Severe 2009 H1N1 influenza in pregnant women in Spain

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Objectives: **To describe the severity of the 2009 influenza H1N1v illness among pregnant women admitted to Spanish intensive care units.**

Design and Patients: **Prospective, observational, multicenter study conducted in 148 Spanish intensive care units. We reviewed demographic and clinical data from the Spanish Society of Intensive Care Medicine database reported from April 23, 2009, to February 15, 2010. We included women of reproductive age (15–44 yrs) with confirmed H1N1v infection admitted to intensive care units.**

Main Results: **Two hundred thirty-four women of reproductive age were admitted to intensive care units, 50 (21.4%) of them pregnant. Seven deaths were recorded in pregnant and 22 in nonpregnant women. Among intensive care unit admissions, there were no statistically significant differences between pregnant women and nonpregnant in Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment scores, chest x-rays, inotrope requirement, or need for mechanical ventilation or steroid therapy. Mortality risk was significantly associated with Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment, and obesity. Viral pneumonia was more frequent in pregnant women than in nonpregnant women, with an odds ratio (adjusted for asthma, time from onset influenza symptoms to hospital admission and obesity) of 4.9 (95% confidence interval: 1.4–17.2). The development of primary viral pneumonia in women of reproductive age appeared to be related to the time of commencement of antiviral treatment, the lowest rates being reported with initiation of antiviral therapy within 48 hrs of symptom onset (63.6% vs. 82.6%, $p = .03$). However, antiviral therapy was started within this time span in only 14% of pregnant women.**

Conclusions: **More than 20% of women of reproductive age admitted to intensive care unit for pH1N1 infection were pregnant. Pregnancy was significantly associated with primary viral pneumonia. Pregnant women should receive prompt treatment with oseltamivir within 48 hrs of the onset of influenza symptoms. (Crit Care Med 2011; 39:000–000)**

Key Words: influenza A/H1N1; pregnancy; pandemic; intensive care unit; pneumonia; complications; mortality

In April 2009, the first cases of severe pneumonia associated with the influenza A/H1N1 virus were reported in Mexico (1) and later in the Southern Cone of South America (especially Argentina [2] and Chile [3]). The illness mainly affected young people aged between 15 and 44 (4) and specific population groups, among them pregnant women. The first reports (5) showed that pregnant women (6–9) had increased pulmonary compromise (10), more frequently required intensive care unit (ICU) admission, and had mortality rates around 10% (11–13).

In June 2009, following the World Health Organization recommendations and in cooperation with the Spanish Ministry of Health, the Spanish Society of Intensive Care Medicine set up a committee to address the current pandemic influenza A/H1N1v. An action protocol was drawn up, and a voluntary registry was created of all patients admitted with influenza A/H1N1v in Spanish.

The aim of this study is to assess whether pregnancy is a risk factor associated with increased incidence of influenza A/H1N1v and whether it is linked to the development of serious complications and a higher mortality rate. We compared the clinical characteristics and progression of two groups of *women of childbearing age*–pregnant and nonpregnant–affected by influenza A/H1N1v and admitted to Spanish ICUs. Our hypothesis was that delayed commencement of oseltamivir due to pregnancy might be associated with higher primary viral pneumonia and worse outcomes.

MATERIALS AND METHODS

Study data were obtained from a voluntary registry created by the Spanish Ministry of Health, the Spanish Society of Intensive Care Medicine after the first reported ICU case. In-

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clusion criteria were: fever (>38°C); respiratory symptoms consistent with cough, sore throat, myalgia or influenza-like illness; acute respiratory failure requiring ICU admission; and microbiological confirmation of novel influenza A/H1N1v. The population analyzed comprised women of reproductive age (15–44 yrs). Data were reported by the attending physician who reviewed medical charts and radiologic and laboratory records. The study analyzed data from the first ICU case until February 15, 2010, and was approved by the ethical board of Joan XXIII University Hospital, Tarragona, Spain. Patients remained anonymous and the requirement for informed consent was waived due to the study's observational. All tests and procedures were ordered by the attending physicians.

