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Safety of influenza vaccination during pregnancy: A review of subsequent maternal obstetric events and findings from two recent cohort studies

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Abstract

Pregnant women and their infants are vulnerable to severe disease and secondary complications from influenza infection. For this reason, annual influenza vaccination is recommended for all pregnant women in the United States. Women frequently cite concerns about vaccine safety as a barrier to vaccination. This review describes the safety of inactivated influenza vaccination during pregnancy with a focus on maternal obstetric events, including hypertensive disorders, gestational diabetes, and chorioamnionitis. Included in the review are new findings from two studies which examined the safety of seasonal inactivated influenza vaccination during pregnancy. The first study enrolled 641 pregnant women during the 2010–2011 season and prospectively followed them until delivery or pregnancy termination. The second study enrolled 1616 pregnant women during the 2010–2011 influenza season, and followed the women and their infants for six months after delivery. No associations between inactivated influenza vaccination and gestational diabetes, gestational hypertension, preeclampsia/eclampsia, or chorioamnionitis were observed in either cohort. When considered as a whole, these studies should further reassure women and clinicians that influenza vaccination during pregnancy is safe for mothers.

Keywords

Pregnancy; Influenza vaccine; Safety; Obstetric outcomes

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1. Introduction

Pregnant women are at increased risk of developing severe illness and secondary complications related to influenza infection [1–3]. This increased risk has been noted both during pandemic and routine influenza seasons. For this reason, the Advisory Committee on Immunization Practices (ACIP) recommends inactivated influenza vaccination for pregnant women during any trimester of pregnancy [4]. These recommendations are supported by the American Academy of Pediatrics, the American Academy of Family Practitioners, and the American College of Obstetrics and Gynecology [5].

Despite this long-standing recommendation and strong support from professional societies, influenza vaccination coverage rates during pregnancy in the United States were generally less than 30% prior to the influenza A (H1N1) pandemic in 2009 [6]. The 2009 pandemic resulted in increased attention to the importance of vaccination during pregnancy, and studies conducted during and after the 2009–2010 season have reported coverage rates ranging from 47% to 63% [7,8]. While the rates have increased, they are still less than the Healthy People 2020 target goal of 80% coverage in the United States [9].

Concern about vaccine safety is often cited as a reason for women declining influenza vaccination during pregnancy [7,10]. However, a growing body of scientific evidence suggests that influenza vaccination is safe for both mothers and fetuses [1–4,11]. In this review, we describe findings from spontaneous reporting systems and epidemiologic studies, focusing on the risk of four relatively common maternal obstetric events: gestational hypertension, preeclampsia/eclampsia, gestational diabetes, and chorioamnionitis. We also present new data from two cohort studies which examined the association between receipt of seasonal inactivated influenza vaccine (IIV) during pregnancy and these four obstetric outcomes.

Pregnancy-related hypertension, which includes gestational hypertension, preeclampsia, and eclampsia, is associated with adverse health effects among both mothers and infants. Pregnancy-related hypertension increases the risk for preterm and cesarean delivery, renal dysfunction, placental abruption, chronic hypertension, maternal death [12,13] and respiratory distress syndrome and fetal growth restriction in the infant [12,14,15]. The prevalence of pregnancy-related hypertension has been reported to range from 1% to 8% and varies by race/ethnicity, with lowest rates reported among white mothers [13,14,16,17].

Gestational diabetes also carries risk for both mothers and infants; it has been found to increase the risk for preterm and cesarean delivery and type 2 diabetes in the mother [18,19] and hyperinsulinemia, future obesity and diabetes in the infant [20–22]. Gestational diabetes occurs in approximately 4% of pregnancies and its prevalence ranges from 1% to 14% among different racial/ethnic groups [23]. Rates of gestational diabetes are also lowest among white mothers [24,25].

