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Receipt of Trivalent Inactivated Influenza Vaccine Not Associated with Early Pregnancy Loss

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Abstract

Background

The safety of influenza vaccine administered during early pregnancy has been inadequately studied. Administration during the first trimester of pregnancy was not recommended until 2004. Between 1997 and 2004, first trimester influenza vaccination was not encouraged to avoid "coincidental association with spontaneous abortion". We performed a retrospective case-control study within the Vaccine Safety Datalink (VSD) to examine the association between early pregnancy loss (EPL) at <20 weeks gestation and receipt of influenza vaccine during the prior four weeks.

Methods

Potential cases were identified among women 18-44 years old who were pregnant during the fall of 2005 or 2006, using electronic ICD-9 codes. Cases of EPL occurring before 20 weeks gestation were confirmed by medical record review; date of fetal demise was obtained from ultrasound when available. Controls with a live birth or stillbirth beyond 20 weeks were individually matched (1:1) to cases by VSD site and date of last menstrual period. The exposure of interest in the primary analysis was influenza vaccination in the 28 days before the date of EPL (fetal demise) of the matched pair. Conditional logistic regression models adjusted for healthcare utilization, maternal age, and parity.

Results

Data from 243 matched pairs were analyzed. Eight-two percent of cases had at least one ultrasound performed; mean gestational age at demise was 7.9 weeks. The mean ages of cases and controls were 32 and 29 years, respectively. Older age was strongly associated with EPL (p<0.0001); 66% of cases were ≥30 years of age, compared to 48% of controls. Thirty-eight (16%) cases and 31 (13%) controls received influenza vaccine prior to the matched date of EPL; 16 (7%) cases and 15 (6%) controls were vaccinated within the 28 day risk window before fetal demise of the matched pair. There was no association between EPL and influenza vaccination in the primary analysis (adjusted odds ratio 1.2, 95% confidence interval [CI] 0.5-2.7, p=0.66).

Conclusions

We found no association between influenza vaccination and pregnancy loss during the first 20 weeks of gestation.

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Introduction

Background

- The Advisory Committee on Immunization Practices (ACIP) revised their recommendations for influenza vaccination during pregnancy in 2004, expanding the recommendation to the first trimester.
- There is inadequate safety data regarding influenza vaccination in early pregnancy.

Published Studies of Influenza Vaccine Safety in Pregnancy

- Largest study to date: Heinonen, et al. (1973); 2291 vaccinated women but no mention of first trimester vaccination or early pregnancy loss as outcome.
- First trimester safety data: (1) Hulfka (1964)--363 vaccinated women, 19 in first trimester; and (2) Deinard, et al. (1981)--189 vaccinated women, 41 in the first trimester.
  - Studies did not use ultrasound to determine date of fetal demise.

Vaccine Safety Datalink (VSD)

- Partnership between the Centers for Disease Control and Prevention (CDC), America's Health Insurance Plans (AHIP) and ten managed care organizations (MCO); established in 1990 to conduct post-licensure vaccine safety studies.

Objective

To determine if unintentional pregnancy loss at <20 weeks gestation (spontaneous abortion) is associated with prior receipt of same-season trivalent inactivated influenza vaccine (TIV).

Methods

Study Design

- Retrospective case-control; individually matched on last menstrual period (LMP) and VSD site

Study Population

- Women aged 18-44 years at 6 VSD sites

Study Periods

- LMP July through December 2005 and LMP July through December 2006

Study Definitions

- Case: documentation in medical record of fetal demise following confirmed pregnancy
- Control: documentation in medical record of live birth or stillbirth at >20 weeks gestation
- Event date: date of fetal demise within the matched pair, confirmed by ultrasound when available
- Primary exposure: vaccine receipt 1-28 days before event date

Analytic Approach

- Matched odds ratios using conditional logistic regression
- Adjustment for potential confounders (maternal age/parity, healthcare utilization, smoking)
- Primary analysis: 3-tier categorical variable for influenza vaccine exposure relative to the risk window (1-28 days before event date)
  1) Exposed within 28 day risk window
  2) Exposed >28 days before event date
  3) Unexposed as of event date
- Assuming 80% power, 233 matched pairs needed to detect odds ratio of 2.0
- Analyses performed using SAS 9.2

