Original article

Prognosis of 2009 A(H1N1) influenza in hospitalized pregnant women in a context of early diagnosis and antiviral therapy

José Ramón Paño-Pardo[1†], Jesús Rodríguez-Baño[2†], Nuria Martínez-Sánchez[1], Diego Viasus[3], M Carmen Fariñas[4], María Leyes[5], Francisco López-Medrano[6], Jerónimo Pachón[7], Julián Torre-Cisneros[8], José Antonio Oteo[9], Tomás Pumarola[10], Mercedes García-Gasalla[11], Lucía Ortega[12], Ferrán Segura[13], Jordi Carratalá[3], the Novel Influenza A(H1N1) Study Group of the Spanish Network for Research in Infectious Diseases (REIPI)[‡]*

[1]Hospital Universitario La Paz - IDIPAZ, Madrid, Spain
[2]Hospital Universitario Virgen Macarena and University of Sevilla, Sevilla, Spain
[3]Hospital Universitari de Bellvitge - IDIBELL, Barcelona, Spain
[4]Hospital Universitario Marqués de Valdecilla, Santander, Spain
[5]Hospital Universitario Son Espases, Palma de Mallorca, Spain
[6]Hospital Universitario 12 de Octubre, Madrid, Spain
[7]Hospital Universitario Virgen del Rocío, Sevilla, Spain
[8]Hospital Universitario Reina Sofía, Córdoba, Spain
[9]Hospital San Pedro - CIBIR, Logroño, Spain
[10]Hospital Clinic Universitari, Barcelona, Spain
[11]Hospital Son Llátzer, Palma de Mallorca, Spain
[12]Hospital de Barcelona, Barcelona, Spain
[13]Hospital Parc Taulí, Sabadell, Barcelona, Spain

*Corresponding author e-mail: jesusrb@us.es
†These authors made an equal contribution to this work
‡See Additional file 1 for a list of the other members of the Novel Influenza A(H1N1) Study Group

Background: Initial reports suggested that novel A(H1N1) influenza virus (2009 A[H1N1]v) infection was significantly more severe in pregnant than in non-pregnant women. In Spain, antiviral therapy was recommended for pregnant women from the beginning of the 2009 pandemic.

Methods: The prospective cohort study included consecutive pregnant and non-pregnant women of reproductive age with a proven diagnosis of 2009 A(H1N1)v admitted to any of the 13 participating Spanish hospitals between 12 June and 10 November 2009.

Results: In total, 98 pregnant and 112 non-pregnant women with proven 2009 A(H1N1)v hospitalized during the study period were included. Influenza was more severe among non-pregnant patients than pregnant patients with respect to outcomes of both intensive care unit admission (18% versus 2%; $P<0.001$) and death (5 versus 0; $P=0.06$). Pregnant women had fewer associated comorbid conditions other than pregnancy (18% versus 44%; $P<0.001$); they were also admitted earlier than non-pregnant women (median days since onset of symptoms: 2 versus 3; $P<0.001$) and a higher percentage received early antiviral therapy (41% versus 28%; $P=0.03$). Neither a multivariate nor a matched cohort analysis found pregnancy to be associated with greater severity than that associated with hospitalized, seriously ill non-pregnant women.

Conclusions: 2009 A(H1N1)v influenza was not associated with worse outcomes in hospitalized pregnant women compared with non-pregnant ones of reproductive age in a context of early diagnosis and antiviral therapy.

Introduction

Although novel H1N1 influenza A virus 2009 A(H1N1)v was first identified in respiratory samples obtained in Southern California, USA in April 2009, the first reported cases occurred in Veracruz, México in February 2009 [1]. As of 17 February 2010, at least 15,921 deaths have been reported relating to 2009 A(H1N1)v and more than 212 countries and overseas territories or communities have reported laboratory-confirmed cases [2].

Although influenza is typically a mild disease, the likelihood of developing complicated influenza, whether in seasonal influenza [3,4] or more frequently in pandemics, has been shown to be higher in pregnant women than in women of reproductive years in the general population [5–8]. Preliminary data from the USA and Australia obtained during the first wave of A(H1N1)v suggested that pregnancy was also associated with a greater risk of complications owing to the 2009 A(H1N1)v virus infection [9–11]. During the 2009 pandemic, protocols for managing influenza in patients at risk of complications or presenting with severe disease were launched in Spain by the Ministry of Health and the Health Services of the Autonomous Communities, including early antiviral therapy in these patients. Specifically, it was recommended that oseltamivir be offered to all pregnant women with complicated disease caused by pandemic influenza or with additional risk factors for complications [12]. The Spanish Network for Research in Infectious Diseases (REIPI) conducted a prospective observational study to compare the clinical and epidemiological features of proven 2009 A(H1N1)v infection in hospitalized pregnant women with those in non-pregnant women of reproductive age.

