Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

No association between influenza vaccination during pregnancy and adverse birth outcomes

Ousseny Zerbo [a,*], Sharareh Modaressi [a], Berwick Chan [a], Kristin Goddard [a], Ned Lewis [a], Karin Bok [b], Bruce Fireman [a], Nicola P. Klein [a], Roger Baxter [a]

[a] Kaiser Permanente Vaccine Study Center, 1 Kaiser Plaza, 16B, Oakland, CA 94612, USA
[b] National Vaccine Program Office, Office of the Assistant Secretary for Health, US Department of Health and Human Services, USA

ARTICLE INFO

Article history:
Received 4 March 2017
Received in revised form 21 April 2017
Accepted 25 April 2017
Available online xxxx

Keywords:
Maternal
Influenza
Vaccination
Pregnancy
Small for gestational age
Preterm birth
Low birth weight
Immortal time bias

ABSTRACT

Background: Pregnant women are recommended to receive inactivated influenza vaccination anytime during pregnancy. Studies have investigated the impact of influenza vaccination during pregnancy on birth outcomes and results on preterm birth have been inconsistent.
Methods: We conducted a retrospective cohort study among children born at a gestational age ≥ 24 weeks from January 1, 2010 to December 31, 2015 at Kaiser Permanente Northern California facilities (KPNC). We evaluated the association between maternal influenza vaccination during pregnancy and risk of preterm birth, small and large for gestational age, admission to the neonatal intensive care unit (NICU), respiratory distress syndrome, low birth weight, and low Apgar score. We ascertained the dates of maternal influenza vaccination, conception, and delivery, as well as birth outcomes from KPNC inpatient and outpatient databases. Conditional multivariate Cox regression and logistic regression analyses were used to determine the association between maternal vaccination during pregnancy and risk of each birth outcome.
Results: The study included 145,869 children. Maternal influenza vaccination during pregnancy was not associated with risk of small or large for gestational age births, preterm birth, need for mechanical ventilation at birth, respiratory distress syndrome, admission to the NICU, low birth weight, or low Apgar score. However, when we did not control for immortal time bias, the risk of preterm birth (odds ratio [OR] = 0.69, 95% confidence interval [CI] 0.66–0.72) was lower among infants of vaccinated mothers.
Conclusion: We found no association between maternal influenza vaccination during pregnancy and adverse birth outcomes. When investigating preterm birth outcome in association with vaccination during pregnancy, immortal time bias should be taken into account in the analysis.

1. Introduction

Influenza viruses can cause serious morbidity and mortality in people of all ages [1]. Severe complications resulting in hospitalization mainly occur in high-risk groups, including younger children, older adults and pregnant women [2–8]. The most effective way to prevent influenza-associated disease is through vaccination.

In the United States, the Center for Disease Control and Prevention (CDC) has recommended since 2004 that pregnant women receive inactivated influenza vaccines regardless of gestational age [9]. Despite studies showing that the vaccination is safe [10–17], rates of vaccination for influenza among pregnant women remain below the Healthy People 2020 target goal of 80%coverage, possibly due to perceived concerns about the vaccine's potential effect on fetal development [18]. Numerous studies have investigated the association between maternal influenza vaccination and adverse birth outcomes [10,14,17,19–34]. With the exception of one study which reported an increased risk of preterm birth following maternal influenza vaccination (mean decrease in gestational age in the exposed pregnancies was approximately three days, which is not clinically important) [22], all studies have found no increased risk of preterm births or small for gestational age after maternal influenza vaccination. Rather, the majority of studies either found no association between maternal influenza vaccination and risk of preterm birth, low birth weight or small for gestational age [10,14,17,19–21,23,24,27,28,31,35], or reported a protective effect [26,30,32–34,36]. A meta-analysis including 5 studies on seasonal influenza vaccination and 13 studies on A/H1N1pdm09 pandemic influenza vaccination reported that

* Corresponding author.
E-mail address: ousseny.x.zerbo@kp.org (O. Zerbo).

http://dx.doi.org/10.1016/j.vaccine.2017.04.074
0264-410X/

influenza vaccination during pregnancy decreased the likelihood of preterm birth and low birth weight but had no impact on small for gestational age birth [29]. However a systematic review of 19 studies on the same topic concluded that maternal influenza vaccination during pregnancy was not associated with increased or decreased risk of preterm births [25]. Recent studies suggested that the apparent protective effect of the association between influenza vaccination and preterm births was due to confounding factors including the time-dependent nature of exposure to vaccination during pregnancy [28,35,37].

We conducted a retrospective matched cohort study among live birth children at Kaiser Permanente Northern California (KPNC) between 2010 and 2015 to further assess for an association between influenza vaccination during pregnancy and birth outcomes. Birth outcomes included small and large for gestational age, preterm birth, low birth weight, need for mechanical ventilation after birth, admission to the neonatal intensive care unit (NICU), respiratory distress syndrome, and low Apgar scores.