Definitions. The following variables were recorded: demographic data, comorbidities, time of illness onset and hospital admission, time to first dose of antiviral delivery, microbiological findings, and chest radiology findings at ICU admission. Intubation and mechanical ventilation requirements, adverse events during ICU stay (e.g., need for vasopressor drugs or renal replacement therapies), and laboratory findings at ICU admission were also recorded. To establish illness severity, the Acute Physiology and Chronic Health Evaluation II score (14) was determined in all patients within 24 hrs of ICU admission. Organ failure was assessed using the Sequential Organ Failure Assessment scoring system (15). Obese patients were defined as those with a body mass index over 30 kg/m^2.

Definition of community-acquired pneumonia was based on the current guidelines of the American Thoracic Society and Infectious Disease Society of America (16). Patients who presented healthcare-associated pneumonia were excluded from the study. Etiological investigations for patients with community-acquired pneumonia included urine test for *Streptococcus pneumoniae* and *Legionella pneumophila*, cultures from blood and respiratory samples, and pleural fluid if present. Bronchoalveolar lavage was not systematically performed because of the high risk of generating aerosols. Respiratory cultures were based on tracheal aspirates obtained immediately after intubation.

Nasopharyngeal-swab specimens were collected at admission, and lower respiratory secretions were also obtained in intubated patients. Real-time polymerase chain reaction testing was performed in accordance with the Centers for Disease Control and Prevention's published guidelines (17). Novel influenza A/H1N1 testing was performed at each institution or centralized in a reference laboratory when not available. A "confirmed case" was defined as an acute respiratory illness with laboratory-confirmed pandemic H1N1 virus infection identified by real-time polymerase chain reaction or viral culture (18). Only confirmed cases were included in the study. Primary viral pneumonia was defined in patients presenting illness with acute respiratory distress and unequivocal pulmonary opacities involving two or more lobes with negative respiratory and blood bacterial cultures during the acute phase of the influenza virus. Coinfection was considered in patients with confirmation of influenza virus infection showing recurrence of fever, increase in cough and production of purulent sputum plus positive bacterial/fungal respiratory or blood cultures (19). Acute renal failure was defined as the need for renal replacement therapy according to the International Consensus Conference guidelines (20). Oseltamivir was administered orally in accordance with Centers for Disease Control and Prevention recommendations and the regimen (150 m/24 h or 300 mg/24 h) was chosen by the attending physician (21). The ICU admission criteria and treatment decisions for all patients, including determination of the need for intubation and type of antibiotic and antiviral therapy administered, were not standardized and were decided by the attending physician.

Statistical Analysis. Differences in clinical variables between pregnant and nonpregnant ICU admissions were assessed with chi-square, Fisher's exact, trend in proportions, Student's *t*, and Mann-Whitney *U* tests, according to the nature of the variables. Their relationship with primary pneumonia and the occurrence of death, in addition to the bivariate analysis with the previous tests, was assessed through logistic regression models. To avoid spurious associations, the variables entered into the regression models were the ones that presented a relationship in the univariate analysis ($p \leq .05$) or a plausible relationship with the dependent variable. Potential explanatory variables were checked for colinearity before inclusion in the regression models using the Tolerance and Variance Inflation Factor. Data analysis was performed using SPSS for Windows 13.0 (SPSS, Chicago, IL).

RESULTS

From a total of 916 adult ICU patients with confirmed influenza A/H1N1v, 50 (5.4%) were pregnant women and 184 (20%) nonpregnant women of childbearing age. Seven pregnant and 22 nonpregnant women of childbearing age died. Table 1 displays epidemiologic and clinical characteristics of pregnant and nonpregnant women of childbearing age. Pregnant women were younger (31 vs. 33 yrs, $p = .005$), and had lower rates of obesity (14% vs. 41%, $p = .001$) and asthma (10% vs. 22%, $p = .096$). Pregnant women presented fewer comorbidities than nonpregnant women. Creatinine and urea values were significantly lower in pregnant women. However, no significant differences were found in acute renal failure.

