Maternal Influenza Vaccine and Risks for Preterm or Small for Gestational Age Birth

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Objective To study the impact of influenza vaccine administered to pregnant women during all trimesters on the rates of preterm and small for gestational age (SGA) births, evaluating both increased and decreased risk.

Study design This retrospective observational matched cohort study involved 7 Vaccine Safety Datalink sites across the US for the 2004-05 through 2008-09 influenza seasons. Cohort eligibility and outcomes were determined from administrative, claims, medical records, and birth data. In propensity score– and vaccine exposure time–matched analyses, ORs for preterm and SGA births were calculated.

Results Among 57 554 matched vaccinated and unvaccinated pregnant women, including 16 240 women in the first trimester, maternal vaccination was not associated with increased or decreased risk for preterm birth (OR for delivery at <37 weeks gestation, 0.97 [95% CI, 0.93-1.02]; for delivery at ≤32 weeks gestation, 0.98 [95% CI, 0.86-1.12]; and for delivery at ≤34 weeks gestation, 0.96 [95% CI, 0.88-1.04]) or SGA birth (OR for <5th percentile weight for gestational age, 1.02 [95% CI, 0.96-1.09], and for <10th percentile weight for gestational age, 1.00 [95% CI, 0.96-1.04]). Similarly, first trimester vaccination was not associated with increased or decreased risk for preterm or SGA birth.

Conclusion Receipt of trivalent inactivated influenza vaccine during pregnancy was not associated with increased or decreased risk of preterm or SGA birth. These findings support the safety of vaccinating pregnant women against influenza during the first, second, and third trimesters, and suggest that a nonspecific protective effect of the influenza vaccine for these outcomes does not exist. *(J Pediatr 2014;164:1051-7)*.

Numerous studies have evaluated the relationship between influenza vaccination during pregnancy and birth outcomes.[1-10] This research has evaluated the safety of both the seasonal trivalent inactivated influenza vaccine (TIV)[1,2,6,9] and the 2009 monovalent influenza A virus (H1N1) pandemic influenza vaccine.[3,5,7,8,10] To date, no studies have detected an increased risk for preterm or small for gestational age (SGA) birth following maternal influenza vaccination; however, none of these studies has reported on a large cohort vaccinated during the first trimester.[1-10]

Several reports have documented potential nonspecific protective effects of influenza vaccination during pregnancy, including decreased risk of preterm birth,[3,7,9,10] beneficial effects on birth weight,[1,6] or both.[2,4,5] The H1N1 studies were started either late in or after the second wave of the pandemic, and thus exposure to the H1N1 virus was minimal.[11] Therefore, any protective effect of maternal H1N1 vaccination on birth outcomes presumably would be related to a nonspecific response, independent of vaccine efficacy.

Two studies of maternal TIV exposure showed improved birth outcomes after maternal vaccination during periods of influenza virus circulation.[1,2] One of these studies was a randomized trial,[1] and together the studies provide evidence of vaccine effectiveness.

Two recently reported studies do not support the theory that maternal vaccination provides a nonspecific protective effect on birth outcomes. Using multiple strategies to control for potential confounding and bias, Pasternak et al[8] found no effect of the H1N1 vaccine on preterm or SGA birth. Similarly, in a reanalysis of the Mother's Gift Project, (a randomized trial of influenza vaccination of pregnant women in Bangladesh), Steinhoff et al[1] found no effect of maternal influenza vaccination on preterm or low birth weight deliveries during periods when the influenza virus was not circulating.

Using a large, geographically diverse cohort, our group is currently conducting a systematic study of TIV safety during pregnancy,[12] and an absence of acute maternal or obstetric events after TIV vaccination in this cohort has been reported previously.[13,14] The goals of the present study were to evaluate the possibility of increased or decreased risk of preterm and SGA births by trimester of maternal TIV vaccination.

H1N1	Influenza A virus
SGA	Small for gestational age
TIV	Trivalent inactivated influenza vaccine
VSD	Vaccine Safety Datalink

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Methods

In this retrospective observational cohort study, we assessed ORs for preterm and SGA births in propensity score–matched and vaccine exposure time–matched TIV-vaccinated and unvaccinated pregnant women in the Vaccine Safety Datalink (VSD), as part of a larger study of TIV vaccine safety.[12] The VSD is a collaboration between the Centers for Disease Control and Prevention's Immunization Safety Office and several integrated health care systems across the US. The VSD evaluates vaccine safety issues using large standardized linked databases.[15] This study was approved by the Institutional Review Boards at each participating site, as well as by the Centers for Disease Control and Prevention.

