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Safety of Quadrivalent Human Papillomavirus Vaccine (Gardasil®) in Pregnancy: Review of Non-manufacturer reports in the Vaccine Adverse Event Reporting System, 2006 – 2013

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Abstract

Background: In 2006, quadrivalent human papillomavirus (HPV4; Gardasil, Merck & Co. Inc.) vaccine was licensed in the US for use in females aged 9 to 26 years. HPV4 is not recommended during pregnancy; however, inadvertent administration during pregnancy may occur.

Objectives: To evaluate and summarize reports to the Vaccine Adverse Event Reporting System (VAERS) in pregnant women who received HPV4 vaccine and assess for potentially concerning adverse events among non-manufacturer reports.

Methods: We searched the VAERS database for non-manufacturer reports of adverse events (AEs) in pregnant women who received HPV4 vaccine from 6/1/2006–12/31/2013. We conducted clinical review of reports and available medical records.

Results: We found 147 reports after HPV4 vaccine administered to pregnant women. The most frequent pregnancy-specific AE was spontaneous abortion in 15 (10.2%) reports, followed by elective terminations in 6 (4.1%). Maternal fever was the most frequent non-pregnancy-specific AE in 3 reports. Two reports of major birth defects were received. No maternal deaths were noted. One hundred-five (71.4%) reports did not describe an AE.

Conclusions: This review of VAERS non-manufacturer reports following vaccination with HPV4 in pregnancy did not find any unexpected patterns in maternal or fetal outcomes.

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Keywords

adverse events; epidemiology; quadrivalent human papillomavirus vaccine; pregnancy; surveillance; vaccine safety

Introduction

Quadrivalent human papillomavirus (HPV4; Gardasil, Merck & Co. Inc.) vaccine was licensed in June 2006 by the Food and Drug Administration (FDA) for use in females aged 9 to 26 years [1]. In 2007, the Advisory Committee on Immunization Practices (ACIP) recommended HPV4 for routine vaccination of girls aged 11 to 12 years, with catch-up vaccination for females aged 13 to 26 years who have not been previously vaccinated [2]. HPV4 is a pregnancy category B product [Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women;. animal reproduction studies are not always predictive of human response]. Given the limited safety data in pregnancy, HPV4 is not recommended for use in pregnant women [2], although no intervention is indicated if HPV4 vaccine is administered during pregnancy. Because catchup vaccination is recommended in women of reproductive age, the possibility of inadvertent exposure during pregnancy exists. As part of vaccine safety monitoring Merck established the Gardasil Pregnancy Registry during 2006 through 2012. No safety concerns were noted in this registry, which stopped enrolling patients by the end of 2012 [3]. To further evaluate the safety of HPV4 in pregnant women, we conducted a review of non-manufacturer reports to the Vaccine Adverse Event Reporting System (VAERS) of pregnant women who received HPV4 during June 2006 through December 2013. We excluded manufacturer reports from our analysis as their findings have already been reported [3].

Material and Methods

Data Sources

VAERS is a spontaneous reporting system co-administered by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) [4]. Established in 1990, VAERS accepts adverse event (AE) reports following receipt of any US-licensed vaccine. VAERS is not designed to assess causal associations between vaccines and AEs; its primary purpose is to detect potential vaccine safety signals that may need to be further investigated in more rigorous epidemiological studies [4,5]. VAERS reports may be submitted voluntarily by any health care provider or member of the public; vaccine manufacturers are required to report all AEs of which they become aware [4]. AE signs and symptoms recorded in each VAERS report are coded using an internationally standardized terminology from the Medical Dictionary for Regulatory Activities (MedDRA) [6]. Each report can be coded with one or more MedDRA terms. Reports are coded as serious based on the Code of Federal Regulations [7] if the AE resulted in death, hospitalization, prolongation of hospitalization, life-threatening illness, or persistent or significant disability. Reports describing maternal exposure during pregnancy with no adverse event may be reported. In this study the definition of serious was slightly modified and did not include

reports on hospitalizations for delivery (vaginal or via cesarean section) unless they required prolonged stay in a hospital due to delivery complications or post-partum conditions. Medical records are routinely requested for all serious VAERS reports except those submitted by the vaccine manufacturer.

