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Chorioamnionitis Following Vaccination in the Vaccine Adverse Event Reporting System

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Abstract

Background: In October 2012, the Advisory Committee on Immunization Practices (ACIP) recommended a dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) during each pregnancy, irrespective of the patient's prior history of receiving Tdap. A retrospective cohort study to assess the safety of Tdap vaccination in pregnant women in two Vaccine Safety Datalink (VSD) sites during 2010-2012 found a small but statistically significant increased risk of chorioamnionitis.

Objective: We conducted a review of the VAERS database to describe reports of chorioamnionitis following receipt of any vaccines.

Methods: We searched the VAERS database for reports of chorioamnionitis after any vaccine in the United States during the period from July 1, 1990 through February 2, 2014.

Results: VAERS received 31 reports of chorioamnionitis out of 3,389 pregnancy reports. The three most common vaccines administered were 2009 H1N1 inactivated influenza, quadrivalent human papillomavirus (HPV4), and Tdap vaccines in 32%, 29% and 26% of reports, respectively. Fifty-eight percent of reports had at least one risk factor for chorioamnionitis. Chorioamnionitis was identified in 3 reports of spontaneous abortions and 6 stillbirths, 6 reports of preterm birth (two of whom died) and 16 reports of term birth; maternal outcomes included two reports of postpartum hemorrhage and one report of maternal admission to the intensive care unit. No maternal deaths were reported.

Conclusion: Chorioamnionitis was found to be uncommonly reported, representing 1% of pregnancy reports to VAERS. A majority of reports had at least one risk factor for chorioamnionitis.

Keywords

adverse event; chorioamnionitis; pregnancy; vaccine safety; surveillance; Tdap; HPV4; 2009 H1N1 inactivated influenza vaccine

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Introduction

Tetanus, diphtheria, and acellular pertussis vaccine (Tdap) was licensed by the Food and Drug Administration (FDA) in 2005 for booster immunization against tetanus, diphtheria, and pertussis for adolescents and adults and is available in the United States from two manufacturers: Adacel (Sanofi Pasteur, Swiftwater, PA) [1] and Boostrix (GlaxoSmithKline Biologicals, Rixensart, Belgium) [2]. Due to the serious and life-threatening complications of pertussis infection in infants less than 6 months, the Advisory Committee on Immunization Practices (ACIP) in June 2011 recommended using a single dose of Tdap for pregnant women who previously had not received Tdap in order to provide the young infant with maternal transplacental passive antibody protection against pertussis during the early postnatal months [4]. This recommendation was further modified in October 2012 to recommending a dose of Tdap during each pregnancy, irrespective of the patient's prior history of receiving Tdap [5]. To maximize maternal antibody response and passive antibody transfer to the infant, the optimal timing of administering Tdap was recommended to occur between 27 to 36 weeks of gestation, although it could be given at any time during pregnancy. The Centers for Disease Control and Prevention (CDC) implemented enhanced safety monitoring studies to look for any potential safety concerns with Tdap given during pregnancy. No unusual or unexpected pattern of maternal, fetal, or infant outcomes were found in reports of pregnant women who received Tdap vaccine before and after the routine Tdap recommendation in pregnancy and whose AEs were reported to the Vaccine Adverse Event Report System (VAERS), a national spontaneous reporting system for adverse events after vaccines [6,7]. A retrospective, observational, cohort study during 2010–2012 in two California Vaccine Safety Datalink (VSD) sites found no increased risk for adverse birth outcomes, including preterm birth, among pregnant women vaccinated with Tdap [9]. However, a small but statistically significant increased risk for chorioamnionitis (RR 1.19;95% CI, 1.13–1.26) after adjusting for maternal age and comorbidities, was found in pregnant women receiving Tdap, compared with unvaccinated pregnant women, although no adjustment for risk factors for chorioamnionitis was done. Although not meeting strict statistical criteria, another VSD study also found a slightly higher risk of chorioamnionitis among women vaccinated with influenza vaccine [8]. The clinical importance of of the chorioamnionitis findings in both studies is unclear.

