90	100.0	81	100.0	171	100.0
1 month						
None	90	100.0	81	100.0	171	100.0
TOTAL	90	100.0	81	100.0	171	100.0

No data were statistically significant.

using blocks of 2 repetitions of 2 groups (4 observations per block); thus, 51 blocks were randomly selected for the 6 possible combinations.

Statistical methods

Descriptive statistics were calculated for the percentages and frequencies of demographic data, maternal and child factors. Safety outcome measures were described by frequency proportion. The geometric mean concentration was determined to evaluate antibody titers against PT and PRN and plotted using 95% CIs. Groups were compared using the Mann-Whitney test for non-normal data distribution with a $P < .05$ being significant. An intention to treat analysis was not done because responses from the primary outcome were missing.

The primary analysis of immunogenicity included participants who received 2 injections (one vaccine and one saline placebo) and contributed both pre- and post-vaccination blood samples for testing. No imputation was carried out for missing data.

Results

There were 171 active participants, 90 in the experimental group and 81 in the control group. For 113 participants, all 6 of the required samples were collected. Of all 953 blood samples, 171 were collected from the pregnant women before administration of the vaccine or placebo; 161 were collected one month after application, 147 were collected from the umbilical cord, and 162, 159 and 153 were collected from the children at 2, 4 and 6 months of age, respectively.

The days of collection of the 4th blood sample (corresponding to the children's 2nd month of age) ranged from 69.2 (SD 11.7) to 68.7 (SD 9.3); 5th sample (4th month) ranged from 128.7 (SD 14.1) to 129 (SD 13.3), and the 6th sample (6th month) from 191.3 (SD 22.0) to 186.1 d (SD 14.7) in the vaccine and control groups, respectively, with no significant difference.

The motheŕs mean age was 24.2 y (SD 5.0) in the experimental group and 23.8 y (SD 5.0) in the control group. Most of the participating women had a secondary school level, a marital status of cohabiting and were housewives. There were no significant differences between the experimental and placebo groups (Table 1). Most of the women had received pertussis vaccines during childhood.

They denied a history of pertussis or being in contact with someone diagnosed with or suspected of having pertussis during the previous month.

Few adverse reactions after the application of the vaccine/placebo occurred; local reactions predominated (Table 2).

The geometric means of IgG against PRN and PT for both groups are shown in Table 3. A statistically significant difference was observed in favor of the experimental group except before vaccination. Fig. 3 shows the levels of IgG against PRN for the 6 groups of blood samples collected from both the experimental and the placebo groups. An increase in IgG in the serum of the mothers 14 times greater than baseline was found; this increase was even greater in cord serum although it subsequently decreased showing a cord:2-month old child serum

Table 3. Geometric means of antipertactin and antipertussis toxin antibodies in both groups.

		Antipertactin Antibodies				Antipertussis Toxin Antibodies			
Treatment	Var	GM	95CI-L GM	95CI-U GM	P	GM	95CI-L GM	95CI-U GM	P
Tdap	MBV	8.53	6.71	10.85	0.908	5.93	4.55	7.74	0.138
Placebo	MBV	8.08	6.11	10.68		7.90	5.92	10.54	
Tdap	MAV	112.08	89.79	139.91	0.001	24.04	18.39	31.43	0.001
Placebo	MAV	7.16	5.38	9.53		7.06	5.24	9.50	
Tdap	CORD	127.51	104.15	156.12	0.001	28.25	21.06	37.90	0.001
Placebo	CORD	8.07	5.84	11.14		8.02	5.84	11.00	
Tdap	CH2M	71.41	56.80	89.77	0.001	10.95	8.71	13.77	0.001
Placebo	CH2M	6.93	5.52	8.72		6.20	4.96	7.73	
Tdap	CH4M	35.35	27.59	45.29	0.001	14.77	12.35	17.66	0.008
Placebo	CH4M	5.07	4.15	6.19		20.45	16.71	25.03	
Tdap	CH6M	16.75	12.94	21.68	0.001	49.09	40.86	58.99	0.007
Placebo	CH6M	4.51	3.80	5.35		69.13	59.10	80.87	

Var = Variable; GM = Geometric mean; 95CI-L GM and 95CI-U GM = lower and upper limits of the 95% confidence interval for the geometric mean; *P* = Mann-Whitney test to compare Tdap vs placebo.