Methods

Setting, patients and study design

A prospective cohort study was conducted in 13 tertiary Spanish hospitals. All adult women of reproductive age (15 to 45 years), admitted to hospital for at least 24 h with a confirmed 2009 A(H1N1)v infection between 12 June and 10 November 2009, were prospectively recruited and followed up. Cases were identified on a daily basis by reviewing the microbiological reports. A confirmed case was defined as a patient with an influenza-like illness and 2009 A(H1N1)v infection documented by real-time (RT)-PCR or viral culture in a respiratory sample (a nasopharyngeal aspirate or nasal plus pharyngeal swab for all patients and samples from lower respiratory tract in selected cases). 2009 A(H1N1)v testing was performed in every institution. Written informed consent was obtained from participants who remained in hospital at the time when investigators reviewed their clinical data. Because of the short hospital stay of many patients, no informed consent was obtained from those discharged before investigators could review clinical data. Informed consent was waived for this subset of patients given the observational nature of the study and the retrospective acquisition of data in a context of an ongoing epidemic. The study was approved by Hospital de Bellvitge's (Barcelona, Spain) Institutional Review Board (PR 182/09).

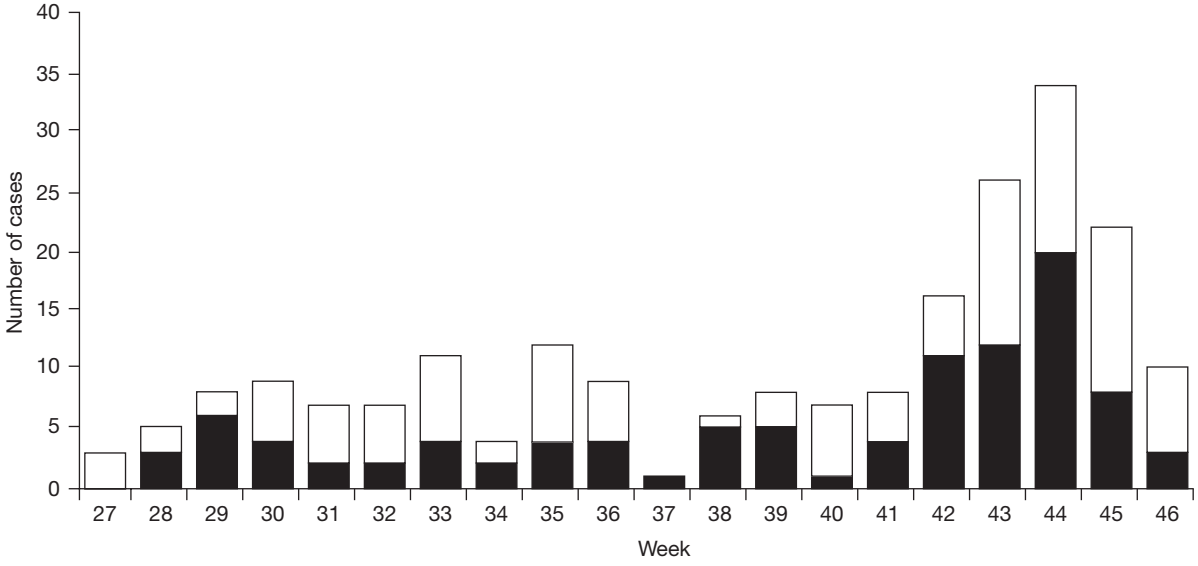
Clinical assessment and follow up

During their hospital stay, patients were followed in each centre by one or more investigators. Demographic and baseline data as well as clinical, radiological, laboratory and microbiological features were collected.

Definitions

The severity of underlying conditions was assessed using the Charlson index [13]. Pneumonia was defined as the presence of a new infiltrate on a chest radiograph; pneumonia severity scores, specifically the Pneumonia Severity Index (PSI) [14] and the CURB-65 score [15], were calculated. Decisions regarding hospitalization and intensive care unit (ICU) admission, microbiological workup and treatment were made by the attending physician at each centre. Because criteria for hospital admission across the centres or during the study period were not homogeneous, we retrospectively defined hospital admission as being clinically driven when any of the following were present on admission: hypoxemia ($PaO_2 \leq 70$ mmHg or oxygen saturation on room air ≤95%); tachypnea (≥24 breaths per min); altered mental status; hypotension (systolic blood pressure ≤90 mmHg); decompensation in underlying condition requiring hospital management (typically, respiratory insufficiency in patients with chronic respiratory disease, worsening of renal function in patients with chronic renal disease, decompensated cirrhosis and metabolic complications of diabetes mellitus); complicated pregnancy course leading to hospitalization for monitoring; and any sign of new or previously unknown organ damage occurring on admission, including new renal insufficiency (glomerular filtration rate <60 ml/min), new heart failure (New York Heart Association class II or higher), or new liver failure (encephalopathy, prolonged prothrombine time >20 s or International Normalized Ratio >1.5). The criteria for clinically driven admission were separately assessed by two investigators (JRP-P and JR-B) who were blinded to the pregnancy status of the patients; discrepancies were resolved by agreement after discussion. Time to clinical stability was evaluated as described by Halm *et al.* [16]. The composite outcome 'severe complication' included in-hospital mortality and ICU admission during the hospital stay.

Figure 1. Distribution of cases during the study period by week of year 2009



Black bars represent pregnant women and white bars represent non-pregnant women.