Chorioamnionitis, the inflammation of the amniotic fluids, membranes, or placenta due to bacterial infection, occurs in approximately 8% of pregnancies [26]. It is associated with significant maternal and fetal morbidity, including stillbirth, rupture of membranes, premature labor, developmental delay, and childhood asthma [26,27].

Inflammation may contribute to the etiology of pregnancy-related hypertension and gestational diabetes. Christian et al. have demonstrated that influenza vaccination can act as a trigger for mild, transient inflammation in pregnant women [28]. Specifically, they report elevations in C-reactive protein and tumor necrosis factor-α within one week of vaccination. This inflammatory response following vaccination was usually milder and more transient than the response seen with influenza infections; however, there was variability in individual responses which suggests that vaccination could induce an inflammatory response in certain women that could lead to the development of adverse events during pregnancy. The potential underlying mechanism for vaccine-associated chorioamnionitis is unknown and unclear. We decided to include chorioamnionitis in this review because it has been described in several of the studies discussed below.

2. Review of the literature

To identify studies reporting on the safety of influenza vaccination during pregnancy, we searched Ovid and PubMed using combinations of the following terms: “pregnancy”, “vaccination”, “influenza”, “safety”, “diabetes”, “hypertension”, and “chorioamnionitis”. We identified both observational studies and reports from spontaneous reporting systems published in 1993 through 2013. References of relevant articles were reviewed, and from those lists additional studies were examined and included when applicable. We included studies of inactivated influenza vaccination (trivalent and monovalent) and live, attenuated influenza vaccination.

3. Spontaneous reporting systems

Summaries of spontaneous reporting systems in the United States (US) and Taiwan have reported few adverse obstetric events following influenza vaccination in pregnancy [29–31]. Moro and colleagues characterized reports to the US Vaccine Adverse Events Reporting System (VAERS) among pregnant women who received seasonal and pandemic influenza vaccines. Seasonal influenza vaccine receipt between July 1990 and June 2009 resulted in a total of 175 reported events, 21 of which were deemed serious. There was one reported case of gestational diabetes and one case of gestational hypertension following receipt of trivalent IIV; none of the pre-specified obstetric events were reported following receipt of live attenuated influenza vaccine [29]. Through February 2010 a total of 294 reports were received by VAERS following receipt of the 2009 monovalent influenza A (H1N1) vaccine among pregnant women. Two cases of preeclampsia were reported [30]. While incidence rates cannot be calculated from these surveillance data, the spontaneous reports did not identify patterns of obstetric events following influenza vaccination among pregnant women in the United States. The Taiwanese national spontaneous reporting system tracked reported adverse events following vaccination with the 2009 monovalent influenza A (H1N1) vaccine among 14,474 pregnant women. Thirty five adverse events were reported, including two cases of chorioamnionitis-associated stillbirth. No other pre-specified obstetric events were reported [31]. As in the United States, spontaneous reports in Taiwan did not reveal any concerning pattern of adverse obstetric events following influenza vaccination.

4. Observational studies

Lack of association between influenza vaccination during pregnancy and adverse maternal obstetric events has also been demonstrated in several recent observational studies (Table 1) [32–39]. These studies examined receipt of unadjuvanted [35,36] and adjuvanted [33–35,37,39] monovalent inactivated influenza vaccine (IIV), in addition to trivalent IIV [32,38]. Of the adverse obstetric outcomes included in this review, the most thoroughly examined was preeclampsia/eclampsia. Kharbanda et al. reported similar rates of both mild preeclampsia and severe preeclampsia or eclampsia among 74,292 women following vaccination with trivalent IIV, compared to 144,597 unvaccinated women [38]. In a large study of active duty US military women, Conlin and colleagues found no significant differences in preeclampsia or eclampsia rates between two vaccination groups: unadjuvanted monovalent IIV and trivalent IIV (adjusted hazard ratio 1.10, 95% CI 0.97–1.26) [36]. Kallan et al. reported a similar lack of association with the AS03-adjuvanted monovalent IIV using Swedish register data [37]. Smaller studies reported lower than expected rates of preeclampsia following vaccination [33], or similar lack of differences as reported above [32,34,35,39].