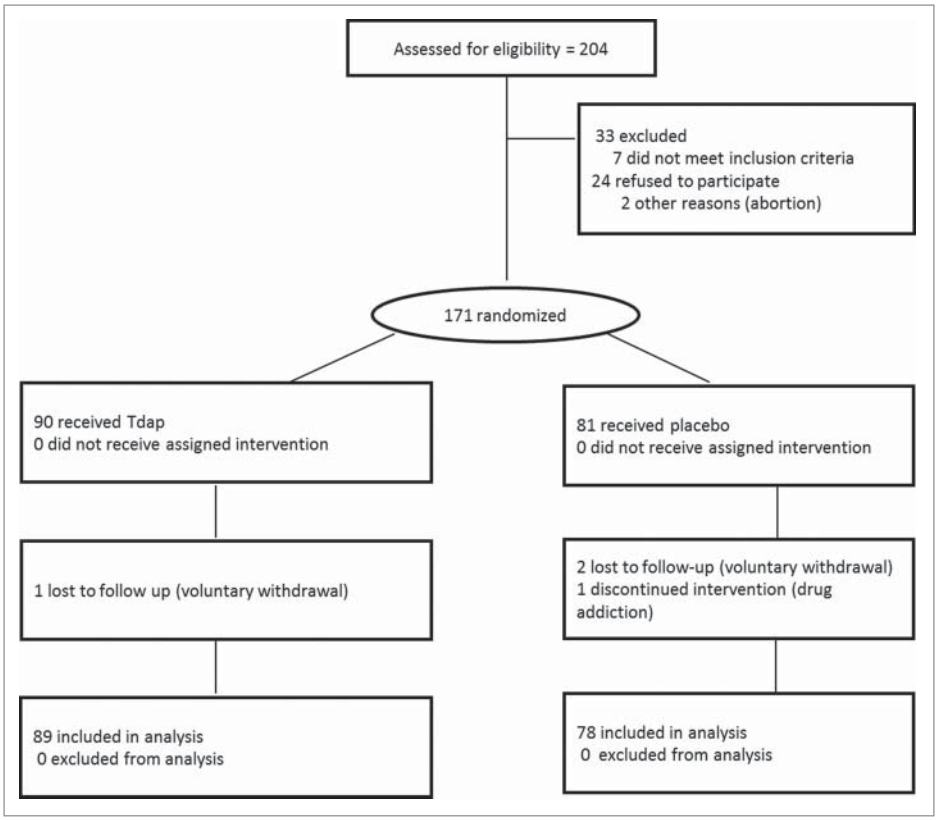

Figure 1. CONSORT flow diagram of the phases of of the study.