Statistical analyses

The results were analysed using a commercially available statistical software package (SPSS, version 15.0; SPSS Inc., Chicago, IL, USA). Comparisons between groups were performed for categorical variables using the χ^2 or Fisher exact tests as appropriate, and the Mann–Whitney U test for continuous variables. All reported *P*-values are two-tailed. To evaluate pregnancy as a risk factor for severe complications, we performed two types of analysis aiming to control for possible confounding factors resulting from differences in the criteria leading to hospitalization of pregnant and non-pregnant women. First, variables associated with the composite outcome were analysed in the cohort of women with clinically driven admission criteria (see *Definitions*) and in the whole cohort. Crude relative risk (RR) and 95% CIs were calculated. Multivariate analysis was performed using logistic regression and variables were selected using a stepwise backward procedure. The second type of analysis was a matched cohort analysis in which non-pregnant patients were matched 1:1 with pregnant women on the basis of the following variables: a pneumonia diagnosis, existence of any comorbidity increasing the risk of complications, and initiation of antiviral therapy during the first 48 h after onset of disease. Whenever more than one non-pregnant woman fulfilled the matching criteria, the one with the number of days between disease onset and hospital admission most closely matched to that of the corresponding pregnant patient was selected. If there was still more than one eligible candidate, the one closest in age was selected. Selection of matched patients was performed without knowledge of clinical outcomes. Comparison of matched pairs was performed by McNemar test or conditional logistic regression.

Results

All 210 women of reproductive age admitted with confirmed 2009 A(H1N1)v infection to the participating centres were included in the analysis; 98 (47%) were pregnant. The distribution of cases throughout the study period is shown in Figure 1. Among pregnant patients, 14 (14.3%) were in their first trimester, 34 (34.7%) in the second and 50 (51%) in the third.

The demographic features and underlying conditions of the patients in the study are shown in Table 1. Current smoking and underlying conditions other than pregnancy were significantly more frequent (smoking, 27% versus 12% and other underlying conditions, 44 versus 18%; $P<0.001$) in non-pregnant women than in pregnant women, respectively. The most common underlying condition in both groups was asthma; chronic heart, liver, or obstructive lung disease and morbid obesity were only present in non-pregnant patients. The median time between onset of symptoms and admission was shorter for pregnant women and their illness

Table 1. Demographic features and underlying conditions of women of reproductive age admitted with pandemic 2009 influenza A (H1N1)

Factor	Pregnant (*n*=98)	Non-pregnant (*n*=112)	*P*-value
Age in years, median (range)	29 (16–44)	32 (16–45)	0.07[a]
Current smoker	11 (12)	30 (27)	0.005
Influenza seasonal vaccine	2 (2)	10 (10)	0.06[b]
Pneumococcal vaccine, previous 5 years	1 (1)	3 (3)	0.6[b]
Any underlying condition	18 (18)	49 (44)	<0.001
Charlson index >1	4 (4)	13 (12)	0.04
Chronic pulmonary disease	13 (13)	25 (22)	0.08
Asthma	13 (13)	22 (20)	0.2
Chronic obstructive pulmonary disease	0	3 (3)	0.2[b]
Chronic heart disease	0	4	0.1
Chronic renal failure	1 (1)	2 (3)	1.0
Chronic liver disease	0	7 (6)	0.01[b]
Diabetes mellitus	4 (4)	5 (5)	1.0
Immunosuppressed	3 (3)	10 (9)	0.09
Cancer	1 (1)	4 (4)	0.3[b]
Morbid obesity	0	8 (7)	0.008[b]

Data are expressed as *n* (%) unless otherwise indicated. *P*-values were calculated using χ^2 test, except for [a]Mann–Whitney U test and [b]Fisher test. Morbid obesity is classified as a body mass index >35 kg/m^2.

severity less, compared with non-pregnant patients (Table 2). Non-pregnant women showed a higher frequency of shortness of breath, tachypnea, wheezing, pleuritic chest pain, diarrhoea and vomiting at hospital admission, whereas pregnant women had rhinorrhoea in a higher proportion (Table 2). Leukopenia, thrombocytopenia and increased levels of serum alanine aminotransferase (ALT), creatinine phosphokinase and C reactive protein, as well as respiratory insufficiency, were more frequent in non-pregnant women. Among those in whom chest radiography was performed, pneumonia was diagnosed in 10 (10.2%) of the pregnant and 62 (55.4%) of the non-pregnant women (*P*<0.001). Overall, clinically driven admission, mainly owing to respiratory distress and hypoxaemia, was twice as frequent in non-pregnant women as in pregnant women (66% versus 33%; *P*<0.001).

Antiviral therapy (oseltamivir in all cases) was more frequently administered to non-pregnant women, although it was administered earlier to the pregnant women (Table 3). Oseltamivir was well tolerated in all treated women, with no reported serious adverse events. In crude comparisons, early antiviral therapy (administered <48 h after illness onset versus later or no therapy) was not significantly associated with a decrease in new-onset complications (10% versus 8.5%, respectively; *P*=0.8), time to clinical stability (median days [range]: 1 [0–7] versus 1 [0–58]; *P*=0.1) or total duration of hospital stay (4 [1–12] versus 5 [1–65]; *P*=0.5); stratification by pregnancy status showed similar results (data not shown). Five out of the 113 patients who did not receive early therapy died (4%), whereas none of those receiving early therapy died (4% versus 0; *P*=0.1 by Fisher test). The five patients who died were non-pregnant women who had not received early therapy. Time to clinical stability and length of hospital stay were shorter for pregnant patients (Table 3). Of 22 patients (10.4%) requiring ICU admission, two were pregnant. Two pregnant women had preterm deliveries with no other complications.

