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Safety of influenza vaccination on adverse birth outcomes among pregnant women: A prospective cohort study in Japan

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ABSTRACT

Background: Pregnant women are in the highest priority group for receiving influenza vaccination. However, they may be reluctant to receive the vaccination due to concerns about the influence of vaccination on the fetuses.
Methods: This prospective cohort study of 10 330 pregnant women examined the safety of influenza vaccination in terms of adverse birth outcomes. Influenza vaccination during pregnancy was determined from questionnaires before and after the 2013/2014 influenza season. All subjects were followed until the end of their pregnancy. Adverse birth outcomes, including miscarriage, stillbirth, preterm birth, low birth weight, and malformation, were assessed by obstetrician reports.
Results: Adverse birth outcomes were reported for 641 (10%) of the 6387 unvaccinated pregnant women and 356 (9%) of the 3943 vaccinated pregnant women. Even after adjusting for potential confounders, vaccination during pregnancy showed no association with the risk of adverse birth outcomes (odds ratio 0.90, 95% confidence interval 0.76–1.07). Vaccination during the first or second trimester displayed no association with adverse birth outcomes, whereas vaccination during the third trimester was associated with a decreased risk of adverse birth outcomes (odds ratio 0.70, 95% confidence interval 0.51–0.98).
Conclusions: Influenza vaccination during pregnancy did not increase the risk of adverse birth outcomes, regardless of the trimester in which vaccination was performed, when compared to unvaccinated pregnant women.

Introduction

In November 2012, the World Health Organization presented a position paper placing pregnant women in the highest priority group to receive influenza vaccination, due to the expectations of vaccine effectiveness in preventing influenza among mothers and their infants (World Health Organization, 2012). Indeed, several epidemiological studies have indicated that maternal influenza

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vaccination provides effective protection against infant influenza (Benowitz et al., 2010; Black et al., 2004; Ohfuji et al., 2018; Steinhoff et al., 2012; Zaman et al., 2008). In general, however, pregnant women tend to be concerned about the influence of vaccines on the fetuses, which may lead to some reluctance to undergo vaccination. In fact, a previous study identified concerns about vaccine safety as the most significant reason for pregnant women not undergoing influenza vaccination (Prospero et al., 2019). Particularly in Japan, influenza vaccination for pregnant women is performed as 'voluntary vaccination'. In this situation, positive vaccination behaviors among pregnant women are likely to remain suboptimal until the safety concerns regarding effects on fetuses can be addressed.

A review of previous reports on the safety of influenza vaccination among pregnant women revealed no studies examining the influence of influenza vaccination among Japanese pregnant women on adverse birth outcomes. Since the Japanese population tends to show greater concern about vaccine safety than other populations (Hanley et al., 2015; Nakayama, 2019), this lack of evidence among the relevant population might present a barrier to achieving adequate coverage with influenza vaccination for pregnant women. Additionally, the proportions of preterm delivery, low birth weight infants, and malformed infants vary between countries (Källén, 2012; Morisaki et al., 2017; Sepkowitz, 1995).

We therefore conducted a prospective cohort study to examine vaccine safety in comparison with the incidence of adverse birth outcomes (including miscarriage, stillbirth, preterm birth, low birth weight, and congenital malformation) between vaccinated and unvaccinated pregnant women in Japan. In general, pregnant women who receive influenza vaccination are likely to be older or to have an underlying illness such as hypertension or diabetes, representing conditions that may bring about a higher incidence of adverse birth outcomes. In this study, the safety of influenza vaccination in pregnant women was evaluated with consideration of the effect of differences in such background characteristics.

Methods

Study subjects

This study was conducted with the cooperation of 117 maternity hospitals and clinics affiliated with the Obstetrical Gynecological Society of Osaka, Japan. Study subjects comprised Japanese pregnant women (regardless of gestational week) attending the collaborating hospitals and clinics before the beginning of the 2013/14 influenza season (i.e., between October and December 2013). In Japan, pregnant women typically undergo influenza vaccination at a maternity clinic or primary care clinic between October and December, as a voluntary vaccination. All study subjects received an explanation of the study from their obstetrician and verbally provided informed consent prior to participation.