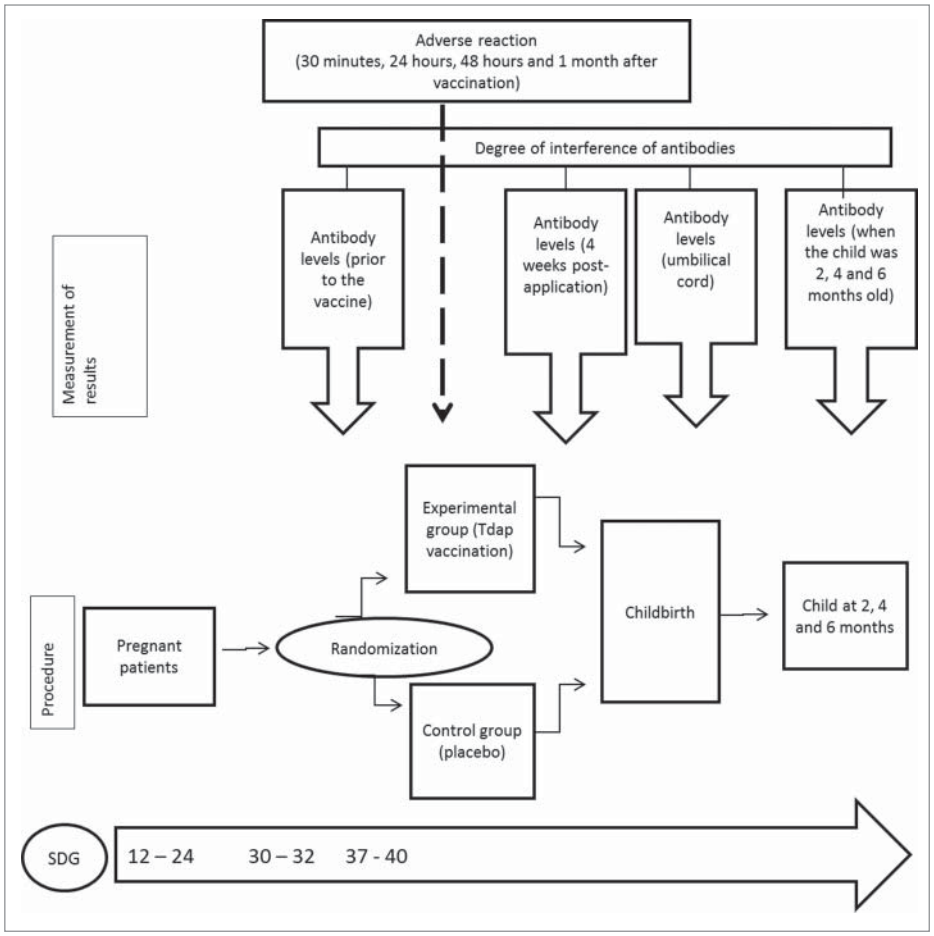

Figure 2. Flow diagram of the experimental procedure.

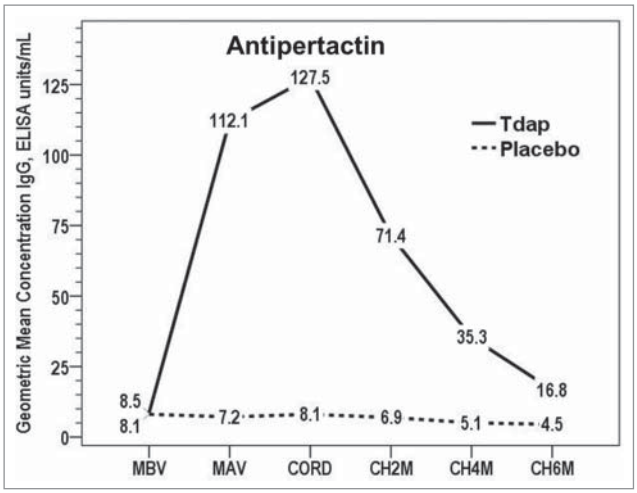

Figure 3. Antipertactin Antibodies in the Experimental and Placebo Groups. IgG levels vs. pertactin in 6 collected blood samples from the experimental and placebo groups. MBV, mother before vaccination; MAV, mother after vaccination; COR, umbilical cord; CH2M, child at 2 months of age; CH4M, child at 4 months of age; CH6M, child at 6 months of age.

ratio for PRN of 1.78. Fig. 4 shows the IgG versus PT levels for all time points and conditions. The elevation of PT is less marked in the serum of the mothers after vaccination. This increase also occurred in cord serum descending to a cord:2-month old child serum ratio of 2.5.

