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ORIGINAL RESEARCH ARTICLE

The PREGVAXGRIP Study: a Cohort Study to Assess Foetal and Neonatal Consequences of *In Utero* Exposure to Vaccination Against A(H1N1)v2009 Influenza

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Abstract

Background In October 2009, in the context of an A(H1N1)v2009 influenza pandemic, a vaccination campaign was launched in France, in which one of the priority groups was pregnant women, on account of the high risk of developing complications following infection by this virus.

Objective The aim of this multicentric, prospective, observational study was to assess safety and pregnancy outcomes in a cohort of pregnant women when receiving the A(H1N1)v2009 influenza pandemic vaccine.

Methods This was a prospective study that followed up pregnant women recruited mainly in vaccination centres and maternity departments. Following the expected delivery date, follow-up data were collected concerning the delivery, the infant, and, if appropriate, the reasons why the pregnancy did not reach its term.

Results Between 1 November 2009 and 31 March 2010, 2,415 pregnant women were included at the time of vaccination; 97.6 % of women received a vaccine without adjuvant and 2.4 % received an adjuvanted vaccine. Ninety-two (3.9 %) women were vaccinated during the first trimester of pregnancy, 1,090 (46.5 %) during the second trimester, and 1,162 (49.6 %) during the third trimester. One hundred and thirty-three adverse events (5.5 % of women) were reported, of which 12 were unexpected or

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serious. There were 2,246 (93.0 %) known pregnancy outcomes with 12 spontaneous abortions (0.5 %), 6 stillbirths (0.3 %), and 4 therapeutic abortions (0.2 %). There were 65 neonates with congenital anomalies, among which 31 were major. But only one congenital malformation (1.4 %) was reported for the 92 women vaccinated in their first trimester. Of the women, 93.3 % were delivered full term and 6.7 % preterm. For 96 (4.2 %) neonates, a disorder was reported in the neonatal period and 130 (5.6 %) were transferred to the neonatology department.

Conclusions This study suggests that exposure to the A(H1N1)v2009 pandemic influenza vaccine during pregnancy does not increase the risk of adverse pregnancy outcomes. However, because of the relatively small number of women exposed during the first trimester, other studies are needed to exclude an increased risk of malformation.

1 Introduction

The first cases of A(H1N1)v2009 influenza appeared in April 2009 in Mexico. This strain, originating from pigs, infected large numbers of people in Mexico and then in the USA, leading to several deaths. Unlike the usual patterns observed in seasonal influenza epidemics, during which 90 % of the deaths are among the elderly, most of the serious forms and most of the deaths relating to the A(H1N1)v2009 influenza epidemic were among individuals under 60 years of age. In addition, around a third of the deaths occurred among subjects without associated co-morbidity [1].

On 11 June 2009, WHO officially declared a state of pandemic for A(H1N1)v2009 influenza. In France, the first cases were isolated in May 2009, with an epidemic wave in September 2009 [2]. At the time of the peak of the epidemic (the end of November 2009), around 750 consultations per 1,000,000 inhabitants per week for suspected A(H1N1)v2009 influenza were reported. In addition, the number of people infected was estimated to be between 7.7 and 14.7 million (i.e. 12 to 23 % of the French population) with 31 deaths attributed to A(H1N1)v2009 influenza [2].

As expected on the basis of earlier pandemics, pregnant women were identified as more liable to develop complications following infection by this influenza virus, in particular respiratory distress and death [3, 4]. This greater susceptibility of the mother and foetus towards influenza infection in pregnancy can be explained by a fall in the immune response in pregnant women, in particular in the third trimester of pregnancy [5]. Influenza-linked morbi-mortality in pregnant women has indeed been found to be higher in both seasonal epidemics and previous pandemics [3, 5–7].

In a recent review covering all publications relating to pregnant women and A(H1N1)v2009 influenza, the authors evaluated the proportion of pregnant women infected by the virus who were hospitalised to be at 52.3 %, among whom 23.3 % were admitted to intensive care [8]. Pregnancy also seems to be a risk factor for A(H1N1)v2009 influenza-related deaths, since, in the same review, the death rate among pregnant women following infection by the A(H1N1)v2009 influenza virus was estimated to be 8 %, and pregnant women accounted for 5.7 % of A(H1N1)v2009 influenza-related deaths. In France, some authors [9] confirmed a high incidence of complications among infected pregnant women, in particular in the third trimester of pregnancy, but the morbi-mortality rate was below that initially described, in the USA and Australia in particular [10–12].