The study protocol was approved by the Ethics Committee at the Osaka City University Graduate School of Medicine, and was performed in accordance with the Declaration of Helsinki.

Information collection

At the time of recruitment, study subjects completed a self-administered questionnaire to provide the following information: date of recruitment, age, gestational age at recruitment, expected date of birth, height and weight before pregnancy, smoking and alcohol drinking habits, underlying illnesses, influenza vaccination status for the 2013/14 season, and month of vaccination for vaccinated subjects. The accuracy of gestational age at recruitment was confirmed by referring to the expected date of birth. To collect information on receipt of influenza vaccination after responding to the questionnaire at recruitment, the study subjects were sent a second questionnaire after the end of the 2013/14 influenza season (May 2014). In this post-season questionnaire, besides vaccination status for the 2013/14 season and month of vaccination, we also asked the following questions about pregnancy outcomes and their babies: date of delivery and birth weight and height of their babies. To confirm these self-reported pregnancy outcomes and neonatal characteristics, the obstetrician-in-charge was contacted and asked to provide the following information from the medical records of each subject: pregnancy outcome (live birth, miscarriage, or stillbirth), and if a live birth was delivered, the date of delivery, gestational week at delivery, birth weight and height, Apgar scores at 1 min and 5 min, and presence and name of any congenital malformations. In addition, information on pregnancy-induced complications (i.e., multiple pregnancy, pregnancy-induced hypertension, gestational diabetes, hospitalization due to threatened miscarriage, placenta previa, fetal growth restriction, abruptio placentae, and intrauterine infection) was also collected by their obstetricians.

Statistical analysis

The primary exposure was influenza vaccination during pregnancy, determined from information on the month of vaccination and month of delivery. Subjects who received vaccination in the same month as the delivery, or for whom information on the month of vaccination was unavailable were excluded from the analysis.

The study outcome was adverse birth outcomes including miscarriage (termination of pregnancy before gestational week 22), stillbirth (dead at birth or after gestational week 22), preterm birth (live birth at less than gestational week 37), and/or low birth weight (birth weight <2500 g) for all study subjects. Miscarriage and stillbirth included therapeutic abortions. Information on low birth weight was primarily based on information from the obstetrician. If information was unavailable from the obstetrician, complementary data were obtained from the self-administered questionnaire. In addition, Apgar scores at 1 min and 5 min were also assessed using three categories: 0–3, very low; 4–6, low; 7–10, healthy. Also, for women in the first trimester, congenital malformation was assessed as another study outcome. Genetic and chromosomal abnormalities were not included in congenital malformation, because these occur at conception and are uninfluenced by vaccination. For detailed analyses, congenital malformations were classified into 10 categories by organ system (i.e., central nervous system; ophthalmological, otological, or orofacial; cardiac; respiratory; cleft lip and/or cleft palate; gastrointestinal; genitourinary or renal; muscular or limb defects; or other), according to International Classification of Diseases 10th revision (ICD-10) codes, and were compared between unvaccinated and vaccinated women.

With regard to explanatory variables, age was categorized into <30, 30–34, and >34 years old. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2), and then classified into three categories according to conventional cut-off values. Gestational age was defined as gestational week at the time of vaccination for vaccinated women or at the time of recruitment for unvaccinated women, and was categorized into first trimester (<16 weeks), second trimester (16–27 weeks), and third trimester (>27 weeks). Gestational age at vaccination was calculated using the information on the month of vaccination, gestational age at recruitment, and date at recruitment, and considering the date of vaccination as the 15th day (median) of the month. Calendar month at the start of pregnancy was calculated by information on

the date of recruitment and gestational age at recruitment, and was classified into four seasons. The following influenza-related high-risk conditions were included according to a previous report: chronic respiratory disorders (including asthma), cardiovascular disorders (excluding isolated hypertension), kidney disease, liver disease, neurological disorders, blood disorders, metabolic disorders (including diabetes), immunocompromised states (such as malignant tumors, connective tissue disorders, inflammatory bowel disease, and chronic rheumatism), and obesity (BMI $\geq$ 25.0 kg/m^2) (Centers for Disease Control and Prevention, 2013). Underlying obstetric and gynecological illnesses were included as infertility, myoma uteri, ovarian diseases, endometriosis, diseases in the neck of the uterus including severe dysplasia or cancer, endometrial polyp, adenomyosis uteri, habitual miscarriage, etc.

