

Epidemiological and Clinical Reasons for Vaccination Against Pertussis and Influenza in Pregnant Women

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Abstract

Vaccinations in pregnancy are an important aspect of prenatal care for improving both maternal health and neonatal outcomes. Despite the fact that protection against some infectious diseases for pregnant women can be easily provided through immunizations, current coverage rates are low. Two vaccines are notably recommended during pregnancy: influenza and the combined tetanus, diphtheria and acellular pertussis (Tdap) vaccine. In this review the authors discuss current recommendations for vaccination against pertussis and influenza in pregnant women in terms of epidemiological, clinical, and immunological reasons, taking into account safety and effectiveness. Promoting patients' awareness about pertussis and influenza and encouraging general practitioners, nurses and obstetricians to recommend the pertussis booster and influenza vaccine will hopefully increase the number of pregnant women who choose to become vaccinated.

Keywords

Prophylaxis • Maternity • Whooping Cough

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Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ACIP	Advisory Committee on Immunization Practices Centers for Disease Control and Prevention
CDC	Centers for Disease Control and Prevention
DTaP	tetanus diphtheria and acellular pertussis vaccine with not reduced doses of antigens, used in infants and children
ECDC	European Centre for Disease Control and Prevention
FDA	Food and Drug Administration
ICU	Intensive Care Unit
Tdap	tetanus diphtheria and acellular pertussis vaccine with reduced doses of antigens, used in adolescents and adults
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink
WHO	World Health Organization

1 Introduction

Effective protection against some infectious diseases for pregnant women and their children can be provided through immunization administered during pregnancy. This means that vaccinations during pregnancy are an important aspect for both maternal and prenatal care, improving the health safety of neonates. Two vaccines are notably recommended during pregnancy: the influenza vaccine and the combined tetanus, diphtheria and acellular pertussis (Tdap) vaccine. We present the current recommendations for immunization against pertussis and influenza in pregnant women in terms of epidemiological, clinical, and immunological reasons. The safety and effectiveness issues for both women and infants are also discussed.

2 Influenza

2.1 Epidemiology and Clinical Course of Influenza in Pregnant Women and Their Children

Influenza is one of the most prevalent viral diseases and a major cause of morbidity and mortality in many regions around the world. The World Health Organization (WHO) estimates between 330 million and 1.575 billion people may suffer from influenza each year, while between 500 thousand and one million people die annually due to influenza and its complications (WHO 2009).

Although the incidence rates of influenza are similar among pregnant and non-pregnant women, pregnant women have an increased risk of experiencing a severe and complicated course of influenza. Factors increasing the severity and risk of complications are associated with physiological changes mainly occurring during the third trimester of pregnancy, including: changes in the immune system (cellular immunodeficiency, selective suppression of Th1 cells), increased cardiac ejection fraction, increased oxygen consumption, and reduced lung volume (Creanga et al. 2010; Steinhoff et al. 2010; Puck et al. 1980).

A severe course of influenza in pregnancy was first reported during the pandemic of 1918, when 1,350 cases in pregnant women, who had an influenza-like illness, were evaluated and when pneumonia complicated 43 % of the cases. In 52 % of these patients, pregnancy was prematurely terminated. The mortality rate was 23 % and it was highest in the last 3 months of pregnancy (Harris 1919).

During the influenza epidemic of 1957, pregnant women accounted for nearly half of the deaths of women of childbearing age. All deaths were attributed to respiratory insufficiency secondary to pulmonary edema and pneumonia (Greenberg et al. 1958). Mullooly et al. (1986) reviewed influenza complicating pregnancy from 1975 to 1979. There were four epidemics during

that 5-year period. Pregnant women sought outpatient medical attention for acute respiratory disease during the influenza season significantly more often than non-pregnant women. However, unlike the previously reported epidemics, there were no maternal deaths attributable to influenza, and the hospitalization rate was low at 2 per 1,000 (Mullooly et al. 1986).

