Vaccine 34 (2016) 4443–4449

Contents lists available at ScienceDirect

Vaccine

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

Safety of the 2010–11, 2011–12, 2012–13, and 2013–14 seasonal influenza vaccines in pregnancy: Birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants, a study from the cohort arm of VAMPSS ☆

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ARTICLE INFO

Article history:
Received 1 March 2016
Received in revised form 13 June 2016
Accepted 16 June 2016
Available online 20 July 2016

Keywords:
Influenza vaccine
Pregnancy
Birth defects
Preterm delivery
Small for gestational age
Spontaneous abortion
Safety

ABSTRACT

Introduction: There is a need for pregnancy safety information overall and for each seasonal formulation of the influenza vaccine.
Methods: As part of the cohort arm of the Vaccines and Medications in Pregnancy Surveillance System, vaccine-exposed and unexposed women in the U.S. or Canada were recruited during pregnancy in the 2010–2014 vaccine seasons and followed to pregnancy outcome. For the four seasons combined, crude and adjusted relative risks (RRs) were estimated with 95% confidence intervals (CIs) for major birth defects overall and infants small for gestational age. Crude and adjusted hazard ratios (HRs) were estimated with 95% CIs for spontaneous abortion and preterm delivery. Specific influenza season subanalyses were also conducted.
Results: Of 1730 women, 1263 were exposed to an influenza vaccine and 467 were unexposed to any influenza vaccine. Among pregnancies with first-trimester exposure excluding lost-to-follow-up, 26/457 (5.7%) resulted in an infant with a major birth defect compared to 13/427 (3.0%) in the unexposed (RR 1.87, 95% CI 0.97, 3.59). No specific pattern of defects was evident in the vaccine-exposed cohort. The overall risk of spontaneous abortion was not elevated (HR 1.09, 95% CI 0.49, 2.40). Adjusted HRs for preterm delivery approximated 1.0 (adjusted HR 1.23, 95% CI 0.75, 2.02). RRs for small for gestational age infants on weight, length and head circumference ranged from 1.19 to 1.49 with all CIs including 1. Season-by-season analyses resulted in variation by season; however, estimates were based on small numbers.
Conclusions: Combining the 2010–2014 influenza seasons, we found a moderately elevated RR for major birth defects overall, but no evidence of a specific pattern; 95% CIs included 1, and this finding could be due to chance. In the combined seasons, we found no meaningful evidence of an increased risk for spontaneous abortion or preterm delivery following exposure to the seasonal influenza vaccine.

1. Introduction

Influenza vaccination for women who are or who will become pregnant is recommended by the Advisory Committee on Immunization Practices and the American College of Obstetricians and Gynecologists. Despite the recommendation that women be vaccinated regardless of trimester, vaccination coverage continues to fall far short of the target. In the 2012–2013 and 2013–2014

☆ This project has been funded in whole or in part with Federal funds from the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, Department of Health and Human Services, under Contract No. HHS0100201000029C and by a research contract from BioCSL (Seqirus).
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http://dx.doi.org/10.1016/j.vaccine.2016.06.054
0264-410X/

influenza seasons respectively, 50.5% and 52.2% of current or soon to be pregnant respondents to a CDC survey indicated they had been vaccinated [1,2]. Reported barriers to vaccination consistently include mother's concerns about the safety of the vaccine for the developing fetus [3].

Since 2012, a small number of reports considered risks of first-trimester exposure and congenital malformations. Reviewed by Polyzos et al., only two studies focused on this concern among U.S. populations since 2009; one prospective cohort and one case control study (both from our group) addressed congenital malformations following maternal influenza vaccinations given in the U.S. in the 2009 season or later [4–6]. While reassuring, these results are not readily generalizable to each season and all subsequent seasonal vaccine formulations. Data regarding other adverse outcomes following maternal vaccination have largely been reassuring but not uniformly so. Vaccine Safety Datalink sites across the U.S. compiled data from five seasons inclusive of 2004–2005 through 2008–2009 and found no association between seasonal influenza vaccine and preterm birth or small for gestational age infants [7]. In contrast, Ahrens et al. noted an elevated risk for preterm delivery in the 2009–2010 season that was not evident in data from the previous 2006–2007 and 2007–2008 seasons [8].