A logistic regression model was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for associations between influenza vaccination during pregnancy and adverse birth outcomes. The multivariate model included all variables related to vaccination status (i.e., exposure variables) or adverse birth outcomes (i.e., outcome index) showing values of $p < 0.05$ in the univariate analyses. The Chi-square test and Wilcoxon rank-sum test were used where appropriate.

In addition, in order to separately evaluate the influence of influenza vaccination on adverse birth outcomes according to gestational week, stratified analyses by trimester were conducted.

All analyses were two-tailed and were conducted using SAS version 9.3 software (SAS Institute, Cary, NC, USA).

Results

Of the 20 420 pregnant Japanese women recruited, 12 838 responded to the post-season questionnaire. Among these, 301 vaccinated women were excluded, because vaccination had been performed in the month of delivery; whether the vaccination had been performed before or after delivery was thus unclear. Another 233 vaccinated women were excluded because of a lack of information on the month of vaccination. Information on birth outcomes was then obtained for 10 330 women from their obstetricians, and these women therefore comprised the subjects for analysis (Figure 1). Table 1 shows the characteristics of the study subjects. A total of 3943 women (38%) received influenza vaccination during pregnancy. Among these, about one-third had received the vaccination during each of the first, second, and third trimesters. Vaccinated women were older and more likely to have underlying obstetric and gynecological illnesses, whereas unvaccinated women appeared to show higher frequencies of obesity, hypertension, or fetal growth restriction as pregnancy-induced complications, and of having smoking or alcohol drinking habits during pregnancy.

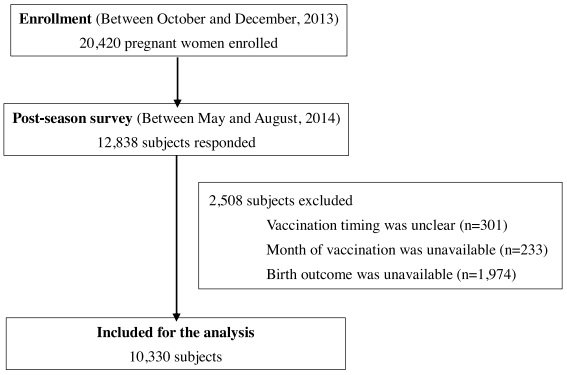

Figure 1. The enrollment process for the study.

Table 2 shows birth outcomes for the study subjects. Miscarriage or stillbirth was reported for 0.1% of subjects, each with similar proportions in unvaccinated and vaccinated women. Preterm birth occurred in 4.1% of subjects, again with similar proportions in the two groups. On the other hand, low birth weight was significantly more frequent among unvaccinated women than among women vaccinated during pregnancy (8% vs. 7%).

A total of 997 subjects (10%) reported miscarriage, stillbirth, preterm birth, and/or low birth weight as adverse birth outcomes (Table 3). Women who had received influenza vaccination during pregnancy reported slightly fewer adverse birth outcomes compared with unvaccinated women, although the difference was not significant (9% vs. 10%, respectively; $p = 0.09$). In addition, pregnant women $\geq$30 years old, with BMI <18.5 kg/m^2, underlying obstetric and gynecological illnesses, pregnancy-induced complications, or a smoking habit during pregnancy were significantly more likely to present with adverse birth outcomes. After considering the effects of these potential confounders in the multivariate analysis, vaccination during pregnancy did not show any significant association with adverse birth outcomes when compared to unvaccinated women (OR 0.90, 95% CI 0.76–1.07). However, age $\geq$30 years, lower BMI before pregnancy, and some pregnancy-induced complications were significantly associated with adverse birth outcomes.

