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Association of influenza vaccination during pregnancy with birth outcomes in Nicaragua

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ABSTRACT

Background: Studies have shown that influenza vaccination during pregnancy reduces the risk of influenza disease in pregnant women and their offspring. Some have proposed that maternal vaccination may also have beneficial effects on birth outcomes. In 2014, we conducted an observational study to test this hypothesis using data from two large hospitals in Managua, Nicaragua.

Methods: We conducted a retrospective cohort study to evaluate associations between influenza vaccination and birth outcomes. We carried out interviews and reviewed medical records post-partum to collect data on demographics, influenza vaccination during pregnancy, birth outcomes and other risk factors associated with adverse neonatal outcomes. We used influenza surveillance data to adjust for timing of influenza circulation. We assessed self-reports of influenza vaccination status by further reviewing medical records of those who self-reported but did not have readily available evidence of vaccination status. We performed multiple logistic regression (MLR) and propensity score matching (PSM).

Results: A total of 3268 women were included in the final analysis. Of these, 55% had received influenza vaccination in 2014. Overall, we did not observe statistically significant associations between influenza vaccination and birth outcomes after adjusting for risk factors, with either MLR or PSM. With PSM, after adjusting for risk factors, we observed protective associations between influenza vaccination in the second and third trimester and preterm birth (aOR: 0.87; 95% confidence interval (CI): 0.75–0.99 and aOR: 0.66; 95% CI: 0.45–0.96, respectively) and between influenza vaccination in the second trimester and low birth weight (aOR: 0.80; 95% CI: 0.64–0.97).

Conclusions: We found evidence to support an association between influenza vaccination and birth outcomes by trimester of receipt with data from an urban population in Nicaragua. The study had significant selection and recall biases. Prospective studies are needed to minimize these biases.

1. Introduction

Infection with influenza during pregnancy and its association with adverse birth outcomes has been documented since the early 1900s [1,2]. For instance, infection with influenza virus during pregnancy may prompt an inflammatory [cascade] response that is associated with preterm birth [3,4]. Influenza vaccination has been shown to reduce the risk of influenza virus disease and its complications among pregnant women and their infants [5–15]. Furthermore, some studies have found a beneficial effect of influenza vaccination on birth outcomes, specifically a decreased likelihood of delivering a baby preterm or small for gestational age [16–22]. Other studies, however, have found no evidence to support this hypothesis [23–30]. Published studies have differed substantially from one another in design and in ability to account for variations in circulating influenza viruses, vaccine components, target population, and place of study, making cross-study comparisons difficult [31].

Historic influenza surveillance data from Nicaragua shows that influenza circulates between June and November [32]. Since 2007, the Nicaraguan Government has provided influenza vaccination to

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women with high-risk pregnancies in the month of May, following the vaccination schedule for countries with southern hemisphere circulation of influenza viruses [33,34]. In May 2014, Nicaragua expanded influenza vaccination to all pregnant women in the country. With the aim of evaluating the hypothesis that influenza vaccination has a beneficial effect on birth outcomes, we collected birth outcome data, current influenza vaccination status, and risk factors for adverse pregnancy outcomes by interviewing postpartum women at two large hospitals in Managua.

2. Methods

2.1. Survey

2.1.1. Sample size calculation

Sample size planning was informed by calculating sample needs in order to detect a 40% reduction of low birth weight among newborns of vaccinated (regardless of vaccination trimester) compared to unvaccinated mothers [20,21], assuming a two-sided 95% confidence level, 80% power, and a ratio of unvaccinated to vaccinated of 2:5 [33]. A design effect of 1.5 was considered to account for any potential biases. The sample size required was estimated to be 2769 (1938 vaccinated and 831 unvaccinated pregnant women).

2.1.2. Inclusion criteria

We selected two large public hospitals, Hospital Aleman Nicaragüense and Hospital Bertha Calderon Roque. Inclusion criteria were being a resident of the Department of Managua and having a singleton birth. Exclusion criteria were delivering a stillborn or newborn with congenital or neonatal anomalies, receiving influenza vaccination before May 1st, 2014 -the start date for the national influenza vaccination campaign [32]- or less than 14 days before delivery, and having a gestational age <28 or >42 weeks at delivery which are the viability and post-term cut-offs, respectively [35,36]. The study was designed as an observational study where a cohort of women who provided informed consent were interviewed between July 21st and December 4th 2014, within 48 h after delivery. Participants were selected in a convenience manner.

