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Safety of Pandemic Influenza A (H1N1) 2009 Vaccination during Pregnancy in Japan

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The U.S. Center for Disease Control and Prevention (CDC) and American College of Obstetricians and Gynecologists (ACOG) have recommended that the influenza vaccination be given to pregnant women who are in the high-risk group of influenza infection. However, because to date there is little data on the influenza vaccine use in pregnant women and the safety for pregnant women in Japan has not been well studied, the influenza vaccination during pregnancy has not been recommended. However, following reports of severe cases of influenza, including death, among pregnant women in other countries during the influenza A (H1N1) pandemic in 2009, the limitations regarding the vaccination for pregnant women listed in the Japanese influenza vaccine package insert have been relaxed, and the Japanese government has expressed the recommendation for pregnant women to have the influenza A (H1N1) 2009 vaccine. We investigated 416 pregnant women who were vaccinated by the influenza A (H1N1) 2009 vaccine, and 716 non-vaccinated pregnant women from 2009 through 2010, in order to evaluate the safety of the influenza A (H1N1) 2009 vaccination during pregnancy in Japan. No significant association between the influenza A (H1N1) 2009 vaccination and miscarriages, stillbirths, malformations, emergency cesareans, premature delivery or low birthweight infants was observed. Our study indicated the safety of influenza A (H1N1)2009 vaccination during pregnancy.

Key Words: Influenza, Pregnancy, Influenza A (H1N1), Safety, Vaccination

Introduction

Examples of pandemics of influenza during the 20th century include Spanish flu (H1N1) from 1918 to 1919, Asian flu (H2N2) from 1957 to 1958, and Hong Kong flu (H3N2) from 1968 to 1969. It was reported that the mortality rate of pregnant women was higher than that of the general population in the pandemics of Spanish flu and Asian flu[1,2]. Influenza is a respiratory tract infection spread by droplets from the respiratory tract of the infected patient and contact infection of a virus; it has been reported that the influenza infection during pregnancy is readily elicits complications and is easily aggravated[3-5]. The influenza pandemic of swine origin, which stemmed from Mexico in the spring of 2009, quickly spread worldwide, just as the influenza pandemics which have occurred in the past. At the outbreak of pandemic influenza A (H1N1) 2009 in Japan, there were more than 20 million influenza A (H1N1) 2009 patients. However, it is noteworthy that only 198

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death cases have been reported nationwide and no death case among pregnant women was reported in Japan[6]. Although there was no death and very few serious cases among influenza A (H1N1) 2009 infected pregnant women in Japan, cases of death or serious cases among influenza A (H1N1) 2009 infected pregnant women were reported in other countries[7-9]. This may be because the prompt administration of anti-influenza medicine in Japan in the early stage following influenza diagnosis was effective.

It has been reported that oseltamivir and zanamivir are effective for the treatment of influenza A (H1N1) 2009 viruses[10] and both drugs are safe for the fetus with administration during pregnancy[11]. The effectiveness and safety of use during pregnancy of the anti-influenza drug have been reported, however prevention with influenza vaccination before an epidemic season is also very important to study.

Since infectious diseases can readily become severe due to lowered immune response during pregnancy, the influenza vaccination is important to prevent influenza infection. In studies from many other countries on influenza vaccination during pregnancy, the influenza vaccination during pregnancy has been shown to have no harmful effects on fetal development and delivery of the newborn, and the safety and benefit of an influenza vaccination during pregnancy have been evaluated[12-17]. Therefore, the U.S. Center for Disease Control and Prevention (CDC) and American College of Obstetricians and Gynecologists (ACOG) has recommended influenza vaccination to pregnant women who are one of the high-risk groups of influenza infection[18,19]. On the other hand, influenza vaccination for pregnant women has not been recommended in Japan. This is because 1) there are few data available on the safety of influenza vaccination during pregnancy, and 2) the description in the package leaflet of the Japanese influenza vaccine states: "Vaccination of pregnant women or women who may be pregnant is, principally, not recommended since the safety of vaccination during pregnancy has not been established". Similarly, since there are few studies on the influenza vaccine use in pregnant women and since influenza vaccination during pregnancy could not be considered securely safe in many European countries[20], influenza vaccination during pregnancy in Japan has not been recommended. However, following reports of death and serious cases of influenza infection during pregnancy at the outbreak of pandemic influenza A (H1N1) in 2009, the description in the package insert of the influenza vaccines approved in Japan stating "Do not vaccinate in principle" was deleted and the description included the following new addition: "A small sample size study reported that the incidence of congenital anomaly in newborns of vaccinated pregnant women was not higher than that of the spontaneous incidence rate". Subsequently, the Japanese government policy regarding the influenza vaccination during pregnancy was changed as mentioned above, and influenza vaccination of pregnant women is now strongly recommended even in Japan[21]. However, very few reports are available on verifying the safety of the influenza vaccination during pregnancy in Japan.