Adverse birth outcomes were examined separately in subgroups according to the trimester at vaccination for vaccinated women or at recruitment for unvaccinated women (Table 4). In the first trimester, although congenital malformation was regarded as one of the adverse birth outcomes, no significant difference in these adverse birth outcomes was seen between unvaccinated and vaccinated women (13% each). In the second trimester, the proportion of adverse birth outcomes was broadly similar among unvaccinated and vaccinated women. In the third trimester, however, vaccinated women had significantly fewer reports of adverse birth outcomes (6% vs. 9%, respectively), especially for low birth weight (6% vs. 8%, respectively), than unvaccinated women. Even in the multivariate analysis with consideration of the effect of potential confounders, women who received vaccination during the first or second trimester showed no significant elevation in adverse birth outcomes compared with unvaccinated women (first trimester: OR 1.07, 95% CI 0.81–1.40; second trimester: OR 0.87, 95% CI 0.65–1.16). On the other hand, women who received vaccination during the third trimester showed a significantly decreased OR for adverse birth outcomes when compared with unvaccinated women (OR 0.70, 95% CI 0.51–0.98).

Discussion

The study findings demonstrated that influenza vaccination during pregnancy was not associated with any increase in adverse effects on the fetus. This result is consistent with previous studies from other countries. To date, several randomized controlled trials of pregnant women have shown that the incidences of miscarriage, stillbirth, preterm birth, low birth weight, and congenital malformations among influenza vaccination groups were similar to those in placebo groups (Michikawa et al., 2018; Osaka City, 2019; Steinhoff et al., 2012). Most cohort studies have also shown that vaccinated and unvaccinated pregnant women display similar incidences of miscarriage, stillbirth, preterm birth, low birth weight, or congenital malformation in their babies (Baum et al., 2015; Black et al., 2004; Chambers et al., 2013; Chambers et al., 2016; Cleary et al., 2014; de Vries et al., 2014; Fabiani et al., 2015; Fell et al., 2012; Fell et al., 2017; Kharbanda et al., 2017; Ma et al., 2014; Madhi et al., 2014; McHugh et al., 2017; Nordin et al., 2014a;

Table 1
Characteristics of the pregnant women ($N = 10\ 330$).[a]

Characteristics		Total *n* (%)	Unvaccinated *n* (%)	Vaccinated *n* (%)	*p*-Value
Total		10 330 (100)	6387 (62)	3943(38)	
Gestational age at recruitment or vaccination (weeks)	<16 (first trimester)	2826 (27)	1705 (27)	1121 (28)	<0.01
	16–27 (second trimester)	3328 (32)	1738 (27)	1590 (40)	
	>27 (third trimester)	4176 (40)	2944 (46)	1232 (31)	
Calendar month at pregnancy start	March–May (Spring)	3506 (34)	1997 (31)	1509 (38)	<0.01
	June–August (Summer)	2908 (28)	1434 (22)	1474 (37)	
	September–November (Autumn)	1997 (19)	1215 (19)	782 (20)	
	December–February (Winter)	1919 (19)	1741 (27)	178 (5)	
Age (years)	Median (range)	32 (15–51)	32 (15–51)	33 (16–47)	<0.01
	<30	3273 (32)	2273 (36)	1000 (25)	<0.01
	30–34	3673 (36)	2154 (34)	1519 (39)	
	>34	3384 (33)	1960 (31)	1424 (36)	
Body mass index before pregnancy (kg/m^2)	<18.5	1636 (16)	1007 (16)	629 (16)	0.04
	18.5–24.9	7585 (75)	4640 (74)	2945 (76)	
	>24.9	960 (9)	640 (10)	320 (8)	
Influenza-related high-risk conditions	Present	2321 (22)	1456 (23)	865 (22)	0.31
Underlying obstetric and gynecological illness	Present	1916 (19)	1075 (17)	841 (21)	<0.01
Pregnancy-induced complications		*n*/*N* (%)	*n*/*N* (%)	*n*/*N* (%)	
Multiple pregnancy	Present	149/10 328 (1)	91/6386 (1)	58/3942 (1)	0.85
Pregnancy-induced hypertension	Present	338/10 302 (3)	234/6367 (4)	104/3935 (3)	<0.01
Gestational diabetes	Present	276/10 322 (3)	185/6383 (3)	91/3939 (2)	0.07
Hospitalization due to threatened miscarriage	Present	526/10 318 (5)	324/6379 (5)	202/3939 (5)	0.91
Placenta previa	Present	41/10 325 (0.4)	28/6384 (0.4)	13/3941 (0.3)	0.39
Fetal growth restriction	Present	271/10 315 (3)	190/6377 (3)	81/3938 (2)	<0.01
Abruptio placentae	Present	36/10 324 (0.4)	25/6384 (0.4)	11/3940 (0.3)	0.35
Intrauterine infection	Present	81/10 313 (1)	54/6376 (1)	27/3937 (1)	0.37
Smoking habit	Present during pregnancy	306/9645 (3)	261/5983 (4)	45/3662 (1)	<0.01
Alcohol drinking habit	Present during pregnancy	66/9661 (0.7)	54/5996 (0.9)	12/3665 (0.3)	<0.01

