Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Assessing the safety of hepatitis B vaccination during pregnancy in the Vaccine Adverse Event Reporting System (VAERS), 1990–2016

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ARTICLE INFO

Article history:
Received 25 June 2017
Received in revised form 13 November 2017
Accepted 14 November 2017
Available online xxxx

Keywords:
Adverse event
Epidemiology
Hepatitis B vaccine
Surveillance
Vaccine safety

ABSTRACT

Background: The safety of hepatitis B vaccination during pregnancy has not been well studied.
Objective: We characterized adverse events (AEs) after hepatitis B vaccination of pregnant women reported to the Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting surveillance system.
Methods: We searched VAERS for AEs reports involving pregnant women who received hepatitis B vaccine from January 1, 1990–June 30, 2016. All reports and available medical records were reviewed by physicians. Observed AEs were compared to expected AEs and known rates of pregnancy outcomes to assess for any unexpected safety concern.
Results: We found 192 reports involving pregnant women following hepatitis B vaccination of which 110 (57.3%) described AEs; 12 (6.3%) were classified as serious; one newborn death was identified in a severely premature delivery, and there were no maternal deaths. Eighty-two (42.7%) reports did not describe any AEs. Among pregnancies for which gestational age was reported, most women were vaccinated during the first trimester, 86/115 (74.7%). Among reports describing an AE, the most common pregnancy-specific outcomes included spontaneous abortion in 23 reports, preterm delivery in 7 reports, and elective termination in 5 reports. The most common non-pregnancy specific outcomes were general disorders and administration site conditions, such as injection site and systemic reactions, in 21 reports. Among 22 reports describing an AE among infants born to women vaccinated during pregnancy, 5 described major birth defects each affecting different organ systems.
Conclusion: Our analysis of VAERS reports involving hepatitis B vaccination during pregnancy did not identify any new or unexpected safety concerns.

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1. Introduction

Five hepatitis B vaccines are licensed in the United States: two single antigen vaccines, Recombivax HB® (Merck & Co., Inc., Whitehouse Station, New Jersey) and Engerix-B® (GlaxoSmithKline Biologicals, Rixensart, Belgium) [1,2], and three combination vaccines, Twinrix® [HepA-HepB] (GlaxoSmithKline Biologicals, Rixensart, Belgium) [3], Comvax® [Hib-HepB] (Merck & Co., Inc., Whitehouse Station, New Jersey) and Pediarix® [DTaP-HepB-IPV] (GlaxoSmithKline Biologicals, Rixensart, Belgium) [4,5]. Comvax® and Pediarix® are indicated only for children [6].

The recommendations of the Advisory Committee on Immunization Practices (ACIP) for hepatitis B vaccination during pregnancy state that this vaccine is not contraindicated during pregnancy. The indications for hepatitis B vaccination are also applicable to pregnant women and these include: universal hepatitis B vaccination for all unvaccinated adults in settings in which a high proportion of adults have risks for hepatitis B infection (e.g., sexually transmitted disease/human immunodeficiency virus testing and treatment facilities). In other primary care and specialty medical settings in which adults at risk for hepatitis B virus (HBV) infection receive care, health-care providers should inform all patients about the health benefits of vaccination, including risks for HBV infection and persons for whom vaccination is recommended, and vaccinate adults who report risks for HBV infection and any adults requesting protection from HBV infection [6,7].

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https://doi.org/10.1016/j.vaccine.2017.11.039
0264-410X/Published by Elsevier Ltd.

Hepatitis B vaccines have a well-established safety record among infants, children, adolescents, and adults [6,7]. The most frequently reported adverse events (AEs) are pain at the injection site and fever [6]. Pregnancy is not a contraindication to vaccination [7]; however, there are limited data on the safety of Hepatitis B during pregnancy [8]. A review in the Vaccine Adverse Event Reporting System (VAERS) assessed the safety of Twinrix [9] in pregnancy and did not find any disproportionate reporting or unexpected AEs [9]. For the other hepatitis B vaccines, we are not aware of safety studies among pregnant women. To address this knowledge gap, we conducted a review of VAERS reports involving pregnant women for hepatitis B vaccines approved for use in women of reproductive age.