To evaluate the safety of the influenza A (H1N1) 2009 vaccination during pregnancy in Japan, during the season from 2009 through 2010, we investigated pregnancy outcome of vaccinated pregnant women and non-vaccinated pregnant women.

Subjects and Methods

1. Subjects

The study population included all pregnant women and newborns delivered in St. Luke's International Hospital (Tokyo, Japan) during October 1, 2009, to September 30, 2010 (n=1157). A total of 1132 cases were investigated; 24 sets of twins and one set of triplets were excluded from the study.

2. Study design

We performed a retrospective electronic chart search from October 1, 2009, to September 30, 2010, at St. Luke's International Hospital in Tokyo, Japan.

3. Methods

The age at delivery, clinical history, race, and medicine use during pregnancy were used as basic information. Among the investigated pregnant women, the pregnant women who received the influenza A (H1N1) 2009 vaccine during pregnancy were defined as the vaccinated group and the

pregnant women who did not receive the influenza A (H1N1) 2009 vaccine during pregnancy were defined as the non-vaccinated group. Vaccination time and the days of pregnancy at the time of vaccination were investigated in the influenza A (H1N1) 2009 vaccinated group. We investigated the presence of influenza A (H1N1) 2009 vaccination during pregnancy and the following factors: age at delivery, gestation length, influenza infection during pregnancy, the anti-influenza medicine administration during pregnancy, miscarriage, stillbirth, malformation, emergency cesarean section, premature delivery (under 37 weeks), birthweight and pregnancy-induced hypertension. The influenza A (H1N1) 2009 vaccine administered in this study was "A Influenza HA Vaccine: H1N1 (Kitasato Institute)" (without any adjuvants or preservatives).

4. Statistical analyses

In order to compare subject characteristics and pregnancy outcome between the influenza A (H1N1) 2009 vaccinated group and the non-vaccinated group, a chi-square test for comparison of percentage, a t-test and a one-way layout analysis of variance (ANOVA) for comparison of average value was performed. If a statistically significant result was found in the one-way layout analysis of variance, a test for the honestly significant difference (HSD) of Tukey was performed. All of the statistics analyses were performed using SPSS software version 18.0 (IBM Japan Ltd., Tokyo, Japan); the level of statistical significance was $p<0.05$ in all the statistics analyses.

5. Ethical consideration

This study was approved by the Institutional Review Board (IRB) of St. Luke's International Hospital.

Results

1. Characteristics of the subjects

Regarding age, 51.3% of the 1132 subjects were over 35 years old age at the time of delivery. There was nothing that was particularly frequent seen in the clinical history of the pregnant woman of investigation, and 97.3% of the 1132 subjects were Japanese (Table 1).

As for the teratogenic agent use during pregnancy, only one subject (vaccinated group, no malformation) used carbamazepine for epilepsy treatment during the entire pregnancy period.

		n (%)
Age at delivery (years)		
	20 - 24	7 (0.6)
	25 - 29	95 (8.4)
	30 - 34	449 (39.7)
	35 - 39	386 (34.1)
	≧ 40	195 (17.2)
Clinical history		
	Asthma	56 (5.0)
	Hypertension	5 (0.4)
	Diabetes	2 (0.2)
Race		
	Japanese	1101 (97.3)
	Others	31 (2.7)

Table 1 : Characteristics of 1132 pregnant women

2. Number of vaccination given monthly and average days of pregnancy at the time of vaccination.

The vaccination against influenza A (H1N1) 2009 in the season from 2009 through 2010 was given to the subjects from November 2009 to March 2010; 59.4% of all vaccination was given in November 2009. The average days of pregnancy at the time of vaccination against influenza A (H1N1) 2009 was 179.9 days (Table 2).