Primary viral pneumonia was more frequent in pregnant women (94% vs. 75%, $p = .006$) and coinfection was more frequent in nonpregnant women (10% vs. 0%, $p = .016$) (Table 1). Pulmonary opacities (number of quadrants affected) did not differ significantly between the two groups ($p = .474$).

Patients with primary viral pneumonia presented higher lactate dehydrogenase values (median 650 vs. 389, $p = .021$) and a delay of one day from symptom onset to hospital admission (median 4 vs. 3, $p < .001$). Among asthmatic women, primary viral pneumonia was less frequent (60.0% vs. 83.6%, $p = .001$). In addition, the development of primary viral pneumonia appeared to be related to the commencement of antiviral treatment, with a lower rate for primary viral pneumonia when antiviral therapy was started within the first 48 hrs of symptom onset. This relationship was observed in the entire group of women (63.6% vs. 82.6%, $p = .034$), as well as in pregnant (80% vs. 100%, $p = .139$) and in nonpregnant (60.7 vs. 76.7 $p = .157$) subgroups. In the multivariate analysis, primary viral pneumonia was independently associated with pregnancy (odds ratio [OR] 4.90, 95% confidence interval [CI]: 1.40–17.19) with time from onset of influenza symptoms to hospital admission (OR per day: 1.30; 95% CI: 1.08–1.56) and obesity (with marginal significance) (OR: 2.03; 95% IC: 0.93–4.41), and negatively with asthma (OR: 0.34; 95% CI: 0.16–0.74) (Table 2).

In women of childbearing age, ICU mortality was 13%, with nonstatistically significant differences between pregnant and nonpregnant women (14% vs. 12%, $p = .86$). All pregnant women who died (n = 7) presented primary viral pneumonia, as did in 16 out of the 22 nonpregnant women who died (73%); the other six patients presented fulminant myocarditis (n = 3), hepatic failure (n = 2), and exacerbated chronic obstructive pulmonary disease (n = 1).

Patients who died in the ICU had higher Acute Physiology and Chronic Health Evaluation II (median 14 vs. 10, $p < .001$), Sequential Organ Failure Assessment (7 vs. 4, $p < .001$), and procalcitonin scores (0.97 vs. 0.26, $p = .006$), and higher rates of obesity (55% vs. 32%, $p = .013$) and shock (72% vs. 36%, $p < .001$). In the multivariate analysis, ICU mortality was associated with obesity (OR: 2.78, 95% CI: 1.04–7.44) and, very

Table 1. Characteristics of pregnant and nonpregnant women of reproductive age (≥15–44 yrs) with A/H1N1v influenza admitted to Spanish intensive care units from June, 2009 to February 15, 2010