Results

Figure 1. Case and control ascertainment

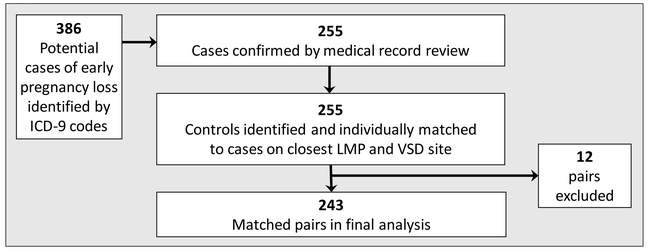


Table 1. Descriptive characteristics of cases and controls

	Cases (n=243)	Controls (n=243)
Mean age, years (SD)	31.7 (6.0)	29.3 (5.4)
≥1 prior live birth	156 (64%)	154 (63%)
≥1 prior miscarriage	80 (33%)	66 (27%)
Smoked while preg.	24 (10%)	25 (10%)
Median no. physician visits in 12 months before LMP (IQR)	3 (1,5)	2 (1,5)

* SD=standard deviation; IQR=interquartile range

Table 2. Influenza vaccination status of cases and controls

	Cases (n=243)	Controls (n=243)
No. (%) vaccinated any time before event date	39 (16)	31 (13)
No. (%) vaccinated 1-28 days before event date	16 (7)	15 (6)
No. (%) vaccinated before conception [LMP +14]	22 (9)	11 (5)

Table 3. Odds of influenza vaccination prior to pregnancy loss (date of fetal demise)

	No. discordant pairs	Crude OR	Adjusted OR*	95% confidence interval	p-value
Exposed 1-28 days before event date (PRIMARY)	27	1.10	1.15	0.50 – 2.67	0.74
Exposed >28 days before event date	28	1.51	1.82	0.79 – 4.22	0.16

* Adjusted for maternal age (spline), parity, smoking status, and healthcare utilization (spline).

Table 4. Odds of influenza vaccination prior to pregnancy loss (date of fetal demise), limited to cases in which the date of demise was confirmed by ultrasound

	Adjusted OR*	95% confidence interval	p-value
Exposed 1-28 days before event date	1.35	0.45 – 4.02	0.59
Exposed >28 days before event date	3.31	0.83 – 13.25	0.09

* Adjusted for maternal age (spline), parity, smoking status, and healthcare utilization (spline).

Secondary Analysis

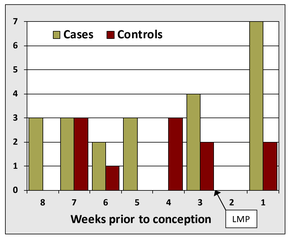
- Secondary analysis: 3-tier categorical variable for influenza vaccine exposure relative to the pregnancy status
  1) Exposed between conception and reference date ("while pregnant")
  2) Exposed prior to conception ("before pregnant")
  3) Unexposed as of event date
- Conception was defined as LMP +14 days for this analysis.

Table 5. Odds of influenza vaccination by pregnancy status

	No. disc. pairs	Crude OR	Adjusted OR*	95% CI	p-value
Exposed while pregnant	31	0.80	0.80	0.37 1.74	0.57
Exposed before pregnant	24	2.55	2.99	1.14 7.86	0.03

* Adjusted for maternal age (spline), parity, and healthcare utilization (spline).

Figure 2. Exposure to influenza vaccine by week prior to conception



Strengths

- Largest influenza vaccine safety study to date focusing on early pregnancy; only study to look specifically at the association between influenza vaccine and early pregnancy loss.
- Medical records were reviewed for all cases and controls; pregnancies and outcomes were confirmed by medical record.
- Ultrasound data were used to determine date of fetal demise, when available.

Limitations

- Precision of gestational age determinations were dependent on availability of ultrasound data.
  - Gestational age measurements via ultrasound were unavailable for 39% of cases.
- Possible unmeasured confounding.
- Study was underpowered for stratified analyses.

Conclusions

- This study works toward filling a critical gap in influenza vaccine safety data.
- Influenza vaccination was not associated with early pregnancy loss in our primary analysis.
  - These results support current vaccination policy, which recommends influenza vaccination during pregnancy regardless of trimester.
- Further research may be needed to assess risk by different gestational age groups and within smaller time intervals surrounding the event.

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