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ORIGINAL ARTICLE

The Impact of Early Postpartum Maternal Pertussis Vaccination on the Protection of Infants: A Randomized Clinical Trial

Ayşe Kılıç[1*], Gülçin Otar Yener[1], Aylin Yetim[1], Mustafa Özçetin[1], Gülbin Gökçay[2], Asuman Çoban[3], Zeynep Ince[3], Beril Yaşa[3], Lütfiye Öksüz[4], Funda Güngör Uğurlucan[5], Nezahat Gürler[4]

[1]Department of Pediatrics, Istanbul Medical School, [2]Istanbul University Institute of Child Health, [3]Department of Neonatology, Istanbul Medical School, [4]Department of Microbiology, Istanbul Medical School, [5]Department of Obstetrics and Gynecology, Istanbul Medical School, Istanbul University, Istanbul, Turkey

ABSTRACT

Background: Despite primary vaccination, infants under six months run a risk of infection with pertussis. **Objective:** To determine the impact of early postpartum maternal pertussis vaccination on protecting infants from the disease. **Methods:** All mothers (n=405) who gave birth to healthy term infants were educated on the cocoon strategy. The mothers who consented were immunized with the tetanus-diphtheria-acellular pertussis vaccine within the first three postpartum days. All infants received their pertussis vaccines according to the national schedule. The anti-pertussis IgG titers of infants of thirty vaccinated mothers were compared with those of thirty unvaccinated mothers. **Results:** The pertussis antibody levels in the infants of vaccinated mothers were significantly higher than those of unvaccinated mothers at the mean infant age of 5.6 ± 1.2 months. Only 6 infants of vaccinated mothers exhibited pertussis-like symptoms, none of whom had positive pertussis PCR. Seventeen infants of unvaccinated mothers had pertussis-like symptoms, and 4 tested positive for pertussis PCR. **Conclusion:** Our results showed that maternal pertussis vaccination, administered within the first three postpartum days, may protect infants against pertussis in their first ten months.

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*Corresponding author: Dr. Ayşe Kılıç, Department of Pediatrics, Istanbul Medical School, Istanbul University, Istanbul, Turkey, e-mail: draysekilic@gmail.com

INTRODUCTION

Pertussis is an acute, contagious respiratory tract infection (1,2). Pertussis infections in infancy can cause permanent respiratory tract damage and neurological sequelae. Despite many years of routine infant vaccination, pertussis is still one of the leading causes of vaccine-preventable deaths (2). In Turkey, a routine vaccination schedule for pertussis has been recommended since 1968. Acellular pertussis vaccine has been administered since 2007. Infants are vaccinated with the DTaP-IPV-Hib vaccine a total of four times (at 2, 4, 6, and 18 months); at 6 years of age, they are further vaccinated with the DTaP-IPV vaccine (3-5). Studies have shown that protective antibody levels are reached after 3 doses of pertussis vaccine (6). Therefore, infants are more vulnerable to contagion under 6 months of age, prior to developing sufficient antibodies. The source of pertussis infection for such infants, in 50% of the cases, has been commonly found to be adult relatives or parents, primarily mothers (7-9). Cocooning refers to the vaccination of mothers and other contacts of newborns and infants in order to prevent the transmission of pertussis to infants who may not have completed their primary vaccination series. A recent study has shown that in addition to reducing the prevalence of pertussis in adults, the cocoon strategy decreases the incidence of pertussis by 91% in young infants (10). In a current review, it is stated that adding booster doses of a cellular pertussis vaccine to the current national immunization practices with whole-cell vaccines for young adults and pregnant women seems to be a good option for controlling mortality and morbidity among high-risk groups such as very young infants (11). The Advisory Committee on Immunization Practices (ACIP) recommends that adults such as parents, grandparents, healthcare staff, babysitters, who are or will be in contact with an infant younger than 12 months, be vaccinated with a single dose of tetanus-diphtheria-acellular pertussis (Tdap) vaccine in order to protect both themselves and the infants (12). Vaccination with a single dose Tdap is also recommended by the ACIP for pregnant women in the third trimester (12). Despite this recommendation, parents may refuse the pertussis vaccination during pregnancy believing it harms the fetus, hence the low acceptance frequency of pertussis vaccination during pregnancy (13). In this study, we aimed to investigate the impact of pertussis vaccine, administered to mothers in the postpartum period prior to leaving hospital.