	Number n (%)	Days of pregnancy mean ± SD
Nov-2009	247 (59.4)	202.0 ± 53.8
Dec-2009	100 (24.1)	161.5 ± 58.0
Jan-2010	43 (10.3)	132.7 ± 43.6
Feb-2010	18 (4.3)	119.2 ± 31.5
Mar-2010	8 (1.9)	119.1 ± 32.2
Total	416 (100.0)	179.9 ± 60.0

SD : standard deviation.

Table 2 : Number of vaccinations given monthly and average days of pregnancy at the time of vaccination

3. Comparison of subject's characteristics and pregnancy outcome between influenza A (H1N1) 2009 vaccinated and non-vaccinated groups.

There was no statistically significant difference in the average age at the time of delivery, the percentage of the subjects who were 35 years and older at the time of delivery, the percentage of the anamnesis and the percentage of the race between the influenza A (H1N1) 2009 vaccinated group and the non-vaccinated group.

The average delivery days was significantly longer in the influenza A (H1N1) 2009 vaccinated group than in the non-vaccinated group ($p<0.05$) (Table 3).

No statistically significant difference was found among both groups regarding the rate of influenza infection during pregnancy, the anti-influenza medicine administration during pregnancy, miscarriage, stillbirth, malformation, emergency cesarean section, premature delivery, low birthweight infants, and pregnancy-induced hypertension. An average birthweight, in the influenza A (H1N1) 2009 vaccinated group was significantly heavier than that in a non-vaccinated group ($p<0.05$) (Table 4). The anti-influenza medicine which was administered to subjects in both groups was Oseltamivir only.

4．Comparison of subject's characteristics and pregnancy outcome according to the term of vaccination in the influenza A (H1N1) 2009 vaccinated group.

By the term of vaccination in influenza A (H1N1) 2009 vaccinated group (n=416), there was no statistically significant difference in the average age at the time of delivery and the percentage of the subjects who were 35 and older at the time of delivery. The average delivery days for the subjects who were vaccinated during the third trimester was significantly longer than in the subjects who were vaccinated during the second trimester ($p<0.05$) (Table 5). No statistically significant difference was found according to the term of vaccination in the rate of influenza infection during pregnancy, the anti-influenza medicine administration during pregnancy stillbirth, malformation, emergency cesarean section, low birthweight infant,

	Vaccinated group (n = 416)	Non-vaccinated group (n = 716)	*P* value
Age at delivery (years, mean ± SD)	35.6 ± 4.0	35.4 ± 4.4	0.469
Age at delivery ≧35 (n (%))	211 (50.7)	370 (51.7)	0.757
Gestation length (days, mean ± SD)	276.8 ± 10.7	274.5 ± 13.4	0.030
Clinical history (n (%))			
Asthma	22 (5.3)	34 (4.7)	0.686
Hypertension	3 (0.7)	2 (0.3)	0.280
Diabetes	1 (0.2)	1 (0.1)	0.697
Race (n (%))			
Japanese	407 (97.8)	694 (96.9)	0.366

SD：standard deviation.

Table 3：Characteristics of pregnant women in vaccinated and non-vaccinated groups

	Vaccinated group (n = 416)	Non-vaccinated group (n = 716)	*P* value
Influenza infection during pregnancy (n (%))	6 (1.4)	9 (1.3)	0.793
Anti-influenza medicine administration during pregnancy (n (%))	10 (2.4)	12 (1.7)	0.392
Miscarriage (n (%))	2 (0.5)	6 (0.8)	0.489
Stillbirth (n (%))	2 (0.5)	11 (1.5)	0.108
Malformation (n (%))	9 (2.2)	14 (2.0)	0.811
Emergency cesarean section (n (%))	41 (9.9)	93 (13.0)	0.116
Premature delivery (<37 weeks, n (%))	18 (4.3)	48 (6.7)	0.100
Birthweight (g, mean ± SD)	3017.3 ± 498.2	2916.2 ± 618.4	0.005
Low birthweight infants (<2500g, n (%))	43 (10.3)	91 (12.7)	0.100
Pregnancy-induced hypertension (n (%))	14 (3.4)	26 (3.6)	0.815

SD：standard deviation.

Table 4：Pregnancy outcome in vaccinated and non-vaccinated groups

pregnancy-induced hypertension and the average birthweight. There was a statistically significant difference in the rate of miscarriage and premature delivery ($p<0.05$) (Table 6).

