OBSTETRICS

Reports to the Vaccine Adverse Event Reporting System after hepatitis A and hepatitis AB vaccines in pregnant women

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OBJECTIVE: To characterize adverse events (AEs) after hepatitis A vaccines (Hep A) and hepatitis A and hepatitis B combination vaccine (Hep AB) in pregnant women reported to the Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting surveillance system.

STUDY DESIGN: We searched VAERS for AEs reports in pregnant women who received Hep A or Hep AB from Jan. 1, 1996-April 5, 2013. Clinicians reviewed all reports and available medical records.

RESULTS: VAERS received 139 reports of AEs in pregnant women; 7 (5.0%) were serious; no maternal or infant deaths were identified. Sixty-five (46.8%) did not describe any AEs. For those women whose gestational age was available, most were vaccinated during the first trimester, 50/60 (83.3%) for Hep A and 18/21 (85.7%) for Hep AB. The most common pregnancy-specific outcomes following Hep A or Hep AB vaccinations were spontaneous abortion in 15 (10.8%) reports, elective termination in 10 (7.2%), and preterm delivery in 7 (5.0%) reports. The most common nonpregnancy specific outcome was urinary tract infection and nausea/vomiting with 3 (2.2%) reports each. One case of amelia of the lower extremities was reported in an infant following maternal Hep A immunization.

CONCLUSION: This review of VAERS reports did not identify any concerning pattern of AEs in pregnant women or their infants following maternal Hep A or Hep AB immunizations during pregnancy.

Key words: hepatitis A hepatitis B combined vaccine, hepatitis A vaccine, pregnancy, surveillance, vaccine safety

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The first inactivated hepatitis A vaccines (Hep A) (Havrix; GlaxoSmithKline Biologicals, Rixensart, Belgium; Vaqta; Merck & Co., Whitehouse Station, NJ) and hepatitis A and hepatitis B combination vaccine (Hep AB) (Twinrix; GlaxoSmithKline Biologicals) were licensed for use in the US in 1995, 1996, and 2001, respectively.[1] Hep A is routinely recommended for young children and is also recommended for certain groups at increased risk for Hep A infection, including vaccination during community outbreaks.[1] Hep AB is indicated for vaccination of persons aged ≥18 years against Hep AB. Any person in this age group having an indication for both Hep AB vaccination can be administered Twinrix.[2] The Advisory Committee on Immunization Practices has assessed that no evidence exists to suggest that administration of inactivated vaccines during pregnancy is associated with a risk to the fetus.[3] The Advisory Committee on Immunization Practices recommends that Hep A should be considered for pregnant women at increased risk for this infection; similarly Hep B is recommended for pregnant women who have an indication for Hep B vaccination.[1,3] Pregnancy is not a contraindication to vaccination with Hep B vaccine. Although few studies have assessed the safety of Hep B vaccine during pregnancy the limited data available suggests that developing fetuses are not at risk for adverse events (AEs) when Hep B vaccine is administered to pregnant women.[4-6]

Currently, there are limited data on the safety of Hep A or Hep AB in pregnancy. Although there is a pregnancy registry maintained by GlaxoSmithKline to collect data on pregnancy and infant outcomes following vaccination with Hep AB,[7] no data has yet been published. To assess the safety of Hep A or Hep AB in pregnant women and their infants exposed during pregnancy, we conducted a review of reports to the Vaccine Adverse Event Reporting System (VAERS) during 1996-2013.

Materials and Methods

Data sources

VAERS is a spontaneous reporting system coadministered by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA).[8] Established in 1990, VAERS monitors vaccine safety and accepts AE reports following receipt of any US-licensed vaccine.[9] 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.[10] VAERS accepts reports from vaccine

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manufacturers, health care providers, vaccine recipients, and others. Healthcare providers are required to report any AE from the reportable events table[11] and are encouraged to report any AE they consider to be clinical significant, whether they believe it was caused by the vaccine. 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.[12] It does not specifically collect information on pregnancy status. AE signs and symptoms recorded in each VAERS report are coded by trained staff using an internationally standardized terminology from the Medical Dictionary for Regulatory Activities (MedDRA).[13] Each report can be coded with 1 or more MedDRA terms. Reports are also classified as serious based on the Code of Federal Regulations[14] 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. For this study, we excluded reports on routine hospitalizations for delivery from the "serious" category. Medical records are routinely requested for all serious VAERS reports except those submitted by the vaccine manufacturer. Some reports only describe exposure to vaccine during pregnancy without an AE.