MATERIALS AND METHODS

Identification and Evaluation of the Study Group. Randomly selected and included in the study were mothers who gave birth to healthy term infants in the first three days of every week between December 2013 and April 2014 in the Obstetrics Department of Istanbul Medical School. Informed consent was obtained from all parents, and Ethical approval was obtained from the Research Ethics Committee of Istanbul University (no. 2012/631-1034). During the study period, 551 deliveries occurred. 101 infants were excluded from the study due to prematurity, major congenital anomalies, chromosome abnormalities, and critical illnesses. A total of 450 mothers were educated on the cocoon strategy and given a brochure containing information on the adult type acellular pertussis vaccine (Tdap). Of these mothers, 45 declined to participate in the study, 205 mothers consented to vaccination, and 200 mothers did not accept vaccination but agreed to participate in the study. The infants of the 205 vaccinated mothers constituted

the study group and the infants of the 200 unvaccinated mothers constituted the control group (Figure 1). Sociodemographic data were obtained from the mothers via questionnaire. The mothers in the study were vaccinated with Tdap –IPV (tetanus, adult type diphtheria, adult type acellular pertussis and inactivated polio vaccine) (Adacel Polio®, Sanofi Pasteur, France) and monitored for side effects for 30 minutes following vaccination.

The phone numbers of physicians and nurses were given to the mothers in both groups prior to leaving the hospital. All participants were asked to call the study staff if the infants started coughing, and we also called them near the 1st day of each calendar month to check the infants for signs of coughing via telephone. Infants with coughs were examined in the pediatric outpatient clinic of the Istanbul Medical School. ThoInfants presenting with pertussis-like symptoms, such as paroxysmal coughs or coughs lasting longer than two weeks, had nasopharyngeal aspirates taken for assessment.

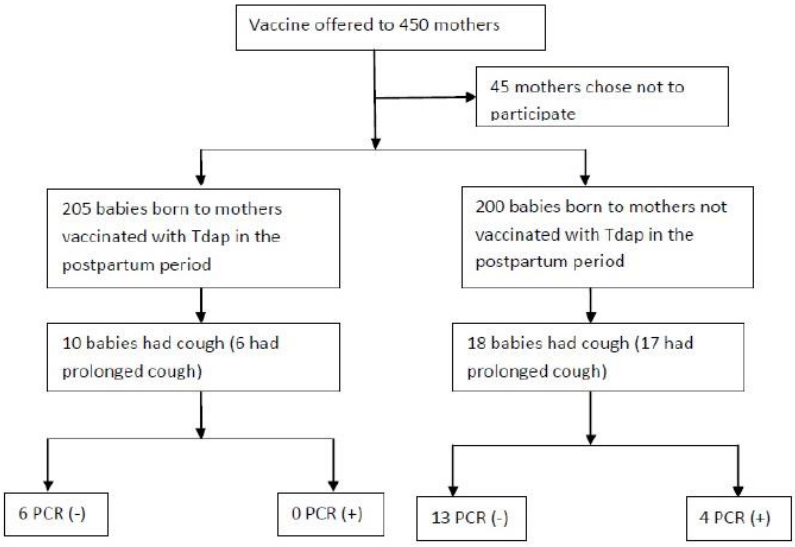

Figure 1. Flowchart for sampling.

Microbiological Samples and Polymerase Chain Reaction (PCR) Analysis. All the microbiological analyses were performed in the Microbiology Department of Istanbul Medical School. Nasopharyngeal aspirate samples were taken from the posterior wall of the nasopharynx by rotating a rayon-tipped, flexible handle swab for 3-5 seconds. The swabs were transported in Amies medium with charcoal to the Microbiology Department. Pertussis infection was investigated in nasopharyngeal aspirates using a rapid diagnostic polymerase chain reaction (PCR) test (GenoQuick® Bordetella, HAIN Lifescience, Germany). Chromosomal regions targeted by PCR in this test included repetitive insertion sequences IS481 for B. pertussis and IS1001 for B. parapertussis. Briefly, the single stranded amplicons hybridized with specific probes were visualized by a gold labeling. According to the validation data of manufacturer, the sensitivity and

specificity of the fast identification kit are 100% and 98%, respectively (14). For the procedure, nasopharyngeal aspirates in a transport medium suitable for pertussis were initially suspended in 300 µl lysis buffer, after being kept at 95°C for 10 minutes. They were centrifuged at 13.000 rpm for 5 minutes; DNA was then extracted from the supernatant, followed by amplification with Bordetella-specific primers. As a result, the appearance of all three bands (conjugate control, amplification control, and Bordetella) was accepted as positive.