The analysis of risk factors for severe complications (ICU admission or death) was carried out on the whole cohort and those with clinically driven admission criteria. This subset comprised 106 patients (32 pregnant [30%] and 74 non-pregnant [70%]), and included all 22 patients who developed severe complications. The univariate analysis is shown in Table 4. Because only 22 patients acquired the outcome variable, a limited number of variables could be included in the multivariate analysis. Instead of including each underlying condition, we opted to include the variable 'significant comorbidity', which included any underlying condition that has been recognized to increase the risk of complications in the course of influenza. Several stratified analyses were performed to investigate effect modification and to decide on which variables to include. The variables finally included in the multivariate analysis were: significant comorbidity, pregnancy, multilobar pneumonia, bacterial coinfections and early antiviral therapy. Pregnancy was retained in the final models. Variables selected as independent risk factors were: significant comorbidity (adjusted odds ratio [OR]=6.2; 95% CI 1.7, 21.4; *P*=0.004) and multilobar pneumonia (adjusted OR=8.0; 95% CI 2.5, 25.8; *P*<0.001); pregnancy was not associated (adjusted OR=0.2; 95% CI 0.05, 1.5; *P*=0.1). The analyses were repeated using a forward selection

Table 2. Clinical features of women of reproductive age admitted with pandemic 2009 influenza A(H1N1)v

Factor	Pregnant (*n*=98)	Non-pregnant (*n*=112)	*P*-value
Median days from onset to hospitalization (range)	2 (1–15)	3 (1–20)	<0.001[a]
Reported symptoms			
Cough	87 (89)	99 (89)	0.9
Shortness of breath	27 (28)	56 (50)	<0.001
Myalgia	54 (55)	68 (61)	0.3
Sore throat	41 (42)	38 (34)	0.2
Headache	44 (45)	38 (34)	0.1
Rhinorrhoea	44 (45)	22 (20)	<0.001
Diarrhoea	3 (3)	11 (10)	0.05[b]
Vomiting	11 (11)	24 (21)	0.04
Pleuritic chest pain	8 (8)	20 (18)	0.03
Physical findings on admission			
Fever (≥38.0°C)	41 (44)	52 (49)	0.4
Hypotension (systolic blood pressure ≤90 mmHg)	2 (2)	7 (7)	0.1[b]
Tachycardia (≥90 beats/min^{-1})	65 (76)	63 (65)	0.1
Tachypnea (≥24 breaths/min^{-1})	12 (16)	27 (40)	0.001
Wheezing	8 (8)	30 (27)	0.001
Impaired consciousness	1 (1)	4 (4)	0.2[b]
Laboratory findings on admission			
Leukopenia (leukocyte count <4,000 per mm^3)	2 (2)	25 (23)	<0.001
Leukocytosis (leukocyte count ≥12,000 per mm^3)	10 (10)	16 (15)	0.3
Anaemia (hematocrit <36%)	67 (69)	31 (29)	<0.001
Thrombocytopenia (platelets <150,000 per mm^3)	13 (14)	31 (29)	0.01
Creatine phosphokinase >240 IU/l	0	6 (19)	0.07
Serum creatinine >1.3 mg/dl	0	3 (3)	0.2[b]
C reactive protein >20 mg/l	40 (64)	60 (85)	0.005
PaO_2/FiO_2<300 or oxygen saturation <90%	5 (6)	30 (31)	<0.001
Radiographic findings			
Chest radiography performed at admission	57 (58)	111 (99)	<0.001
Infiltrates on chest radiography[c]	10 (18)	62 (56)	<0.001
Bilateral infiltrates[d]	6 (60)	31 (50)	0.5
Pleural effusion[c]	1 (2)	7 (6)	0.1[b]
CURB-65>1[e]	1 (10)	7 (11)	0.9[b]
Pneumonia Severity Index III–V[e]	1 (10)	9 (15)	0.7[b]
Bacterial coinfection	2 (2)	9 (8)	0.05[b]
Clinically driven admission[f]	32 (33)	74 (66)	<0.001
Hypoxaemia	5 (5)	30 (27)	<0.001
Tachypnea	12 (16)	27 (40)	0.001
Altered mental status	1 (1)	4 (4)	0.1[b]
Hypotension	2 (2)	7 (7)	0.1[b]
Decompensated underlying condition	16 (16)[g]	26 (23)[h]	0.2
New other organ damage	1[i]	4 (4)[j]	0.2[b]