The purpose of our study was to evaluate the fetal risk and relative safety of the seasonal influenza vaccine overall and secondarily season by season from 2010–2014 using data from the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), a research program developed specifically to evaluate medications and vaccines used by pregnant women [9]. The VAMPSS program is composed of two complementary study designs, a prospective cohort study and case-control surveillance, each of which is conducted in parallel with coordination provided by the American Academy of Allergy, Asthma & Immunology. In 2009, VAMPSS initiated a study of the influenza vaccine in pregnancy and results of the first three years of data collection 2009–2012 were reported previously [5,6]. This report describes results of the cohort arm of VAMPSS with the addition of new data from two seasons to the combined analysis and for the secondary analysis of season by season estimates covering the years 2010–2011 through 2013–2014; results of the case-control arm are described separately [10].

2. Methods

2.1. Design and setting

MotherToBaby studies conducted by the Organization of Teratology Information Specialists (OTIS) are prospective pregnancy cohort studies involving study participants across the U.S. and Canada. The methods of MotherToBaby OTIS cohort studies have been described previously [11,12]. In brief, MotherToBaby services, located in academic institutions or hospitals throughout the U.S. and Canada, provide counseling to women and their providers who contact the services with questions about the risks of exposures in pregnancy. Pregnant women who contact a service with a question about any exposure whether the exposure has already taken place or is anticipated (e.g., cosmetic products, occupational exposures, infections, household chemicals, over-the-counter medications, vitamin supplements, or prescription medications) are screened for exposure to one of the vaccines or medications currently under study by MotherToBaby OTIS. Those women who meet preliminary criteria for participation in either an exposed or unexposed cohort for a given study are referred to the OTIS Research Center at the University of California San Diego where they are screened, consented to participate and where all subsequent data collection takes place. Additional methods of recruitment are also employed, including physician referrals and direct-to-consumer marketing through social media and the MotherToBaby website. In all cases, however, the pregnant woman is the individual consented into the study and the primary source of exposure data.

2.2. Participants

The sample available for the current analysis was enrolled in the VAMPSS cohort study starting in 2010 and continuing through 2014 and thus were exposed or not exposed to the seasonal vaccine in the 2010–2011, 2011–2012, 2012–2013, or 2013–2014 seasons. Previously published analyses of pooled data from the VAMPSS cohort arm included 485 exposed pregnancies and 155 unexposed pregnancies from the 2010–2012 seasons that are now incorporated into this updated overall and season-by-season analysis. This study was approved by the institutional review board of the University of California San Diego.

Women met the inclusion criteria if they had received an influenza vaccine at any time in pregnancy from the first day of the last menstrual period (LMP) to the end of pregnancy, were currently pregnant, had not previously had prenatal diagnosis indicating that the fetus had a major birth defect, and had not enrolled in this study with a previous pregnancy. Women met the inclusion criteria for the comparison group if they had received no influenza vaccine in pregnancy, were currently pregnant, had not previously had prenatal diagnosis indicating they were carrying a fetus with a major birth defect, and had not enrolled in this study with a previous pregnancy.

2.3. Maternal interviews

Women in both the exposed and unexposed cohorts completed one to three telephone interviews during pregnancy and one interview at the completion of pregnancy. These were administered by trained study staff in English or Spanish. The first interview obtained information on demographic, pregnancy and family medical history, tobacco, alcohol and caffeine consumption, and illicit drug use, as well as infections, fever, and prenatal tests. Data regarding dates of exposure were collected on all vaccines and dates and dosages of medications (prescription, over-the-counter), vitamins/minerals, and herbal products used/administered from LMP through the date of the interview. Subsequent maternal interviews elicited information on additional exposures or events since the last interview. The Slone Epidemiology Center's Drug Dictionary was used to code exposures [13].

Methods that were used for verifying vaccine exposure from medical or vaccine records and for obtaining brand, lot number and single syringe vs. multi-dose vial have been described previously [14].

2.4. Exposure definitions

We classified women exposed to a seasonal influenza vaccine into one of four categories by timing of exposure: (1) the two weeks between LMP and date of conception, (2) conception to 13 weeks' gestation, (3) >13–26 weeks' gestation, or (4) >26 weeks' gestation. In cases where the date of vaccination was uncertain, we assigned the exposure based on the midpoint of possible dates. The comparison group consisted of women who received no influenza vaccine of any type throughout pregnancy.