Antibody Response to Vaccine. We randomly selected the infants of similar age and gender (30 infants from vaccinated mothers and 30 from unvaccinated mothers) who visited our outpatient clinic. We measured and compared their anti-pertussis (Anti-PT) IgG titers, and blood samples were immediately centrifuged. Serums were analyzed for Anti-PT IgG titers using enzyme-linked immunosorbent assay (ELISA) kits (Statens Serum Institut, Denmark). The Bordetella pertussis IgG-PT ELISA kit is a quantitative test for the detection of IgG antibodies against pertussis toxin in human serum samples. The specificity and sensitivity of the test were declared by the manufacturer to be 96% and 81%, respectively.

Statistical Analysis. The (SPSS) software version 15.0 was used for statistical analyses. Further employed were descriptive statistical methods, the chi-square test, and Fisher's exact test for the comparison of categorical variables, and *Student's t-test*, and Mann-Whitney U test for the comparison of continuous variables. The results were assessed at a 95% confidence interval, and the significance was evaluated at $p<0.05$.

RESULTS

The 205 mothers who consented to vaccination were vaccinated in the postpartum period at a mean time of 25.4 ± 6.7 hours after delivery. No significant side effects were observed after vaccination, although 7 mothers did report pain at the injection site, a minor, expected side effect. The mean age, gestational age, birth weight of the children, and maternal and paternal age were similar between the control and test groups. The average education level of mothers and fathers in the unvaccinated group was higher than that of the vaccinated group. Whereas the number of housewives was higher in the vaccinated group compared with the unvaccinated group, the number of health care workers was higher in the unvaccinated group. Table I shows the sociodemographic characteristics of the families and infants in the vaccinated and unvaccinated groups.

Comparison of pertussis PCR results in infants with pertussis-like symptoms.

Of the 405 (6.9%) infants, 28 had coughs in the follow-up period, 10 belonging to the vaccinated mothers, and 18 to the unvaccinated ones. The incidence of cough symptoms was similar in both groups ($X^2=2.673$; $p>0.05$). The infants had coughs at a mean age of 4.2 ± 2.3 months. The onset time of the cough was similar between the vaccinated and unvaccinated groups, as well as between the pertussis PCR negative and pertussis PCR positive cases. Six of the 10 infants in the vaccinated mothers group and 17 of the 18 infants in the unvaccinated mothers group had suffocative coughs, or coughs lasting longer than two weeks. The five remaining infants had neither suffocative coughs nor coughs lasting longer than two weeks. Pertussis PCR analyses of nasopharyngeal aspirates were only performed on the 23 cases of suffocative or long-lasting coughs.

Pertussis PCR results were positive in 4 of these cases (17.4%), all belonging to the unvaccinated mothers group (Table II).

Table I. Sociodemographic characteristics of the infants of the vaccinated and unvaccinated mothers.

	Infants of vaccinated mothers (n=205)	Infants of unvaccinated mothers (n=200)	t or X^2 value	p-value
Birth weight (mean ± SD)	3058.17±718.97	3128.74±507.17	-1.139	0.253
Gestational age (week, mean ± SD)	38.33±1.87	38.50±1.59	-0.973	0.331
Maternal age (mean ± SD)	30.03±5.59	30.95±5.34	-1.683	0.093
Paternal age (mean ± SD)	33.41±5.91	34.52±5.94	-1.876	0.061
Education of mother, n (%)				
Illiterate	10 (4.9)	5 (2.5)		
Primary school	117 (87.1)	70 (35.0)	24.464	<0.001
High school	36 (17.6)	54 (27.0)		
University	42 (20.5)	71 (35.5)		
Profession of mother, n (%)				
Housewife	154 (75.1)	111 (55.5)		
Teacher	9 (44.4)	12(6.0)		
Health care worker	14 (6.8)	32 (16.0)	19.977	0.001
Public officer	16 (7.8)	23 (11.5)		
Worker	7 (3.4)	8 (4.0)		
Other	5 (2.4)	14 (7.0)		
Education of father, n (%)				
Illiterate	1 (0.5)	1 (0.5)		
Primary school	110 (53.7)	65 (32.5)	21.916	<0.001
High school	56 (27.3)	63 (31.5)		
University	38 (18.5)	71 (35.5)		
Profession of father, n (%)				
Public officer	38 (18.5)	40 (20)		
Worker	63 (30.7)	36 (18)	17.412	0.002
Health care worker	7 (3.4)	23 (11.5)		
Shop owner	88 (42.9)	86 (43.0)		
Other	9 (4.4)	15 (7.5)		
Siblings of caregivers, n (%)				
Yes	22 (10.7)	9 (4.5)	5.562	0.014
No	183 (89.3)	191 (95.5)		