Chorioamnionitis is a polymicrobial aerobic and anaerobic infection of the amniotic fluid, fetal membranes, placenta, and/or uterus which can affect 1–2% of term and 5–10% of preterm pregnancies [10,11]. Some recognized risk factors for chorioamnionitis include: longer duration of rupture of membranes; prolonged labor; nulliparity; African American ethnicity; internal monitoring of labor; multiple vaginal examinations; meconium-stained amniotic fluid; smoking, alcohol or drug abuse; immunocompromised states; epidural anesthesia; colonization with group B streptococcus (GBS); and bacterial vaginosis [10]. To further assess if choriamnionitis represented a safety concern following vaccination in pregnant women, we conducted a review of VAERS reports of chorioamnionitis.

Methods

VAERS is a national spontaneous reporting system co-administered by CDC and FDA [12]. Established in 1990, VAERS monitors vaccine safety and accepts adverse event (AE) reports following receipt of any US-licensed vaccine [13]. VAERS is not designed to assess causal associations between vaccines and AEs; its primary purpose is to detect potential vaccine safety concerns that may warrant further investigations in defined populations [14]. Reports of vaccination errors with no occurrence of an AE may also be reported (i.e., administration of live attenuated influenza vaccine to a pregnant woman) [15].VAERS accepts reports from healthcare providers, vaccine recipients, vaccine manufacturers, and others. Healthcare providers are required to report any AE designated on the VAERS Table of Reportable Events Following Vaccination [16] and those listed as contraindications in the package insert, and are also encouraged to report any AE they consider to be clinically significant, whether they believe it was caused by the vaccine or not. Manufacturers are required to report all AEs of which they become aware. The VAERS report form collects patients' demographic and past medical history as well as details of the AEs and information on vaccinations [17]. It does not specifically collect information on pregnancy status. AE signs and symptoms recorded in each VAERS report are coded using an internationally standardized terminology from the Medical Dictionary for Regulatory Activities (MedDRA) [18]. Each report can be coded with one or more MedDRA terms. Reports are also classified as serious based on the Code of Federal Regulations [19] if they contain information that the AE resulted in death, hospitalization, prolongation of hospitalization, life threatening illness, or resulted in a persistent or significant disability. Medical records are routinely requested for all serious VAERS reports except those submitted by the vaccine manufacturer.

We searched the VAERS database for reports of chorioamnionitis after any vaccine in the United States during the period from July 1, 1990 through February 2, 2014. We conducted an automated search using the following criteria: MedDRA Preferred Terms (PT) "chorioamnionitis," "amniotic cavity disorder," "funisitis," and "amniotic cavity infection"; and a text string search for the terms: "chorio," "amnio," and "funi". We reviewed all available reports and medical records and analyzed reports by demographic characteristics, frequencies of AEs, vaccines given, trimester of vaccination and other characteristics. The onset interval from vaccination to chorioamnionitis was calculated based on time to first symptoms and/or date of delivery. Based on information provided in the VAERS form and/or the medical records (if available), we classified chorioamnionitis reports into clinical, histological, or both [10]. Clinical chorioamnionitis was defined [10] as patients presenting with fever ≥38○C, and two or more of the following signs or symptoms: uterine tenderness, foul-smelling lochia, maternal tachycardia (>100 bpm), fetal tachycardia (>160 bpm), or maternal leukocytosis (WBC >16,000 cells/mm3). Histological chorioamnionitis were those reports with pathology findings describing polymorphonuclear leukocytes on microscopic examination of placenta and fetal membranes.