During the last pandemic caused by the influenza A(H1N1) pdm09 virus in 2009, using a passive surveillance system in the USA, it was found that pregnant women were 7.2 times more likely to be hospitalized and 4.3 times more likely to be admitted to an intensive care unit (ICA) than non-pregnant women (Creanga et al. 2010). Among all deaths from influenza that year, 4.3 % were reported in pregnant women. This risk was higher if they had an underlying medical condition, were older, or were infected in the third trimester. Severe illness occurred in all pregnancy trimesters, but most cases (55 %) occurred in the third trimester. In a study by Neuzil et al. (1998), women in the third trimester were three to four times more likely to be hospitalized for an acute cardiopulmonary illness during influenza season than postpartum women. Asthma in pregnant women increased the rate of hospitalizations for a respiratory illness tenfold during influenza season. Bogers et al. (2011) also investigated the pregnancy outcomes and complications in all hospitalized pregnant women infected in 2009 by influenza A/H1N1 in the Netherlands. Most women were admitted from 28 weeks of gestation onward, which could have been due to the concern about the fetal condition, but more likely resulted from decreased pulmonary capacity caused by diaphragmatic elevation and decreased chest wall compliance. Pre-term birth was a recognized complication of the 2009 influenza A/H1N1 infection (Bogers et al. 2011). The perinatal outcomes of the 2009 influenza A/H1N1 in the United Kingdom were reported by Pierce et al. (2011). The authors found 10 deaths among 256 infants and increased risk of perinatal mortality in the infected women compared with the uninfected ones.

The effect of the influenza infection on the fetus is not clear. However there is an increased risk of spontaneous abortion, still birth, or prematurity. There is a distinct lack of prospective data on the effects of intrapartum, laboratory-confirmed influenza on the fetal outcome. Influenza has been associated with limb reduction and neural tube defects, including anencephaly (Lynberg et al. 1994; Aro et al. 1984; Coffey and Jessop 1959), although anencephaly has not been uniformly confirmed (Saxen et al. 1990). Irving et al. (2000) found no significant difference in the incidence of congenital malformations between women who had serum-confirmed influenza and controls. Widelock et al. (1963) studied the influenza epidemics between 1957 and 1960. They found neither the increased incidence of fetal death nor malformations in pregnant women who had influenza. In contrast, some studies unraveled the increased incidence of schizophrenia in people who were born 2–3 months after the influenza epidemic, which implies that maternal exposure to influenza in the second trimester, when fetal neurons are migrating, is a risk factor (Sham et al. 1992; Mednick et al. 1988). There have also been reports of an increased incidence of cleft lip (Leck 1963, 1969). Unfortunately, many studies are limited by recall and selection bias, making it unclear if there truly is a link. However, a direct teratogenic effect of influenza viruses appears unlikely and it is presumed that the fetus is affected by the infection indirectly through fever. In a study by Acs et al. (2005) the risk of congenital anomalies was reduced by the use of anti-fever drugs.

It should be highlighted that influenza is a clinical problem not just for pregnant women but also for the infant care due to their young age precluding vaccination against influenza. Mothers (or households in general) may be a source of influenza viruses for unprotected infants. Data from the 2003/2004 epidemic season in the United States indicated that the death rate from influenza in infants aged 0–6 months was 88/100,000 and only one third of the deaths occurred in children affected by chronic diseases,

such as bronchial asthma, chronic lung disease, or cardiovascular conditions (Glass et al. 2009).

2.2 Safety of Influenza Vaccination in Pregnant Women

Inactivated split or subunit influenza vaccines have been given to millions of pregnant women around the world with no harmful effects either for the mother or the child. The incidence of adverse reactions was similar among vaccinated and unvaccinated women and there was no increased risk of complications during pregnancy or a higher number of cesarean deliveries in vaccinated women.

The Centers for Disease Control and Prevention (CDC), in collaboration with the Food and Drug Administration (FDA), conducted a search of reports in the Vaccine Adverse Event Reporting System (VAERS) for pregnant women who received seasonal influenza vaccines from 1990 to 2009 to address the potential vaccine safety concerns. The study concluded that no unusual patterns of pregnancy complications or adverse fetal outcomes were observed in the VAERS reports on pregnant women after being given the influenza vaccine. The CDC is also conducting studies on flu vaccine safety and pregnancy through the Vaccine Safety Datalink (VSD). The study's findings provide reassurance that the flu vaccine given to pregnant women during the first trimester of pregnancy does not increase the risk of spontaneous abortion (CDC 2013a).