2. Materials and methods

2.1. Vaccine Adverse Events Reporting System (VAERS)

VAERS is a national vaccine safety surveillance system, co-administered by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). It receives spontaneous (passive) reports of AEs following vaccination [10] submitted by healthcare providers, vaccine recipients, vaccine manufacturers, and other reporters. The VAERS report form collects information on the age, sex, vaccines administered, AE experienced, medical conditions at the time of vaccination and medical history. Signs and symptoms in VAERS reports are coded using Medical Dictionary for Regulatory Activities (MedDRA) terms, a clinically validated, internationally standardized medical terminology [11]. AEs in a VAERS report may be assigned one or more MedDRA preferred terms (PT). A MedDRA PT is a distinct descriptor for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, or medical, social, or family history characteristic [12]. MedDRA PTs are not medically confirmed diagnoses. System Organ Class (SOC) is the highest level of the MedDRA hierarchy that provides the broadest classification for AEs [9] (e.g. nervous system disorders). The definition of serious reports, based on the Code of Federal Regulations, is a report that includes one of the following: death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability [13]. This definition is based on the reporter's assessment of the condition, and for pregnancy reports, it often is based on conditions in the mother and not necessarily the fetus or live born infant (e.g., a report of spontaneous abortion may not be classified as serious if it was not life threatening to the woman or did not result in hospitalization). Medical records are routinely requested for reports classified as serious and reported by non-manufacturers. Reports describing only a vaccination error (e.g., vaccine administered to a person who is of an age not recommended for vaccination) and no report of an AE are assigned appropriate MedDRA PTs for medication errors.

We searched the VAERS database for reports of pregnant women vaccinated in the United States with hepatitis B vaccine from January 1, 1990 through June 30, 2016. To identify pregnancy reports, we conducted an automated search using the following three approaches: i) MedDRA terms in two system organ classes (SOC), "Pregnancy, Puerperium, and Perinatal Conditions" and "Congenital, Familial, and Genetic Disorders"; ii) MedDRA PTs "Drug exposure during pregnancy", "Maternal exposure during pregnancy", and "Exposure during pregnancy"; and iii) a text string search for the term "preg" in the report. Reports that met at least one of these criteria were included for analysis. We included reports of women vaccinated with hepatitis B vaccine during pregnancy where the primary AE being reported (or the focus of the report) was in the live born infant.

2.2. Clinical reviews

Physicians from the FDA (FB) and CDC (YZ, PM, MC) reviewed all United States reports identified through the automated search of the VAERS database to ascertain pregnancy status at time of vaccination, calculate gestational age, and characterize AEs. For each report, a primary diagnosis was assigned. If more than one AE was reported for the same individual, we assigned the diagnosis based on what we believed was the primary health event of concern, and classified the pregnancy-specific event as the primary event unless information suggested otherwise. Non-pregnancy-specific medical conditions were categorized by SOC. We excluded reports where upon review we determined the subject was not pregnant or that hepatitis B vaccine was administered prior to the last menstrual period. Gestational age at the time of vaccination and at the time of the AE were calculated based on: (1) clinical determination by the health care provider as stated in the report, (2) earliest ultrasound assessment (if the former was not available), or (3) last menstrual period, estimated delivery date, or estimated date of conception (if the first two options were unavailable) in the VAERS report and/or medical records. We used the following definition for trimesters: first (0–13 weeks), second (14–27 weeks), and third ($\geq$28 weeks). Spontaneous abortion (SAB) was defined as fetal demise <20 weeks gestation; stillbirth was defined as fetal demise $\geq$20 weeks gestation, and preterm delivery was defined as a live birth <37 weeks gestation [14]. Observed AEs were compared to expected AEs and known rates of pregnancy outcomes to assess for any unexpected safety concern. Expected AEs were those deemed as such by subject matter experts [YZ, FB], and published sources [14,15].

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 or informed consent requirements.

3. Results

From January 1, 1990 through June 30, 2016, VAERS received 192 reports involving hepatitis B vaccination of pregnant women. A total of 110 reports described AEs; the remaining 82 (42.7%) reports did not described an AE; in 48 of these 82 reports a live vaccine (contraindicated during pregnancy) was concomitantly administered and in one report the hepatitis B vaccine was given intravenously. A total of 12 (6.3%) reports were classified as serious. Characteristics of the pregnant women and AEs reported are shown in Tables 1 and 2. Most (191; 99%) reports involved administration of a single antigen Hepatitis B vaccine. In 93 (48.4%) hepatitis B vaccine was given concurrently with other vaccines; 39 (43%) with known age were children and adolescents The top three vaccines given concurrently with Hepatitis B vaccine were varicella, measles, mumps, rubella, and hepatitis A vaccines, respectively. Vaccine manufacturers submitted the most reports (83, 43.2%) followed by healthcare providers (43, 22.4%).

Among 115 (59.9%) reports where information on trimester of pregnancy when vaccinated was available, 86 (74.7%) stated that hepatitis B vaccine was received in the first trimester. A supplementary table shows the adverse events according to the trimester of vaccination. No maternal deaths were reported. One death in an infant of a woman vaccinated during pregnancy was reported; the child was born prematurely at 27 weeks gestation and died at 54 days of age. The infant presented with small perforations in the small intestine and had mild hyaline disease. The most common pregnancy-specific AEs were spontaneous abortion in 23 (20.9%) of 110 reports, followed by preterm delivery in 7 (6.4%) and elective termination of pregnancy in 5 (4.5%) reports. Circumstances

Please cite this article in press as: Moro PL et al. Assessing the safety of hepatitis B vaccination during pregnancy in the Vaccine Adverse Event Reporting System (VAERS), 1990–2016. Vaccine (2017), https://doi.org/10.1016/j.vaccine.2017.11.039