Data are expressed as *n* (%) unless otherwise indicated. *P*-values were calculated using χ^2 test, except for [a]Mann–Whitney U test and [b]Fisher test. [c]Only patients with chest radiography performed are considered. [d]Only patients with pulmonary infiltrate are included. [e]Only patients with pneumonia are considered. [f]Patients might have more than one criterion for clinically driven admission. [g]Asthma (14 patients), preterm labour (2). [h]Asthma (22 patients), chronic pulmonary disease (3), chronic renal failure (1), chronic liver disease (1). [i]Renal insufficiency. [j]Heart insufficiency (2), renal insufficiency (2).

method, adding different variables to pregnancy. Pregnancy did not significantly modify the predictions of the model when significant comorbidity and multilobar pneumonia were present. Because pneumonia can be interpreted as an intermediate step in the evolution of the disease, a multivariate model was built that did not include pneumonia and that included chronic pulmonary disease and morbid obesity as individual variables. The variables selected were chronic pulmonary disease (adjusted OR=3.2; 95% CI 1.1, 9.7; *P*=0.03), morbid obesity (adjusted OR=8.1; 95% CI 1.0, 51.3; *P*=0.02), and pregnancy (adjusted OR=0.06; 95% CI 0.04, 1.0; *P*=0.06). The inclusion of specific criteria for clinically driven admission did not change the results. Similar results were obtained when the whole cohort of women was analysed (data not shown).

Table 3. Therapies and outcomes for women of reproductive age admitted with influenza A (H1N1)v

Factor	Pregnant (*n*=98)	Non-pregnant (*n*=112)	*P*-value
Therapy			
Antiviral therapy (oseltamivir)	73 (75)	109 (97)	<0.001
Median number of days from symptom onset to antiviral therapy (range)	2 (1–15)	4 (1–20)	0.003[b]
Early treatment (≤48 h after symptom onset)	40 (41)	30 (28)	0.03
Antibacterial treatment	25 (26)	86 (78)	<0.001
Corticosteroids	7 (7)	28 (26)	<0.001
Clinical outcomes			
Median days to clinical stability (range)	0 (0–12)	2 (0-58)	<0.001[a]
Median days of hospital stay (range)	3 (1–11)	6 (1-65)	<0.001[a]
Complications			
Shock on/after admission	0	7 (6)	0.01[b]
Nosocomial infections	0	3 (2)[c]	0.2[b]
Heart failure	0	2 (2)	0.5[b]
Acute respiratory distress syndrome	0	10 (9)	0.002[b]
Intensive care unit admission	2 (2)	20 (18)	<0.001
Intubation and mechanical ventilation	1 (1)	12 (11)	0.01[b]
Non-invasive mechanical ventilation	2 (2)	3 (3)	1.0[b]
Preterm delivery	2 (2)	–	–
Mortality	0	5 (5)	0.06[b]

Data are expressed as *n* (%), unless otherwise indicated. *P*-values were calculated using χ^2 test, except for [a]Mann–Whitney U test and [b]Fisher test. [c]Ventilator-associated pneumonia (2 cases), catheter-related bacteraemia (1 case).

When only patients with a definite diagnosis of pneumonia were considered, severe complications occurred in 5/45 (11%) versus 11/27 (41%) of patients with 0 or ≥1 points in the CURB-65 index, respectively (*P*=0.003), and in 9/62 (15%) versus 7/10 (70%) classified as I–II or III–V according to PSI, respectively (*P*<0.001). The low number of pregnant patients with definite pneumonia (10) precluded any other analysis.

Our matched analysis was able to match 37 pairs of pregnant and non-pregnant patients, meaning that 62% of pregnant patients were not included. The Charlson index was >1 in 3 (6%) and 11 (11%) of pregnant and non-pregnant women, respectively (*P*=0.3, McNemar test); 1 woman in each group had a PSI class ≥III and 3 in each group had a CURB-65 index ≥1. In the matched cohort, 8 patients developed severe complications (2 pregnant and 6 non-pregnant women; RR=0.3; 95% CI 0.07, 1.5; *P*=0.2). Again, significant comorbidity (OR=12.1; 95% CI 1.5, 90.9; *P*=0.003) and multilobar pneumonia (OR=4.2; 95% CI 1.2, 15.1; *P*=0.03) were associated with an increased risk of severe complications.

Discussion

We found a low frequency of severe complications in the 98 consecutive pregnant patients admitted to 13 Spanish hospitals because of 2009 A (H1N1)v infection. Overall, only two (2%) patients required ICU admission (both of them had comorbid conditions) and none died. Pregnancy was not independently associated with an increased risk for severe complications among hospitalized women of reproductive age in a context of early diagnosis and antiviral therapy, partly owing to a high awareness of the importance of influenza in pregnant women. Our results contrast with other recent studies suggesting that pregnant women were at a significantly increased risk of severe complications with mortality rates of approximately 5% and ICU admission rates of 20% among admitted patients [9–11,17,18]. The possibility of a selection bias in these studies overestimating the influence of pregnancy in the development of complications has been acknowledged and should be considered. The three US studies [7,9,14] are based on passive case reporting and severe cases might be overrepresented. ICU admission as a surrogate marker of disease severity might not be as good in pregnant women: the threshold for ICU admission could be lower in these patients because of an increased awareness of clinicians of the severity risk for pregnant women compared with that for non-pregnant patients. Possibly, deaths or complicated cases in non-pregnant women might have been underreported. Of note, the initial report by Jamieson *et al.* [9] found that 13% of the deaths reported to the CDC between 15 April and 16 June 2009 as being due to pandemic 2009 A(H1N1)v infections were of pregnant women, whereas data from the Spanish Registry indicated that 2.5% (3/118) of deaths from the A(H1N1)v influenza infection occurred in pregnant women [19]. During the