[a] Data are expressed as the number (%) unless indicated otherwise.

Table 2
Birth outcomes of the study subjects.[a]

Birth outcomes		Total *n* (%)	Unvaccinated *n* (%)	Vaccinated *n* (%)	*p*-Value
Pregnancy outcomes	Live birth	10 305 (99.8)	6370 (99.7)	3935 (99.8)	0.38
	Miscarriage	11 (0.1)	6 (0.1)	5 (0.1)	
	Stillbirth	14 (0.1)	11 (0.2)	3 (0.1)	
Gestational age at delivery (weeks)	22–36 (preterm birth)	421 (4.1)	258 (4.1)	163 (4.2)	0.81
	37–41	9839 (95.5)	6084 (95.5)	3755 (95.4)	
	42+	45 (0.4)	28 (0.4)	17 (0.4)	
Birth weight (g)	Median (range)	3030 (428–4670)	3032 (484–4670)	3030 (428–4615)	0.39
	<2500 (low birth weight)	812 (7.9)	531 (8.3)	281 (7.1)	0.03
	≥2500	9493 (92.1)	5839 (91.7)	3654 (92.9)	
Apgar score at 1 min	0–3	58 (0.6)	43 (0.7)	15 (0.4)	0.01
	4–6	155 (1.5)	105 (1.7)	50 (1.3)	
	7–10	10 078 (97.9)	6212 (97.7)	3866 (98.3)	
Apgar score at 5 min	0–3	10 (0.1)	8 (0.1)	2 (0.1)	0.16
	4–6	32 (0.3)	22 (0.3)	10 (0.3)	
	7–10	10 233 (99.6)	6323 (99.5)	3910 (99.7)	

[a] Data are expressed as the number (%) unless indicated otherwise.

Olsen et al., 2016; Omon et al., 2011; Oppermann et al., 2012; Oskovi Kaplan and Ozgu-Erdinc, 2018; Pasternak et al., 2012; Regan et al., 2016; Steinhoff et al., 2017; Sugiura-Ogasawara et al., 2019; Vazquez-Benitez et al., 2016). In a previous case–control study, no association was identified between influenza vaccination during pregnancy and miscarriage (Ludvigsson et al., 2013).

In general, concerns have been raised regarding the effect of maternal medications, including vaccination, on the fetus within the first trimester, since the first trimester is a crucial period for embryogenesis of the major organs. However, the present study showed that even pregnant women who received influenza vaccination during the first trimester showed similar incidences of miscarriage, stillbirth, preterm birth, low birth weight, and congenital malformations when compared with unvaccinated women. The results suggest no adverse influences on the fetus, even when providing influenza vaccination to pregnant women in the first trimester.