2.5. Outcomes

Outcomes were collected by maternal interview and by medical records obtained from the obstetrician, pediatrician, and delivery

hospital as well as pathology reports if relevant. Data were collected on outcome status of each pregnancy (live birth, stillbirth, spontaneous abortion, elective termination), gestational age at outcome, mode of delivery, sex and number of infants, birth weight, length, and head circumference and the presence or absence of major birth defects detected up through the first year of life. Maternal report of major birth defects was confirmed by medical record review.

Major birth defects were classified using the Metropolitan Atlanta Congenital Defects Program coding system [15]. Spontaneous abortion was defined as spontaneous pregnancy loss at <20 gestational weeks. Preterm delivery was defined as delivery at <37 gestational weeks. Ultrasound dating was used to correct gestational weeks, as necessary, using a standard algorithm, or if the LMP was unknown. Small for gestational age was defined as <10th centile for sex and gestational age in live born infants using standard U.S. growth charts for full and preterm infants [16–18].

2.6. Statistical methods

All statistical comparisons were performed between the group of women exposed to the seasonal influenza vaccine in the relevant gestational time period and the women with no exposure to any influenza vaccine in pregnancy. Exact methods were used to calculate crude relative risks (RRs) and their 95% confidence intervals (CIs) for the pregnancy outcomes of live birth, stillbirth, elective termination, major birth defects overall, and small for gestational age infants. Adjusted RRs and their 95% CIs were estimated using logistic regression with the adjusted odds ratios (ORs) calculated and used as an approximation of the adjusted RRs. First-trimester exposure to an influenza vaccine was considered the relevant exposure window for major birth defects.

For spontaneous abortion, the subset of those women who enrolled in the study prior to 20 weeks' gestation was used for the analysis. Kaplan Meier estimates at 20 weeks of gestation were used to estimate the probability of spontaneous abortion accounting for left truncation due to varying gestational timing of enrollment, and data were censored at 20 weeks' gestation [19]. As demonstrated in previous work, for time-to-event endpoints such as spontaneous abortion, in order to avoid selection bias it is also crucial to account for the fact that women may receive vaccination after enrollment in the study [19]. Therefore, Cox proportional hazards modeling with time-varying exposure to vaccine was used to estimate hazard ratios (HRs) and their 95% CIs. Similar methods were used for preterm delivery, where the sample was restricted to live births among women who enrolled prior to 37 weeks' gestation, and data were censored at 37 weeks' gestation. Twins were excluded in the analyses of preterm delivery and small for gestational age infants due to higher risk in multiple gestations.

Control for confounding was conducted where numbers permitted. All relevant covariates specific to each outcome, including maternal age, race, ethnicity, socioeconomic status, tobacco, alcohol, pre-pregnancy body mass index, use of vitamin supplements, pregnancy history, infection, fever, asthma, depression, autoimmune disease, other known human teratogens, and hypertension were considered as possible confounders.

Using a criterion of $\geqslant$10% change in the estimate of the RR or the HR of vaccine exposure with the addition of each covariate in a model containing exposure, potential confounders were selected for each outcome. If one confounder was identified, direct adjustment was performed. If two or more confounders were identified for a particular outcome, a propensity score was created incorporating the identified confounders for that outcome with the propensity score predicting exposure to the influenza vaccine [20]. Given the modest sample size, the propensity score approach was used as a method of reducing the number of covariates required for inclusion in the model to a single adjustment factor based on identified confounders. We employed the selection process described above to ensure that those variables that were strongly correlated with the exposure but only weakly correlated with the outcome were not included in the propensity scores [21]. Propensity scores were computed for each specific outcome using logistic or Cox regression depending on the outcome, and all confounders as covariates [20,21]. Adjusted RRs or HRs were then computed using logistic or Cox regression. All analyses were conducted using R open-source statistical software.

3. Results

There were 1730 subjects available for analysis; 1263 were exposed to a seasonal influenza vaccine in pregnancy, and 467 were unexposed to any influenza vaccine in pregnancy. The lost-to-follow-up rate was 4.9%. Women in the exposed cohort were more likely to enroll in the study later in gestation, to have comorbidities such as psychiatric conditions, and less likely to reside in Canada (Table 1).

