Birth Defects Among Infants Born to Women Who Received Anthrax Vaccine in Pregnancy

Margaret Ryan, MD, MPH
Tyler Smith, MS, PhD
Carter Sevick, MS
William Honner
Rosha Loach, MPH
Cynthia Moore, MD, PhD
David Erickson, DDS, PhD, MPH

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

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Anthrax Vaccine and Birth Defects

Background

- Concerns have been raised about the use of anthrax vaccine in US military professionals; civilians share concerns.
- Concerns have included reproductive health issues, even though there may be little biologic plausibility for inactivated vaccines causing reproductive harm.
- Anthrax vaccine originally considered by FDA as Pregnancy Category C.
- US military has vaccinated >1M healthy young adults since 1998, and observational data are available on their reproductive health experiences.

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Objective

- To evaluate infants born to military women who were inadvertently vaccinated against anthrax in early pregnancy, and compare the prevalence of major birth defects with that of infants born to military women who were vaccinated against anthrax, but not in early pregnancy.

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General methodology

- Link data from the central Department of Defense (DoD) vaccine database to data from the DoD Birth and Infant Health Registry.
- Multivariable logistic regression modeling adjusted for confounding by other variables, including: maternal age, race/ethnicity, marital status, service branch, military pay grade, infant plurality, infant gender, and gestational age.

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DoD Birth and Infant Health Registry

- Evaluates data on all live births, and healthcare encounters in the first year of life, among all infants born to DoD beneficiaries.
- Includes all recorded inpatient and outpatient care from civilian and military facilities. Leverages ICD-9-CM codes for diagnoses.

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Preliminary Results (2001-02)

- Original regression model (using only 1998-99 data) revealed a small, marginally significant association between anthrax vaccination in the first trimester of pregnancy and birth defects.
- Preliminary results shared DoD and civilian policymakers in 2001.
  - Anthrax vaccine consent form, given to civilians in Dec 2001, included information about birth defect concerns.
  - MMWR published "Notice to Readers: Status of US Department of Defense Preliminary Evaluation of the Association of Anthrax Vaccination and Congenital Anomalies," Feb 2002 / 51(06);127
  - Manufacturer's product insert included reference to findings.
  - FDA reclassified anthrax vaccine as Pregnancy Category D.

Limitations and Concerns

- Vaccination status and dates are based on military vaccine databases.
- 1st trimester exposure window is based on ICD-9-CM coding related to gestational age.
- Birth defects diagnoses are based on ICD-9-CM coding.

Addressing Limitations and Concerns, 2002-2007

- Validation of a large sample of vaccine records against archived paper records in VA Records Management Center in St Louis (n ~ 12,000)
- Obstetric records reviewed for cases in which gestational age could affect exposure classification (n ~ 5500)
- Pediatric birth and healthcare records were reviewed by professionals (blinded to exposure status) to validate ICD-9-CM coded birth defects (n ~ 200)

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Updated Analyses: Results

Among 115,169 infants born to military women 1998-2004,

37,140 infants born to women ever vaccinated against anthrax

3,465 infants born to women vaccinated in the first trimester

- Birth defects were slightly more common in infants born to women vaccinated in the first trimester of pregnancy (OR=1.18, 95% CI=0.997-1.41)
- This association was only statistically significant when alternative referent groups were used.

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Updated Analyses: Results (continued)

Comparison of Primary and Alternative Models: Adjusted Odds of Birth Defects Among Infants of Military Women, by Maternal Anthrax Vaccination Status, 1998-2004.

Exposure Groups with Associated Odds Ratios and 95% Confidence Intervals	Referent Group for Maternal Vaccination					
	Vaccinated outside of 1st trimester (primary model)		Vaccinated post-pregnancy		Never vaccinated	
	1st trimester vaccinated	1.18 (0.997, 1.41)	1st trimester vaccinated	1.20 (1.005, 1.43)	1st trimester vaccinated	1.20 (1.02, 1.42)
			Pre-pregnancy vaccinated	1.09 (0.98, 1.22)	Pre-pregnancy vaccinated	1.08 (0.99, 1.17)
			Late-pregnancy vaccinated	0.86 (0.58, 1.27)	Late-pregnancy vaccinated	0.86 (0.59, 1.26)
					Post-pregnancy vaccinated	1.02 (0.95, 1.10)
					Ever-vaccinated	1.05 (0.98, 1.12)

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Updated Analyses: Results (continued)

- Among individual defects, only atrial septal defect (ASD) was significantly associated with first trimester anthrax vaccination (OR=1.38, 95% CI=1.04-1.82). This finding was not statistically significant if cases of isolated ASD in preterm infants were excluded, as may be clinically appropriate. Also, this finding was not statistically significant if adjustment for multiple comparisons was applied.

- Maternal vaccination pre-pregnancy or in late-pregnancy was not associated with an increased risk of birth defects.

Discussion and Challenges

- Alternative explanations exist for finding a small association between any exposure that is also associated with late-recognition of pregnancy and adverse outcomes.

- Conclusions:

  "Although the small observed association may be unlikely to represent a causal relation between vaccination in early pregnancy and birth defects, this information should be considered when making decisions about administering anthrax vaccine to pregnant women."

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Primary Reference:

Ryan MAK, Smith TC, Sevick C, Honner WK, Loach RA, Moore CA, Erickson JD. Birth defects among infants born to women who received anthrax vaccine in pregnancy. American Journal of Epidemiology 2008;168(4):434-42.

Email contacts:

Margaret.ryan@med.navy.mil

Tyler.c.smith@med.navy.mil

Carter.sevick@med.navy.mil

cam0@CDC.GOV

erickson.jdavid@gmail.com