Table 4. Univariate analysis of factors associated with severe complications in 106 patients with clinically driven criteria for hospital admission

Factor	Number of women with severe complications (%)	RR (95% CI)	*P*-value
Period			
Weeks 27–36	10 (23)	0.8 (0.4, 1.8)	0.6
Weeks 37–46	12 (19)		
Age			
≤35 years	16 (23)	1.3 (0.5, 3.0)	0.5
>35 years	6 (17)		
Pregnancy			
Yes	2 (6)	0.2 (0.05, 0.9)	0.01
No	20 (27)		
Charlson index			
0–1	18 (19)	1.9 (0.7, 4.7)	0.2
>1	4 (36)		
Significant comorbidity[a]			
Yes	17 (34)	3.9 (1.5, 9.9)	0.001
No	5 (9)		
Chronic pulmonary disease			
Yes	9 (36)	2.2 (1.0, 4.7)	0.03
No	16 (16)		
Immunosuppression			
Yes	3 (43)	2.2 (0.8, 5.8)	0.1[b]
No	19 (19)		
Morbid obesity			
Yes	4 (68)	3.7 (2.0, 7.4)	0.01
No	18 (18)		
Seasonal influenza vaccine			
Yes	2 (29)	1.5 (0.4, 5.2)	0.6[b]
No	17 (19)		
Pneumococcus vaccine			
Yes	1 (33)	1.6 (0.3, 8.7)	0.4[b]
No	18 (20)		
Pneumonia			
Yes	16 (28)	2.2 (0.9, 5.2)	0.05
No	6 (13)		
Multilobar pneumonia			
Yes	15 (43)	4.3 (1.9, 9.7)	<0.001
No	7 (10)		
Leukocytes >12,000/mm^3			
Yes	7 (39)	2.2 (1.0, 4.7)	0.05[b]
No	15 (17)		
ALT>40 IU/l			
Yes	7 (41)	4.0 (1.4, 10.7)	0.01[b]
No	5 (10)		
Serum sodium <135 mEq/l			
Yes	10 (37)	2.5 (1.2, 5.2)	0.01
No	11 (15)		
Serum creatinine >1.3 mg/dl			
Yes	2 (67)	3.3 (1.3, 8.3)	0.1[b]
No	20 (20)		
Bacterial coinfection			
Yes	4 (40)	2.1 (0.9, 5.2)	0.2[b]
No	18 (19)		

[a]Significant comorbidities include: chronic pulmonary disease, diabetes mellitus, chronic renal insufficiency, liver cirrhosis, chronic cardiovascular disease (except hypertension), severe neuromuscular disease, morbid obesity and immunosuppression. *P*-values were calculated using χ^2 test, except for [b]Fisher test. ALT, alanine aminotransferase; RR, relative risk.

Table 4. Continued

Factor	Number of women with severe complications (%)	RR (95% CI)	*P*-value
Days between onset of symptoms and admission			
≤2 days	11 (24)	1.2 (0.6, 2.7)	0.5
>2 days	11 (19)		
Start of antiviral therapy after onset of symptoms			
<3 days	7 (19)	0.9 (0.4, 2.5)	0.8
≥3 days	14 (22)		

study period, an estimated 6.11% of women of reproductive age were pregnant in Spain [20]; because 33% of women of reproductive age with a clinically driven admission with A(H1N1)v were pregnant, this would suggest that pregnancy actually significantly increased the risk of hospitalization owing to pandemic influenza. Our data indicate, however, that once the women were hospitalized (in a context of high awareness, early diagnosis and therapy), outcome was no worse for pregnant women than it was for non-pregnant women.

Similar to our findings, two studies have not found a high rate of complications among pregnant women infected with A(H1N1)v [21,22]. Both included consecutively diagnosed pregnant women regardless of their in-hospital or ambulatory management. In the study from Singapore among 211 pregnant women with documented A(H1N1)v infection only two patients developed pneumonia, one required ICU admission and no deaths were reported [21]. All but four of these patients received oseltamivir therapy (one received inhaled zanamivir) with a median time of 2 days from symptom onset to initiation, and >70% were managed as outpatients. In the study from La Reunion Island among 127 consecutive pregnant women with A(H1N1) v infection, 6 patients with pneumonia were identified and no ICU admissions or deaths were reported; 86% of the infected patients received antiviral therapy with oselmtamivir with a median delay between onset of symptoms and initiation of oseltamivir of <2 days [22]. Admission rates in the studies were 30% [21] and 60% [22]. Pooling the results of these two studies with ours, among 436 consecutive pregnant women infected with A(H1N1)v, the mortality rate was 0 and the ICU admission rate was 0.6%.

