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CLINICAL OVERVIEW

Pertussis vaccination in pregnancy: Security and effectiveness in the protection of the infant

Vacunación con pertussis en el embarazo: una estrategia segura y efectiva para proteger al lactante menor

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Abstract

Whooping cough is an immune preventable disease that can be life threatening. Despite infant immunization starting at 2 month of age, there are many cases and outbreaks in our country and also around the world, with a high risk of mortality especially in infants under 6 month of age. It has been proposed that antenatal vaccination with acellular pertussis component (Tdap) would be useful, safe and effective since it transfers a high antibody rate to the child, reducing the incidence of pertussis in this group by 85%. No higher incidence of adverse effects has been found in pregnant women with this vaccine. This strategy has been implemented in several developed and Latin American countries. The purpose of this manuscript is to review and discuss the benefits of antenatal vaccination with Tdap. It was concluded that maternal immunization with Tdap vaccine should be promoted to prevent infection and associated mortality in infants under 6 months of age by *Bordetella pertussis*.

Keywords:
Whooping cough, *Bordetella pertussis*, diphtheria-tetanus-pertussis vaccine

Introduction

Pertussis, or whooping cough, is an infectious, contagious and potentially life-threatening disease caused by *Bordetella pertussis* (*B. pertussis*). Its affects exclusively humans and has a worldwide distribution. Its clinical presentation of coughs in accesses and/or apneas is manifested with greater severity and lethality in children younger than 6 months of age[1,2]. If it is severe, its manifestation is distinguished by extreme leukocytosis (> 100,000/mm^3), pulmonary hypertension, respiratory failure and refractory hypoxemia, which usually lead to cardiovascular collapse[3].

The pertussis vaccine has been administered in our country since 1952 and it was incorporated into the national immunization program (PNI) at a later time, as part of the triple bacterial vaccine, associated with diphtheria and teta-

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nus toxoid, showing a clear decrease in the incidence of the disease during time of administration, with seasonal epidemic outbreaks every 3-4 years[2]. Since 2002, the disease has limited its impact, with approximately 7 cases per 100,000 inhabitants, except for the period between 2011 to 2013, when it reached 33.1/100,000. The main affected group was those younger than 1 year old. In 2015, it reached a rate of 137.7/100,000 inhabitants, and from this group, 82% were younger than 6 months, recording a rate of 233.3/100,000, while the age group of 6 to 11 months presented a risk almost six times lower than the first group, with a rate of 42, 6/100,000[2,4]. The mortality rate has remained stationary, without many changes, with about 0.4 per 100,000 inhabitants, corresponding to the fifth cause of immune preventable deaths[1,3]. There are no specific mortality rates available for those children younger than 6 months, however, children of this age group die every year for pertussis[3-6] (figure 1 and table 1).

The evidence obtained from epidemiological studies, have established that the source of pertussis infection in children under 1 year of age, is usually transfer from an adult relative[7-9]. Over the past 20 years, there has been an increase in the age of susceptible cases, including adolescents and young adults[2,10]. For this reason, multiple strategies have been developed in order to try to control this problem[11], reinforcing the coverage of the primary scheme at 2, 4 and 6 months of age, adding also boosters at 18 months, as well as in 1st and 8th grade at primary school *(grades according to Chilean education system, when the child is around 6 years old in 1st grade, and 13 years old in 8th grade).*

These include the cocoon strategy, implemented during 2012 and 2013 in Chilean regions with infants mortality cases, as occurred in Bío-Bío, O'Higgins, Valparaíso and Metropolitan Region. It was decided to vaccinate the postpartum women, as well as parents of every newborn, siblings and relatives of 12 years and older, including caregivers, who lived and shared all day with the newborn, in addition to vaccination of health care providers whom work with pediatric patients. The total coverage reached was 91% in postpartum women and 60% in other groups, however, given the high number of members in chilean families, it is not possible to sustain this strategy over time, due to