The types of malformations in subjects of investigation were as follows in the vaccinated group and the non-vaccinated group. The malformations in the influenza A (H1N1) 2009 vaccinated group were a case of right accessory ear, vulvar hypertrophy, black nevus, 21 trisomy, hypospadias, aproctia, back of the head subcutaneous mass, syndactylism, and 18 trisomy. The malformations in the non-vaccinated group were two cases of cleft lip and palate, a case of paternal uniparental disomy for chromosome 14, 21 trisomy, mandibular congenital tooth, hemangioma, walleye, 18 trisomy, black nevus, spina bifida, anencephaly, auricle hypoplasia, hypospadias, and right accessory ear. All the subjects whose babies had any malformation in the influenza A (H1N1) 2009 vaccinated group had influenza vaccination in the second trimester or later, except for one subject (influenza vaccination at 88 days of pregnancy) whose baby had a hypospadias.

Discussion

In order to evaluate the safety of the influenza A (H1N1) 2009 vaccination during pregnancy in Japan, during the season from 2009 through 2010, we investigated the pregnancy outcome of vaccinated pregnant women and non-vaccinated pregnant women. In this investigation, regarding the average days to delivery, the influenza A (H1N1) 2009 vaccinated group was significantly longer than that of the non-vaccinated group. As for average birthweight, the babies of the influenza A (H1N1) 2009 vaccinated group were significantly heavier than those of the non-vaccinated group. Regarding the timing of vaccination in influenza A (H1N1) 2009 vaccinated group, the average delivery days in the subjects who were vaccinated during the third trimester was significantly longer than that in the subjects who were vaccinated during the second trimester. However, the average delivery days were within the term delivery in the comparison between the vaccination group and non-vaccination group and in the comparison of vaccination term in the vaccination group.

Regarding the ratio of the low birthweight infants, no statistically significant difference was found in the

	1st trimester (n = 43)	2nd trimester (n = 178)	3rd trimester (n = 195)	*P* value
Age at delivery (years, mean ± SD)	35.5 ± 4.1	35.8 ± 4.1	35.2 ± 3.8	0.364
Age at delivery ≧35 (n (%))	25 (58.1)	91 (51.1)	95 (48.7)	0.530
Gestation length (days, mean ± SD)	275.3 ± 15.4	275.5 ± 9.7 ・	278.2 ± 10.3 ・	0.038

SD：standard deviation.　　・：p=0.045

Table 5 : Characteristics of pregnant women according to the vaccination term

	1st trimester (n = 43)	2nd trimester (n = 178)	3rd trimester (n = 195)	*P* value
Influenza infection during pregnancy (n (%))	0 (0.0)	4 (2.2)	2 (1.0)	0.432
Anti-influenza medicine administration during pregnancy (n (%))	0 (0.0)	5 (2.8)	5 (2.6)	0.547
Miscarriage (n (%))	2 (4.7)	0 (0.0)	0 (0.0)	<0.001
Stillbirth (n (%))	0 (0.0)	2 (1.1)	0 (0.0)	0.261
Malformation (n (%))	1 (2.3)	4 (2.2)	4 (2.1)	0.989
Emergency cesarean section (n (%))	2 (4.7)	20 (11.2)	19 (9.7)	0.428
Premature delivery (<37 weeks, n (%))	5 (11.6)	7 (3.9)	6 (3.1)	0.042
Birthweight (g, mean ± SD)	2893.7 ± 757.8	2995.2 ± 504.4	3064.6 ± 410.2	0.093
Low birthweight infants (<2500g, n (%))	6 (14.0)	21 (11.8)	16 (8.2)	0.373
Pregnancy-induced hypertension (n (%))	2 (4.7)	6 (3.4)	6 (3.1)	0.874

SD：standard deviation.

Table 6 : Pregnancy outcome according to the vaccination term

comparison between the influenza A (H1N1) 2009 vaccination group and the non-vaccination group and in the comparison of vaccination term in the vaccination group. Therefore, there seemed to be little influence of the influenza A (H1N1) 2009 vaccination on the weight of the newborn. Although there were only a few cases, a statistically significant difference was observed in the rate of miscarriages according to inoculation term; further investigation will be necessary on this matter.

A statistically significant difference was found regarding the ratio of premature deliveries, but two of the five premature deliveries seen in the first trimester vaccination occurred with pregnancy-induced hypertension. Therefore, the possibility that pregnancy-induced hypertension influenced the premature delivery should be considered, and the further investigation will be necessary.