A matched case-control study of 252 pregnant women who received TIV in the 6 months before delivery determined no adverse events after vaccination among pregnant women and no difference in pregnancy outcomes compared with 826 pregnant women who were not vaccinated (Munoz et al. 2005).

During the 2000–2003 seasons, an estimated 2 million pregnant women were immunized and only 20 adverse events among women who received TIV were reported to VAERS, including nine injection-site reactions and eight systemic reactions (e.g. fever, headache and myalgias). In addition, three miscarriages were reported but

these were not known to be causally related to the vaccination (Iscander et al. 2006). The rate of adverse events associated with TIV was similar to the rate of adverse events among pregnant women who received the pneumococcal polysaccharide vaccine in one small randomized controlled trial in Bangladesh and no severe adverse events were reported in any study group (Zaman et al. 2008). A recent international review of data on the safety of TIV concluded that no evidence exists to suggest harm to the fetus (Mak et al. 2008). There was no increased risk of cesarean section in vaccinated women and no increased risk of complications during pregnancy (Zaman et al. 2008; Munoz et al. 2005; Black et al. 2004).

2.3 Effectiveness of the Influenza Vaccination in Pregnant Women

Pregnant women have protective levels of specific anti-influenza antibodies after immunization (Munoz et al. 2005; Sumaya and Gibbs 1979). The passive transfer of anti-influenza antibodies that might pass the protection from vaccinated women on neonates has also been reported (Steinhoff et al. 2010; Englund et al. 1993; Sumaya and Gibbs 1979). The degree and duration of protection is directly dependent on the mother's influenza antibody titers and placental transfer efficacy, essentially defined by the time elapsed between immunization and delivery. The duration of passively acquired antibodies in infants depends on the initial cord concentration and is probably less than 6 months (Irving et al. 2000). Puck et al. (1980) reported a correlation between the level of cord blood influenza antibodies and the time of culture-documented influenza infection, showing that infants with high levels of influenza antibodies saw a delay in influenza infection.

Poehling et al. (2011) reported that hospitalized infants whose mothers received influenza vaccine during pregnancy were 45–48 % less likely to have laboratory-confirmed influenza during their first influenza season compared with infants of unvaccinated mothers. A prospective observational study among native Americans in

2002–2005 found that infants of immunized mothers had a 41 % decrease in the risk of laboratory-confirmed influenza infection and a 39 % reduction in the risk of hospitalization for an influenza-like illness (Eick et al. 2011).

One randomized controlled trial conducted in Bangladesh in which a flu vaccination was offered to pregnant women during the third trimester demonstrated a 29 % reduction in respiratory illness with fever among the mothers and a 36 % reduction among their infants during the first 6 months of life. In addition, infants born to vaccinated women had a 63 % reduction in laboratory-confirmed influenza illness during the first 6 months of life (Zaman et al. 2008).

Thompson et al. (2014) provided further substantial evidence on the effectiveness of the actual vaccination against influenza in pregnant women. Their study was based on a modern model of case-control study (so-called ‘test negative design’), which minimized systematic errors (selection errors) and therefore had a significant impact on the reliability of the results obtained. The results of the study, demonstrating that influenza vaccination in pregnant women reduced the risk of contracting influenza by 50 %, should be considered noteworthy, contributing to improved influenza vaccination in pregnant women.