Table 1. National rates of incidence and lethality and number of deaths under 6 months of age. Chile, period 2011-2015[4,5]

Year	2011	2012	2013	2014	2015
Incidence rate per 100,000 inhabitants	15	33.1	11.2	6.3	4.1
Lethality rate per 100,000 inhabitants	0.09	0.07	0.02	0.04	0.04
Fatal cases younger than 6 month of age	16	13	3	7	8

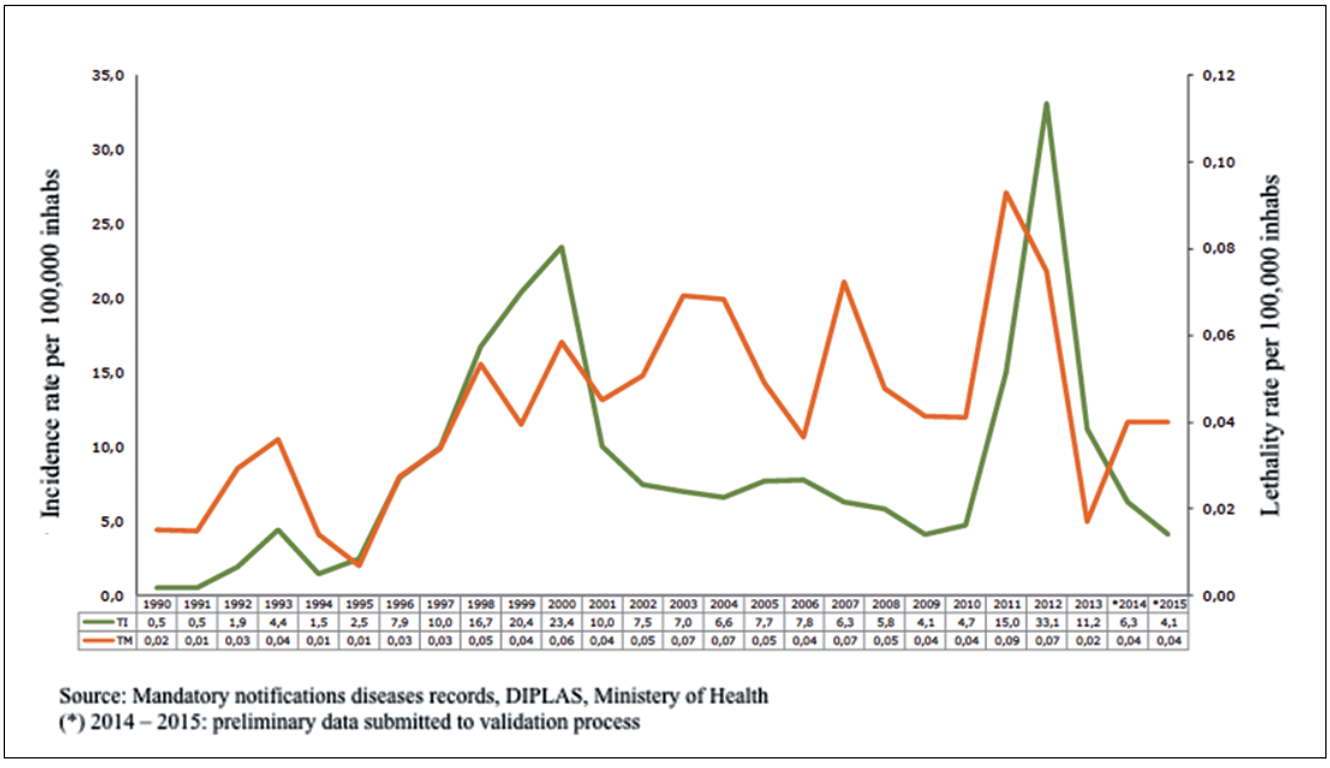

Figure 1. Incidence and mortality rates by pertussis. Chile period 1990-2015[4].

its cost, which is clearly high, and its optimal coverage is very difficult to fulfill, which enables frames of susceptibility for the infant to the *B. pertussis* infection[5,12].