In October 2009, in the context of the influenza pandemic, a major national vaccination campaign was launched in France. In the course of the winter of 2009–2010, more than 5 million individuals were vaccinated, amounting to some 8 % of the general population [2]. In most cases, vaccines were administered in centres dedicated to the pandemic vaccination campaign. Pregnant women were the second priority group (after health professionals) on

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account of the potential severity of the infection in this population.

Vaccination was recommended for all pregnant women from the second trimester of pregnancy, with a non-adjuvanted vaccine. The aim of this measure was to reduce the number of serious forms and the number of deaths, more frequent in the second and third trimesters of pregnancy [1]. A vaccine without adjuvant was recommended in the absence of information about clinical safety of AS03-adjuvanted vaccine during pregnancy.

In earlier studies, it was shown that vaccines against seasonal influenza virus did not present any particular risk for pregnant women [13]. It nevertheless seemed important to study the safety of A(H1N1)v2009 vaccines among pregnant women and any effects on the foetus. In the context of the A(H1N1)v2009 influenza pandemic, we were not able to perform a study with a classic protocol design on account of the time span, so the best alternative was that of a large-scale study.

The aim of this study, named PREGVAXGRIP, using an observational prospective cohort design, was to assess the safety and pregnancy outcomes in a cohort of pregnant women who received the A(H1N1)v2009 influenza pandemic vaccine.

2 Materials and Methods

2.1 Inclusion

The prospective study was observational and followed a cohort of pregnant women who were vaccinated against the A(H1N1)v2009 virus in the course of the French vaccination campaign in the winter of 2009–2010.

Vaccinated pregnant women were recruited by health professionals mainly in the vaccination centres and maternity departments across France between 1 November 2009 and 31 March 2010.

An information sheet and a consent form for participation in the study were issued to the subjects after verbal explanations had been provided. Women who agreed to take part in the study were subsequently contacted by phone by a health professional (doctor or pharmacist) from 1 of the 17 regional pharmacovigilance centres that took part in this study.

At the time of the telephone contact, information was gathered on the current pregnancy, as well as on socio-demographic characteristics, gynaecological and obstetrical history, anti-viral treatment received during pregnancy, information on the vaccination against the A(H1N1)v2009 virus (name of the vaccine, date of vaccination, adverse events subsequent to the vaccination), and the name and address of the facility in which the mother was to give birth.

2.2 Pregnancy Follow-up

After the expected date of the birth, pregnancy follow-up data were obtained from the maternity departments or the physician in charge concerning pathologies having occurred during pregnancy, treatments received, information on the delivery, the infant, and the reasons why any pregnancy did not reach its normal term.

2.3 Data Processing and Statistical Analyses

The inclusion and follow-up data were collected and captured by a health professional in each regional pharmacovigilance centre in a secure and anonymous manner on a dedicated server using the Modalisa® programme, version 4.0 (Kynos, Paris, France). These data were then checked and validated before analysis by the reference regional pharmacovigilance centre of Poitiers. Coherency tests were performed using SAS software version 9.2 (SAS Institute, Cary, NC, USA), and in case of incoherence, clarification was requested from the regional pharmacovigilance centre involved. Certain data were nevertheless not retrieved, despite recalls.

Women for whom the vaccination date or the name of the vaccine were known were retained in the analysis.

Certain pre-existing medical conditions were recorded, such as asthma, diabetes, hypertension, liability to allergy, epilepsy, substance addiction, and HIV infection.

Adverse events linked to vaccination were classified into non-serious expected adverse events, and serious and/or unexpected adverse events, the reporting of the latter to the national French pharmacovigilance database being required in compliance with the legal obligation to notify (decree 95.278, 13 March 1995). According to the French public health code, a serious adverse event was defined as any effect leading to hospitalisation, prolonging hospitalisation, entailing permanent handicap or disability, and life-threatening or fatal condition. These different adverse events were coded according to System Organ Class in the Medical Dictionary for Regulatory Activities (MedDRA®) classification, version 13.0 (MSSO, Chantilly, VA, USA). MedDRA® terminology is the medical terminology developed under the auspices of the International Conference on Harmonization of technical requirements for Registration of Pharmaceuticals for Human Use (ICH).