Discussion

The safety of the Tdap vaccine was demonstrated in the Mexican population because at 30 minutes and one month after application, no reaction was reported. Furthermore, at 24 and 48 hours after administration, 22.2% and 21.0% of the participants in the control group reported local mild pain; thus, these reactions can be considered secondary to the vaccine application technique and not to the action of the biologic.

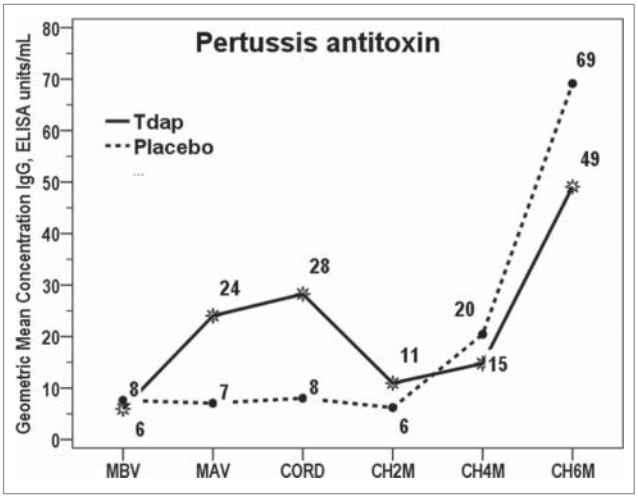

Figure 4. Antibodies against Pertussis Toxin in the Experimental and Placebo Groups. IgG levels versus detoxified pertussis toxin in 6 collected blood samples. Abbreviations: MBV, mother before vaccination; MAV, mother after vaccination; COR, umbilical cord; CH2M, child at 2 months of age; CH4M, child at 4 months of age; CH6M, child at 6 months of age.

A recent study in the United States showed similar results with no reports of adverse events in pregnant women, the fetus or newborns [17], and the safety of the vaccination was confirmed by the infants' birth weight, Apgar scores and neonatal examination.[20] Similar safety indicators were reported among in a study cohort of 20,074 pregnant women in the United Kingdom.[21]

Regarding the first main outcome, the immunogenic capacity of the Tdap vaccine has already been demonstrated in babies born to mothers who received the Tdap vaccine during pregnancy. These infants had a significantly higher concentration of antibodies against pertussis at birth and up to 2 months of age compared with those whose mothers did not receive vaccination.[20]

However, in this study, the vaccine produced an increase in PRN and PT antibodies (especially PRN antibodies) in the pregnant women, and these levels were elevated in the umbilical cord. However, the proportion of antibodies that pass transplacentally to the newborn is much lower.

Specific transplacental transfer of IgG is so variable that it ranges between 20% and 200%.[22] The gestational age at which the vaccine is applied can affect the titer, leading to a 6-fold greater concentration (46 EI/mL) when the vaccine is administered between weeks 27–30 ± 6, according to Abu Raya et al.[23]

In the current study, the vaccine was administered between weeks 28–30 of gestation, which could explain the increase in postvaccine levels of Ig against PT and PRN in the mother (112.0 EI/mL and 24.0 EI/mL, respectively). Therefore, the Center for Disease Control and Prevention recommends Tdap immunization during pregnancy, preferably at 27–36 weeks of gestation.[15] However, pregnant women showed greater production of anti-PRN than anti-PT, which is consistent with results of other authors,[20,24] although antibodies were not completely transferred to the newborn.