2. Method

2.1. Study population

KPNC is an integrated health-care delivery organization that provides health care to approximately 4 million members in metropolitan San Francisco, Sacramento and surrounding counties. KPNC members are broadly socioeconomically representative of the catchment area population except for the extremes of income distribution [38]. The study population was drawn from the KPNC pregnancy database which contains more than 859,699 women and 873,753 children [39]. The database contains the start and end dates of each pregnancy, basic demographic characteristics of mothers and infants, and can be linked to all encounters and medical procedures for each member. For the present study, eligibility was restricted to singleton children who were born at a gestational age of $\geq$24 weeks during January 1, 2010–December 31, 2015 to mothers who did not have gestational diabetes. Children born to women with gestational diabetes were excluded due to potential association between gestational diabetes and macrosomia.

2.2. Exposure: Maternal influenza vaccination

The primary exposure was maternal seasonal inactivated influenza vaccination received from the estimated date of conception to 14 days before the date of delivery. Maternal tetanus, diphtheria and acellular pertussis vaccine (Tdap) was a secondary exposure. Maternal influenza and Tdap vaccination were extracted from the electronic medical record. Estimated date of conception was calculated based on the gestational age at birth.

2.3. Outcomes

Outcomes evaluated include: (1) preterm birth: defined as a gestational age at birth <37 weeks; (2) small for gestational age: defined as weight-for-gestational age <10th percentile or <5th percentile, large for gestational age: defined as weight-for-gestational age >95th percentile based of the Fenton infant growth chart [40]; (3) low birth weight: defined as a birth weight <2500 g; (4) admission to the NICU following birth; (5) respiratory distress: defined based on International Classification of Diseases, Ninth Revision (ICD-9) code 769; (6) need for mechanical ventilation: defined as receipt of assisted breathing at birth; and (7) low Apgar scores: defined as a score <7 at 1 and 5 min.

2.4. Covariates

Covariates included child's sex, calendar year of birth, gestational age in weeks, maternal pre-pregnancy body mass index (BMI < 18.5 = underweight; 18.5 $\leq$ BMI < 25 = normal weight; 25 $\leq$ BMI < 30 = overweight; BMI $\geq$ 30 = obese), maternal age at delivery (18–24, 25–29, 30–34, 35–39 and $\geq$40 years), self-reported maternal race (Asian, Black, Multi-race, Pacific Islander, Native American, Unknown and White), self-reported maternal ethnicity (Hispanics and non-Hispanics), and parity. Additional categorical covariates included pre-pregnancy asthma (ICD-9 codes 493, hypertension (ICD-9 codes 401), preeclampsia (ICD-9 codes 642.4 and 642.7), self-reported smoking status during pregnancy, type of insurance coverage (subsidized/non subsidized), influenza vaccination in previous season, and medical service area where patients received their healthcare, parity ($\leq$1 vs. >1). Covariates were used to adjust the measure of association between maternal influenza vaccination during pregnancy and risk of each outcome in statistical analyses.

2.5. Statistical analysis

Women who received influenza vaccination during pregnancy were frequency matched on age categories (18–24, 25–29, 30–34, 35–39 and $\geq$40 years), gestational age at child birth, service area where they received care, and calendar week of conception with those who were not vaccinated. We assessed the association between maternal influenza vaccination and covariates using Chi-square test for categorical variables and *T*-test for continuous variables. We also assessed the association between covariates and each birth outcome. We conducted conditional Cox proportional hazard regression analyses treating maternal vaccination status as a time varying variable to account for immortal time bias [41,42] to determine the association between maternal influenza vaccination during pregnancy and risk of each birth outcome. We analyzed associations between maternal influenza vaccination and each outcome separately. For preterm and small for gestational age birth outcome, we conducted analyses stratified by maternal race and ethnicity. We also conducted analyses were maternal vaccination status was considered as a time independent variable using conditional logistic regression models. In this analysis, unvaccinated women at any time during the studied pregnancy were the unexposed reference group. Finally, we explored birth outcome risks among women who received both influenza and Tdap vaccines during the studied pregnancy. In all analyses, we considered the results to be statistically significant when $p < 0.05$.

This study was approved by the KPNC Institutional Review Board.

3. Results

The study included 145,869 children and their mothers. The overall influenza vaccination coverage during pregnancy was 44.4%. Among women who received the influenza vaccine during pregnancy, 29.3% received the vaccination in the first trimester, 38.4% in the second, and 32.3% in the third trimester. Vaccinated pregnant women were more likely to be older, diagnosed with asthma and hypertension prior to pregnancy start, and diagnosed with pre-eclampsia during pregnancy as compared with unvaccinated pregnant women. Asian women were more likely to be vaccinated than unvaccinated. Black women were more likely to be unvaccinated than vaccinated. A higher proportion of white women (39.8%) than black women (5.6%) received the influenza vaccine during pregnancy. Vaccinated women were more likely

Please cite this article in press as: Zerbo O et al. No association between influenza vaccination during pregnancy and adverse birth outcomes. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.04.074