Spontaneous abortion (SA) was defined as intrauterine death of a foetus of under 500 g or of gestational age under 22 weeks' amenorrhoea (WA). Stillbirths (SB) were defined as intrauterine death of a foetus of over 500 g or gestational age of more than 22 WA (WHO definitions). Premature childbirth was defined as occurring before 37 WA (WHO).

Congenital malformations were classified as major and minor according to the EUROCAT (European Surveillance

of Congenital Anomalies) guide (Approach to Coding and Classification, Chap. 3.1, p. 84, September 2005, EUROCAT Guide 1.3 and reference documents—instructions for the registration and Surveillance of Congenital Anomalies, issued: September 2005).

Neonatal pathologies were classified according to ICD-10 classification (International Classification of Diseases, 10th edition, WHO, http://apps.who.int/classifications/icd10/browse/2010/en).

A descriptive analysis of data at inclusion and data relating to pregnancies and childbirth was performed.

The quantitative data are presented as means and standard deviation, and qualitative data as numbers and percentages.

The incidence of congenital abnormalities was compared with French data in the general population extrapolated from malformation registries [14] and from rates of neonatal disorders for the general population provided by Audipog data for the year 2006 (sentinel network for maternity departments, French perinatal database, http://www.audipog.net) [15]. The Audipog data were also used for comparison with the SB rate observed in the present study.

This study was performed as part of the mandate of the regional pharmacovigilance centres in France (Code de Santé Publique 2010, article R.5121-167).

3 Results

The data (inclusion and follow-up) were collected between 1 November 2009 and 1 April 2011.

3.1 Inclusion Data

In the course of the study period, 2,415 women were included.

The following percentage values do not include pregnant women for whom the information was not available.

A total of 1,817 (78.0 %) were recruited in a vaccination centre, 302 (13.0 %) in a maternity department, and 209 (9.0 %) in an occupational medicine department by a gynaecologist in ambulatory consultation or on the initiative of the subject.

Mean age at inclusion was 31 years, range 15–48.

The characteristics of women at inclusion are shown in Table 1.

For 755 women (36.9 %), it was the first pregnancy, while 1,192 (58.3 %) had had 1–3 previous pregnancies. Among these women with previous pregnancies, 235 (18.2 %) had already had an SA, and 87 (6.7 %) had had at least two SAs.

Four hundred ninety-four women (20.5 %) had a pre-existing medical condition (Table 1).

Table 1 Maternal characteristics and obstetrical history

Mean maternal age, years (SD) ($N = 2{,}379$[a])	30.8 (4.6)
Previous pregnancies, *n* (%) ($N = 2{,}045$[a])	
0	755 (36.9)
1–3	1,192 (58.3)
≥4	98 (4.8)
Parity, *n* (%) ($N = 1{,}975$[a])	
0	875 (44.3)
1–3	1,069 (54.1)
≥4	31 (1.6)
Spontaneous abortions, *n* (%) ($N = 1{,}290$[b])	
1	235 (18.2)
≥2	87 (6.7)
Elective termination of pregnancy, *n* (%) ($N = 1{,}290$[b])	105 (8.1)
Pre-existing medical conditions, *n* (%) ($N = 2{,}415$)	
Presence of at least one pathology	494 (20.5)
Diabetes	138 (5.7)
Allergy	116 (4.8)
Hypertension	114 (4.7)
Asthma	88 (3.6)
Epilepsy	12 (0.5)
HIV infection	5 (0.2)
Addiction	3 (0.1)

[a] Number of women for whom this item was completed

[b] Number of women having had a previous pregnancy

SD standard deviation

3.2 Vaccine Exposure

Vaccination took place for the women in the cohort between 3 November 2009 and 10 March 2010. Of the women included, 97.6 % were vaccinated with PANENZA® (a vaccine without adjuvant, Sanofi Pasteur, Lyon, France) and 2.4 % with an adjuvanted vaccine (PANDEMRIX®, GlaxoSmithKline Biologicals SA, Rixensart, Belgium, or FOCETRIA®, Novartis Vaccines and Diagnostics SRL, Sienna, Italy). The details of vaccine exposure are given in Table 2.