Comparison of the antibody levels of the infants.

The serum anti-PT IgG levels of 30 infants in each group were measured at the mean infant age of 5.6 ± 1.2 months.

Table II. Bordetalla pertussis PCR results of the infants of vaccinated and unvaccinated mothers.

		Infants of the vaccinated mothers (n=6)		Infants of the unvaccinated mothers (n=17)		p-value
		n	%	n	%	
PCR result	**Positive**	0	0.0	4	17.4	X^2=3.88
	Negative	6	26.1	13	56.5	p=0.049

The mean ages (in months) of the infants who were measured for serum anti-PT IgG levels were similar in both vaccinated and unvaccinated mothers (17 of the infants were between 4-5 months old (9 vaccinated / 8 unvaccinated), 14 were 5-6 months old (7 vaccinated/7 unvaccinated), 14 were 6-7 months old (7 vaccinated/7 unvaccinated), and 15 were 7-8 months old (7 vaccinated/8 unvaccinated)). The mean serum anti-PT IgG level of the infants was higher in the vaccinated mothers (Figure 2).

Table III. Serum pertussis antibody levels of the infants vaccinated with 2 doses and 3 doses of DTaP-IPV-Hib between vaccinated and unvaccinated mothers.

	Serum pertussis antibody level				
	Infants of the vaccinated mothers (n=17)		Infants of the unvaccinated mothers (n=17)		p-value
	Mean	SD	Mean	SD	
Infants vaccinated with 2 doses of DTaP-IPV-Hib	375.62	140.87	99.18	63.47	<0.001
Infants vaccinated with 3 doses of DTaP-IPV-Hib	439.40	113.87	88.99	74.11	<0.001

DTaP-IPV-Hib: Diphteria, acellular pertussis, tetanus, inactive polio- Hemophilus influenza vaccine.

The number of infants who received 3 doses of DTaP-IPV-Hib was higher in the unvaccinated mothers, while the serum anti-PT IgG levels of the infants in the vaccinated mothers group were significantly higher. The serum anti-PT IgG levels of the infants with two vaccine doses of DTaP-IPV-Hib were higher in the infants of the vaccinated mothers group (Table III).

DISCUSSION

The cocoon strategy reduced the incidence of pertussis infection in 9-17% of adults and 70% of infants aged 0-3 months (15). Almost half of the episodes of pertussis in infants may be prevented by the postpartum immunization of their mothers (16). In accordance with the literature, there was no infant with verified pertussis infection in vaccinated

mothers, while all infants with a verified pertussis infection belonged to unvaccinated mothers.

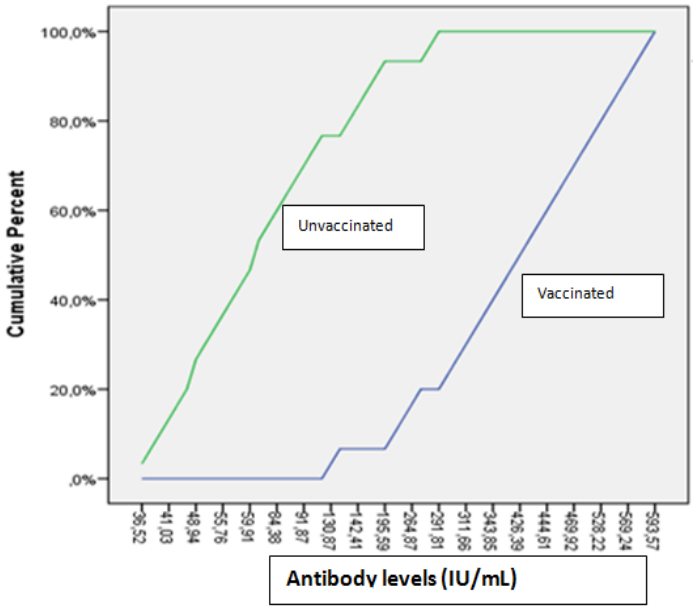

Figure 2. Serum Pertusis antibody levels in the infants of vaccinated and unvaccinated.