Besides, pregnant women who received influenza vaccination during the third trimester were less likely to have babies with low birth weight. This was an unexpected finding. One possible interpretation is that recent advances in medical checkups for pregnancy have enabled better diagnosis of fetal growth restriction during pregnancy. Pregnant women diagnosed with fetal growth restriction during the third trimester might thus have been reluctant to receive influenza vaccination. Such a difference in vaccination behavior might result in apparent increases in babies with low birth weight among unvaccinated pregnant women. However, the present study did not collect information about the

Table 3
Association between background characteristics including influenza vaccination and adverse birth outcomes.[a]

Characteristics		Outcomes *n*/*N* (%)	Univariate OR (95% CI) *p*-Value	Multivariate[b] OR (95% CI) *p*-Value
Total		997/10 330 (10)		
Influenza vaccination during pregnancy	Unvaccinated	641/6387 (10)	1.00	1.00
	Vaccinated	356/3943 (9)	0.89 (0.78–1.02)	0.90 (0.76–1.07)
			0.09	0.24
Gestational age at recruitment or vaccination (weeks)	<16 (first trimester)	291/2826 (10)	1.00	1.00
	16–27 (second trimester)	354/3328 (11)	1.04 (0.88–1.22)	1.25 (0.95–1.65)
			0.06	0.12
	>27 (third trimester)	352/4476 (8)	0.80 (0.68–0.94)	1.05 (0.73–1.51)
			<0.01	0.79
			(Trend $p < 0.01$)	(Trend $p = 0.89$)
Calendar month at pregnancy start	March–May (Spring)	358/3506 (10)	1.00	1.00
	June–August (Summer)	292/2908 (10)	0.98 (0.83–1.16)	1.01 (0.78–1.31)
			0.82	0.93
	September–November (Autumn)	213/1997 (11)	1.05 (0.88–1.26)	1.23 (0.86–1.76)
			0.59	0.25
	December–February (Winter)	134/1919 (7)	0.66 (0.54–0.81)	0.79 (0.60–1.03)
			<0.01	0.08
Age (years)	<30	264/3273 (8)	1.00	1.00
	30–34	380/3673 (10)	1.32 (1.12–1.55)	1.34 (1.09–1.64)
			<0.01	<0.01
	>34	353/3384 (10)	1.33 (1.12–1.57)	1.32 (1.06–1.63)
			<0.01	0.01
			(Trend $p < 0.01$)	(Trend $p = 0.01$)
Body mass index before pregnancy (kg/m^2)	<18.5	206/1636 (13)	1.44 (1.22–1.70)	1.45 (1.18–1.78)
			<0.01	<0.01
	18.5–24.9	689/7585 (9)	1.00	1.00
	>24.9	83/960 (9)	0.95 (0.75–1.20)	0.78 (0.55–1.09)
			0.66	0.14
			(Trend $p < 0.01$)	(Trend $p < 0.01$)
Influenza-related high-risk conditions	Absent	768/8009 (10)	1.00	1.00
	Present	229/2321 (10)	1.03 (0.88–1.21)	1.19 (0.95–1.50)
			0.69	0.13
Underlying illnesses in obstetrics and gynecology	Absent	787/8414 (9)	1.00	1.00
	Present	210/1916 (11)	1.19 (1.02–1.40)	0.97 (0.79–1.19)
			0.03	0.76
Pregnancy-induced complications				
Multiple pregnancy	Absent	894/10 179 (9)	1.00	1.00
	Present	102/149 (68)	22.5 (15.9–32.1)	14.8 (9.73–22.4)
			<0.01	<0.01
Pregnancy-induced hypertension	Absent	894/9964 (9)	1.00	1.00
	Present	99/338 (29)	4.21 (3.29–5.37)	3.81 (2.79–5.21)
			<0.01	<0.01
Gestational diabetes	Absent	957/10 046 (10)	1.00	1.00
	Present	37/276 (13)	1.47 (1.03–2.09)	1.41 (0.92–2.16)
			0.03	0.12
Hospitalization due to threatened miscarriage	Absent	821/9792 (8)	1.00	1.00
	Present	172/526 (33)	5.31 (4.37–6.46)	4.45 (3.49–5.68)
			<0.01	<0.01
Placenta previa	Absent	971/10 284 (9)	1.00	1.00
	Present	24/41 (59)	13.5 (7.25–25.3)	17.2 (8.38–35.1)
			<0.01	<0.01
Fetal growth restriction	Absent	768/10 044 (8)	1.00	1.00
	Present	224/271 (83)	57.6 (41.7–79.5)	66.1 (46.4–94.0)
			<0.01	<0.01
Abruptio placentae	Absent	982/10 288 (10)	1.00	1.00
	Present	13/36 (36)	5.36 (2.71–10.6)	6.22 (2.55–15.2)
			<0.01	<0.01
Intrauterine infection	Absent	977/10 232 (10)	1.00	1.00
	Present	15/81 (19)	2.15 (1.22–3.79)	2.13 (1.11–4.07)
			<0.01	0.02
Smoking habit	Absent	887/9339 (9)	1.00	1.00
	Present during pregnancy	43/306 (14)	1.56 (1.12–2.17)	1.45 (0.96–2.19)
			<0.01	0.08
Alcohol drinking habit	Absent	926/9595 (10)	1.00	1.00
	Present during pregnancy	6/66 (9)	0.94 (0.40–2.18)	1.15 (0.44–2.95)
			0.88	0.78