Ninety-two (3.9 %) women were vaccinated during the first trimester of pregnancy, 1,090 (46.5 %) during the second trimester, and 1,162 (49.6 %) during the third trimester.

Vaccination using the vaccine without adjuvant was mainly performed in the course of the second and third trimesters of pregnancy (97.4 %) while exposure to the vaccine containing adjuvant mainly occurred in the first trimester (56.1 %, $p < 0.0001$).

In addition, 67 women received anti-viral treatment, oseltamivir (56) or zanamivir (5), and the name of the drug

Table 2 Type of vaccine and period of vaccination in the pregnancy

Vaccines (n = 2,397[a]/2,415)	Numbers
PANENZA, n (%)	2,340/2,397 (97.6)
1st trimester of pregnancy	60/2,287 (2.6)
2nd trimester of pregnancy	1,077/2,287 (47.1)
3rd trimester of pregnancy	1,150/2,287 (50.3)
PANDEMRIX, n (%)	56/2,397 (2.3)
1st trimester of pregnancy	31/56 (55.4)
2nd trimester of pregnancy	13/56 (23.2)
3rd trimester of pregnancy	12/56 (21.4)
FOCETRIA, n (%)	1/2,397 (0.04)
1st trimester of pregnancy	1/1 (100)
2nd trimester of pregnancy	0
3rd trimester of pregnancy	0

[a] Number of women for whom the name of the vaccine was recorded

Among the 2,415 women thus included, the date or the name of the vaccine was not recorded for 71 (and the name was unknown for 18 women)

PANENZA, vaccine without adjuvant; PANDEMRIX and FOCETRIA, adjuvanted vaccines

Table 3 Adverse reactions reported with A(H1N1) vaccines

Adverse reactions (N = 2,415), n (%)	133 (5.5)
Non-serious adverse reactions	121 (91.0)
General disturbances and anomalies at the administration site	66 (54.5)
Fever and flu-like symptoms	34
Local reactions (pain at the injection site, etc.)	20
Asthenia	12
Nervous system manifestations	23 (19.0)
Headache	12
Paresthesias	6
Dizziness	5
Musculoskeletal and systemic manifestations	6 (5.0)
Myalgia	6
Vascular manifestations	2 (1.7)
Association of adverse reactions	24 (19.8)
Unexpected adverse reactions	7 (5.3)
Serious adverse reactions	5 (3.7)

System Organ Class classification, MedDRA® version 13.0

was not available for six women. In 77.6 % of these cases, the treatment was preventive.

One hundred and thirty-three women (5.5 %) reported adverse events following vaccination, and 15 were unexpected or serious (Table 3). The non-serious adverse events were mainly general disturbances and anomalies at the administration site, in particular local reactions (20 cases), flu-like syndrome or fever (34 cases), and nervous system manifestations (23 cases). Twenty-four women signalled the occurrence of more than one adverse event following vaccination.

Concerning unexpected adverse events, most were cutaneous reactions, mainly transitory (four cases), a sensation of deafness (one case), and active foetal movement after the vaccination (two cases).

The adverse events considered serious (five) were respiratory difficulties (one case), tachycardia and foetal anasarca (one case), paresthesia (one case), intense back pain (one case), and development of bronchitis (one case).