In the influenza A (H1N1) 2009 vaccinated group and the non-vaccinated group, no statistically significant difference was found regarding the ratio of malformation, and also no specific malformation type was seen. Furthermore, all of the eight subjects whose babies had a malformation in the influenza A (H1N1) 2009 vaccinated group had influenza vaccination in the second trimester or later, except for one subject whose baby had a hypospadias and who had influenza vaccination at 88 days of pregnancy. Because there was no specific type of malformation and teratogenesis did not concentrate in the first trimester which is highest teratogenic risk term during pregnancy, the possibility of the teratogenic risk rise to the fetus with influenza A (H1N1) 2009 vaccination during pregnancy is considered to be a low risk.

Although there are very few reports on influenza A (H1N1) 2009 vaccination of pregnant women in Japan other than the present report, there are some reports being published overseas. In France, during the influenza A (H1N1) pandemic in 2009, the influenza A (H1N1) 2009 vaccination for pregnant women was recommended by the French Health authorities as in Japan, and the vaccination was administered. In the prospective study on the influenza A (H1N1) 2009 vaccination for pregnant women performed in France, the risks of maternal conditions, malformations and neonatal condition were not statistically different compared with those of the general population[22]. Moreover, the prospective cohort study on the adjuvanted split H1N1 (2009) vaccination for pregnant women performed in U.K., reported that the risks of spontaneous abortion, congenital anomalies, preterm delivery, low birthweight neonates, and maternal complications were not increased[23]. These reports agree with the present report that vaccination against influenza A (H1N1) 2009 during pregnancy does not raise the risk for the mother's body or the newborn.

The report following an investigation in U.S. stated that the ratio of preterm delivery and low birthweight infants were high for the mothers who delivered during hospitalization for influenza A (H1N1) 2009 infection in a season from 2009 through 2010[24]. Therefore, the report emphasized that the vaccination of an influenza vaccine is important for pregnant women. Also in Japan, the pregnant women are targeted for priority of the vaccination as a high-risk group for influenza infection[21]. In addition, there is a report which describes the differing policies and practices regarding influenza vaccination for pregnant women in each country in Europe[25]. The report has considered that the differences in pandemic vaccination policy and practice from country to country might explain the variation in perceptions of vaccine efficacy and safety, the vaccination campaign system, and operational issues related to vaccine manufacturing and procurement.

Regarding the campaign of the vaccination of pregnant women in Japan, positive vaccination has come to be recommended by the announcement of the Ministry of Health, Labour and Welfare in November 2009 which states that there is no report of increased risk of miscarriage or congenital anomaly to date, even if an influenza vaccine is administered during pregnancy[21]. The problem with the operative aspect in conjunction with vaccine production and the procurement in Japan, there has been an experience whereby the vaccine quantity ran low during the new influenza pandemic during 2009 through 2010. Therefore, the development of a stable supply system of vaccine will be indispensable together with the accumulation of further safe information for vaccination promotion for pregnant

women in Japan.

As for the safety of the influenza A (H1N1) 2009 vaccination during pregnancy, no increase in clinical risk to pregnancy outcome with the vaccination was recognized by this investigation. However, as for the vaccination against influenza A (H1N1) 2009 during the first trimester and the association of miscarriage and premature delivery, further investigation including a larger number of cases will be necessary.

It is thought that this data might serve as a positive basis to support the safety of recommendation of vaccination for influenza A (H1N1) 2009 for pregnant women, as the concept of positive vaccination recommendation for pregnant women had not been verified to date, due to the scarcity of data on safety for pregnant women. There are the following study limitations: this data is only from one establishment in Japan and delivery for women 35 years old or older accounts for about half which makes for an unbalanced group toward the advanced age side in comparison with 23.8% (2010)[26] of delivery ratios in the Japanese whole 35 years old or older. The data on the safety of the influenza A (H1N1) 2009 vaccination during pregnancy still is not sufficient, even including the overseas reporting[22,23,27,28], therefore research including the accumulation of further future cases is necessary.

Conclusions

To evaluate the safety of the influenza A (H1N1) 2009 vaccination during pregnancy in Japan, we investigated pregnancy outcome of vaccinated pregnant women and non-vaccinated pregnant women.

No significant association was found between the influenza A (H1N1) 2009 vaccination and miscarriages, stillbirths, malformations, emergency cesareans, premature delivery or low birthweight infants. The present study confirmed the safety of influenza A (H1N1)2009 vaccination during pregnancy.

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