OR, odds ratio; CI, confidence interval.
[a] Miscarriage, stillbirth, preterm birth, or low birth weight were included.
[b] Model included variables in this table.

Table 4
Birth outcomes of study subjects according to trimester.

Birth outcomes		First trimester		*p*-Value	Second trimester		*p*-Value	Third trimester		*p*-Value
		Unvaccinated *n* (%)	Vaccinated *n* (%)		Unvaccinated *n* (%)	Vaccinated *n* (%)		Unvaccinated *n* (%)	Vaccinated *n* (%)	
Adverse birth outcomes[a]	Present	229 (13)	142 (13)	0.56	119 (11)	155 (10)	0.11	265 (9)	87 (6)	0.04
Pregnancy outcomes	Live birth	1697 (99.5)	1116 (99.6)	0.61	1733 (99.7)	1588 (99.9)	0.46	2940 (99.9)	1231 (99.9)	1.00
	Miscarriage	6 (0.4)	5 (0.4)		0 (0)	0 (0)		0 (0)	0 (0)	
	Stillbirth	2 (0.1)	0 (0)		5 (0.3)	2 (0.1)		4 (0.1)	1 (0.1)	
Preterm birth	Present	64 (4)	55 (5)	0.12	97 (6)	79 (5)	0.74	97 (3)	29 (3)	0.07
Low birth weight	Present	148 (9)	86 (8)	0.34	155 (9)	125 (8)	0.27	228 (8)	70 (6)	0.02
Congenital malformation	Present	55 (3.2)	33 (3.0)	0.67	–	–		–	–	
Categories by organ system	Central nervous system	0 (0)	1 (0.1)	0.25						
	Ophthalmological, otological or orofacial	1 (0.1)	3 (0.3)							
	Cardiac	7 (0.4)	3 (0.3)							
	Respiratory	0 (0)	1 (0.1)							
	Cleft lip and/or cleft plate	1 (0.1)	1 (0.1)							
	Gastrointestinal	0 (0)	1 (0.1)							
	Genitourinary or renal	5 (0.3)	2 (0.2)							
	Muscular or limb defects	7 (0.4)	1 (0.1)							
	Others	0 (0)	1 (0.1)							
	Unknown	34 (2.0)	19 (1.7)							

[a] Miscarriage, stillbirth, preterm birth, low birth weight, or congenital malformation were included for women in the first trimester. For women in the second or third trimester, miscarriage, stillbirth, preterm birth, or low birth weight were included.

timing of diagnoses of fetal growth restriction. It is thus difficult to determine how such diagnoses affected the vaccination behaviors of pregnant women.

Various limitations need to be considered when interpreting the results of this study. First, to increase the response rate, we decided to collect information on vaccination month instead of vaccination date, resulting in the exclusion of 301 vaccinated women who had received vaccination in the same month as the delivery. Besides, the trimester at vaccination for vaccinated women might have been misclassified into the neighboring category in some subjects, since calculations were made using information on the month of vaccination, date of recruitment, and gestational week at recruitment, and the date of vaccination was regarded as the 15th of each month. Since we lacked accurate information on the date of vaccination from the clinic at which patients received vaccination, this represents the most important limitation of the present study.