Four existing studies have examined the relationship between influenza vaccination during pregnancy and the subsequent development of gestational diabetes. One large retrospective matched cohort found a significantly reduced risk of gestational diabetes among women vaccinated with the trivalent IIV, both using a 42-day risk window (adjusted relative risk 0.89) and a pregnancy-end risk window (adjusted hazard ratio 0.88), compared to unvaccinated women [38]. A similar significant reduced rate of gestational diabetes was discovered following vaccination with the MF59-adjuvanted monovalent vaccine [34]. Two studies with smaller numbers of vaccinated women found no difference in rates of gestational diabetes following AS03-adjuvanted monovalent vaccine [37] or trivalent IIV compared to unvaccinated women [32].

Two large studies found no increased risk of gestational hypertension following trivalent IIV [38] or the AS03-adjuvanted monovalent vaccine, compared to unvaccinated control groups [39]. Tavares and colleagues found a lower than expected rate of gestational hypertension among women vaccinated with the AS03-adjuvanted vaccine, but the conclusion was based on four identified cases and no comparison group [33]. To our knowledge, only one observational study has examined chorioamnionitis following influenza vaccination. Kharbanda et al. found a non-significant higher risk of chorioamnionitis following vaccination with trivalent IIV, compared to unvaccinated pregnant women (adjusted hazard ratio = 1.08, NS) [38].

Of the eight existing observational studies described in this review [32–39], six focused on the 2009 monovalent influenza vaccine. Existing data on seasonal trivalent IIV and its association with these outcomes are limited. Although one of the two studies looking at trivalent IIV was large in size, the exclusive use of electronic medical record data did result in limitations, including potential misclassification of both exposure status and outcomes [38]. The six studies focused on the 2009 monovalent IIV were varied in size, methods, and population. By design, these observational studies were at risk for uncontrolled confounding

[34] and possible selection bias [39]. Three of the studies warn of possible exposure misclassification [34,36,37], and two studies were limited in size [33,35]. One study did not include a control group [33]. Strengths of the existing observational studies include large size [34,36–39], comprehensive data collection [34,37,38], and prospective design [33–35].

5. New findings

To fill some of the gaps in our knowledge about the safety of seasonal IIV during pregnancy and these maternal outcomes, we present new findings from two observational cohort studies sponsored by the Centers for Disease Control and Prevention (CDC) below. Institutional Review Boards at each participating site reviewed and approved the protocols and materials for both studies.

6. Vaccine Safety Datalink (VSD) Cohort

We prospectively enrolled 641 pregnant women in the fall/winter of 2010 within two healthcare delivery systems, Kaiser Permanente Northwest (KPNW) in Oregon and Marshfield Clinic (MFC) in Wisconsin. Detailed information about study methods has been published previously [10]. Briefly, enrollment occurred either in person or by telephone after the participant's initial prenatal visit. Participants were asked to complete a survey at enrollment and a two-week symptom diary following influenza vaccination. A detailed medical record abstraction was conducted after delivery to collect information about maternal and infant outcomes. Information about influenza vaccination was extracted from electronic medical record (EMR) databases and state immunization registries at both sites.

Trained study staff collected detailed information about gestational hypertension, preeclampsia/eclampsia, gestational diabetes, and chorioamnionitis diagnoses, including dates of onset, through manual review of medical records. We identified cases of chorioamnionitis with diagnoses within two weeks of delivery; the other outcomes were limited to diagnoses at ≥20 weeks gestation. We then compared influenza vaccination coverage among cases and the remaining controls from the enrolled cohort using chi-squared tests. We limited vaccine exposures to those occurring during pregnancy and prior to diagnosis among cases; among controls, vaccine exposures were limited to those occurring during pregnancy. We also conducted logistic regression analyses for each outcome adjusting for maternal age and study site.