We searched the VAERS database for non-manufacturer reports of pregnant women vaccinated in the United States with HPV4, with or without other vaccines, between June 1, 2006 and December 31, 2013. To find the reports we conducted an automated search using published criteria [8].

Clinical Reviews

CDC medical officers reviewed all US reports found in the VAERS database using an automated search to ascertain pregnancy status at time of vaccination, calculate gestational age and characterize AEs. Complex reports (e.g. major birth defects, preeclampsia) were reviewed by physicians with expertise in obstetrics and birth defects. If more than one AE was reported for the same person, we selected what we believed was the primary clinical event of concern. Non-pregnancy specific AEs were assigned to a clinical category [9]. Additionally, we abstracted information on vaccine brand name, maternal age, gestational age at the time of vaccination and outcome, concomitant vaccinations, pregnancy outcomes, and neonatal outcomes. Reports that indicated the reported subject was not pregnant or that HPV4 vaccine was administered prior to the last menstrual period were excluded. We also included reports on infants born to women vaccinated with HPV4 during pregnancy.

Gestational age at the time of vaccination and at the time of AE was calculated based on last menstrual period or estimated delivery date found in the VAERS report or medical record. We used the following definition for trimesters: first (0–13 weeks), second (14–27 weeks), and third (28+ weeks) [10]. Spontaneous abortion (SAB) was defined as a fetal demise prior to 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. Causality between reported AEs and HPV4 vaccine was not assessed.

Analysis

Frequencies and proportions of MedDRA terms and selected AEs were calculated using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Because VAERS is a routine, government-sponsored surveillance system that does not meet the definition of research, it is not subject to institutional review board review and informed consent requirements.

Results

From June 1, 2006 through December 31, 2013, VAERS received a total of 18,296 reports after HPV4 administration in females in the United States, 1,572 (0.1%) reports met criteria of pregnancy reports using the automated search. Of these, 1,188 were manufacturer reports which were excluded from further analysis. One hundred forty-five reports were submitted by healthcare providers, vaccinees and other individuals. Two reports described both

maternal and infant AEs in each report, which we treated separately; therefore, there were a total of 147 reports. Median maternal age was 17 years. In most (61;84.7%) of the reports, HPV4 was given during the first trimester of pregnancy. One hundred-five (71.4%) maternal reports did not describe any AEs and the reason for submission was vaccine exposure during pregnancy. No maternal or infant deaths were reported. The most frequent pregnancy-related AE was spontaneous abortion (SAB) described in 15 (10.2%) reports followed by elective termination in 6 (4.1%) reports (Table 1). The most frequent non-pregnancy-specific adverse event was fever (3), and there were two reports each of nausea/vomiting, and non-anaphylaxis allergic reactions. Seven reports described infant outcomes which included two birth defects (Table 1).

Discussion

In our analysis of non-manufacturer VAERS reports submitted by healthcare providers, vaccinees and other individuals administering the vaccine we did not find any concerning pattern of AEs. The majority (71%) of these non-manufacturer reports did not describe an AE. The most common pregnancy-specific outcome in our review was SAB in 15 (10.2%) reports. SAB was also the most common pregnancy-specific outcome reported to VAERS after trivalent inactivated influenza (TIV), influenza A (H1N1) 2009 monovalent vaccine, and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine, all of which are recommended during pregnancy [8,11,12]. SAB is a relatively common event that occurs in about 15–20% of all pregnancies [13].

A pregnancy registry was established shortly after FDA licensed Gardasil® in 2006 to monitor adverse events in pregnant women inadvertently exposed to HPV4 [3]. Enrollment in the registry was discontinued on December 31, 2012 because it fulfilled its regulatory obligation with FDA. Analysis of prospective reports (pregnant women enrolled before the outcome was known) in the registry was found to be re-assuring: the rates of spontaneous abortion, fetal death, and major birth defects were comparable to background rates for these events [14–16]. Although VAERS has received reports from this pregnancy registry we did not include those reports in our analysis since 908 (32%) of 2,802 total registry reports [15] were received by VAERS and the information from these limited number of reports may not reflect the true safety profile of the registry.

Two major birth defects were noted in our review: one report of an infant born without both lower limbs whose mother had also received Hepatitis A vaccine during her pregnancy [17]. A second report involved an infant born with total anomalous pulmonary venous return who was also exposed to Varicella vaccine in utero. The infant had surgery at 4 weeks of age to repair this defect. No further information was provided.