Table 4 Pregnancy outcomes

Pregnancy outcome	2,246
Multiple gestations	45 twins + 1 set of triplets
Delivery resulting in live born, n (%)	2,222/2,246 (98.9)
Pregnancies that did not reach term	24
Spontaneous abortion, n (%)	12 (0.5)
Stillbirth, n (%)	6 (0.3)
Therapeutic termination of pregnancy, n (%)	4 (0.2)
Elective termination of pregnancy, n (%)	1 (0.04)
Not specified, n (%)	1 (0.04)
Delivery resulting in live born	2,222
Caesarean section, n (%)	371/1,890 (19.6)
Premature delivery (<37 WA), n (%)	144/2,145 (6.7)
Mean term, WA (SD)	39.0 (2.0)
Birth characteristics	2,269
Gender male, n (%)	1,094/2,216 (49.4)
Mean birthweight, g (SD)	3,281.2 (560.6)
Low birthweight (<2,500 g), n (%)	154/2,250 (6.8)
Mean stature, cm (SD)	49.5 (2.5)
Mean cranial circumference, cm (SD)	34.4 (1.8)
Malformations, n (%)	65/2,269 (2.9)
Major malformations, n (%)	31/2,269 (1.4)
Neonatal pathologies, n (%)	96/2,269 (4.2)
Transfer to neonatology department, n (%)	130/2,269 (5.6)
Neonatal deaths, n (%)	3/2,269 (0.1)

SD standard deviation, *WA* weeks' amenorrhoea

3.3 Pregnancy Outcome

Among the 2,415 women included in the study, data concerning pregnancy outcome were available for 2,246, giving a follow-up rate of 93.0 %.

Among these 2,246 pregnancies, 46 multiple pregnancies were observed, 45 cases of twins, and 1 case of triplets.

As indicated in Table 4, 2,222 pregnancies reached their term with 2,269 births. Twenty-four pregnancies failed, mainly because of SA (n = 12, 0.5 %), SB (n = 6, 0.3 %), and therapeutic termination of pregnancy (n = 4, 0.2 %). Details concerning these pregnancies (SA and SB) are given in Table 5.

Table 5 Pregnancies that failed to reach their term

Age of the woman (years)	Name of vaccine and trimester of vaccination	Time lapse between vaccination and spontaneous abortion	Gynaecological and obstetrical history	Pathologies	Comments
Spontaneous abortion					
32	PANENZA, 1st trimester	6 weeks	One previous pregnancy: one normal infant		
36	PANENZA, 2nd trimester	7 days	7 previous pregnancies: one voluntary abortion, 2 spontaneous abortions and 4 normal infants		
30	PANDEMRIX, 1st trimester	24 days	No previous pregnancy		Doubts concerning haematoma on the egg
37	PANENZA, 2nd trimester	Non-determined	Non-determined		
31	PANENZA, 1st trimester	2 months	Non-determined		
28	PANENZA, non-determined	Non-determined	No previous pregnancy		
40	PANENZA, 2nd trimester	9 days	3 previous pregnancies: one medical abortion (trisomy 18) and 2 normal infants	Asthma	
31	PANENZA, 2nd trimester	10 days	Non-determined		
29	PANENZA, 3rd trimester	Non-determined	No previous pregnancy		
30	Non-determined, 1st trimester	1 month	2 previous pregnancies: 2 normal infants		
33	PANENZA, 1st trimester	7 weeks	One previous pregnancy One normal infant		
Stillbirth					
35	PANENZA, 2nd trimester	1 month	One previous pregnancy: one normal infant		Dual striction of the umbilical cord with velamentous insertion
26	PANENZA, 3rd trimester	Non-determined	No previous pregnancy		
23	PANENZA, 2nd trimester	2 months and a half	No previous pregnancy		Umbilical cord around the neck
38	PANENZA, 3rd trimester	1 day	4 previous pregnancies: one spontaneous abortion, one stillbirth (Benckiser haemorrhage), two normal infants		
29	PANENZA, 3rd trimester	1 month	No previous pregnancy		Benckiser haemorrhage
31	PANENZA, 3rd trimester	2 months	2 previous pregnancies: 2 normal infants		