This type of vaccination during pregnancy has been considered as one of the most gentle and effective strategies to reduce morbidity and mortality in children younger than 6 months of age[1,13-15]. Its main objective is to promote the transfer of placental antibodies to the fetus and to protect it during the period of greatest risk of a severe pertussis infection, while patient completes its primary immunization schedule with 3 doses[1,5,16].

The purpose of this research is to review and to discuss the benefits of antenatal vaccination with Tdap.

Immunological basis of antenatal Tdap vaccine

At birth, the infant has an immature immune system that has not been exposed to antigens, thus, it is not possible to develop an adaptive kind of immunity on its own, with exclusively IgG-class antibodies transferred through the placenta from the mother during pregnancy, especially during the third trimester[17]. The child is incapable of establishing a suitable protective response against pathogens or other agents, due to his/her immature immune system[18]. For this reason, the transplacental transfer of antibodies is the main defense mechanism during the first 2 months of life.

Several studies have demonstrated that immunization during pregnancy with acellular pertussis vaccine (Tdap) produces an elevation in IgG class antibody titres in pregnant women, and consequently an elevation in antibody titres in newborn plasma as well[1,19-21]. This phenomenon is not observed when maternal immunization is performed prior to pregnancy[22]. The theory that could explain this is that when vaccinating the pregnant mother during the 2nd or 3rd trimester will induce high titers of antibodies that would allow her to effectively and sufficiently transfer them to protect her child while he acquires immunity through the primary regimen of vaccination[23,24].

Effectiveness and safety of Tdap antenatal vaccine

Several studies have provided information regarding the safety and effectiveness of antenatal immunization with Tdap. If this vaccination in pregnant women reaches high coverage, pertussis deaths in children younger than 6 months should decrease and even disappear in children born from mothers already vaccinated during gestation[5,15,18,25,26].

Dabrera et al. demonstrated in a retrospective study that pertussis cases occurred in a lower percentage in the group of mothers immunized with the Tdap vaccine versus the control group[27]. Winter et al., evaluated a cohort of women whose ages were between 14 and 44 in California, who had been mothers in the past 12 months and who received Tdap vaccine in the peripartum period, showing that children born from women vaccinated between 27 and 35 weeks of gestation developed 85% fewer *B. pertussis* infections than the control group[18]. The same group, through a retrospective analysis, showed that children of mothers vaccinated during pregnancy with Tdap and who were infected with pertussis had less severe manifestations of the disease, which it results in a lower rate of hospitalization and/or admission to critical patient unit (95% confidence interval (CI): 49% -85%) and 58% (95% CI: 15% -80%), compared to those who were born from unvaccinated mothers, establishing an effectiveness of 72%, in relation to hospitalization prevention[26]. It is shown that no patient born in the cohort of vaccinated mothers required a connection to mechanical ventilation.

Regarding vaccine safety, a retrospective study was published in 2014, which measured whether vaccination with Tdap causes an increase in obstetric risk, and it analyzed 123,494 pregnant women. It was concluded that vaccination with Tdap in pregnant women did not significantly increase the risk of hypertensive syndrome, chorioamnionitis, preterm (< 37 weeks gestation) or small for gestational age (< p10)[28]. During the same year, a randomized, double-blind and controlled study was published, in which women were vaccinated between 30 and 32 weeks of gestation. The primary aim that was measured was the occurrence of adverse effects on mother and child, the development of whooping cough (pertussis) and child's weight growth up to 13 months of life. It was found that there is no greater incidence of adverse effects in mothers and children of vaccinated women versus placebo. There were no reports of pertussis or significant differences in child growth. In addition, at the moment birth and at two months of age, the children of vaccinated women had significantly elevated antibody titers versus placebo. At 4 months of age, though, this difference was not evident[21].