2.4 Current Recommendations Regarding the Influenza Vaccination in Pregnant Women

In the United States and Canada recommendations for the influenza vaccination in pregnant women in the second and third trimester of pregnancy with the use of inactivated vaccines have been around for more than a decade. They were first published by the CDC in 1997, in 2004 these recommendations were expanded, recommending administration of the influenza vaccination not only in the second and third trimesters, but also in the first trimester of pregnancy (in both healthy women and those affected by chronic diseases which constitute a risk factor for the severe and complicated course of influenza) (CDC

2005). In 2005, the WHO recommended vaccination for all pregnant women in the epidemic season (WHO 2005). Vaccination against influenza in pregnant women has also been recommended by the American College of Obstetricians and Gynecologists (ACOG 2004). Pregnancy-related influenza vaccination recommendations were published during the 2012/2013 season in 23 European Union member states, with 13 countries recommending vaccination in any trimester and 10 countries recommending vaccination in the second or third trimester (ECDC 2013). Vaccination against influenza in pregnant women and postpartum women may be considered a way of protecting not only the mother but also the fetus, newborn and young infant (cocoon vaccination strategy). The only exception is the live attenuated vaccine administered intranasally, which is not recommended for use in pregnant women.

Despite official recommendations from experts, the level of vaccinations against influenza in the population of pregnant women is very low and varies from 2 to 20 % (CDC 2012). The low rate may stem from factors like: lack of physicians’ recommendation, unavailability of vaccine in gynecological–obstetric surgeries, insufficient knowledge about influenza and its complications in pregnant women, insufficient knowledge about the safety and efficacy of the influenza vaccination in pregnant women among medical staff, insufficient knowledge of current recommendations for the influenza vaccination in pregnant women, the common belief among patients that the flu is not a serious disease, the misconception that vaccination against influenza can cause the flu, no reimbursement for the influenza vaccination by insurers. Unfortunately, the results of published studies indicate insufficient knowledge among medical staff regarding influenza vaccination in pregnancy: 40 % of the surveyed doctors and nurses who deal with pregnant women did not know that such women are in a group at higher risk of the complicated and severe course of influenza. Only 65 % of the staff were aware of the recommendations regarding influenza vaccinations for that group of patients (Yudin et al. 2009; Panda et al. 2011; Tong et al. 2011). Therefore, it must be concluded

that intensive educational efforts should be directed at medical staff, especially those taking care of women of childbearing age, to improve the immunization rate against influenza in this patient population.

3 Pertussis

3.1 Epidemiology and Clinical Course of Pertussis in Pregnant Women and Infants

Pertussis is caused by *Bordetella pertussis* and is a highly contagious disease as illustrated by secondary transmission rates as high as 90 % among susceptible household contacts. Despite the availability of effective pertussis vaccines for more than 40 years, pertussis is still endemic in many countries. While developing countries may account for up to 90 % of global reported cases, pertussis remains a public health issue in many developed countries, with high childhood vaccination coverage, which experience a change in the epidemiology characterized by a shift of the incidence over the last decade to older age groups often associated with a resurgence of infantile pertussis (Hewlett and Edwards 2005). However, the incidence of pertussis among pregnant and non-pregnant women remains similar and the infection during pregnancy has not been shown to result in enhanced morbidity (Matlow et al. 2013). In limited case reports, no pertussis-related deaths were reported in pregnant women. Rare reports of fetal morbidity from mothers with pertussis include one case of extradural hematoma (Bonney et al. 2005) and another of laryngotracheal obstruction (Haugen et al. 2000), which apparently have not been related to the mother's pertussis infection.

In the pre-vaccination era, the majority of pertussis cases occurred in children who also represented the major source of transmission. As adults, their immunity was regularly boosted by recurrent exposure in the population. Protection was then passed from mothers on their infants through the placental transfer of antibodies. As maternal antibodies waned, infants became

vulnerable to infection. This pattern is still observed in developing countries where not all children are adequately immunized during infancy (Hewlett and Edwards 2005; Rothstein and Edwards 2005).

After the use of pertussis vaccine had been established, the newly immunized pediatric group became protected. As a result of the widespread vaccine use, the circulation of *B. pertussis* within the community has been reduced and adolescents and adults are less regularly boosted by natural infection. Therefore, an increasing proportion of cases occur in adolescents and adults, who lost their vaccine-induced immunity (waning after the age of 4–12 years) and in infants, who receive fewer passive antibodies than infants did in the pre-vaccination era and who are too young to be immunized (Hewlett and Edwards 2005; Rothstein and Edwards 2005).

