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Safety of inadvertent anthrax vaccination during pregnancy: An analysis of birth defects in the U.S. military population, 2003–2010

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ABSTRACT

Background: Anthrax vaccine adsorbed (AVA) vaccination is compulsory for United States military servicemembers with operational indicators. As the number of female military servicemembers has increased, so has the chance of inadvertent AVA vaccination during pregnancy. Building upon past analyses assessing AVA vaccination during pregnancy and birth defects risk, this study sought to determine if inadvertent AVA vaccination during pregnancy is significantly associated with risk of birth defects after adjusting for other potential risk factors.
Methods: The study population included 126,839 liveborn infants in the Department of Defense Birth and Infant Health Registry (2003–2010). Mothers were categorized by AVA vaccination exposure timing in relation to pregnancy. Infant medical records were assessed for birth defect diagnoses within the first year of life. Multivariable logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).
Results: Infants of first trimester AVA vaccinated mothers versus receipt at any other time point (OR, 1.10; 95% CI, 0.93–1.29) were not at higher odds of birth defects in adjusted models. Infants of mothers vaccinated prepregnancy versus postpregnancy had a 1.11 (95% CI, 1.01–1.22) higher odds of having a birth defect. Vaccination postpregnancy versus never vaccinated revealed a 10% lower odds of birth defects (OR, 0.90; 95% CI, 0.83–0.99).
Conclusions: No strong associations between inadvertent AVA vaccination during pregnancy and birth defects risk were observed. Marginal associations between prepregnancy vaccination or never vaccinated women and birth defects risk was observed when compared to postpregnancy vaccination. These findings may be due to self-selection and/or reverse causation bias when assessing comparisons with postpregnancy vaccination, and a "healthy worker" effect when assessing comparisons with women never vaccinated.

1. Introduction

Anthrax infection is caused by *Bacillus anthracis,* a zoonotic, gram-positive bacterium [1]. Humans may be infected through contact with infected animals or animal tissue, which occurs through inhalation, cutaneous contact, or ingestion of anthrax spores. Natural infection through contact with infected animals is rare in the United States (US), and the true threat that anthrax poses is its potential use as a bioweapon in bioterrorism [2]. Anthrax is an ideal pathogen for bioterrorism as its spores are highly stable, can remain viable for decades in the environment, and are easily aerosolized. Therefore, anthrax vaccine adsorbed (AVA) vaccination is compulsory for US military servicemembers with operational indicators, such as deployment to a high-risk location for 15 days or more, with pregnancy being one of few medical exemptions [3].

Licensed in the US in the early 1970s, AVA is a series of five intramuscularly administered doses (six subcutaneously administered doses prior to December 2008) and annual boosters to sustain protection [4]. The vaccine is made from cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *Bacillus anthracis*. The filtrate results in a mixture of proteins with the main component being protective antigen. As the number of female military servicemembers has increased [5], and since pregnancies are often not recognized until several weeks after conception, there is potential for inadvertent AVA vaccination during

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pregnancy. As an inactivated vaccine, AVA vaccination is not likely to be teratogenic; however, the potential adverse effects on the fetus from exposure to antibodies against protective antigen, or maternal adverse events related to vaccination, are unknown. There are no randomized clinical trials, due to the elevated risk of including pregnant women. Few observational studies assessing safety of AVA vaccination during pregnancy have been conducted, since administration to the general US population is rare [6,7]. Although the results of these studies have been reassuring they have been limited to small sample sizes, and replication of these findings in larger populations is needed.

Currently, the US Food and Drug Administration and the Advisory Committee on Immunization Practices do not recommend AVA vaccination during pregnancy based on preliminary findings utilizing the Department of Defense Birth and Infant Health Registry (Registry) [4,8]. The final published results, assessing the association between inadvertent AVA vaccination during pregnancy and birth defects risk in the Registry (1998–2004), showed an increased odds of birth defects among infants with mothers who were vaccinated in the first trimester of pregnancy in comparison to postpregnancy [Odds Ratio (OR): 1.20, 95% Confidence Interval (CI): 1.01–1.43] or never vaccinated mothers (OR: 1.20, 95% CI: 1.02, 1.42) [9]. Limitations of this previous study include a potential issue with vaccination data validity early in the study, as well as the use of less detailed *International Classification for Diseases,* Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes for determining the beginning date of each pregnancy that were in use at the time. Additionally, uncontrolled confounding by deployment status and lack of pregnancy recognition may have led to significant findings. As AVA is not recommended during pregnancy, pregnancy status at the time of vaccination was likely unrecognized in most cases, and other unaccounted-for high-risk behaviors associated with birth defects (*i.e.*, smoking and alcohol consumption) may have contributed to the results.