The proportion of stillbirths or elective terminations did not differ between exposed and unexposed; however, women who were vaccinated in the first trimester or any trimester were more likely than unvaccinated women to deliver at least one live born infant (Table 2). Among pregnancies ending in live birth, 25 of the 446 (5.6%) who had first-trimester vaccine exposure were diagnosed with major birth defects compared to 12/409 (2.9%) in unexposed (RR 1.91, 95% CI 0.97, 3.75). Among all pregnancies enrolled with outcome, excluding those lost-to-follow-up, there were 26/457 (5.7%) first-trimester exposed pregnancies that resulted in at least one fetus/infant diagnosed with a major birth defect compared to 13/427 (3.0%) in the unexposed (Table 2). Although numbers of events were small in the season-by-season analyses, estimates for the crude RRs ranged from 1.30 in the 2010–11 season to 2.59 in the 2013–14 season with all CIs including the null (Table e1). The specific major defects reported in the vaccine-exposed group by season of exposure are shown in Table e2.

Spontaneous abortion risks in the four seasons combined (Table 3) did not vary by exposure status, with the point estimate of the HR approximating 1.0 for first trimester exposure (adjusted HR 1.12, 95% CI 0.47, 2.65) and for any exposure in pregnancy prior to 20 weeks' gestation (HR 1.09, 95% CI 0.49, 2.40). Crude HRs by season were possible to estimate only in the first two seasons due to small numbers of events (Table e3).

The overall adjusted HR for preterm delivery with exposure at any time in pregnancy through 37 weeks' gestation compared to no exposure was 1.23 (95% CI 0.75, 2.02) and results were similar by trimester of exposure (Table 4). The subanalyses season-by-season resulted in point estimates of the crude HR for anytime in pregnancy exposure that tended to decline with later seasons (Table e4). The crude HR for exposure anytime in pregnancy in the 2010–11 season was 2.04 (95% CI 0.78, 5.34) and in the 2011–12 season the anytime in pregnancy HR was 2.69 (95% CI 0.90, 8.00). In addition, substantially elevated HRs with wide CIs were noted in the 2011–2012 season with 1st trimester exposure (unadjusted HR 3.65, 95% CI 1.16, 11.46). In the subset of women vaccinated in the two weeks prior to the estimated date of conception (LMP-DOC), elevated odds ratios were seen overall, and in three of the four seasons, although estimates were unstable as there were two or fewer preterm events in any one season.

The point estimate of the RR for small for gestational age infants on birth weight for exposure anytime in pregnancy across all four seasons was 1.49 (95% CI 0.93, 2.39). Small for gestational age RRs

Table 1
Selected maternal characteristics of women exposed during pregnancy to seasonal influenza vaccine and pregnant women not exposed to any influenza vaccine, 2010–2014.