We enrolled 362 women at KPNW and 279 women at MFC. The mean maternal age at enrollment was 28.6 years (SD 5.4, range 18–49); women enrolled at KPNW were significantly older than women enrolled at MFC (29.2 years vs. 27.9 years, $p < 0.001$). Overall, 277 (43%) women received 2010–2011 IIV; 266/277 (96%) women were vaccinated while pregnant. Among those vaccinated weeks (SD 9.3, range 5–38). Women enrolled at KPNW were significantly more likely to be vaccinated than women enrolled at MFC (49% vs. 35%, $p < 0.001$). We identified 31 cases of gestational hypertension (4.8% prevalence), 25 cases of preeclampsia/eclampsia (3.9%), 33 cases of gestational diabetes (5.1%), and 15 cases of chorioamnionitis (2.3%) (Table 2). Influenza vaccine coverage during pregnancy did not differ significantly (p-values > 0.05) between cases and controls

for any of these four outcomes. After adjusting for maternal age and study site, no significant associations were observed between vaccination and the maternal outcomes (data not shown).

7. Pregnancy and Influenza Project (PIP) Cohort

We enrolled 1616 pregnant women during the 2010–2011 influenza season at KPNW and Kaiser Permanente Northern California (KPNC), and followed the cohort and their infants until six months after delivery. Detailed information about study methods has been published previously [40]. Participants were identified after a prenatal care visit and were recruited by telephone. Participants completed surveys at enrollment, 1 month after delivery, and 6 months after delivery. Information about influenza vaccination was obtained through both self-report and EMR data.

Maternal outcomes were identified using EMR data and International Classification of Disease, 9th Revision (ICD-9) codes. Preeclampsia/eclampsia (ICD-9 codes 642.4x–642.7x), gestational hypertension (ICD-9 codes 642.3x, 642.9x), and gestational diabetes (ICD-9 codes 648.8x) diagnoses were identified at ≥20 weeks gestation. Women with pre-existing diabetes (ICD-9 codes 250.xx, 251.xx) or hypertension (ICD-9 codes 401.xx, 642.0x–642.3x) were excluded from the gestational diabetes and gestational hypertension analyses, respectively. Chorioamnionitis (ICD-9 codes 658.4x) diagnoses were identified within two weeks of delivery. We then compared influenza vaccination coverage among cases compared to the remaining controls from the enrolled cohort using chi-squared tests. We limited vaccine exposures to those occurring during pregnancy and prior to diagnosis among cases; among controls, vaccine exposures were limited to those occurring during pregnancy. We also conducted logistic regression analyses for each outcome adjusting for maternal age and study site.

Of the 1616 participants, 999 were enrolled at KPNC and 617 were enrolled at KPNW. The mean maternal age at enrollment was 32.1 years (SD 5.2, range 16–49); women enrolled at KPNC were significantly older than women enrolled at KPNW (32.8 years vs. 31.1 years, $p < 0.0001$). Sixty-five percent (1052/1616) of the cohort received 2010–2011 IIV; 924/1052 (88%) were vaccinated while pregnant. Among those vaccinated during pregnancy, the mean gestational age at vaccination was 16.6 weeks (SD 8.5, range 0–40). Vaccination rates did not differ between study sites (66% at KPNC vs. 63% at KPNW, $p = 0.21$). We identified 117 cases of gestational hypertension (7.2% prevalence), 96 cases of preeclampsia/eclampsia (5.9%), 192 cases of gestational diabetes (11.9%), and 121 cases of chorioamnionitis (7.5%) (Table 3). Influenza vaccine coverage during pregnancy did not differ (p-values > 0.05) between cases and controls for any of these four outcomes. After adjusting for maternal age and study site, no significant associations were observed between vaccination and the maternal outcomes (data not shown).