Table 6 Congenital malformations and neonatal pathologies

Malformations[a] ($N = 2,269$), *n* (%)	65 (2.9)
Major	31 (1.4)
Cardiovascular	12
Renal	5
External genital organs	4
Oral region	2
Gastrointestinal	2
Chromosome anomalies	2
Feet and limbs	1
Skin	1
Brain, neural tube defects	1
Pulmonary	1
Minor	31 (1.4)
Feet and limbs	10
Ears	4
Cardiovascular	4
Renal	4
Oral region	2
Brain, neural tube defects	2
External genital organs	2
Eyes	1
Gastrointestinal	1
Other	1
Non-determined	3 (0.1)
Neonatal pathologies[b] ($N = 2,269$), *n* (%)	96 (4.2)
P00–P04	5
Foetus and neonate affected by maternal disorder, complications in pregnancy, labour and delivery	
P05–P08	12
Anomalies linked to the duration of gestation and the growth of the foetus	
P20–P29	27
Respiratory and cardiovascular complaints specific to the perinatal period	
P35–P39	21
Infections specific to the perinatal period	
P50–P61	2
Haemorrhagic and haematological conditions of the foetus and the neonate	
P70–P74	13
Transitory endocrine and metabolic disorders specific to the foetus and the neonate	
P75–P78	5
Disorders of the digestive system specific to the foetus and the neonate	
P80–P83	1
Conditions affecting the tegmina and thermal regulation in the foetus and the neonate	
P90–P96	6
Other disorders originating from the perinatal period	
Others	4

[a] Classification according to the EUROCAT guide (approach to coding and classification. Chap 3.1, p. 84, Sept 2005)

[b] ICD-10 Classification

ICD-10 International Classification of Diseases 10th edition

For pregnancies reaching their term, childbirth occurred on average at 39 WA (Table 4), mainly by normal delivery for 80.4 %, and Caesarean section was performed for 19.6 %. Premature delivery, i.e. before 37 WA, occurred in 6.7 % of cases. One hundred and fifty-four newborns (6.8 %) had a birthweight under 2,500 g (Table 4).

Sixty-five newborns presented a malformation at birth, and 31 of these malformations were major, mainly cardiovascular (12 cases), renal (5 cases), or external genital organ anomalies (4 cases) [Table 6]. But only one (1.4 %) malformation, which was major, was observed in a child born to a woman who had been vaccinated in the first trimester of pregnancy with PANDEMRIX® (adjuvanted vaccine). The malformation was peri-membranous interventricular communication with pulmonary artery hypertension. Respectively, 30 (3.0 %) and 34 (3.0 %) malformations were observed among children born to women vaccinated in the course of the second and third trimesters of pregnancy.

Ninety-six neonatal pathologies (4.2 %) were reported (Table 6). Among these, 27 were respiratory and cardiovascular conditions specific to the neonatal period, mainly concerning episodes of respiratory depression, and 21 were infections specific to the perinatal period. With regard to the vaccination exposure period, the neonatal pathologies were significantly more frequent when the vaccination took place in the course of the first trimester of pregnancy (10.0 % vs. 3.8 % and 4.4 %, respectively, for trimesters 2 and 3, $p = 0.043$). Respectively, 7/96, 38/96 and 50/96 neonatal morbid conditions were observed among women vaccinated in the first, second, and third trimester of pregnancy.

Finally, three deaths were notified, two of which concerned very premature triplets (25 WA) who died following high-grade cerebral haemorrhage. The mother had been vaccinated during the second trimester of pregnancy with a vaccine without adjuvant, and childbirth occurred 2 months after vaccination. The third death was reported for a very premature newborn (25 WA) presenting hyaline membrane disease with pulmonary haemorrhage, severe hypotrophy, and ulcerating-necrotising enterocolitis. In this case, the mother had been vaccinated in the second trimester of pregnancy with a vaccine without adjuvant, and childbirth occurred 1 week after vaccination, in a context of severely retarded intrauterine growth and hypertension.

4 Discussion

In this cohort, we followed 2,415 pregnant women prospectively after vaccination against the A(H1N1)v2009 influenza virus, by way of collaboration across the French network of pharmacovigilance centres. The very small number of pregnancies for which the outcome was

unknown (7.0 %) does not impact the analysis of the results of this study, in particular with respect to pregnancy outcomes. Moreover, there is a very high probability that the pregnancies that were lost to follow-up were uneventful. Indeed, if there had been a negative outcome, there would be a strong incentive for reporting or contacting their physicians.

Overall, recommendations concerning vaccination quoted above were complied with, since most women (2,252) were vaccinated in the course of the last two trimesters of pregnancy (96.1 %) with a vaccine that did not contain adjuvant—PANENZA® for 97.6 %. The uses of a vaccine containing adjuvant (PANDEMRIX® or FOCETRIA®) occurred mainly in the first trimester, and this failure to comply with the recommendations could be explained by the fact that the women concerned did not know they were pregnant at the time of the vaccination and so fell under the measures adopted for the general population, i.e. vaccine with adjuvant. Indeed, in most cases, subjects were aware they were pregnant at the time of vaccination. But a few were included in the cohort after having discovered their pregnancy after vaccination.