Due to the tenuous nature of the earlier findings, follow-up analyses using additional data from more recent years, updated algorithms for case definitions, and additional data on other potential risk factors were warranted. For instance, deployment status during pregnancy and administration of other potentially risky vaccinations during pregnancy, a proxy for lack of pregnancy recognition, were adjusted for in multivariable models to better assess the independent risk of AVA vaccination during pregnancy. We hypothesized that there would be no significant association between inadvertent AVA vaccination during pregnancy and risk of birth defects after adjusting for other potential risk factors.

2. Methods

2.1. Study population

The study population of interest included 128,989 liveborn infants of military mothers, captured in the Registry from 2003 through 2010. The Registry, maintained at the Naval Health Research Center, is a population-based cohort with the mission of providing ongoing birth and infant health surveillance among TRICARE beneficiaries [10]. TRICARE beneficiaries include military personnel, retirees, and their dependents. Briefly, the Registry was developed in 1998 and collects maternal and infant data from the Military Health System Data Repository and Defense Manpower Data Center. Same sex multiple gestations (*e.g.*, twins) are excluded from the Registry because of difficulties in differentiating between their medical records in early life. For the present study, infants of active duty, Reserve, and Guard mothers who served in the Army, Air Force, Navy, or Marines were included. Infants of mothers not present in the demographic data during the month of delivery were excluded (n = 2150). The final analytic population included 126,839 liveborn infants from the Registry. Approval for this study was obtained from the Naval Health Research Center's institutional review board, and collection of informed consent was waived in accordance with 32 CFR § 219.116(d).

Birth defects were defined by ICD-9-CM diagnostic codes captured on inpatient and outpatient administrative electronic medical records from civilian and military treatment facilities. National Birth Defects Prevention Network guidelines for defining and classifying birth defects by ICD-9-CM diagnostic codes, reported in the first year of life, were followed [11]. Infants were defined as a case if they were diagnosed with a birth defect on one inpatient record or two outpatient records on different days, within the first year of life.

2.2. AVA vaccination in relation to pregnancy

AVA vaccination was identified by reporting of administered vaccines in immunization records maintained by the Defense Manpower Data Center. Mothers were classified with respect to time of AVA vaccination in relation to pregnancy, as was done in the previous analysis [9]. Mothers were first categorized as ever or never vaccinated. Mothers who were ever vaccinated were further stratified by time of vaccination: prepregnancy [prior to last menstrual period (LMP)], first trimester [LMP – 13 weeks of estimated gestational age (EGA)], second or third trimester (greater than 13 weeks of EGA up until date of delivery), and postpregnancy (date of delivery or later). The AVA vaccination schedule includes administration of multiple vaccine doses (*i.e.*, up to six doses with annual boosters); therefore, it was possible for mothers to be included in more than one exposure category. To assure these categories were mutually exclusive, the exposure categories hypothesized to have higher risks of birth defects took precedence (*i.e.*, first trimester, followed by second / third trimester, prepregnancy, and postpregnancy vaccination).

2.3. Covariates

Infant covariates included in multivariable models were birth year, sex, and plurality (yes or no). Maternal age at delivery (<35 or ≥35 years of age), race/ethnicity (white, black, Hispanic, or other/unknown), marital status (married or not married), occupation (healthcare related, combat, or other category), military service branch (Army, Air Force, Navy, or Marines), rank (enlisted or officer), reserve status (active duty or activated Reserve/Guard), deployment during pregnancy (yes or no), amount of time deployed prior to LMP (in 60 day increments), and administration of other potentially risky vaccinations in the first trimester of pregnancy (yes or no) were also adjusted for as potential risk factors in multivariable models. Specifically, vaccinations for the following pathogens were defined as potentially risky: measles, mumps, rubella; tuberculosis; varicella; smallpox; influenza (intranasal administration only); poliovirus; rabies; yellow fever; meningococcal; human papillomavirus; herpes zoster; and adenovirus.

2.4. Statistical analysis

The study population was characterized using frequencies and percentages. Multivariable logistic regression, adjusting for potential confounders selected a priori (see above), was used to calculate ORs and 95% CIs for associations between AVA vaccination and birth defects risk. Analyses were conducted comparing the first trimester AVA vaccination group and mothers vaccinated at any other time point followed by multiple sensitivity analyses comparing each of the different vaccination exposure categories with prepregnancy, postpregnancy, and never vaccinated mothers. Indi-

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