Anti-PRN levels declined sharply in infants until 6 months with no response to the usual DTaP vaccine scheme. This is important because it has been established that PRN plays an important role in the opsonization of *Bordetella*.[25]

In this study, anti-pertussis Ig levels showed an abrupt decrease at 2 months; however, in the absence of consensus, it is unclear whether this decrease provides protection against infection with *B. pertussis*.[20] Thus, it is difficult to know the proportion of infants that is unprotected at birth[26], although some authors have established a cutoff of more than 5 EU for PT and more than 10 EU for FHA and PRN. [27] However, in the current investigation, anti PT Ig levels were greater in the Tdap group of children than in the placebo group of children at 2 months. It was also observed that antibodies against PT increased as the number of DPaT doses increased (at 2, 4 and 6 months). Pasetti et al.[28] reported that complete protection is not achieved after 3 doses. This occurs after the first booster has been applied. Another study reported an effectivity of 95.6% (95% CI:89.7%–98.0%) after 3 doses.[29]

Since this study examined infants up to 6 months of age, there were no data on the behavior of antibodies after that time, although an increasing trend was observed. In a study that included children up to 7 months of age under different conditions, the concentration of anti-PT in the children showed no significant difference between groups.[20]

Regarding the second main outcome, there is apparently some interference between maternal antibodies and the endogenous production of anti-PT in response to the DTaP vaccine, as there was a delay in the response at 4 and 6 weeks among the children of women in the experimental group compared with children from the control group, in contrast to findings by Muñoz et al.[20] Published evidence indicates that maternal Ig inhibits antibodies generated by the complete cellular vaccine but not by the acellular vaccine.[30,31]However, some authors have demonstrated that the high concentration of maternal antibodies is bound to specific epitopes of the vaccine, thus avoiding interaction with the child's B cells. A second booster immunization or the administration of a toxoid formulation with new adjuvant has been proposed to overcome this interference.[32] Nonetheless, in a recent contribution, Muñoz et al. clarified that there is no significant difference in titers after application of the booster vaccine.[20]

In contrast, Quinn et al. (2014) recently mentioned a progressive loss of antigenicity in children who received 5 doses of DTaP.[33] More studies are needed on this topic.

Considerations regarding the intervention

Vaccination with Tdap during pregnancy has been shown to be more effective than vaccinations given immediately postpartum. As vaccination during pregnancy was not associated with any safety problems in the mother or child, it appears to be a good alternative to postpartum vaccination. The study was double blind and the experimental group received the Tdap vaccine (Sanofi Pasteur; 0.5 mL) intramuscularly.[16] The control group received a placebo of 0.9% saline solution, which was administered by the same route and in the same dose as the vaccine.

Limitations

In this research, only 2 out of 3 recommended antibodies against *B. pertussis*—PRN and PT—were measured to determine immunogenicity because of technical accessibility problems which prevented measuring the other antigen as was originally planned. However, anti-PT is considered representative of the vaccine's immunogenicity.

The children were not followed up to determine whether they later contracted whooping cough, which would be a solid demonstration of the vaccine's immunogenicity. Ig against PRN decreased rapidly during the child's 2nd month of life; however, it is unknown whether these levels remained protective against the disease.

Future direction

While it is unclear whether the high incidence of whooping cough in the population is caused by a loss of the immunogenic effect of the current Tdap vaccine or whether there is an antigenic change in the *B. pertussis* strain, it is necessary to demonstrate whether the lower levels of antipertussis and anti-PRN Ig in children, especially at 2 and 4 months of age, are sufficient to protect them against this disease before they begin to generate their own antibodies. In the same sense, the effectiveness of early Tdap immunization in children at 6 weeks of age should be investigated.

Conclusions

The children of mothers who were vaccinated with Tdap experience delayed production of antipertussis antibodies for up to 6 months. The vaccination of pregnant women with Tdap generates antibodies in the mother that can be lost within 2 months; however, Tdap vaccination appears to be a feasible and safe strategy for providing their children with antibodies against pertussis, although more studies are needed to demonstrate whether this transfer of antibodies is effective and timely.

