Research Article

Effect of maternal antenatal influenza vaccination on adverse neonatal outcomes in terms of premature birth, small-for-gestational age and low birth weight: A comparative study

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Abstract

Background: Maternal influenza infection can impose significant health risks to pregnant women and their neonates.

Objective: The objective of this study was to assess the effect of maternal antenatal influenza vaccination on adverse neonatal outcomes in terms of premature birth, small-for-gestational age (SGA), and low birth weight (LBW).

Material and Methods: The present cross-sectional retrospective study included women who gave birth to their live third trimester neonates at a secondary care hospital in Saudi Arabia after exposure to the 2013/2014 influenza season in any entire trimester of their pregnancy. Neonatal outcomes of women who received inactivated influenza vaccine in their first, second, or early third trimester have been compared to the neonates of women who did not receive the vaccine throughout pregnancy. Data were collected by chart review.

Results: In the present study, 1237 women were included, of these 347 (28.05%) received the trivalent inactivated influenza vaccine during pregnancy. Neonates born to vaccinated mothers were, on average, 97 g heavier (3279.7934 ± 337.6 compared with 3182.5107 ± 424.06, $P = 0.001$). Adverse neonatal outcomes were significantly lower in the vaccinated group; premature (9.1% compared with 17.6%, $P = 0.001$), SGA (8% compared with 14%, $P = 0.003$), and LBW (6.3% compared with 10.4%, $P = 0.022$). There was no significant increase in birth defects (2.2% compared to 2.6%, $P = 0.711$). Logistic regression analysis revealed that, compared to the neonates of mothers who received the vaccine, neonates of unvaccinated mothers are at almost two-fold increased risk of being premature (OR = 1.957; 95% CI, 1.310–2.923; $P = 0.001$), 40% risk for SGA (OR = 1.409; 95% CI, 0.872–2.275; $P = 0.161$), and 30% risk for LBW (OR = 1.306; 95% CI, 0.773–2.206; $P = 0.319$).

Conclusion: Maternal antenatal influenza vaccination is associated with reduced adverse neonatal outcomes in terms of premature birth, SGA, and LBW. Moreover, it is associated with having heavier babies, and not associated with increased birth defects.

KEY WORDS: Pregnancy, influenza vaccine, neonatal outcomes, premature, birth weight, birth defects, small for gestational age.

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Introduction

Epidemiological studies have shown that pregnant women are at increased risk to a variety of infections with increasing severity.[1–3] Influenza is considered as one of the most transmissible respiratory illnesses that can inflict substantial health hazards. On the basis of data from seasonal influenza and from the influenza pandemics of 1918–1919, 1957–1958, and

2009–2010, pregnant women infected with influenza are more likely to develop severe influenza-related illness compared to the general population. The physiologic changes that increase the severity of influenza in pregnancy include changes in the cardiovascular and respiratory systems, and immunologic alterations result in a shift away from cell-mediated immunity.[4–11] The associated systemic reactions to influenza infection can cause disruptions in fetal homeostasis thus compromising the co-existing fetus and subsequently may have a negative impact on neonatal outcomes.[12,13]

In a recent systematic review and meta-analysis of observational studies, influenza or influenza-like illness in the first trimester was associated with an increased risk of congenital fetal abnormalities such as cleft lip, neural tube defects, hydrocephaly, and congenital heart defects.[14] Hyperthermia is a common clinical manifestation of influenza and a risk factor for certain birth defects and other adverse neonatal outcomes.[15] Also, there is indirect evidence that maternal influenza infection during pregnancy is associated with an increased risk of spontaneous abortion, preterm delivery, low birth weight (LBW), birth of a small-for-gestational age (SGA) infant,[5,6,16–26] and fetal death.[27,28]

Because of the increased severity of influenza in pregnancy, and its associated potential adverse effects on both the mother and fetus, The World Health Organization (WHO) has considered pregnant women at the top priority for influenza vaccination,[29] and the US Centers for Disease Control's (CDC) Advisory Committee on Immunization Practices (ACIP) has recommended that all women who are pregnant or will be pregnant during influenza season should receive inactivated influenza vaccine, either the trivalent or quadrivalent, regardless of trimester of pregnancy.[30]

Influenza vaccination during pregnancy creates a defensive antibody response and reduces clinical illness in both mothers and infants.[31] Pregnant women who received the influenza vaccine were 36% (95% CI 4–57) less likely to have respiratory illness with fever[32] and 24% less likely to seasonal influenza.[33] Many retrospective cohort studies and one prospective randomized controlled trial have investigated the effect of maternal influenza vaccination on neonatal outcomes, including a possible effect on decreased incidence of preterm birth, SGA, and LBW infants.[22,26,34,35]

The present study was purposed to examine whether neonatal outcomes differed between women who received the influenza vaccine during pregnancy and those who did not, with emphasis on outcomes including birth of premature infants, SGA, and LBW.