Characteristic	Exposed *N* = 1263 *n* (%)	Unexposed *N* = 467 *n* (%)
Maternal age (years)[a]		
<25	71 (5.6)	46 (9.9)
25,29	272 (21.6)	107 (23.0)
30,34	433 (34.3)	161 (34.6)
>34	486 (38.5)	151 (32.5)
Maternal race		
White	983 (77.8)	329 (70.4)
Black	47 (3.7)	32 (6.9)
Asian/Pacific Islander	71 (5.6)	34 (7.3)
Indian/Native American	6 (0.5)	2 (0.4)
Other	7 (0.6)	5 (1.1)
Refused	1 (0.1)	0
Missing race due to recoding	148 (11.7)	65 (13.9)
Maternal ethnicity[b]		
Non-Hispanic	1094 (86.8)	390 (83.7)
Hispanic	167 (13.2)	76 (16.3)
Maternal education (years)		
<12 y	51 (4.0)	23 (4.9)
12,15 y	252 (20.0)	119 (25.5)
>15 y	960 (76.0)	325 (69.6)
Family SES[c]		
1	582 (46.8)	168 (36.4)
2	419 (33.7)	167 (36.1)
3	130 (10.5)	66 (14.3)
4	62 (5.0)	42 (9.1)
5	50 (4.0)	19 (4.1)
Country of residence[d]		
U.S.	1175 (93.2)	379 (81.2)
Canada	86 (6.8)	88 (18.8)
Gestational age at enrollment in study		
<13 weeks	224 (17.7)	141 (30.2)
13–26 weeks	570 (45.1)	207 (44.3)
>26 weeks	469 (37.1)	119 (25.5)
Gravidity > 1	762 (60.3)	286 (61.2)
Parity > 0	570 (45.1)	214 (45.8)
Previous spontaneous abortion (any)	327 (25.9)	130 (27.8)
Previous elective termination (any)	89 (7.0)	48 (10.3)
Pre-pregnancy body mass index[e]		
<18.5	37 (2.9)	23 (5.0)
18.5–24.9	778 (62.0)	269 (58.0)
25–29.9	258 (20.6)	105 (22.6)
⩾30	182 (14.5)	67 (14.4)
Alcohol (any)	560 (44.3)	168 (36.0)
Tobacco (any)	53 (4.2)	20 (4.3)
Folic acid containing supplements		
Started prior to conception	910 (72.1)	298 (63.8)
Post-conception only	347 (27.5)	165 (35.3)
Not at all	6 (0.5)	4 (0.9)
History of a child with a birth defect	49 (3.9)	15 (3.2)
Diagnosis of asthma	261 (20.7)	91 (19.5)
Thyroid or other autoimmune disease	427 (33.8)	70 (15.0)
Antidepressant use	112 (8.9)	13 (2.8)
Diagnosis of other psychiatric conditions	222 (17.6)	23 (4.9)
Exposure to other known or suspected Human teratogens	66 (5.2)	18 (3.9)
Pre-gestational hypertension	32 (2.5)	5 (1.1)
Gestational hypertension[f]	97 (8.1)	22 (5.5)
Preeclampsia[g]	60 (5.0)	16 (3.9)
Diagnosed with influenza in pregnancy	40 (3.2)	20 (4.3)
Any non-flu infection in pregnancy[h]	943 (74.7)	327 (70.5)
Vaccine year[i]		
2010–2011	340 (26.9)	135 (28.9)
2011–2012	253 (20.0)	141 (30.2)
2012–2013	379 (30.0)	101 (21.6)
2013–2014	291 (23.0)	90 (19.3)
Gestational age at vaccine exposure		—
<13	495 (39.2)	
13–26	479 (37.9)	
>26	289 (22.9)	

[a] Missing for 1 subject in Exposed Group and 2 subjects in Unexposed Group.
[b] Missing for 2 subjects in Exposed Group and 1 subject in Unexposed Group.
[c] SES was categorized using Hollingshead criteria based on maternal and paternal education and occupation; 1 is highest and 5 is lowest [22]. Values missing for 20 subjects in Exposed Group and 5 subjects in Unexposed Group.
[d] Missing for 2 subjects in Exposed Group.
[e] Missing for 8 subjects in Exposed Group and 3 subjects in Unexposed Group.
[f] Missing for 14 subjects in Exposed Group and 11 subjects in Unexposed Group. Denominator excludes subjects with outcomes of spontaneous abortion, termination, or lost-to-follow-up.
[g] Missing for 3 subjects in Exposed Group. Denominator excludes subjects with outcomes of spontaneous abortion, termination, or lost-to-follow-up.
[h] Missing for 1 subject in Exposed Group and 3 subjects in Unexposed Group.
[i] Vaccine year starts from August 1st of each year. For Exposed Group, vaccine year was based on exposure time, for Unexposed Group, vaccine year was based on enrollment time. Four subjects received two vaccines in one season.

for length and head circumference were close to unity with exposure anytime in pregnancy and in all cases the 95% CIs included 1.0 (Table 5). Season-by-season estimates for these same endpoints in crude analyses were variable (Table e5).

4. Discussion

For the four influenza seasons combined, we found no evidence of a meaningful increase in spontaneous abortion, preterm delivery or small for gestational age infants in exposed compared to unexposed pregnancies. These findings are consistent with the few studies that have been published on seasonal influenza vaccines administered in the U.S. or Canada in these four seasons [4]. We found a modestly elevated risk of 1.87 for major birth defects overall with pregnancy exposure to seasonal influenza vaccine products in the first trimester, with a lower bound of the CI of 0.97. However, the case-control arm of VAMPSS found no increased risk for major birth defects overall (adjusted OR 1.00, 95% CI 0.84, 1.19) [10]. There was no evidence of clustering in the specific defects reported in our cohort study among the vaccine-exposed pregnancies (Table e2). Furthermore, of the defects reported in the cohort study, only one case of craniosynostosis was consistent with those specific defects reported at an adjusted OR of 2.0 or more in any of the four separate seasons the case-control study (craniosynostosis, cleft palate, extra or horseshoe kidney, renal agenesis/dysgenesis, agenesis or dysgenesis of the corpus callosum, tracheoesophageal fistula or omphalocele) [10]. Taken together, these findings suggest that the cohort study findings could be due to chance.

