Vaccine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Brief report

Analysis of pregnancy and infant health outcomes among women in the National Smallpox Vaccine in Pregnancy Registry who received Anthrax Vaccine Adsorbed

Ava Marie S. Conlin*, Anna T. Bukowinski, Gia R. Gumbs,
for the Department of Defense Birth and Infant Health Registry Team

Deployment Health Research Department, Naval Health Research Center, 140 Sylvester Road, San Diego, CA 92106, USA

ARTICLE INFO

Article history:
Received 7 February 2015
Received in revised form 23 April 2015
Accepted 21 May 2015
Available online xxx

Keywords:
Maternal exposure
Anthrax Vaccine Adsorbed (AVA)
Congenital abnormalities
Pregnancy outcome

ABSTRACT

The National Smallpox Vaccine in Pregnancy Registry (NSVIPR) actively follows women inadvertently vaccinated with smallpox vaccine during or shortly before pregnancy to evaluate their reproductive health outcomes. Approximately 65% of NSVIPR participants also inadvertently received Anthrax Vaccine Adsorbed (AVA) while pregnant, providing a ready opportunity to evaluate pregnancy and infant health outcomes among these women. AVA-exposed pregnancies were ascertained using NSVIPR and electronic healthcare data. Rates of pregnancy loss and infant health outcomes, including major birth defects, were compared between AVA-exposed and AVA-unexposed pregnancies. Analyses included AVA-exposed and AVA-unexposed pregnant women who also received smallpox vaccine 28 days prior to or during pregnancy. Rates of adverse outcomes among the AVA-exposed group were similar to or lower than expected when compared with published reference rates and the AVA-unexposed population. The findings provide reassurance of the safety of AVA when inadvertently received by a relatively young and healthy population during pregnancy.

1. Introduction

The US Department of Defense (DoD) is challenged with monitoring and protecting the health of its service members and their families. The compulsory smallpox vaccination policy, initiated in early 2003 [1], introduced a unique occupational exposure to a large population of reproductive-age service members. Aside from extremely rare cases of fetal vaccinia [2–6], documentation on the potential reproductive effects of smallpox vaccine is scant. The National Smallpox Vaccine in Pregnancy Registry (NSVIPR), managed by the DoD Birth and Infant Health Registry [7], closely follows women inadvertently vaccinated with smallpox vaccine within 28 days prior to or any time during pregnancy to evaluate their pregnancy outcomes [8]. Outcomes captured include pregnancy loss and infant health outcomes.

Approximately 65% of participants in the NSVIPR also inadvertently received Anthrax Vaccine Adsorbed (AVA) in pregnancy. The Food and Drug Administration currently indicates that AVA can cause fetal harm when administered to a pregnant woman; as such, it is not recommended for use in pregnancy unless risk of disease outweighs risk of vaccination [9]. Limited research exists, however, leading to concerns that women inadvertently vaccinated with AVA while pregnant may elect to terminate their pregnancy or suffer unnecessary concern should they choose to carry to term. Further research to support or refute the recommendation is important for these and other reasons. Data contained in the NSVIPR provided a ready opportunity to evaluate pregnancy and infant health outcomes of participants who received both the smallpox vaccine shortly before or during pregnancy and AVA during pregnancy, by comparing their outcomes with rates in the published literature. Additional analyses compared smallpox and AVA vaccinated pregnancies with those only exposed to the smallpox vaccine.

2. Methods

Women are eligible for NSVIPR enrollment if they receive the smallpox vaccine within 28 days prior to pregnancy (42 days prior to estimated conception), or any time during pregnancy, with the beginning of pregnancy defined as the first day of a woman's last menstrual period. Pregnant women who have close

* Corresponding author. Tel.: +1 619 417 9614; fax: +1 619 767 4806.
E-mail address: avamarie.s.conlin.ctr@mail.mil (A.M.S. Conlin).

http://dx.doi.org/10.1016/j.vaccine.2015.05.054
0264-410X/

contact with a recent smallpox vaccinee may also be included. Once enrolled, research staff periodically contact the women to obtain outcome data. Data captured include pregnancy losses (miscarriage, stillbirth), voluntary interruption of pregnancy, live birth status (preterm or full-term), and infant health outcomes (birth defects diagnosed through the first year of life, or other outcomes). Women with live births are contacted annually through early childhood (*i.e.* approximately 5 years of age) to evaluate the overall health and developmental progress of their child/children. Enrollment in the registry began in 2003, and at the time of this analysis, 517 women were actively followed in the registry, representing 522 pregnancies. Approximately 95% of these women received the smallpox vaccine before 8 weeks estimated gestational age (EGA). Delivery information was pending on 12 subjects, but 429 of the pregnancies had thus far resulted in live births.

Approximately 65% of the NSVIPR participants also reported inadvertently receiving AVA around the time of smallpox vaccination, so a review of the case files to verify vaccination dates in the supporting documentation was conducted. Documentation included vaccination records, provider-completed referral forms, and self-report referral forms. Dates verified through this review were validated as described below.