Material and Methods

This cross-sectional retrospective study was conducted at a randomly selected large secondary care hospital in Makkah region, Saudi Arabia during the period of October 2014–April 2015. The study was approved by the research and ethics committee of the Faculty of Medicine of Umm Alqura University, and by the hospital's administrative authority.

The study materials used were the medical records of pregnant women who gave birth to their live third trimester neonates during the period of 1 January–30 November 2014. Inclusion criteria were women who have been pregnant in their entire first and/or second and/or third trimester during the 2013/2014 influenza season (from 1 October 2013 to 31 May 2014). This means inclusion of women with the date of the last menstrual period anytime between 1 April 2013 and 1 March 2014. Also, women have been included only if they received their antenatal care at the study setting. Then, women, as identified from their medical records, have been divided into two groups; a vaccinated group included women who have received the trivalent inactivated influenza vaccine (TIIV) during their first, or second, or early third trimester (weeks 29–32) of pregnancy, late third trimester vaccinations (week 33 to the end of pregnancy) were excluded, and unvaccinated group included women who have not received the TIIV at any trimester of pregnancy during the same influenza season.

Women vaccinations with regard to the influenza vaccine were identified by revision of the vaccination sheets in their medical records. Other relevant information about the women's health including socio-demographics, medical risk factors, and any pregnancy complications has been obtained from the medical records. Medical risk factors include: bronchial asthma; anemia (hemoglobin <10 g/dl or hematocrit <30%); hypertension including pregnancy-induced hypertension, chronic hypertension, and pre-eclampsia; gestational or pre-pregnancy diabetes mellitus; cardiac disease; hemoglobinopathy; incompetent cervix; previous large baby >4000 g, previous preterm delivery, previous SGA or low birth weight (LBW). Pregnancy complications include: hydramnios/oligohydramnios; amnionitis; premature rupture membranes; abruptio placentae, placenta previa; and antepartum hemorrhage.

The primary outcomes of the study were comparison between the two groups with regard to neonatal outcomes including premature birth, birth defects, birth weight, SGA, and LBW. These outcomes were documented in the neonatal sheet of every mother's medical record.

Premature birth, also known as preterm birth, is the birth to a baby at less than 37 weeks gestational age.[36,37] Birth defects, also known as congenital malformations, were the structural abnormalities which are present from birth. Functional abnormalities were not included because it could not be identified at birth.[38] SGA was defined as birth weight <10th percentile for gestational age and sex.[39] Birth weight at term delivery between 2500 and 4200 g is normal, while birth weight of less than 2500 g regardless of gestational age is low birth weight (LBW).[40,41]

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) for Windows version 20.0 (Somers, NY, USA). Data were presented using descriptive statistics in the form of frequencies and percentages for qualitative variables, and means ± standard deviation (SD) for quantitative variables. Quantitative continuous variables were

compared using Student *t*-test in case of normal distribution. Qualitative categorical variables were compared using Chi-square test. Logistic regression analysis was performed to evaluate the association of maternal non-immunization with inactivated influenza vaccine and the risk of having adverse neonatal outcomes; premature birth, SGA, and LBW; birth weight <2500 g. Odds ratios were calculated. To check for significant differences between the ratios, the 95% confidence level around each measure was calculated. Statistical significance is set at *P*-value <0.05.

Results

There were 1764 women who gave birth to their neonates during the intended period of study. Of these, 527 have been excluded because they did not receive their antenatal care at the study setting. There was no detection of women receiving the influenza vaccine late in the third trimester to be excluded. Hence, a total of 1237 women met the inclusion criteria, and their medical records have been evaluated during the study period. Of these, 347 women (28.05%) received the TIIV of the 2013/2014 influenza season during pregnancy. Women of both groups gave birth to a total 1300 live third trimester neonates. Vaccinated women gave birth to 363 (r27.9%), and un-vaccinated women gave birth to 937 (72.1%).