The rate of pertussis infection verified by pertussis-PCR (17.4%) was similar to the results of the study conducted in Turkey among the infants with pertussis-like symptoms (17,18). ACIP advises immunization against pertussis in the third trimester of pregnancy period (12), but pregnant women may resist vaccination in that period of time. Therefore, we vaccinated the mothers in the early postpartum period in our study, reducing the number of infants with pertussis. According to our study results, early maternal vaccination in postpartum period (3 days after delivery) may be an effective approach to protecting infants from pertussis. In contrast, Castagnini *et al.* (19) found that the postpartum maternal vaccination did not protect infants against pertussis; their multicenter study, on the other hand, did not mention the exact time the mothers were vaccinated. In our study, the mean vaccination time of mothers was 25.4 ± 6.7 hours following delivery. It is known that the earlier the maternal vaccination occurs in the postpartum period, the more effective it will be in protecting infants from pertussis.

Immunization against pertussis blocks infection through increasing the anti-PT IgG level (20). We observed that early postpartum maternal immunization nearly quadrupled the anti-PT IgG levels of the infants. In the literature, there exist conflicting results regarding the possible effects of maternal immunization during postpartum period on the anti-PT IgG levels of infants. Some studies favor the postpartum maternal immunization due to the higher antibody levels of the infants (21). However, Belloni *et al.* (22) showed how postpartum maternal immunization may reduce the anti-PT IgG levels of fully vaccinated infants. In our study, early postpartum maternal immunization did not depress the antibody response of infants. Further observed was a five-fold

increase in the pertussis antibody levels of infants belonging to vaccinated mothers. Anti-PT IgG levels vary among the studies on cocoon strategy (23-25). Of the reproductive-age females, 57.2% showed an anti-PT IgG level of over 30 EU/ml (26). Pertussis antibody levels depend mainly on previous exposure to pertussis and the PT level of the vaccine. The high levels of antibodies found in our study may be due to the high prevalence of pertussis in Turkey.

Also evaluated in the present study was the additional risk factors for a prolonged cough: maternal and paternal educational levels as well as paternal occupational status. A recent study showed that providing the parent with ample information about cocooning may affect their opinion on maternal vaccination and its perceived benefits and norms (27). Although our nurses directly contacted the families and vaccines were provided free of cost, the rate of participation acceptance was lower than other studies. Cultural concerns and doubts about the benefits of the vaccine may have affected the low acceptance rate of postpartum vaccination in the current research. In the literature, maternal education level is presented as one of the factors that influence the vaccination rates of children (28,29). Smith *et al.* (29) showed that undervaccination was associated with mothers with lower educational status; on the other hand, unvaccination was found to be related to mothers with higher educational status. In our study, it was promising that mothers with lower educational levels or more children in daycare leaned towards accepting immunization. Interestingly, medical personnel and participants with higher education levels showed higher resistance to vaccination. Nationwide projects are required to spread knowledge regarding the importance of postpartum maternal pertussis vaccination. This conduces to dispelling any fears that mothers may have concerning the side effects of the vaccine. The present study encountered certain limitations: primarily , we did not evaluate asymptomatic infants with pertussis PCR due to financial constraints. For a differential diagnosis of acute pertussis infection and vaccine effect, we might measure anti-PT IgA or IgM levels, but pertussis infection was diagnosed via clinical symptoms and PCR analysis. Moreover, we had a limited number of cases, necessitating similar studies with more populations. Lastly, our 10-month follow-up might have been too short to account for all the cases. Despite such limitations, this randomized-controlled study shows the efficacy of early maternal pertussis vaccination. The focus of the present study was on early postpartum maternal vaccination against pertussis and its protective effect on infants in their first 8-10 months of life. As a result, it was observed that vaccination of mothers in the early postpartum period (immediately after birth) had a very high protection ratio in infants. Maternal immunization supported the infants' serum pertussis antibody production. Further research is needed to elucidate the protective effects of early postpartum maternal immunization on infants. Besides, protection of infants against pertussis infection depends on many socioeconomic and sociodemographic factors to be separately analyzed.

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