In this study, we looked for any adverse event potentially linked to vaccination in the pregnant women in our cohort having received the vaccine. The overall percentage of these adverse events was 5.5 %. The non-serious adverse events reported in the cohort are similar to those described for the general population by Caillet et al. [16]. In this study, the authors analysed all adverse events reported by practitioners and patients in regional pharmacovigilance centres in France and registered in the French national pharmacovigilance database. Among the non-serious adverse events reported, "general disturbances and anomalies at the administration site" (65.9 % for PANDEMRIX® and 47.0 % for PANENZA® vs. 54.5 % for cases in our study), and "manifestations of the nervous system" (17.6 % for PANDEMRIX® vs, 16.9 % for cases in our study) were the most often described [16]. The adverse events found in our study were also comparable with those described in a study assessing vaccine safety in a population of healthcare personnel [17]. Generally, the profile of undesirable side effects is not specific to this particular vaccine, since it is also noted for other vaccines, in particular that for seasonal influenza [18, 19].

Among the 2,246 women whose pregnancy was followed up, 2,222 pregnancies (98.9 %) reached their term with 2,269 births.

Concerning SA, the proportion observed in our study (0.5 %) is well below the overall rate reported in the general population, which varies according to study from 10 to 15 % [20–24]. This very marked difference could be explained by the fact that the pregnant women were recruited at the time of vaccination, that is to say, as noted earlier, in the second and third trimesters of pregnancy. SA is much more frequent in the early weeks of pregnancy, and decreases between the 8th and 12th week of gestation [20, 22, 24]. Thus, in the present study, given the small number of women vaccinated in the first trimester, it seems difficult to conclude to any effect of the vaccine on the risk of SA. Concerning SB, the proportion found by the present study (0.3 %) is below the rate observed in the general population, estimated at 0.7 % according to Audipog data. Again, it is difficult to draw conclusions, since 1,162 (49.6 %) of women were vaccinated in the third trimester, which could partly explain why the proportion is so small. This study therefore shows that vaccination against A(H1N1)v2009 influenza probably does not increase the risk of spontaneous miscarriage (SA and SB combined).

This result appears to confirm data from the French national pharmacovigilance database analysed in a recent publication [25]. In this study, the authors noted 30 serious adverse events observed in pregnant women and notified to regional pharmacovigilance centres. Among these, there were 13 cases of SB and 12 cases of SA, which is well below the proportions expected in the general population, thus leading to the conclusion that there was no reason for concern for this vaccination among pregnant women, despite limitations inherent in this type of surveillance (under-reporting).

Regarding pregnancies that reached their term, deliveries were mainly normal, since the proportion of Caesarean section was estimated to be 19.6 %, a proportion that is superimposable on that for the general population, estimated at 18.8 % (Audipog 2006). Delivery occurred at 39 WA on average, and prematurity was observed in 6.7 % of cases, which is close to the figure of 7.1 % reported by Audipog. Finally, no difference was found in birthweight (3,281 g vs. 3,282 g in the general population, Audipog) and stature (49.5 cm vs. 49.6 cm in the general population, Audipog) compared with the general population.

Congenital abnormalities were reported for 2.9 % of the neonates, and this proportion does not differ from that expected in the general population. However, if solely the women vaccinated in the first trimester of pregnancy are considered, only one malformation was observed, amounting to a rate of 1.4 %, which is below that expected in the general population. Indeed, according to a French weekly epidemiological bulletin published in 2008 in France, congenital malformations concern around 3 % of live births. This incidence is estimated from 4 French registries performing epidemiological surveillance of pregnancy outcomes in 14 French administrative areas, accounting for around 16 % of French births. To the 65 congenital anomalies observed in this study should be added 4 cases of therapeutic abortion, 2 of which followed disclosure of chromosome abnormalities (trisomy 18 and

21), 1 on account of a renal disorder (anamnios), and 1 for retarded growth. In the last instance, the termination was selective, on a twin with a serious malformation (details not available). The pregnant women had all been vaccinated in the second trimester of pregnancy using a vaccine without adjuvant with the exception of the last case, which occurred in the third trimester also using a vaccine without adjuvant.