Table 1 shows that there were no significant statistical differences between the two groups (vaccinated and unvaccinated) with regard to mean age, nationality, body mass index (BMI), parity, pregnancy complications, maternal medical risk factors including hypertension, diabetes, cardiac disease, multiple pregnancy, and other medical risk factors (Table 1, *P* > 0.05%), except bronchial asthma. The likelihood of receiving influenza vaccine was higher for women at a higher level

Table 1: Maternal characteristics by receipt of inactivated influenza vaccine during pregnancy

Characteristics	Vaccinated [*n* = 347 (28%)	Unvaccinated [*n* = 890(72%)]	Chi-square or *t*-test	*P*-value
	No. (%)	No. (%)		
Age: mean±(SD); (*t*-test)	28.2161±(4.02)	27.9191±(4.61)	1.053*	0.293
Nationality				
Saudi	192 (55.3%)	521 (58.5%)	1.052	0.305
Non-Saudi	155 (44.7%)	369 (41.5%)		
Education				
Primary	12 (3.5%)	137 (15.4%)	74.801	0.001
Secondary	119 (34.3%)	422 (47.4%)		
High	216 (62.2%)	331 (37.2%)		
*BMI***				
Underweight	18 (5.2%)	36 (4.0%)	1.294	0.731
Average	86 (24.8%)	241 (27.1%)		
Overweight	213 (61.4%)	538 (60.4%)		
Obese	30 (8.6%)	75 (8.4%)		
Parity				
Primigravida	82 (23.6%)	213 (23.9%)	0.012	0.911
Multigravida	265 (76.4%)	677 (76.1%)		
Bronchial asthma	81 (23.3 %%)	45 (5.1%)	91.260	0.001
Hypertension	38 (11.0%)	99 (11.1%)	0.008[a]	.931
Diabetes Mellitus	53 (15.3%)	142 (16.0%)	0.087	0.768
Cardiac disease	10 (2.9%)	29 (3.3%)	0.116	.733
Multiple pregnancy (during current gestation)	16 (4.6%)	47 (5.3%)	0.232	.630
Other medical risk factors***	42 (12.1%)	112 (12.6%)	0.053	0.818
Any pregnancy complications©	72 (20.7%)	199 (22.4%)	0.378	0.538

* Statistical t est used is the *t*-test.

** BMI: Body Mass Index.

***Other medical risk factors include anemia (hemoglobin <10 g/dl or hematocrit <30%); Rh sensitization; incompetent cervix; renal disease; hemoglobinopathy; previous baby >4000 g; previous preterm, SGA, or low birth weight delivery; and rubella.

©Includes fetal or placental problems affecting maternal management; polyhydramnios; oligohydramnios, premature rupture of membranes; antepartum hemorrhage; abruptio placentae, and placenta previa; and antepartum complications.

of education, and women with history of bronchial asthma (P <0.001%).

Table 2 shows significant statistical differences between the two groups regarding neonatal outcomes including delivery of a premature infant, mean birth weight, small for gestational age, and giving birth to low birth weight infants <2500 g (P <0.05%). There was no significant statistical difference between the two groups with regard to birth defects (P = 0.342). Newborns of vaccinated women were, on average, 97 g heavier than newborns of unvaccinated women (3279 versus 3182 g; P = 0.001).

Logistic regression analysis (Table 3) shows that newborns whose mothers did not receive antenatal influenza vaccine were almost at double-fold increased risk of being premature (OR = 1.957; 95% CI, 1.310–2.923; P = 0.001), about 40% risk of being SGA (OR = 1.409; 95% CI, 0.872–2.275; P = 0.161), and about 30% risk of being LBW (OR = 1.306; 95% CI, 0.773–2.206; P = 0.319) compared with neonates of vaccinated mother.

Discussion

The present study demonstrated a low rate of maternal vaccination with inactivated influenza vaccine during pregnancy (28.05%). Black et al in 2004, and France et al in 2006 reported a very low rate of antenatal influenza vaccination (7.5% and 20%, respectively), while Omer et al demonstrated a rate of 19.2%, and Richards et al demonstrated a rate of 41.5%.[42,43,25,35]

Despite the recommendations from WHO, CDC, and American College of Obstetrics and Gynecology (ACOG), the rate of vaccination with influenza vaccine during pregnancy remains low for many years.[44–46] ACOG reported a rate below 50% for maternal vaccination with influenza.[45] Studies have shown that concern about vaccine safety is the most commonly mentioned reason for refusing the vaccine.[47–49] Fetal safety is of high importance for healthcare providers, public health officials, and the general public.[50]

The current study addressed the safety of antenatal influenza vaccine in terms of birth defects where there were no increased birth defects among neonates of vaccinated mothers. This finding is supported by previous evidences of antenatal influenza vaccine safety.[25,44,51–54]

Also, the current study found that neonates of vaccinated mothers weight, on average, 97 g heavier than neonates of un-vaccinated mothers. This finding is supported by results from earlier studies in the United States, Canada, and Bangladesh showing that maternal influenza infection is associated with decreased birth weight, and maternal influenza vaccination is associated with increased birth weight.[23–25,35]