Abbreviations

Tdap	Tetanus, diphtheria, and pertussis vaccine
Anti-PRN	Antibodies against *Bordetella pertussis* pertactin
Anti-PT	Antibodies against pertussis toxin
DPT	Diphtheria, pertussis and tetanus

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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DPT Group Nuevo León: Celina Gómez Gómez, Dr med, Irasema Rodríguez Rodríguez, MD, Azucena Maribel Rodríguez González, M.D., Marco Antonio Rodríguez Moreno, M.D., Martha Lilia Pérez Sosa, M.D., Ulises Hernández Torres, M.D., Amalia González Salas, RN, José Marcos Salazar Rodríguez, M.D., Martha Alicia Martínez Núñez, RN, Mónica B. Segovia Rodríguez, M.D., Felipe N. Matehuala Leos, M.D., Roberto Leal Leal, M.D., Ernesto Luna Sepúlveda, M.D., Roberto Rivera Rivera, M.D., Gabriel Hernán de Sánchez, M.D., Alicia Luna Alcántar, NURS, Félix Martínez Lazcano, M.D., Juan Amaro Alaffa Lucero, M.D., Mónica Morales Ramírez, M.D., Maritza Ibarra Balderas, M.D., Reveca García Hernández, ASN, María Leonor Álvarez Zúñiga, ASN, María Asunción Cadena Colunga, ASN, Martha Alicia González Rodríguez, M.D., María Antonia Gutiérrez Muñoz, ASN, Alma Rosa Zertuche González, M.D., María Cristina Díaz Charles, RN, José Guadalupe Sánchez Hernández, M. D., Nora Allen Hermosillo, RN, Martha Alicia Moreno Ríos, M.D., Lucía Elizeth Cantú Ramírez, ASN, Martha Elida Chávez Vázquez, M.D., María Margarita Palacios M., ASN, José Luis Rivera Palacios, M.D., María Josefa Berumen Correa, ASN, Myrna Ortiz de Osio, M.D., José Luis Frausto Treviño, M.D., Acención Rodríguez Estrada, ASN, Fernando O. Reyna Hernández, M.D., Jorge D. Ochoa Chapa, M.D., María Flor González Soto, RN, Brenda Gabriela Lozano Castillo, BSW, Sandra Esthela Hernández Leal, BSW, María Candelaria Meza Colunga, BSW, María de Los Ángeles Zermeño Zuñiga, ASN, Amada Briones Ramírez, RN, Micaelina Carvajal Laguna, RN, Enf. Rebeca García Gutiérrez, RN, Verónica Moreno Encinia, RN, Myrna Alejandra Martínez Guerrero, RN, María Guadalupe Rodríguez Méndez, RN, María de los Ángeles Mata Briseño, M.D., Graciela Cantú González, BSCh, Sandra L. Pimentel Urquidi, BSCh, Litsy Aurora Menchaca Salgado, BSCh, Sonia Maricela González González, BSCh, José Perales Dávila, M.D., José Guillermo Pons Muñoz, M.D., Fidel Cisneros Rivera, M.D., Raúl Piña Cano, M.D., Reyes Amador Pérez Rodríguez, M. D., José Francisco Guajardo García, M.D., Ulises Castillo Gloria, M.D., Edgar Iván Galindo Galindo, BSCh, María Romelia Ballesteros Elizondo, BSCh, María Rita Moreno Juárez, BSCh, Michelle de J. Zamudio Osuna, MSc, Ana María Villarreal Herrera, M.D., María Luisa Saldaña Chávez, BSNtr

Author contributions

JZVP and JMRA contributed equally to the work. JMRA and MDOC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: JMRA, JPD, MDOC, FJGE.

Acquisition, analysis, or interpretation of data: JZVP, JMRA, JPD, MJZO, FJGE, MRBE.

Drafting of the manuscript: JMRA, AMRG, MRBE.

Critical revision of the manuscript for important intellectual content: JZVP, MJZO, MVGM, AMRG, MDOC.

Statistical analysis: MVGM, JMRA, AMRG.

Obtained funding: JZVP JMRA, and FJGE

Administrative, technical, or material support: JZVP, JMRA, MDOC, MVGM, AMRG.

Study supervision: JZVP, JMRA, FJGE.

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