8. Discussion

We found no significant associations between influenza vaccination during pregnancy and four maternal obstetric events (gestational hypertension, gestational diabetes, preeclampsia/

eclampsia, and chorioamnionitis) in the VSD and PIP analyses. These new findings are consistent with other published studies showing no elevated risk of these events following vaccination [32–39]. The VSD and PIP studies each enrolled a relatively large number of participants, and followed participants through delivery using the comprehensive EMR data available at participating sites to monitor outcomes and vaccine exposures.

The new data presented here focused on the safety of seasonal IIV during pregnancy. The majority of existing literature on the safety of inactivated influenza vaccine during pregnancy focuses on pandemic H1N1 monovalent IIV. The recent study by Kharbanda and colleagues is the largest study of seasonal trivalent IIV and maternal obstetric events to date and found results consistent with the VSD and PIP findings [38]. Kharbanda and colleagues report a significantly lowered risk of gestational diabetes among women who receive IIV during pregnancy. Similarly, we observed lower IIV coverage among gestational diabetes cases in the VSD study relative to controls, but this difference was not statistically significant ($p = 0.06$). However, this trend was not present in the PIP analysis. Kharbanda and colleagues also report a statistically non-significant elevated risk of chorioamnionitis associated with vaccination. In the VSD analyses, vaccination coverage was higher among 15 chorioamnionitis cases compared to controls (60% vs. 43%, $p = 0.18$), but this trend was not seen in the PIP analyses which included a larger number of cases.

The prevalence rates of the obstetric events in the PIP study were higher than those from the VSD study, which likely reflects differences in the methods used to identify these outcomes. Diagnoses were manually abstracted by medical records reviewers in the VSD study. This method could have introduced differential misclassification bias; however, abstractors were blinded to the participant's vaccination status during the review. The PIP study extracted ICD-9 coded diagnoses from EMR databases, which could have introduced misclassification of outcomes by including miscoded or "ruled out" diagnoses. Although the data collection methods differed between the two studies, all of the prevalence rates reported in these two analyses are consistent with the prevalence ranges reported by other studies of these maternal events [13,14,16,17,23,26].

Participant recruitment for both the VSD and PIP studies occurred during slightly different periods of time at KPNW, but there were several months of overlap which resulted in 87 participants simultaneously enrolled in both studies. A small number ($n = 1–9$ per outcome) of these participants developed the four maternal events of interest. Excluding these participants from the analyses did not affect the findings from either study (data not shown).

We have focused our review and analyses on four common maternal obstetric events following influenza vaccination during pregnancy because data about these outcomes were collected in both the VSD and PIP studies. We did not include other important pregnancy outcomes, such as spontaneous abortion or Cesarean delivery, nor did we include infant outcomes, such as preterm delivery, low birth weight, and congenital anomalies. Neither the VSD nor PIP studies were designed to examine spontaneous abortion since both required participants to have had at least one prenatal visit, which usually occurs at 10–12 weeks gestation after a significant proportion of spontaneous abortions occur. Data about the mode of delivery (e.g., vaginal vs. cesarean section) were not consistently collected across the

VSD and PIP studies, nor was the follow-up of infant outcomes consistent, so these outcomes were not included. A separate analysis of infant outcomes and vaccination is underway in the PIP study. A growing body of scientific literature in this area suggests no adverse association between influenza vaccination during pregnancy and these other important pregnancy and infant outcomes [2,3,11,36,39,41].

Each of the studies presented here has its own methodological strengths and limitations. A large, randomized, placebo-controlled trial of IIV during pregnancy would provide the most robust safety data; however, it is not ethically possible to conduct such a study in the United States or other countries where the vaccination is recommended for all pregnant women. When considered as a whole, the existing surveillance reports and observational studies, and the new VSD and PIP findings reported here, should offer further reassurance to women and providers about the safety of inactivated influenza vaccination during pregnancy.