Among non-pregnancy specific AEs, conditions such as nausea and/or vomiting, and fever were mostly reported. These are relatively common conditions during pregnancy. Nausea and/or vomiting can affect as many as three-fourths of pregnant women, mainly during the first half of the pregnancy [10].

Although HPV4 is not recommended in pregnancy there are some limited data on its safety in pregnant women. A pooled analysis of five randomized clinical trials during which some women were inadvertently vaccinated with HPV4 while pregnant found no safety pattern of concern [18]. In this pooled analysis, 1,796 HPV4 vaccine and 1,824 placebo recipients became pregnant. No significant differences were noted overall for the proportions of pregnancies resulting in live births, fetal loss, or spontaneous abortion. The rate of congenital anomalies among HPV4 recipients (2.1%) was not statistically higher than that found for the placebo group (1.4%).

As a national surveillance system, VAERS may be used to detect signals of potential vaccine safety concerns, which can be further explored in carefully designed epidemiological studies. VAERS has inherent limitations of all passive surveillance systems including under or over-reporting, reporting biases, and inconsistency in quality of reports. Events from other studies or systems may be reported to VAERS and may confound certain safety findings. VAERS does not collect data on the number of pregnant women vaccinated, therefore it is not possible to directly calculate incidence/prevalence or reporting rates of AEs. Events that occur temporally closer to the time of vaccination are more likely to be reported to VAERS [4]; conversely, events diagnosed months after the vaccination (e.g., birth defects) may be underreported. Therefore, VAERS data must be interpreted with caution and cannot generally be used to assess causality.

The burden and cost of HPV-associated disease and cancer remain an important public health problem. Monitoring the safety of HPV vaccine is an important part of the HPV vaccination program [19].

Although HPV4 is not recommended in pregnant women, inadvertent exposure to vaccine during pregnancy may occur since this vaccine is routinely recommended in women 11–12 years and for catch-up vaccination in women aged 13 – 26 years, a period when many women initiate sexual activity [2]. This review of VAERS reports comprising more than 6 years of monitoring found no safety concern among pregnant women or their infants who received this vaccine during pregnancy. Findings of this review will serve as a baseline for future efforts to monitor the safety of HPV4 vaccine in VAERS which is particularly relevant now that the Gardasil pregnancy registry has been discontinued.

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Table 1.

Reported adverse events[a] in pregnant women and their infants following receipt of Quadrivalent human papillomavirus (HPV4) vaccine, Vaccine Adverse Event Reporting System (VAERS), non-manufacturer reports, January 1, 2005 through December 31, 2012 (N=147)

Adverse Events	N	%
Pregnancy-specific AEs[†]		
Spontaneous abortion	15	10.2
Elective termination	6	4.1
Oligohydramnios	1	0.7
Stillbirth	1	0.7
Therapeutic abortion	1	0.7
Abortion (unspecified)	1	0.7
Breech presentation	1	0.7
Vaginal bleeding	1	0.7
Total	27	18.4
Non-pregnancy specific outcomes		
Fever	3	2.0
Nausea with/without vomiting	2	1.4
Non-anaphylaxis allergic reactions	2	1.4
Syncope	1	0.7
Dyspnea, abdominal pain, pruritus	1	0.7
Injured arm	1	0.7
Total	10	6.8
Infant/neonatal outcomes		
Absence of lower extremities[b]	1	0.7
Total anomalous pulmonary venous return[c]	1	0.7
Test positive for Down's syndrome	1	0.7
Right testicular torsion in newborn	1	0.7
Upper respiratory infection (at 4 months)	1	0.7
Jaundice, gastroenteritis (at 5 months)	1	0.7
Respiratory problems/fluid in lungs[d]	1	0.7
Total	7	4.8
No Adverse Event Reported	105	71.4

[a]Adverse events are based on primary reported diagnosis identified during clinical review. Maternal and infant outcomes in 2 reports were treated as separate reports

[b,c]Major birth defects;

[b]gestational age at vaccination was 4 weeks;

[c]gestational age at vaccination was 5 weeks

[d]Required hospitalization in the neonatal intensive care unit

† Defined as adverse events that can only occur in a pregnant woman