In the present analysis, we did not note an overall increase in preterm delivery in the four seasons combined. We had previously reported a 2–3-fold elevated risk for preterm delivery with vaccination in the 2009–2012 seasons combined, with some suggestion that the 2009–2010 seasonal risk was higher [5]. In the current analysis which excluded the 2009–2010 season, adjusted HRs by trimester and overall were close to the null. In contrast to the observations of Louik et al. [10], in our season-by-season analysis, we did not see an elevated risk in the 2011–2012 season for second trimester exposure (unadjusted HR 0.82, 95% CI 0.15, 4.48 based on 2 events in 75 exposed women). Instead, we saw an elevated HR for 1st trimester exposure in that season (unadjusted HR 3.65,

Table 2
Pregnancy outcomes of women exposed to seasonal influenza vaccine by gestational timing of exposure compared to women not exposed to any influenza vaccine, 2010–2014.

Outcome	Unexposed N = 467 n (%)	Vaccine exposed LMP-DOC[a] N = 23 n (%)	RR (95% CI)	Vaccine exposed 1st trimester N = 477 n (%)	RR (95% CI)	Vaccine exposed any trimester N = 1240 n (%)	RR (95% CI)
Live birth	409 (87.6)	20 (87.0)	0.99 (0.84, 1.17)	446 (93.5)	1.07 (1.02, 1.11)	1185 (95.6)	1.09 (1.05, 1.13)
Male, Singleton	219 (55.4)	11 (57.9)	1.04 (0.70, 1.55)	228 (52.8)	0.95 (0.84, 1.08)	564 (49.6)	0.89 (0.80, 0.99)
Twin	13 (3.2)	1 (5.0)	1.57 (0.12, 8.38)	14 (3.1)	0.99 (0.47, 2.08)	47 (4.0)	1.25 (0.68, 2.28)
Stillbirth	2 (0.4)	0	0 (0.00, 39.66)	2 (0.4)	0.98 (0.13, 7.62)	2 (0.2)	0.38 (0.05, 2.95)
Termination	1 (0.2)	0	0 (0.00, 150.60)	0	0 (0.00, 7.84)	0	0 (0.00, 2.80)
Lost-to-Follow-up	40 (8.6)	2 (8.7)	1.02 (0.23, 3.31)	20 (4.2)	0.49 (0.29, 0.82)	43 (3.5)	0.4 (0.27, 0.61)

Birth defects	Unexposed n/N (%)	Vaccine exposed LMP-DOC[a] n/N (%)	Crude RR (95% CI)	Vaccine exposed 1st trimester n/N (%)	Crude RR (95% CI)	Adjusted RR[b] (95% CI)
Major birth defects in live born infants	12/409 (2.9)	1/20 (5.0)	1.70 (0.13, 9.27)	25/446 (5.6)	1.91 (0.97, 3.75)	–
Major birth defects in all pregnancies[c]	13/427 (3.0)	1/21 (4.8)	1.56 (0.12, 8.47)	26/457 (5.7)	1.87 (0.97, 3.59)	–

[a] LMP-DOC is defined as exposure between 1st day of last menstrual period and estimated date of conception.
[b] No adjusted RR was calculated because no confounder was identified.
[c] The denominator includes all pregnancies with outcome: live births, stillbirths, terminations, and spontaneous abortions.

Table 3
Estimated probabilities of spontaneous abortion for those enrolled and exposed prior to 20 weeks' gestation to seasonal influenza vaccine compared to women enrolled prior to 20 weeks' gestation and not exposed to any influenza vaccine, 2010–2014.

Vaccine exposure	Number of subjects	Number of spontaneous abortions	Kaplan meier estimate (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Unexposed	267	15	15.9% (8.9, 27.5%)	Reference	Reference
LMP-DOC[b]	16	1	11.1% (1.6, 56.7%)	1.12 (0.15, 8.46)	–
1st Trimester	253	9	14.4% (6.6, 29.6%)	0.89 (0.39, 2.04)	1.12 (0.47, 2.65)
Prior to 20 weeks' gestation	380	11	11.6% (5.5, 23.5%)	1.09 (0.49, 2.40)	–

[a] No adjusted HR was calculated for LMP-DOC due to the small number of events. The 1st trimester HR was adjusted for a propensity score comprised of pre-pregnancy body mass index and influenza season year. No adjusted HR was calculated for the group exposed anytime in pregnancy prior to 20 gestational weeks because no confounder was identified.
[b] LMP-DOC is defined as exposure between 1st day of last menstrual period and estimated date of conception.