In this study, adverse neonatal outcomes; preterm birth, SGA, and LBW (<2500 g) were significantly lower in neonates of antenatal influenza vaccinated mothers. This finding of reduced adverse neonatal outcomes is in context with multiple observational and experimental studies which support this conclusion.[5,6,16–26,28,34] It has been reported that maternal seasonal influenza vaccination was protective against SGA birth during periods of widespread influenza activity.[25] In the prospective study in Bangladesh, receipt of TIV during pregnancy was associated with an increased birth weight of 200 g and decreased incidence of SGA by 34%. Retrospective studies have also shown a decreased risk of premature birth with both H1N1 vaccine and TIV administration during pregnancy.[26,28] Results from the South African study demonstrate efficacy in both pregnant women and their infants.[55,56] However, Richards et al[35] although they demonstrated reduced risk of premature birth with antenatal influenza immunization;

Table 2: Comparison between neonatal outcomes of vaccinated and unvaccinated mothers with trivalent inactivated influenza vaccine during pregnancy

Outcome	Neonates ofvaccinated mother [n = 363 (28.9%)]	Neonates ofunvaccinated [n = 937(71.1%)]	Chi square or t-test	P-value
Premature delivery	33 (9.1%)	165(17.6%)	14.654	0.001
Birth defects	8 (2.2%)	24 (2.6%)	0.137	0.711
Small for gestational age	29 (8%)	131 (14%)	8.668	0.003
Mean birth weight (t-test)*	3279.7934 ± 337.6	3182.5107 ± 424.06	3.916*	0.001
Low birth weight (<2500 g)	23 (6.3%)	98 (10.4%)	5.245	0.022

*Statistical test used is the t-test.

Table 3: Odds Ratios for adverse neonatal outcomes of unvaccinated mothers with inactivated influenza vaccine

Outcome	Neonates of unvaccinated mothers	95% C.I.	P-value
Premature birth	1.957	1.310–2.923	0.001
Small for gestational age	1.409	0.872–2.275	0.161
Low birth weight (<2500 g)	1.306	0.773–2.206	0.319

they did not demonstrate such similar association with SGA and LBW.

The current study revealed that the odds of having a premature third trimester neonate is almost double fold for neonates of unvaccinated mothers compared to neonates of mothers who received the vaccine, a finding comparable to previous reports from multiple studies.[5,6,16–26,28,34,35] Neonatal prematurity was the most significantly encountered adverse outcome with non-vaccination. Only one study in the literature reported an increased risk of premature birth associated with antenatal influenza vaccination. Although, the risk rise was high (HR = 3.28; 95% CI, 1.28–8.63); however, the CI was very wide and the researchers noted that the average decrease in gestational length was only 3 days, which they hypothesized may not be of significant clinical consequence.[57] Omer et al[25] and Richards et al[35] described a significantly reduced risk of premature birth in neonates of vaccinated mothers compared to non-vaccinated group by about 70%. A recent systematic review by Fell et al[58] concluded that, several studies generally reported modestly decreased risks of premature birth among neonates of influenza vaccinated. They also concluded that these results may be biased by methodological shortcomings of observational studies of influenza vaccine effectiveness.

Prematurity is a major public health problem, with increased stress to the family, and increased cost to the health authority.[59]

The current study findings suggest that at least a portion of premature births, and other adverse neonatal outcomes including SGA and LBW, may be preventable through maternal antenatal influenza vaccination.

Recommendations

Health care providers involved in antenatal care including obstetricians and family physicians are encouraged to counsel pregnant women regarding vaccination with the inactivated influenza vaccine during pregnancy for the purpose of improvement of birth outcomes, with emphasis on safety of the influenza vaccine. Further studies are recommended to evaluate the effect of the trimester of vaccination on neonatal outcomes.

Limitations

This was an observational study without controlling, and subsequently liable for possible residual confounding variables. Although effectiveness of influenza vaccine is thought to be through prevention of influenza infection during pregnancy, however, this was not possible to be assessed in this study due to the behavior of fragmentation of health care in the setting of the study. Also, this study omitted to evaluate the effect of trimester of vaccination on neonatal outcomes; however, it conditioned inclusion of early third trimester vaccination to give a chance for the vaccine effect and protection. Also, the current study included only third trimester live births, and did not include second trimester births and stillbirths which might have an impact on the studied outcomes.

Conclusions

This study demonstrated that maternal vaccination with inactivated influenza vaccine during pregnancy is safe in terms of congenital birth defects, and is associated with significant reduction of adverse neonatal outcomes in terms of premature birth, small for gestational age, and low birth weight. The reduced risk for premature baby was the most prevailing finding of this study. Moreover, it was associated with increased birth weight.

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