Household contacts, especially mothers with older siblings, are responsible for up to 75 % of *B. pertussis* infections in infants (Wendelboe et al. 2007). Mothers with pertussis at the time of delivery have a high chance of infecting newborns. Nooitgedagt et al. (2009) found serological evidence of current or recent pertussis in 2.5 % and 3.8 % of pregnant women, respectively. The authors suggested an efficient placental transfer of existing maternal IgG pertactin (PT) antibodies in pregnant women. There is evidence that maternal antibodies offer protection against pertussis in neonates (Healy et al. 2004) and low IgG–PT levels correlate with increased susceptibility to pertussis (Storsaeter et al. 2003). However, depending on the time of the onset of the mother's infection, the neonate may not be protected by maternal antibodies acquired through placental transfer.

It must also be emphasized that unvaccinated or incompletely vaccinated infants aged under 6 months have the highest risk of severe and life-threatening complications and death. Recent outbreaks of pertussis in Costa Rica (Ulloa-Gutierrez and Avila-Aguero 2008), California (Roehr 2010), and Saskatchewan (Lawrence 2010) have also been linked with increased reports of infant deaths.

In 2012, the CDC received more than 41,000 reports of pertussis infection in the US with 18 deaths reported, most of them in unvaccinated infants younger than 3 months (CDC 2013b). In Canada, approximately 2,500 cases were reported in 2012 with one fatality in a 1-month old infant (Alphonso 2012). These epidemiological data support the need for immunization against pertussis in pregnant women and women of childbearing age.

3.2 Safety of Pertussis Vaccination in Pregnant Women

The FDA classifies the Tdap vaccine as a pregnancy category C drug because there is insufficient evidence on the safety of its administration during pregnancy. Data are also insufficient on concerns about blunting the infant's immune response with the combined diphtheria, tetanus toxoid, and acellular pertussis (DTaP) vaccines. Nevertheless, the ACIP concluded that vaccination of pregnant women (who had not previously received Tdap) late in the second trimester or third trimester is an acceptable risk for both mother and fetus (CDC 2013b).

The safety of the Tdap vaccine during pregnancy is quite well established. Data from the Vaccine Adverse Event Reporting System, Sanofi Pasteur, and GlaxoSmithKline pregnancy registries, along with minor studies, have not suggest any increased frequency or unusual patterns of adverse events in pregnant women who received Tdap. However, the ACIP's conclusion is that administration of Tdap after 20 weeks of gestation is preferable in order to minimize the risk of uncommon adverse events and the possibility that any spurious association between Tdap-related adverse events and another illness might appear causative (ACIP 2013).

Zheteyeva et al. (2012) did not identify any consistent patterns in maternal, infant, or fetal outcomes after administration of the Tdap vaccine in pregnant women. The authors searched the VVAERS for the years 2000–2005 and identified 132 reports of Tdap administered to pregnant women. There were no adverse

events found in 55 (42 %) of the reports, no maternal or infant deaths were reported. The most frequent pregnancy-specific adverse event was spontaneous abortion in 22 (16.7 %) reports, injection-site reactions were the most frequent non-pregnancy-specific effect in 6 (4.5 %) reports, and one report identified a major congenital anomaly (gastroschisis).

The ACIP (2013) concluded that experience with tetanus-toxoid containing vaccines suggests no excess risk of severe adverse events for women receiving Tdap with every pregnancy. However, there is a need for safety studies on adverse events when Tdap is given during subsequent pregnancies.

3.3 Effectiveness of Pertussis Vaccination in Pregnant Women

Maternal pertussis immunization with Tdap vaccines seems more effective than postpartum vaccination of infant's close contacts. The cocoon strategy of pertussis immunization has been recommended in France and Germany, but there has been little compliance with the recommendation (Matlow et al. 2013). In Costa Rica, where the strategy was more aggressively implemented, infant deaths from pertussis decreased but it was unclear whether that was due to the effect of the immunization strategy or the natural waning of the outbreak (Ulloa-Gutierrez and Avila-Aguero 2008). A pilot project in Houston to immunize postpartum women before they left hospital was successful but was very resource-consuming (Healy et al. 2011).