Gestational age at the time of vaccination and at the time of the AE was calculated based on the last menstrual period or estimated delivery date found in the VAERS report or medical records. If this information was not provided, we used other information available from the VAERS report or medical record indicative of gestational age (e.g., ultrasound report). We

used the following definition for trimesters: first (0–13 weeks), second (14–27 weeks), and third (28 or more weeks) [11]. Spontaneous abortion was defined as a fetal demise before 20 weeks gestation, stillbirth was defined as fetal demise at or after 20 weeks gestation, and preterm delivery was defined as a live birth before 37 weeks gestation [11]. Causality between vaccination and chorioamnionitis was not assessed. Characteristics of some of the chorioamnionitis reports after 2009 inactivated H1N1 influenza vaccine described in the current study were previously described [20].

Because VAERS is a routine, government-sponsored surveillance system that does not meet the definition of research, this investigation was not subject to institutional review board review nor informed consent requirements.

Results

During July 1, 1990 through February 2, 2014, among a total of 3,389 pregnancy reports VAERS received 841 US reports that met the specified search criteria for chorioamnionitis; 83 were duplicate reports. We reviewed the remaining 758 reports and 31 were found to be chorioamnionitis reports. Eighteen reports met criteria for clinical chorioamnionitis, 9 for histological, 3 for both, and one was undetermined. Nineteen of the 31 reports had medical records available to supplement information provided in the VAERS report. Table 1 shows characteristics of chorioamnionitis reports identified. The largest number of reports (10/31; 32.3%) was received during the 2009–2010 influenza season. The most common vaccines (90%) documented in chorioamnionitis reports were inactivated vaccines, and the three most common were: 2009 H1N1 inactivated influenza, quadrivalent human papillomavirus (HPV4), and Tdap vaccines in 32%, 29% and 26% of reports, respectively. Fifty-eight percent of reports had at least one risk factor for chorioamnionitis [10,21]. Seventy-four percent of reports had chorioamnionitis onset more than two weeks after vaccination (Table 1). 2009 H1N1 inactivated vaccines were administered in all reports with an onset interval less than 2 weeks.

Adverse pregnancy and neonatal outcomes among chorioamnionitis reports included the following: nine (29%) reports of fetal death (3 spontaneous abortions and 6 stillbirths); 22 live births (71%) which included 6 (19%) reports of preterm birth and 16 (52%) reports of term birth; two (6%) reports of postpartum hemorrhage and one (3%) report of maternal admission to the intensive care unit (ICU). No maternal deaths were reported. Among the six preterm births, two resulted in infant deaths, one occurring soon after birth and the second required admission to the neonatal intensive care unit (ICU) for prematurity, sepsis, nutritional and breathing support, with death occurring one month after delivery.

Discussion

In our review of chorioamnionitis reports in VAERS we found that this condition is an uncommon AE, observed in 1% of pregnancy reports submitted to VAERS. We found that almost 60% of women with chorioamnionitis in the VAERS reports had at least one risk factor for this condition. Reports of chorioamnionitis were fairly evenly distributed among 2009 inactivated H1N1, HPV4, Tdap, and the trivalent inactivated influenza (IIV3) vaccines,

which are the vaccines most commonly associated with reports in pregnant women in general (CDC, unpublished data). Reporting patterns and onset interval to chorioamnionitis were consistent with other AEs described among pregnant women receiving H1N1 at a time of stimulated AE reporting in VAERS [20].

Kharbanda et al [9] found a small increased risk of chorioamnionitis among women who received Tdap vaccine during pregnancy. Although chorioamnionitis is often found associated with preterm birth [10], in the study by Kharbanda et al, most of the women who had chorioamnionitis following Tdap vaccination did not have preterm births. In addition chart review was able to confirm only 50% of the chorioamnionitis diagnoses [9]. Chorioamnionitis has been described in a few other studies, but no statistically significant association has been observed with any vaccine. Although not meeting strict criteria for statistical significance, a VSD study of the 2002–2009 influenza seasons found a small increased risk of chorioamnionitis among women who received influenza vaccine [21]. In a combined report of studies in two managed care organizations, IIV3vaccination coverage among pregnant women was not significantly higher among vaccinated women with chorioamnionitis compared to controls [22]. A study using a passive surveillance system to monitor AEs after vaccination in Taiwan described two reports of chorioamnionitis among stillbirths from a total of 35 AEs in pregnant women vaccinated with 2009 H1N1 [23].