2.1.3. Questionnaire

The questionnaire included demographic information (age, race, living environment, education level, type of fuel used for cooking, number of persons in the household, delivery hospital), antenatal care (number of antenatal visits, vaccinations received during pregnancy, consumption of antenatal supplements), presence of medical conditions prior to pregnancy (obesity, diabetes, asthma, renal disease, liver disease, blood disease, neurologic disease), any complications during pregnancy (hospitalization for any specific complication such as preeclampsia, eclampsia, hemorrhage, sepsis, urinary infection, diabetes, severe acute respiratory infection, or influenza-like illness), other risk factors for adverse pregnancy outcomes (alcohol consumption and smoking before and during pregnancy), obstetric characteristics of the mother (number of parturitions, number of abortions, number of livebirths and stillbirths, type of delivery), and characteristics of the offspring (sex, weight, gestational age at delivery). Pregnancy and birth outcome data were obtained from antenatal and hospital medical records and included date of last menstrual period (LMP), gestational age calculated by ultrasound when LMP was not available from antenatal medical records, delivery date, and birth weight. Influenza vaccination was self-reported; however, interviewers validated this information using vaccination cards and/or antenatal medical records if available.

2.1.4. Assessing self-reported influenza vaccination

We assessed the validity of self-reporting influenza vaccination or non-vaccination through random sampling of the self-reported vaccinated and unvaccinated group. Sample size of the random sample, per group, was calculated using the formula to estimate a proportion assuming that 90% of those who self-reported being vaccinated or unvaccinated status were truly vaccinated or unvaccinated, respectively [37]. The sample size in each group was 123 and 128 for the vaccinated and unvaccinated groups, respectively. For each selected mother, we reviewed vaccination records of the Expanded Program on Immunization at the Health Unit where the mother received antenatal care and/or we contacted the mother and documented the vaccination date directly from the vaccination card (during a home visit) or as reported by the mother reading from the card (by telephone); influenza vaccination was considered confirmed if an exact date for vaccination could be provided by any of these methods. Likewise, non-vaccination status was corroborated if no information on vaccination including specific date for vaccination was identified from these sources. The positive predictive value (PPV) and negative predictive value (NPV) of self-reporting vaccination and non-vaccination status were then calculated. Out of all participants randomly selected for this assessment who self-reported receiving influenza vaccination (n = 123), 61% (75) had evidence of vaccination. Of the total (n = 128) of participants who self-reported not receiving influenza vaccination, only 2 (2%), had evidence of influenza vaccination. Thus, PPV was 61% (75/123) for self-reporting receiving influenza vaccination, and NPV was 98% (126/128) for self-reports of being unvaccinated. Due to the low PPV and high NPV, we excluded from further analyses women who self-reported vaccination status but did not present evidence of vaccination, and we included all participants who self-reported non-vaccination status.

2.2. Data analysis

2.2.1. Variable definitions

Age was categorized into three groups: <18, 18–34 and ≥35 years old. A proxy variable was calculated for cumulative influenza exposure using influenza surveillance data from Nicaragua [38]. This variable was calculated in stages, first by dividing the number of positive influenza samples by the total number of samples tested per week from the surveillance data and then assigning the cumulative sum of the influenza positive proportions per week to the weeks that women were pregnant; we dichotomized this variable by high or low exposure using the median cumulative influenza exposure as a cutoff. Birth outcome data were defined and calculated as follows: (1) gestational age at delivery was calculated using LMP, if available, or gestational age at any ultrasound obtained from antenatal medical records (see Supplementary material A1 for gestational age calculation algorithm); (2) small for gestational age (SGA) was calculated from weight and gestational age at delivery according to the International Fetal and Newborn Growth Consortium for the 21st Century, or intergrowth-21st standards [36]; (3) preterm birth (PTB) was defined as born with <37 weeks of gestational age; and (4) low birth weight (LBW) was defined as born weighing <2500 g.

2.3. Statistical analysis

We compared all variables by vaccination status using chi-square test to compare differences between vaccinated and unvaccinated women regardless of trimester of receipt of influenza vaccination. We performed multivariable logistic regression (MLR) analyses per birth outcome (SGA, PTB and LBW) as the variable of interest and influenza vaccination as the exposure variable. We used the Akaike Information criterion (AIC) to identify the most