Only those NSVIPR subjects who received the smallpox vaccine as part of their military service and who were not enrolled in the BioThrax® (Anthrax) Vaccine in Pregnancy Registry were included in this analysis. The NSVIPR records were queried to identify subjects who reportedly also received AVA. Subjects' exposure to AVA during pregnancy (defined as on or after the first day of the last menstrual period) was determined first using Defense Manpower Data Center (DMDC) data; in cases with discrepant dates between self-report and DMDC data, vaccination dates in pregnancy were taken from Armed Forces Health Longitudinal Technology Application (AHLTA); when no in-pregnancy AVA dates were found in either DMDC or AHLTA data, vaccination dates were taken from self-reported NSVIPR data. Subjects with no record of AVA vaccination in pregnancy in the DMDC or NSVIPR data sources were considered AVA-unexposed. Subjects who reported receiving AVA but did not provide a precise date, and for whom no record of in-pregnancy AVA vaccination was found in either DMDC or AHLTA data, were excluded from analyses ($n = 20$). Also excluded were subjects with discrepant vaccination data in multiple sources ($n = 1$), subjects with unknown pregnancy outcomes (those lost to follow-up before delivery ($n = 8$), and those with delivery information still pending ($n = 12$).

In the primary analysis, in order to maximize the number of subjects included in the study, both AVA-unexposed and AVA-exposed subjects who received smallpox vaccine within 28 days prior to or any time during pregnancy were included. A secondary analysis limited the AVA-unexposed/exposed subjects to those who had received smallpox vaccine *during* pregnancy (Fig. 1). In addition, for a small number of the excluded subjects with unknown pregnancy outcomes, outcomes could be ascertained from other DoD data sources. Supplementary analyses were performed including these subjects.

Outcome rates and 95% Clopper–Pearson exact confidence intervals were calculated for the following outcomes: ectopic pregnancy, spontaneous abortion, stillbirth, preterm birth, low birth weight, male sex of infant, and major birth defects diagnosed through the first year of life. For elective abortions, the ratio of elective abortions to 100 live births, the standard reporting for this metric, and a 95% Wald confidence interval were calculated. For the birth weight outcome, the mean and standard normal 95% confidence interval were calculated. Outcomes were compared between the AVA-exposed group and expected values determined by a literature review. Additional comparisons were made between the AVA-exposed and AVA-unexposed groups.

This research, performed under Naval Health Research Center Institutional Review Board-approved protocol 2003.0018, work units 61132/N1226, was conducted in compliance with all applicable federal regulations governing the protection of human subjects in research.

3. Results

There were 463 women (155 AVA-unexposed, 308 AVA-exposed) included in the primary analysis; 5 women had twin pregnancies, yielding 468 total fetal outcomes (Fig. 1). The average ages among the AVA-unexposed and AVA-exposed groups were 22.9 years and 22.8 years, respectively. Among the AVA-exposed women, 78.9% received AVA before 4 weeks EGA, the time after

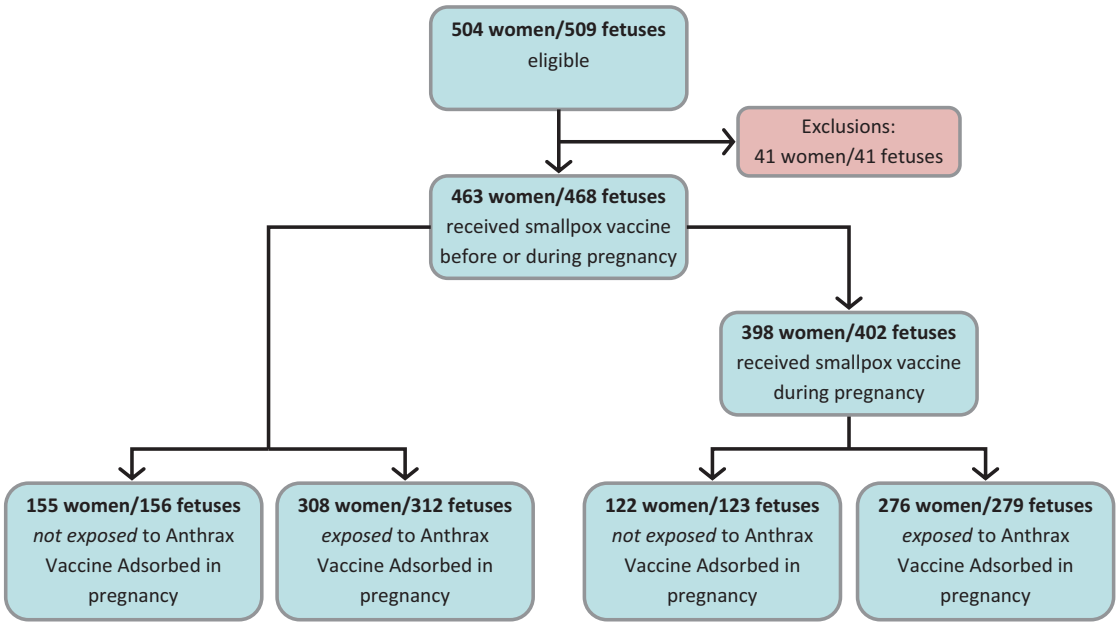

Fig. 1. National Smallpox Vaccine in Pregnancy Registry (NSVIPR) subjects included in analyses.

Please cite this article in press as: Conlin AMS, et al. Analysis of pregnancy and infant health outcomes among women in the National Smallpox Vaccine in Pregnancy Registry who received Anthrax Vaccine Adsorbed. Vaccine (2015), http://dx.doi.org/10.1016/j.vaccine.2015.05.054