It is difficult to identify a biological mechanism for chorioamnionitis following vaccination. It has been hypothesized that inflammatory processes may contribute to certain maternal pregnancy outcomes such as gestational hypertension and preeclampsia [10]. It has also been shown that vaccination with IIV3 can elicit a measurable and variable inflammatory response in pregnant women [24]. However, this response is considered to be mild and transient and there is no evidence that such an inflammatory response leads to a medical condition or adverse event. Nevertheless, this is an area that may merit further research.

Our study had several limitations. VAERS is a passive surveillance system that may be prone to biased reporting (over- or underreporting) and inconsistency in the completeness and quality of reports [13]. Because VAERS accepts reports from any reporter, the information provided by individuals with little or no medical training, may adversely affect the quality of the report. Events that occur close to the time of vaccination are more likely to be reported. VAERS also generally cannot determine whether a vaccine caused an AE [13]. Stimulated reporting can occur after publicity around a potential AE. VAERS does not collect data on the number of individuals vaccinated therefore it is not possible to calculate the incidence or prevalence of AEs. Nonetheless, VAERS has been shown to be useful for detecting unexpected AEs or safety signals that may be further explored in other epidemiological studies [25].

In conclusion, over a period of 25 years few cases of chorioamnionitis following receipt of any vaccine were reported to VAERS. CDC and FDA will continue to regularly monitor the safety of Tdap and other vaccines given to pregnant women to ensure the safety of mother and infant.

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the centers for Disease Control and Prevention and Food and Drug Administration

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Table 1.

Characteristics of chorioamnionitis reports (N=31) in the Vaccine Adverse Event Reporting System (VAERS), July 1, 1990 - February 2, 2014

Characteristics	
Median age (range), years	29 (15 – 42)
Median onset interval (range), days	86 (0-635)[a]
	N (%)
Overall onset interval (intervals between vaccination and chorioamnionitis)	
0-1 day	2 (7)
2-14 days	5 (19)
>14 days	20 (74)
Age groups (in years)	
≤18 years	7 (23)
19 - 25 years	6 (19)
26 - 34 years	11 (35)
≥35 years	7 (23)
Trimester of vaccination (n = 27)	
First (0–13 weeks)	14 (45)
Second (14–27 weeks)	7 (23)
Third (≥28 weeks)	5 (16)
Risk factors for Chorioamnionitis (n = 31)	
No risk factors identified	13 (42)
At least one risk factor identified	18 (58)
Nulliparity	9
Preterm premature rupture of membranes	5
Prolonged labor	5
Lower genitourinary infections	2
Internal fetal monitoring	1
Type of vaccines administered	
Inactivated only	28 (90)
Live only	2 (6)
Both	1 (3)
Vaccines administered	
HPV4 only	8 (25.8)
2009 inactivated H1N1 only	7 (22.6)
Tdap only	5 (16.1)
2009 inactivated H1N1 + IIV3	3 (9.7)
IIV3 only	2 (6.4)
IIV3 + Tdap	2 (6.4)
HPV4 + Tdap	1 (3.2)
Hepatitis B vaccine + varicella + Td	1 (3.2)
MMR + VAR	1 (3.2)

Characteristics	
VAR only	1 (3.2)

[a]Twenty four reports (74%) had a median onset interval >14 days

HPV4: Human papillomavirus vaccine (quadrivalent)

Tdap: Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed

IIV3: Trivalent inactivated influenza vaccine

MMR: Measles, mumps, and rubella vaccine

VAR: Varicella vaccine