During 2016, a retrospective study was published, in which 36,884 women were included and the safety in the coadministration of the Tdap vaccine and influenza vaccine was measured. The occurrence of adverse effects of vaccination and obstetric adverse effects were evaluated, concluding that coadministration of vaccines had no higher incidence of severe adverse events in vaccination or in the development of preterm delivery, small for gestational age, versus patients who received administration sequentially[29]. A retrospective study of

Table 2. Safety studies on administration of Tdap vaccine in pregnancy

Author, country, journal and year	Objectives	Design, sample size	Conclusions
Kharbanda E et al. EEUU JAMA, 2014[28]	Risk of preterm birth, small newborn for gestational age, chorioamnionitis and hypertensive syndrome of pregnancy	Retrospective, observational cohort study n = 123,494	There was no increase in risk in relation to the primary objectives, measured in pregnant women vaccinated with Tdap
Muñoz F et al. EEUU JAMA, 2014[21]	Occurrence of adverse events in women and children. Development of pertussis and weight gain at 13 months of age	Phase 1-2, randomized, double-blind, placebo-controlled study n = 48 healthy pregnant women and their newborns; and 32 healthy non-pregnant women	There was no increase in adverse events due to Tdap vaccine in pregnant women or their children. No cases of pertussis were reported. There were no differences in weight growth
Sukumaran L et al. EEUU JAMA, 2015[30]	Occurrence of acute adverse events and obstetric adverse events (preterm birth, small newborn for gestational age and low birth weight for gestational age) in women vaccinated with Tdap during pregnancy who had previously received tetanus	Retrospective study n = 29,155 pregnant women	There was no higher incidence of acute adverse events or obstetric events in women who had previously received tetanus
Sukumaran L et al. EEUU Obstet Gynecol. 2015[29]	Occurrence of acute adverse events in coadministration of Tdap and influenza vaccine. Occurrence of preterm birth, small newborn for gestational age and low birth weight for gestational age	Retrospective cohort study n = 36,844 pregnant women	There was no increase in the incidence of adverse events when co-administering Tdap and influenza vaccines compared to their sequential vaccination. Coadministration of these vaccines does not increase the risk of obstetric pathology studied

same authors measured the risk of acute adverse events and adverse events at birth in women receiving Tdap vaccine during pregnancy, and who had previously received tetanus vaccine. It was concluded that prior vaccination with tetanus vaccine does not increase the risk of acute adverse effects or the incidence of preterm or small gestational age in patients receiving Tdap vaccine during pregnancy[30]. Table 2 summarizes the safety evidence presented.

In our country, there are two vaccines against Tdap registered by the Institute of Public Health: GlaxoSmithKline's Boostrix®, which suggests in its information to prescribe the possibility of being used during pregnancy based on safety data previous to its commercialization[31], and Adacel® from Sanofi Pasteur, with international experience with both for these purposes.

In order to evaluate the cost-effectiveness of introducing maternal immunization with Tdap into Brazil's PNI, a study was conducted in 2011, with one-year follow-up comparing the maternal immunization model versus the usual practice (non-maternal immunization), as well as an evaluation of direct medical and non-medical costs and indirect costs. It was concluded that maternal immunization would prevent 661 cases of pertussis and 24 deaths, saving 1,800 lives per year and about $29,000 dollars, considering the 78% of vaccine effectiveness[32]. Starting in 2011, the Advisory Committee on Immunization Practices (ACIP) in the United States recommended to vaccinate pregnant women who had not been immunized, ideally after 20 weeks of gestation. After the appearance of new evidence, in 2013, ACIP updated also its recommendation, indicating that all pregnant women should be immunized between 27 and 36 weeks of gestation, regardless of their previous vaccination record. If patient does not receive the vaccine, it should be given in the immediate postpartum. From 2011 to 2015 this strategy has also been performed in England, Wales, Ireland, Belgium, Australia, Portugal, New Zealand, Israel, Argentina, Costa Rica, Colombia, Mexico and Uruguay, among others. In August 2015, the World Health Organization, regarding vaccination against pertussis, mentions the vaccination strategy for pregnant women, including cost-effectiveness and safety, and recommended that PNI should incorporate it into their main objectives during the third trimester and at least 15 days before delivery, which was a decision shared by the vaccine and immunization advisory committee in our country, Chile[1,6].