Our aim was to investigate whether pregnancy alone increased the risk of severe complications in admitted patients, and thus we compared the occurrence of severe complications in pregnant women with those in non-pregnant women of reproductive age. Although a crude analysis showed that the pregnant women were at less risk of severe complications, we soon realized that a selection bias opposite to the one potentially affecting the earlier studies needed to be controlled for, because RT-PCR for 2009 A(H1N1)v influenza virus was recommended for all pregnant women with influenza-like symptoms in Spain and the influence of initial reports might have lead to a lower threshold for hospital admission in pregnant women. In two other studies, 43% and 58% of admitted pregnant women with A(H1N1)v had no clear clinical reason for hospitalization [21] or were non-complicated influenza infections [10]. In our study, the percentage of pregnant women with comorbid conditions was much lower than in previous reports. To control this, we used two types of analysis to investigate the importance of pregnancy as a risk factor in the development of severe complications: we restricted our analysis to the subset of women admitted on clinical grounds according to pre-defined clinical and analytical data examined by two investigators and we also performed a matched cohort analysis. Both showed similar results, indicating that pregnancy was not associated with the outcome variable in this context, and that the main variables influencing the occurrence of severe complications were the presence of other underlying conditions and multilobar pneumonia. Among young women with pneumonia, those with a CURB-65 score >1 or group III or higher in the PSI index had a higher frequency of severe complications. It should be noted, however, that these indexes have shown a limited capability to predict severity in patients with 2009 A(H1N1) influenza [23,24]. In our study, one quarter of non-pregnant women received corticosteroids, mainly because of complicated asthma, but corticosteroids have not been associated with improved outcomes in A(H1N1)v influenza [25] and some recent data even suggest that they might be harmful [26].

The percentage of pregnant women in our series who received early therapy with oseltamivir (41%) was higher than that reported by Hewegama *et al.* [10] (27%) and similar to that reported by Louie *et al.* [11] (50%) and by Lim *et al.* [20] (50.3%). The high rate of early antiviral therapy in our study might have been influenced by an increased awareness of clinicians about the severity of 2009 A(H1N1) influenza in pregnant women, given the initial reports and the impact of mass media. Of note, the first registered death in Spain

caused by A(H1N1)v was a pregnant woman to whom antiviral therapy was delayed. Thus, our results should not be interpreted as that A(H1N1)v was not associated with higher risk of complications in pregnant women; indeed, the high proportion of pregnant women among the clinically driven admitted patients (about one third) would suggest an increased severity of influenza for pregnant women at the population level. Furthermore, our study and others found that most hospitalized pregnant patients with 2009 A(H1N1) influenza were either in the second or the third trimester, which might reflect a higher severity of influenza in advanced pregnancy.

We hypothesize that earlier diagnosis and antiviral therapy might have influenced the better outcomes in our study. This hypothesis is also consistent with the results of Siston *et al*. [17] who found mortality to be significantly lower among pregnant patients who received antiviral therapy within 48 h of symptom onset. If no further safety concerns on the effect of oseltamivir on the offspring of pregnant women treated arise, an aggressive management of pregnant patients with influenza-like illness, consisting of early antiviral therapy, should be the most appropriate strategy to manage these patients [27,28].

Our study has some limitations and strengths. We think it is highly improbable that pregnant patients with severe disease were not included because the Spanish Health System provides free universal medical attention and the participating hospitals attend to all patients requiring hospital admission in their area of influence; RT-PCR for 2009 A(H1N1)v was readily available in all participating centres. All the consecutive cases diagnosed were recruited prospectively, and the association of pregnancy and severe complications was analysed in several ways. Although our cohort of admitted pregnant women is one of the largest to date, the numbers were small, however, which limits the statistical power of the study. The specific context in which our study was performed (a public healthcare system with free universal access and high awareness of the potential importance of influenza in pregnant women) should be taken into account when considering the external validity of our results. We did not investigate the population-based incidence of pneumonia, admission or severe complications, nor were immunological and virological studies performed.

In conclusion, we did not find that pregnancy by itself seemed to be an additional risk factor for the occurrence of severe complications in a context of early admission and therapy for 2009 A(H1N1)v. Comorbid conditions and presentation with multilobar pneumonia were associated with admission to the ICU or death in women of reproductive age. Furthermore, our findings suggest that pregnancy, especially in the second and third trimester, is a risk factor for severe influenza illness and complications leading to hospitalization when the prevalence of pregnancy is considered at the population level.

Additional file

Additional file 1: A list of the other members of the Novel Influenza A(H1N1) Study Group can be found at http://www.intmedpress.com/uploads/documents/AVT-11-OA-2028_Pano-Pardo_Add_file1.pdf

Acknowledgements

This work was funded by Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III, cofinanced by European Development Regional Fund 'A way to achieve Europe' ERDF, Spanish Network for the Research in Infectious Diseases (REIPI RD06/0008).

Disclosure statement

The authors declare no competing interests.