Table 4
Estimated probabilities of preterm delivery in women enrolled and exposed prior to 37 weeks' gestation to seasonal influenza vaccine compared to women enrolled prior to 37 weeks' gestation and not exposed to any influenza vaccine, 2010–2014.

Vaccine exposure	Number of subjects	Number of preterm deliveries	Kaplan meier estimate (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Unexposed	379	21	5.9% (3.8, 8.9%)	Reference	Reference
LMP-DOC[b]	18	4	22.2% (9.0, 48.9%)	4.07 (1.40, 11.86)	2.48 (0.25, 24.88)
1st Trimester	422	31	7.7% (5.5, 10.8%)	1.33 (0.77, 2.32)	–
2nd Trimester	418	23	6.2% (4.1, 9.2%)	1.04 (0.58, 1.88)	1.23 (0.59, 2.57)
3rd Trimester	234	14	6.8% (4.0, 11.2%)	1.52 (0.76, 3.05)	1.28 (0.63, 2.58)
Anytime in pregnancy	1092	72	7.2% (5.8, 9.1%)	1.39 (0.85, 2.27)	1.23 (0.75, 2.02)

[a] The LMP-DOC HR was adjusted for a propensity score comprised of pre-pregnancy body mass index, maternal education, socioeconomic status, gestational hypertension, infection, and influenza season year. No adjusted HR was calculated for the 1st trimester comparison because no confounder was identified. The 2nd trimester HR was adjusted for a propensity score comprised of influenza season year and use of corticosteroids. The 3rd trimester HR was adjusted directly for gestational hypertension.
[b] LMP-DOC is defined as exposure between 1st day of last menstrual period and estimated date of conception.

95% CI 1.16, 11.46, based on 11 events in 92 exposed women, Table e4). These isolated findings with small numbers of events among multiple comparisons could be due to chance. In addition, the inconsistency of our findings compared to the Louik et al. study by specific trimester of exposure and vaccine season do not support causality. However, the seasonal variation we have noted in associations of influenza vaccine with preterm delivery does suggest that further season by season research is needed, and further exploration of exposure in the window of time just prior to conception is warranted.

VAMPSS has proposed criteria to guide the identification of risk and safety signals [9]; these include "no evidence of risk" when a RR or HR approximates 1.0 with an upper 95% CI $\leqslant$ 4.0 and "evidence of relative safety" when a RR or HR approximates 1.0 with an upper 95% CI $\leqslant$ 2.0. Applying these guidelines, we found that spontaneous abortion and preterm delivery in the combined seasons included in this study met the criteria of "no evidence of risk".

Our study has several strengths and some limitations. We recruited women during pregnancy before the outcome was known and evaluated pregnancies for a range of endpoints. We

Table 5
Small for gestational age (SGA) infants[a] born to women exposed to seasonal influenza vaccine compared to women not exposed to any influenza vaccine, 2010–2014.

Vaccine exposure	Number of subjects[b]	Number SGA (%)	Crude RR (95% CI)	Adjusted RR[c] (95% CI)
Weight				
Unexposed	395	20 (5.1)	Reference	Reference
LMP-DOC[d]	19	1 (5.3)	1.04 (0.07, 5.29)	–
1st Trimester	430	32 (7.4)	1.47 (0.86, 2.53)	–
2nd Trimester	433	35 (8.1)	1.60 (0.94, 2.72	–
3rd Trimester	272	19 (7.0)	1.38 (0.75, 2.54)	1.76 (0.87, 3.53)
Anytime in pregnancy	1154	87 (7.5)	1.49 (0.93, 2.39)	–
Length				
Unexposed	377	13 (3.4)	Reference	Reference
LMP-DOC[d]	19	0	0 (0.00, 5.29)	–
1st Trimester	421	17 (4.0)	1.17 (0.58, 2.38)	0.93 (0.43, 2.04)
2nd Trimester	415	18 (4.3)	1.26 (0.62, 2.53)	1.41 (0.67, 2.99)
3rd Trimester	266	13 (4.9)	1.42 (0.67, 3.01)	–
Anytime in pregnancy	1121	48 (4.3)	1.24 (0.68, 2.27)	1.40 (0.73, 2.69)
Head circumference				
Unexposed	288	38 (13.2)	Reference	Reference
LMP-DOC[d]	13	1 (7.7)	0.58 (0.04, 2.66)	–
1st Trimester	343	60 (17.5)	1.33 (0.92, 1.93)	–
2nd Trimester	338	55 (16.3)	1.23 (0.84, 1.81)	–
3rd Trimester	232	30 (12.9)	0.98 (0.63, 1.53)	1.09 (0.64, 1.85)
Anytime in pregnancy	926	146 (15.8)	1.19 (0.86, 1.66)	–