Conclusion

Pertussis is a potentially life-threatening acute respiratory infection caused by *B. pertussis*, which may be a very severe, particularly in children younger than 3 months. Currently, it is the fifth preventable cause of death in Chile. Maternal immunization is a proven, safe and cost-effective system to reduce this disease in children younger than 6 months and its associated mortality, and should be administered in each pregnancy during the 2nd or 3rd trimester, continuing until at least 15 days prior to delivery, regardless of the interval from prior vaccination with dT or Tdap, in order to transfer high titers of antibodies. That is the main reason why, since 2013, it is included among the international recommendations related to vaccines administered during gestation, to which Chile should definitely join.

Conflicts of Interest

Authors state that any conflict of interest exists regards the present study.

References

1. WHO. Pertussis vaccines: WHO position paper, August 2015. Recommendations. Vaccine; 2016;34(12):1423-5.
2. Departamento de epidemiología, Ministerio de Salud de Chile. Boletín Epidemiológico Trimestral, 2016;112(2):1-4. Disponible en: http://epi.minsal.cl/wp-content/uploads/2016/08/BET-coqueluche-enero-julio-2016.pdf, accedido el 14 Septiembre 2016
3. Donoso A, Arriagada D, Cruces P. Coqueluche grave: Estado del arte. Rev Chil Infectol. 2012;29(3):290-306.
4. Departamento de epidemiología Ministerio de Salud de Chile. Situación epidemiológica de coqueluche (CIE-10 A37). Chile. 2015;1-14. Disponible en: http://epi.minsal.cl/wp-content/uploads/2016/05/Informe-anual-coqueluche-final.pdf, accedido el 27 de Abril del 2017
5. Cofré J. ¿Es tiempo de vacunar a la mujer embarazada contra la Coqueluche? Rev Chil infectología. 2016;33(1):55-8.
6. Avendaño L, Dabanch DJ, Inostroza J, María D, Navarrete S. Sesión ordinaria del CAVEI 10 Nov 2016;1-4. Disponible en: http://vacunas.minsal.cl/wp-content/uploads/2017/01/Acta-CAVEI-10-noviembre-2016.pdf, accedido el 27 de Abril del 2017
7. Bisgard K, Pascual F, Ehresmann KR, Miller CA, Cianfrini C, Jennings CE, Rebmann CA, Gabel J, Schauer SL LS. Infant pertussis: who was the source? Pediatr Infect Dis J. 2004;23(11):2004.
8. Godoy P, Toledo D, Carmona G, Caylà JA, Alsedà M, Àlvarez J, et al. Factors influencing the spread of pertussis in households : a prospective study , Catalonia and Navarre , Spain , 2012 to 2013. Euro Surveill. 2013;21(45):1-10.
9. de Greeff SC, de Melker HE, Westerhof A, Schellekens JF, Mooi FR van BM. Estimation of household transmission rates of pertussis and the effect of cocooning vaccination strategies on infant pertussis . Epidemiology. 2012;23(6):23018969.
10. Wirsing von König C-H. Pertussis diagnostics: overview and impact of immunization. Expert Rev Vaccines. 2014;13(10):1167-74.
11. Poland GA. Pertussis outbreaks and pertussis vaccines: New insights, new concerns, new recommendations? Vaccine. 2012;30(49):6957-9.
12. Comité asesor de vacunas e inmunizaciones. Estrategias para el control del coqueluche. 2012;1-21. Disponible en: http://web.minsal.cl/portal/url/item/c9098adc64cfbccae040010165013c8a.pdf, accedido el 14 de Mayo 2017
13. Sawyer, M; Liang, JL; Messonnier, N; Clark T. 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(7):131-5.
14. Atkins K, Fitzpatrick M, Galvani A, Towsend J. Cost-Effectiveness of Pertussis vaccination during pregnancy in the United States. Am J Epidemiol. 2016;183(12):1159-70.
15. Vizzotti C, Neyro S, Katz N, Juárez MV, Pérez Carrega ME, Aquino A, et al. Maternal immunization in Argentina: A storyline from the prospective of a middle income country. Vaccine; 2015;33(47):6413-9.
16. Krishnaswamy S, Wallace E, Buttery J, Giles M. Antenatal pertussis vaccination: Are we implementing best evidence into practice? Aust New Zeal J Obstet Gynaecol. 2016;56(6)
17. Torres LS, Gamboa DÁ. Inmunología perinatal Resumen. FEMINA. 2014;42(4):185-92.
18. Winter K, Nickell S, Powell M, Harriman K. Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis. Clin Infect Dis. 2017;64:3-8.
19. Abu Raya B, Srugo I, Bamberger E, Kessel A. The avidity of pertussis antibodies following gestational acellular pertussis immunization. Vaccine; 2015;33(42):5490-1.
20. Maertens K, Caboré RN, Huygen K, Vermeiren S, Hens N, Van Damme P, et al. Pertussis vaccination during pregnancy in Belgium: Follow-up of infants until 1 month after the fourth infant pertussis vaccination at 15 months of age. Vaccine; 2016;34(31):3613-9.
21. Munoz FM, Bond NH, Maccato M, Pinell P, Hammill HA, Swamy GK, 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(17):1760-9.
22. 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(4):539-44.
23. Eberhardt CS, Blanchard-Rohner G, Lemaître B, Boukrid M, Combescure C, Othenin-Girard V, et al. Maternal immunization earlier in pregnancy maximizes antibody transfer and expected infant seropositivity against pertussis. Clin Infect Dis. 2016;62(7).
24. Eberhardt CS, Blanchard-rohner G, Lemaître B, Combescure C, Othenin-girard V, Chilin A, et al. Pertussis antibody transfer to preterm neonates after second versus third trimester maternal immunization. 2017;64:1129-32.

25. Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: An observational study. Lancet; 2014;384(9953):1521-8.
26. Winter K, Cherry JD, Harriman K. Effectiveness of Prenatal Tetanus , Diphtheria , and Acellular Pertussis Vaccination on Pertussis Severity in Infants. Clin Infect Dis. 2017;64:9-14.
27. Dabrera G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. Clin Infect Dis. 2015;60(3):333-7.
28. Kharbanda EO, Vázquez-Benítez G, Lipkind HS, Klein NP, Cheetham TC, Naleway A, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. Jama. 2014;312(18): 1897-904.
29. Sukumaran L, Mccarthy NL, Kharbanda EO, Li R, Klein NP, Hambidge SJ. Safety of tetanus, diphtheria, and acellular pertussis and influenza vaccinations in pregnancy. Obs Gynecol. 2016;126(5):1069-74.
30. Sukumaran L, McCarthy NL, Kharbanda EO, McNeil MM, Naleway AL, Klein NP, et al. Association of Tdap vaccination with acute events and adverse birth outcomes among pregnant women with prior tetanus-containing immunizations. JAMA. 2015;314(15):1581-7.
31. Kline GS. boostrix_combinada_1.pdf. Folleto de información al profesional. Boostrix vacuna combinada contra difteria, tétanos y pertussis acelular. Suspensión inyectable. 2016. Disponible en: http://www.ispch.cl/sites/default/files/boostrix_combinada_1.pdf, accedido el 27 de Abril del 2017
32. Sartori AMC, de Soárez PC, Fernandes EG, Gryninger LCF, Viscondi JYK, Novaes HMD. Cost-effectiveness analysis of universal maternal immunization with tetanus-diphtheria-acellular pertussis (Tdap) vaccine in Brazil. Vaccine.; 2016;34(13):1531-9.