For the 2011 ACIP recommendations, a decision analysis model was developed to assess the impact and cost effectiveness of the Tdap vaccination during pregnancy compared with vaccination immediately postpartum. The model showed that Tdap vaccination during pregnancy would prevent more infant cases, hospitalizations, and deaths compared with the postpartum dose. Based on the mathematical model, the Tdap vaccination during pregnancy might prevent 906 (range: 595–1,418) infant cases, 462 (range: 261–736) hospitalizations, and nine (range: 4–17)

deaths; a postpartum dose might prevent 549 (range: 361–860) infant cases, 219 (range: 124–349) hospitalizations and three (range: 1–6) deaths (ACIP 2013).

In a 2011 study, newborns whose mothers received Tdap during pregnancy were significantly more likely to have protective antibodies against pertussis than newborns whose mothers did not receive Tdap during pregnancy (Gall et al. 2011).

3.4 Current Recommendations Regarding Pertussis Vaccination in Pregnant Women

In January of 2013, the ACIP (2013) released a revised adult immunization schedule and recommended administering a dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) to all women during each pregnancy, regardless of their immunization history and stating that the optimal time for Tdap administration is between 27 and 36 weeks of gestation, although Tdap may be given at any time during pregnancy. It is worth noting that after receiving Tdap, a minimum of 2 weeks is required for a maximum immune response to the vaccine's antigens (Halperin et al. 2011; Kirkland et al. 2009) and the active transport of maternal immunoglobulin G does not take place in great quantities before the 30th week of gestation (Englund 2007). Additionally, new data indicate that maternal antipertussis antibodies are short-lived; therefore, the Tdap vaccination in one pregnancy will not provide high levels of antibodies to protect newborns during subsequent pregnancies (Healy et al. 2013). That is a change from the 2008 and 2011 recommendations, which advised that only women who had never received Tdap or those for whom it was 10 or more years since the previous boosters should get a dose of Tdap during pregnancy (ACIP 2008, 2011). Both sets of recommendations advised that a dose of Tdap be administered immediately after delivery if a woman did not receive the vaccine during pregnancy. The ACOG Committee on Obstetric Practice supports the 2013 revised ACIP

recommendations on the use of the Tdap vaccine during pregnancy (ACOG 2013).

The importance of vaccinating during each pregnancy is emphasized by the case of a 40-day old baby who died from pertussis; the baby's mother had received a postpartum Tdap dose 2 years earlier, but she developed a coughing illness 1 week before delivery (Matlow et al. 2013). Since the 'cocoon' method of vaccinating parents and all close contacts immediately after delivery has been shown ineffective and resource-heavy, Tdap vaccination for pregnant women might be a more feasible option for reducing pertussis transmission to unvaccinated newborns (ACIP 2012; Matlow et al. 2013).

The recommendation to vaccinate during each pregnancy is based on considerations of high pertussis rates, low vaccination rates in pregnant women, and hesitancy among health care providers to vaccinate when the mother's Tdap history is unknown (Matlow et al. 2013). Since the 2011 ACIP vaccination recommendations, the uptake of Tdap among pregnant women remains low. A survey of 1,231 women estimated that only 2.6 % of them received Tdap during their last pregnancy (ACIP 2013). The pertussis vaccination coverage rate among Korean women is even lower, amounting to 0.8 % (Seon et al. 2013). A low Tdap vaccine coverage among pregnant women is a result of lack of awareness among both patients and medical professionals. It should be pointed out that 80 % of patients would agree to the pertussis vaccination during pregnancy if that were recommended by an obstetrician-gynecologist (Varan et al. 2014), which underscores the role of medical professionals in the promotion of vaccinations.

4 Conclusions

Immunization during pregnancy is a well-established method for providing protection for both the mother and the newborn infant. Maternal vaccinations with Tdap and trivalent inactivated influenza vaccines have been shown

to be immunogenic and safe. Promoting patients' awareness about pertussis and influenza diseases and vaccine effectiveness, and encouraging the medical staff to recommend vaccination ought to increase the rate of vaccinated pregnant women and to reduce the risk of infections.

Conflicts of Interest Authors declare no conflict of interests in relation to this article.

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