References

1. Fraser C, Donnelly CA, Cauchemez S, *et al*. Pandemic potential of a strain of influenza A (H1N1): early findings. *Science* 2009; **324:**1557–1561.
2. World Health Organization. Global alert and response (GAR). Pandemic (H1N1) 2009 – update 88 (Updated 19 February 2010. Accessed 11 February 2011.) Available from http://www.who.int/csr/don/2010_02_19/en/index.html
3. Kort BA, Cefalo RC, Baker VV, Simonsen L, Griffin MR. Fatal influenza A pneumonia in pregnancy. *Am J Perinatol* 1986; **3:**179–182.
4. Neuzil KM, Reed GW, Mitchel EF, *et al*. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol* 1998; **148:**1094–1102.
5. Harris J. Influenza occurring in pregnant women. *JAMA* 1919; **14:**978–980.
6. Greenberg M, Jacobziner H, Pakter J, Weisl BA. Maternal mortality in the epidemic of Asian influenza, New York City, 1957. *Am J Obstet Gynecol* 1958; **76:**897–902.
7. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol* 1998; **148:**1094–1102.
8. Rasmussen SA, Jamieson DJ, Bresee JS. Pandemic influenza and pregnant women. *Emerg Infect Dis* 2008; **14:**95–100.
9. Jamieson DJ, Honenin M, Rasmussen S, *et al*. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009; **374:**451–458.
10. Hewagama S, Walker SP, Rhonda L, *et al*. 2009 H1N1 Influenza A and pregnancy outcomes in Victoria, Australia. *Clin Infect Dis* 2010; **50:**686–690.
11. Louie JK, Acosta M, Jamieson D, Honein MA, California Pandemic (H1N1) Working Group. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med* 2010; **362:**27–35.
12. Comité Asesor, Ministerio de Sanidad y Política Social y Consejo Interterritorial. Gobierno de España. [Prevention and treatment of infection due to novel influenza A(H1N1) virus in pregnant women, with particular attention to workers and healthcare centers]. (Updated September 2009. Accessed 11 February 2011). Available from http://www.msc.es/profesionales/saludPublica/gripeA/guiasProtocolosInf/pdf/09-10-09_Embarazada.pdf. Spanish.

13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40:**373–383.
14. Fine MJ, Auble TE, Yealy DM, *et al*. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; **336:**243–250.
15. Lim WS, van der Eerden MM, Laing R, *et al*. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; **58:**377–382.
16. Halm EA, Fine MJ, Marrie TJ, *et al*. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications to practice guidelines. *JAMA* 1998; **279:**1452–1457.
17. Siston AM, Rasmussen S, Honey MA, *et al*. Pandemic 2009i A(H1N1) virus illness among pregnant women in the United States. *JAMA* 2010; **303:**1517–1525.
18. The ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System. Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study. *BMJ* 2010; **340:**c1279.
19. [Human cases of influenza caused by pandemic virus (H1N1) 2009. Descriptive analysis of dead patinets in Spain]. (Updated 12 December 2009. Accessed 11 February 2011.) Available from http://www.msc.es/profesionales/saludPublica/gripeA/docs/informacionFallecidosH1N1_091201.pdf. Spanish.
20. Spanish National Statistics Institute Database. (Updated 26 November 2011.Accessed 2 September 2011.) Available from http://www.ine.es/inebmenu/indice.htm#7
21. Lim ML, Chong CY, Tee WSN, Lim WY, Chee JJ. Influenza A/H1N1 (2009) infection in pregnancy – an Asian perspective. *BJOG* 2010; **117:**551–556.
22. Gérardin P, El Amrani R, Cyrille B, *et al*. Low clinical burden of 2009 pandemic influenza A (H1N1) infection during pregnancy on the island of La Réunion. *PLoS ONE* 2010; **5:**e10896.
23. Mulrennan S, Tempone SS, Ling IT, *et al*. Pandemic influenza (H1N1) 2009 pneumonia: CURB-65 score for predicting severity and nasopharyngeal sampling for diagnosis are unreliable. *PLoS ONE* 2010; **5:**e12849.
24. Muller MP, McGeer AJ, Hassan K, Marshall J, Christian M, Toronto Invasive Bacterial Disease Network. Evaluation of pneumonia severity and acute physiology scores to predict ICU admission and mortality in patients hospitalized for influenza. *PLoS ONE* 2010; **5:**e9563.
25. Viasus D, Paño-Pardo JR, Cordero E, *et al*. Effect of immunomodulatory therapies in patients with pandemic influenza A (H1N1) 2009 complicated by pneumonia. *J Infect* 2011; **62:**193–199.
26. Kim SH, Hong SB, Yun SC, *et al*. Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. *Am J Respir Crit Care Med* 2011; **183:**1207–1214.
27. Centers for Disease Control. Updated Interim Recommendations for Obstetric Health Care Providers Related to Use of Antiviral Medications in the Treatment and Prevention of Influenza for the 2009–2010 Season. (Updated 29 December 2009. Accessed 7 March 2010.) Available from http://www.cdc.gov/H1N1flu/pregnancy/antiviral_messages.htm
28. World Health Organization (WHO). Pandemic influenza in pregnant women. (Updated 31 July 2009. Accessed 30 January 2011.) Available from http://www.who.int/csr/disease/swineflu/notes/h1n1_pregnancy_20090731/en/index.html

Accepted 10 September 2011; published online 16 December 2011