Second, since information on vaccination status and explanatory variables was based on self-reports from pregnant women, some data such as body weight before pregnancy, smoking, and alcohol drinking status might have been underreported. However, the present design using a prospective cohort study is less susceptible to misclassification due to recall errors than a case–control study design. Besides, to confirm the accuracy of self-reported data, the date of delivery and birth weight, which were obtained using two methods (self-report and obstetrician report), were examined by comparing information from both sources. Among the subjects for whom the date of delivery was available from both self-report and obstetrician report ($n = 8227$), the correlation coefficient between self-report and obstetrician report was 0.988 ($p < 0.01$). Among subjects for whom birth weight was available from both reports ($n = 8273$), the correlation coefficient was 1.000 ($p < 0.01$). Based on these confirmations, the self-reported information used in the present study was expected to be relatively reliable.

Third, the subjects analyzed comprised 10 330 women who answered the post-season questionnaire and had birth outcomes provided by their obstetricians, from among the 20 420 women recruited before the season. This follow-up proportion might have affected the study results. For example, if women who experienced miscarriage or stillbirth as the pregnancy outcome tended to be less likely to answer the post-season questionnaire, a selection bias for study subjects would have been present. Actually, considering the number of stillbirths and livebirths in Osaka of 1621 and 69 968 in 2014 (Håberg et al., 2013), the proportion of miscarriage or stillbirth among the present study subjects (0.1%) appeared lower than among the general population (2%). On the other hand, the proportions of preterm birth, low birth weight, or congenital malformation in Japan were reported as 5.1%, 8.3%, and 3–5%, respectively, in 2013 (Nordin et al., 2014b), representing proportions broadly comparable to those in the present study. The possibility of selection bias thus appears low in the assessment of preterm birth, low birth weight, or congenital malformations, but the possibility of selection bias due to study dropout in the assessments of miscarriage or stillbirth cannot be ruled out.

Fourth, since the study subjects were pregnant women under clinical follow-up at obstetric facilities in Osaka Prefecture before the beginning of the 2013/14 influenza season, some concerns remain about the generalizability of the results. Further investigations of different seasons and regions is desirable to confirm the validity of the present study findings.

This study has the following strengths. First, with the cooperation of the Obstetrical Gynecological Society of Osaka, it was possible to investigate the safety of influenza vaccination among pregnant women in a large cohort exceeding 10 000 study subjects, covering 15% of pregnant women in the study area. This also enabled the examination of the effects of the timing of influenza vaccination on adverse birth outcomes. Second, since information on pregnancy outcomes was based on reports from the obstetricians of the study subjects, the accuracy of information was considered high. In fact, the proportions of preterm birth, low birth weight, congenital malformations, and pregnancy-induced complications in the present study were comparable to those of the general population in Japan (Munoz et al., 2005; Nordin et al., 2014b; Sheffield et al., 2012). Additionally, maternal age, BMI, and the proportion of smokers during pregnancy were similar in another study in Japan (Munoz et al., 2005). In addition, the present study detected known risk factors for adverse birth outcomes, such as maternal age, pregnancy-induced complications, and smoking during pregnancy (Irving et al., 2013). These findings suggest the reliability of the study results.

In conclusion, this cohort study indicates that influenza vaccination of pregnant women had no adverse effects on the fetus regardless of the trimester in which the vaccination was performed. The safety of influenza vaccination among pregnant women in Japan was also suggested.

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Conflict of interest

SO reports personal fees from speaking and/or teaching arrangements, outside the submitted work; TK reports personal fees from the BIKEN Foundation, outside the submitted work; WF reports personal fees from royalties, personal fees from consulting, personal fees from speaking and/or teaching arrangements, personal fees from scientific advisory committee, and grants outside the submitted work; YH reports grants from the Ministry of Health, Labor, and Welfare, during the conduct of the study; all other authors declare no conflicts of interest.

Author contributions

SO contributed to the study design, data management, statistical analysis, data interpretation, and drafting of the work or revising it critically for important intellectual content. MD, DT, MK, TT, and all members listed in the Appendix contributed to data acquisition and data interpretation. TY and AU contributed to the study design and data management. KI, TK, AM, KK, and WF contributed to the study design and data interpretation. YH contributed to the conception of the design, overall management, data interpretation, and manuscript editing. All authors provided comments on the drafts and have read and approved the final manuscript.

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