The absence of any difference between malformation rates in the general population and in the present study population suggest that there is no causal link between the appearance of the abnormalities and vaccine exposure. Further to this, the risk of morphological effects is highest in the course of the first trimester, the period of organogenesis. It is therefore difficult to attribute the anomalies observed in the study to the administration of the vaccine, given that the exposure mainly occurred in the course of the second and third trimesters. Conversely, it is also difficult to conclude the absence of any teratogenic effect of the vaccine on account of the small number of subjects vaccinated in the first trimester. Moreover, the follow-up data were collected mainly 1 week after the delivery data, so that certain minor malformations that are not always immediately detected at birth may have been missed. Moreover, in most files there was no information on whether or not the patient was taking folates, but we consider that our study population was representative of the general population in France. Indeed, an overprescription of folates in our population is unlikely considering the fact that, in France, the prescription of folates during pregnancy is not usual. Another parameter that was not taken into account in our study is that use of potential teratogenic medication was not an exclusion criterion.

Finally, 96 newborns (4.2 %) presented a neonatal disorder, which is a proportion that is well below that found in the general population (25.3 %, Audipog). Several hypotheses could explain this difference, such as lack of homogeneity in the definition of the disorder, difficulty in diagnosing the disorder, and the fact that some regional pharmacovigilance centres might have not taken the usual pathologies observed in neonates into account, such as neonatal jaundice (0.2 % in our study vs 9.2 % in Audipog).

This study aimed to gain knowledge about any possible repercussions of mass vaccination against A(H1N1)v2009 influenza in a particular population, that of pregnant women, since data on the clinical safety of vaccines in this population are often sparse [26–33]. It entails certain limitations. Indeed, as mentioned earlier, it appears difficult to draw certain conclusions, for instance on any teratogenic effect, because the vast majority of the women were vaccinated in the second or third trimester of pregnancy, i.e. after the organogenesis phase. Likewise, it is also difficult to assess the impact of vaccination on the occurrence of SA, given the period of vaccine exposure among the women in the cohort. The small number of women exposed in the first trimester included in the present study is accounted for by the fact that the recommendation was for vaccination in the second and third trimesters. Among women vaccinated during the first trimester, 31 received the adjuvanted vaccine (PANDEMRIX) with one SA and one major congenital abnormality, which was not different compared with the general population, but the number of women vaccinated with PANDEMRIX was too small to allow us to draw a conclusion.

The second main limitation of this study is the lack of a control group. Indeed, in the setting of a pandemic the establishment of a control group was not possible because of the time span. We therefore compared our results with data from the general population of pregnant women extrapolated from the Audipog perinatal network or from data recorded in the malformations registry.

It is also difficult to determine from this study whether or not the population of women included, who had decided or were advised to accept vaccination, were comparable from all points of view with the general population of pregnant women, in particular for age, social characteristics, risk factors, or gynaecological and obstetrical history, which are factors that can have an influence on the occurrence of spontaneous miscarriage [19, 22, 23]. Indeed, despite recommendations, according to health watchdog figures, only 22.7 % of pregnant women were vaccinated during the vaccination campaign of the winter of 2009–2010 [2].

The strength of our study is the large number of French women included and a very good follow-up rate of 93 %, reflecting marked interest from pregnant women and physicians for this study and considerable involvement and effort by the French network of regional pharmacovigilance centres, explaining this good follow-up rate.

5 Conclusions

This study conducted on a large sample of pregnant women via collaboration with the French network of regional pharmacovigilance centres has made it possible to show that vaccination against A(H1N1)v2009 influenza does not appear to increase the risk of miscarriage or the occurrence of congenital malformations compared with rates observed in the general population of pregnant women, despite the fact that the number of women vaccinated in the first trimester of pregnancy was insufficient for final conclusions to be reached. The impact of this data is important because of the demonstrated risk of severe complications for mother and foetus following infection by the A(H1N1)

virus and the fact that vaccination at present appears to be the best means of preventing these complications in pregnancy.

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Conflict of interest The authors declare that they have no conflict of interest.

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