[a] Small for gestational age (SGA) defined as <10th centile for sex and gestational age using NCHS 2000 growth curves or Lubchenko [16–18].
[b] Numbers of subjects vary for each outcome measure due to missing values.
[c] The RRs for LMP-DOC were not adjusted in any comparison due to the small number of events. The RRs for weight were not adjusted for the 1st and 2nd trimester or anytime in pregnancy because no confounder was identified. The RR for weight in the 3rd trimester was adjusted for a propensity score comprised of maternal age and pre-pregnancy body mass index. The RR for length was not adjusted for the 3rd trimester because no confounder was identified. The RR for length for the 1st trimester was adjusted for a propensity score comprised of antidepressant use in pregnancy and other psychiatric conditions; for 2nd trimester and anytime in pregnancy, the RRs for length were directly adjusted for pre-pregnancy body mass index. The RRs for head circumference were not adjusted for 1st and 2nd trimester or anytime in pregnancy because no confounder was identified. The RR for head circumference for 3rd trimester was directly adjusted for maternal thyroid or autoimmune disease.
[d] LMP-DOC is defined as exposure between 1st day of last menstrual period and estimated date of conception.

experienced very low lost-to-follow-up rates. We collected information on vaccination exposure directly from the woman during pregnancy which allowed us to identify exposures that might not be recorded in medical or claims records if the vaccine was given in a non-traditional setting such as a pharmacy, school, community center, etc. Although it is possible that some women were misclassified as unexposed if they failed to report being vaccinated, the direct method of questioning the mother specifically about influenza vaccination (gestational timing of vaccination and the setting in which given) during the maternal interviews suggests this would be unlikely to occur. Our study involved a volunteer sample that was not population-based and we had imbalances in some covariates in the vaccinated vs. non-vaccinated women; however, we concurrently recruited comparison women and addressed confounding on those measured covariates that were relevant. Our ability to identify risks for specific birth defects is limited in a cohort study of this size; however, the complementary nature of the VAMPSS system allows both study designs to test hypotheses using different methods. The overall findings of this study provide general reassurance regarding influenza vaccine safety in pregnancy. However, the season-by-season findings demonstrate considerable variability and reinforce the need for continued surveillance of seasonal influenza vaccine in each season and ultimately for specific influenza products.

Conflict of interest

Dr. Christina D. Chambers receives research funding from GlaxoSmithKline who manufactures a Quadrivalent Influenza Vaccine. Dr. Chambers also receives research funding from the following industry sponsors: AbbVie; Amgen Inc.; Apotex, Barr Laboratories, Inc.; Bristol-Myers Squibb; Celgene; GlaxoSmithKline; Janssen Pharmaceuticals; Kali Laboratories, Inc.; Pfizer, Inc.; Hoffman La Roche-Genentech; Sandoz Pharmaceuticals; Genzyme Sanofi-Aventis; Seqirus; Takeda Pharmaceutical Company Limited; Teva Pharmaceutical Industries Ltd.; and UCB, USA. Dr. Allen A. Mitchell is a member of Biogen's Tecfidera Pregnancy Registry Advisory Committee. All other authors do not have any Conflicts of Interest to declare.

Acknowledgements

We are indebted to the members of the VAMPSS Vaccine and Asthma Advisory Committee for their contributions to the design, conduct, and analysis of this study: Margaret Honein (chair), Dixie Snider, Robert Glynn, James Mills, Elizabeth Conradson Cleary, Joseph Bocchini, and Peter Gergen. We make special note of the continuing support of Jo Schweinle and Tanima Sinha at BARDA and for the ongoing support provided by Lauri Sweetman and Sheila Heitzig at AAAAI.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.06.054.

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