We searched the VAERS database for reports involving pregnant women who had received Hep A or Hep AB in the United States, with or without other vaccines, during Jan. 1, 1996, through April 5, 2013. We conducted an automated search using the following criteria: MedDRA terms in System Organ Classes (SOC) "Pregnancy, Puerperium, and Perinatal Conditions" and "Congenital, Familial, and Genetic Disorders", the MedDRA terms "Drug Exposure during Pregnancy" or "Maternal Exposure During Pregnancy", and a text string search for the term "preg" in the report. Reports of pregnant women or their infants exposed in utero that had at least 1 of these criteria were included in the dataset for further evaluation.

Clinical reviews

CDC and FDA medical officers reviewed all US reports identified in the VAERS database using the automated search to confirm pregnancy status at time of vaccination, calculate estimated gestational age and characterize AEs. For each report we assigned a primary diagnosis. If more than 1 AE was reported for the same individual, we assigned the diagnosis based on what we believed was the primary clinical event of concern and assumed the primary event was a pregnancy-specific event unless information suggested otherwise. Complex reports (eg, major birth defect, preeclampsia) were reviewed by physicians on the study team with expertise in obstetrics and neonatology. For purposes of AE description, if a VAERS report described AEs in more than 1 person (eg, mother and exposed infant), we treated each person as a separate report. Reports that indicated the reported subject was not pregnant or that Hep A or Hep AB vaccine was administered before the last menstrual period were excluded.

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 (eg, ultrasound report, reporter's note, hospital records). We used the following definition for trimesters: first (0-13 weeks), second (14-27 weeks), and third (28+ weeks).[15] Spontaneous abortion (SAB) 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. Causality between reported AEs and Hep A or Hep AB was not assessed.

Proportional reporting ratios

To assess for disproportionately higher reporting of AEs after Hep A or Hep AB administered to pregnant women, we calculated proportional reporting ratios (PRRs)[16,17] compared with inactivated influenza vaccines, which have been determined to have an acceptable safety profile in pregnancy.[18,19] We combined Hep A and Hep AB vaccine reports and compared proportions of MedDRA terms after these vaccines with proportions of the same MedDRA terms after trivalent inactivated influenza vaccines and influenza A (H1N1) 2009 monovalent vaccine (used during the 2009-10 pandemic) administered without Hep A or Hep AB vaccine to pregnant women. For trivalent inactivated influenza vaccines and monovalent vaccines administered in pregnancy, we used VAERS reports analyzed in previous studies[18,19] as well as reports received during 2010-2013. We excluded reports from analysis if no AE was reported or if live vaccines (contraindicated during pregnancy[3]), or anthrax vaccine (not recommended during pregnancy[20]) were administered concomitantly. We identified MedDRA terms with disproportionately higher reporting after Hep A or Hep AB by applying Evans' criteria (PRR $\geq$2.0, Yates χ^2 $\geq$4.0, and number of reports $\geq$3 in reports of HEP A or Hep AB).[16] Clinical reviews were conducted for all MedDRA terms with a PRR $\geq$2.0.

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 Jan. 1, 1996 through April 5, 2013, VAERS received a total of 21,606 US reports after Hep A or Hep AB vaccination; 134 reports (0.6%) met criteria of pregnancy reports using the automated search and manual review (102 reports after Hep A and 32 after Hep AB). Five reports described maternal and infant AEs in each report, which we treated separately; therefore, there were a total of 139 reports. No maternal or infant deaths were reported.

Characteristics of VAERS reports are presented in Table 1. Sixty-five Hep A and Hep AB reports (47%) did not describe