Seven VSD sites contributed data for this study: Group Health Cooperative, HealthPartners Institute for Education and Research, Kaiser Permanente Colorado, Kaiser Permanente Northwest, Kaiser Permanente Northern California, Kaiser Permanente Southern California, and Marshfield Clinic Research Foundation.

As described previously,[12] pregnant women enrolled in the participating sites were identified using an algorithm developed and validated by Hornbrook et al[16] and adapted for use in the VSD by Naleway et al.[17] The algorithm uses a hierarchical approach to identify pregnancy episodes, pregnancy outcomes (ie, live birth, stillbirth, spontaneous abortion, or therapeutic abortion), and gestational age at pregnancy outcome, using claims and administrative data. The gestational age at delivery was then used to assign an estimated pregnancy start date, equivalent to the estimated last menstrual period.

Pregnancies with a lapse in insurance enrollment from 6 months before pregnancy start through the end of pregnancy were excluded from our analysis. Additional exclusion criteria were multiple gestation pregnancy, ectopic pregnancy, gestational trophoblastic disease, therapeutic abortion, pregnancy in which the outcome could not be determined from available data, and receipt of the live attenuated influenza virus vaccine while pregnant. Also excluded were women who received TIV within 2 weeks of their last menstrual period, owing to the estimated nature of the pregnancy start date, and women vaccinated in their last week of pregnancy, to ensure that postpartum administrations were not included. Women with no outpatient medical claims during pregnancy were excluded as well (**Figure 1**; available at www.jpeds.com).

For the larger VSD study of TIV vaccination of pregnant women, those aged 14-49 years meeting the previously mentioned inclusion criteria who received TIV during the 2002-03 through the 2008-09 influenza seasons were matched 1:2 with replacement to unvaccinated women using a variable optimal matching algorithm.[18] Match variables included age at pregnancy outcome (±1 year), estimated pregnancy start date (±30 days), and VSD site. From this larger sample, a smaller sample was drawn comprising all pregnancies during the 2004-05 through 2008-09 influenza seasons ending in a live birth, with birth data available, a birth weight of ≥500 g, and gestational age of ≥22 weeks. Women from the earlier seasons were excluded because they predate Advisory Committee on Immunization Practices recommendations for vaccination throughout pregnancy. This sample of pregnant women is referred to as the main cohort (**Figure 1**).

The exact date of receipt of TIV was identified from the VSD vaccine files. Data sources for these files include vaccines captured through claims and site-based vaccine registries. Data on vaccination at nontraditional sites (eg, pharmacies) were available when manually entered by a health care provider based on patient report. Timing of vaccination was stratified by trimester,[19] with first trimester defined as <14 weeks gestation, second trimester as 14 to <28 weeks, and third trimester as ≥28 weeks.

Outcomes

The 2 primary study outcomes were preterm birth and SGA birth. Gestational age and pregnancy start date were obtained from the clinical estimate of gestational age on the birth record.[19] Preterm birth was defined as delivery before 37 weeks gestation. Very and moderately preterm births were defined as delivery at ≤32 and ≤34 weeks gestation, respectively. Weight-for-gestational age percentiles were obtained from Oken et al,[20] who provide comprehensive reference values for distributions of birth weights at 22-44 completed weeks of gestation derived from broadly based nationwide data, stratified by sex. Using these standards, we defined 2 cutoffs for SGA birth, <10th and <5th percentiles.

Covariates

All data on relevant covariates or risk factors for preterm or SGA birth that were available in the VSD files were gathered. Preexisting conditions were identified from *International Classification of Diseases, Ninth Revision, Clinical Modification* codes recorded in electronic health care records at inpatient, outpatient, or emergency department visits for the period starting 6 months before conception through the end of the pregnancy (**Table I**; available at www.jpeds.com). Preexisting conditions included hypertension, diabetes, cardiovascular disease, and renal disease. Health care utilization was measured by receipt of medical care during the first trimester and the Kotelchuck Adequacy of Prenatal Care Utilization Index.[21,22] Health care utilization measures were identified from electronic health care data. The number of hospitalizations during the first 2 trimesters was used as a proxy of complication during pregnancy. Infant race/ethnicity was identified from birth data and used as a proxy for maternal race/ethnicity. In the absence of socioeconomic data at the individual level, we used census tract poverty level, defined for each subject as the percentage of families in his or her census tract with annual income below 150% of the federal poverty level.[23] When maternal address was missing, data on poverty were imputed using the expectation maximization algorithm.[24] This algorithm was based on a regression model that includes health care utilization covariates, demographic