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Table 1

Summary of data on adverse obstetric events following influenza vaccination during pregnancy.

Study	Design	Study group	Control group	Vaccine(s) studied	Adverse obstetric outcome(s)
Munoz et al. [31]	Retrospective matched cohort	225 vaccinated pregnant women	826 unvaccinated pregnant women	Trivalent inactivated influenza	No significant difference in rates of gestational diabetes or preeclampsia
Tavares et al. [32]	Prospective cohort	267 vaccinated pregnant women	None	AS03-adjuvanted A/H1N1 (2009)	Four women (1.5%) diagnosed with preeclampsia/ hypertension within 181 days of vaccination; lower than expected rate
Heikkinen et al. [33]	Prospective matched cohort	2295 vaccinated pregnant women	2213 unvaccinated pregnant women	MF59-adjuvanted A/H1N1 (2009)	No difference in rates of preeclampsia (3.5% vaccinated, 3.4% unvaccinated; aOR 1.12, NS). Significantly lower rate of gestational diabetes among vaccinated (1.1% vs 2.2%; aOR 0.48)
Oppermann et al. [34]	Prospective matched cohort	323 vaccinated pregnant women	1329 unvaccinated pregnant women	AS03-adjuvanted A/H1N1 (2009), A/H1N1 (2009)	No difference in rates of preeclampsia (3.2% vaccinated, 4.5% unvaccinated; aOR 1.15, NS)
Conlin et al. [35]	Retrospective matched cohort	10,376 A/H1N1 (2009)-exposed pregnant women	7560 pregnant women vaccinated with seasonal influenza vaccine	A/H1N1 (2009)	No difference in rates of preeclampsia or eclampsia between vaccination groups (5.8% A/H1N1 vs. 5.2% seasonal)
Kallan et al. [36]	Retrospective matched cohort	18,612 vaccinated pregnant women	136,914 and 83,298 unvaccinated pregnant women	AS03-adjuvanted A/H1N1 (2009)	No significant difference in rates of gestational diabetes or preeclampsia delivery diagnoses
Kharbanda et al. [37]	Retrospective matched cohort	74,292 vaccinated pregnant women	144,597 unvaccinated pregnant women	Trivalent inactivated influenza	No difference in rates of gestational hypertension or preeclampsia/eclampsia; significantly lower risk of gestational diabetes among vaccinated, non-significant higher risk of chorioamnionitis among vaccinated
Rubinstein et al. [38]	Retrospective matched cohort	7293 vaccinated pregnant women	23,195 unvaccinated pregnant women	MF59-adjuvanted A/H1N1 (2009)	No significant difference in rates of pregnancy induced hypertension, preeclampsia, or eclampsia

Table 2

Maternal obstetric events and influenza vaccination coverage, 2010–2011 influenza season, Vaccine Safety Datalink (n = 641).

	Number of cases	Vaccinated cases, *n* (%)	Number of controls	Vaccinated controls, *n* (%)	*p*-value
Gestational hypertension	31	11 (35%)	610	264 (43%)	0.39
Preeclampsia/eclampsia	25	12 (48%)	616	263 (43%)	0.60
Gestational diabetes	33	9 (27%)	608	266 (44%)	0.06
Chorioamnionitis	15	9 (60%)	626	268 (43%)	0.18

Table 3

Maternal obstetric events and influenza vaccination coverage, 2010–2011 season, Pregnancy and Influenza Project (n = 1616).

	Number of cases	Vaccinated cases, *n* (%)	Number of controls	Vaccinated controls, *n* (%)	*p*-value
Gestational hypertension	117	69 (59%)	1499	855 (57%)	0.68
Preeclampsia/eclampsia	96	58 (60%)	1520	866 (57%)	0.51
Gestational diabetes	192	101 (53%)	1424	823 (58%)	0.17
Chorioamnionitis	121	68 (56%)	1495	856 (57%)	0.82