Characteristics	Pregnant (n = 50)	Nonpregnant (n = 184)	*p*
Real–time polymerase chain reaction (positive rapid test)	All	All	
No. (%) of indicated age			.007[a]
15–19 yr	2 of 50 (4)	11 of 184 (6)	
20–24 yr	10 of 50 (20)	20 of 184 (11)	
25–29 yr	10 of 50 (20)	29 of 184 (16)	
30–34 yr	16 of 50 (32)	38 of 184 (21)	
35–39 yr	11 of 50 (22)	37 of 184 (20)	
40–44 yr	1 of 50 (2)	49 of 184 (27)	
Median age (range) (yr)	31 (17–43)	33 (15–44)	.005[b]
Median Acute Physiology And Chronic Health Evaluation II (range)	10 (3–26)	10 (1–38)	.936[b]
Median Sepsis–Related Organ Failure Assessment (range)	4 (0–17)	4 (0–23)	.630[b]
Median MODS (range)	31 of 50 (62)	97 of 183 (53)	.331
Median time from symptom onset to hospitalization (range) (days)	4 (1–9)	4 (0–15)	.511[b]
Median time from hospitalization to diagnosis (range) (days)	2 (1–12)	1 (0–13)	.140[b]
Median time from hospitalization to intensive care unit admission (range) (days)	1 (1–10)	1 (0–18)	.273[b]
No. with indicated chronic coexisting illness/total (%)			
Asthma	5 of 50 (10)	40 of 184 (22)	.096
Chronic pulmonary disease	0 of 50 (0)	4 of 184 (2)	.581[c]
Chronic heart failure	0 of 50 (0)	5 of 184 (3)	.587[c]
Renal disease	1 of 50 (2)	4 of 183 (2)	1.000[c]
Hematologic disease	0 of 50 (0)	4 of 184 (2)	.581[c]
Obesity	7 of 50 (14)	75 of 184 (41)	.001
Diabetes mellitus	2 of 50 (4)	6 of 184 (3)	.681[c]
Human immunodeficiency virus/acquired immunodeficiency syndrome	0 of 50 (0)	4 of 184 (2)	.581[c]
Neurologic disorder: neuromuscular disease; muscular dystrophy	1 of 50 (2)	6 of 184 (3)	1.000[c]
Autoimmune disease	0 of 50 (0)	9 of 184 (5)	.211[c]
Viral pneumonitis: no./total no. (%)	47 of 50 (94)	138 of 184 (75)	.006
Secondary bacterial pneumonia: no./total (%)	0 of 50 (0)	18 of 184 (10)	.016[c]
Bacterial coinfection: no./total (%)	1 of 33 (3)	19 of 118 (16)	.077[c]
Health care infections: no./total (%)[d]	2 of 50 (4)	9 of 184 (5)	1.000[c]
Acute renal failure: no./total(%)	3 of 35 (9)	12 of 123 (10)	1.000[c]
Global mortality: no./total (%)	7 of 49 (14)	22 of 182 (12)	.866
Mortality patients with primary pneumonia: no./total (%)	7 of 46 (15)	16 of 136 (12)	.724
Mortality inpatient without pneumonia primary: no./total (%)	0 of 3 (0)	6 of 43 (13)	.67[c]
Median time from symptom onset to death (range) (days)	15 (3–49)	15 (1–35)	.307[b]
Infiltrates/quadrants on chest radiography or computed tomography: no. (%)	35	126	.474[a]
0 of 4	2 of 35 (6)	11 of 126 (9)	
1 of 4	8 of 35 (23)	18 of 126 (14)	
2 of 4	11 of 35 (31)	42 of 126 (33)	
3 of 4	10 of 35 (29)	28 of 126 (22)	
4 of 4	4 of 35 (11)	27 of 126 (21)	
Median lactate dehydrogenase (range): U/L	613 (20–22,067)	530 (146–4,794)	.910[b]
Median TGO (range): U/L	51.5 (12–1,158)	48 (10–524)	.366[b]
Median TGP (range): U/L	37 (8–290)	30 (9–420)	.551[b]
Median creatine phosphokinase (range): U/L	178 (17–1,397)	148 (13–11,170)	.494[b]
Median no. leukocytes (range): no./mm^3	7,200 (1,800–20,000)	5,700 (280–29,800)	.344[b]
Median no. platelets (range): no./mm^3	142,000 (42,000–280,000)	161,500 (138–458,000)	.288[b]
Median creatinine (range) (mg/dL)	.5 (.10–3.35)	.70 (.05–2.7)	<.001[b]
Median urea (range) (mg/dL)	14.0 (.20–182.0)	25.5 (.36–108)	<.001[b]
Median procalcitonin (range) (ng/mL)	.5 (.0–23.7)	.5 (.0–39.7)	.921[b]
Median C–reactive protein (range) (mg/dL)	17.45 (1.8–189.0)	25.150 (1.4–354.4)	.111[b]
Median fibrinogen (range) (mg/dL)	504.0 (116–742)	528.0 (113–1,040)	.629[b]

[a]Test tendencies in proportions. If not marked as Mann-Whitney *U* test or Fisher's exact test, results are from a two-tailed chi-square test, with correction of continuity; [b]Mann-Whitney *U* test; [c]Fisher's exact test; [d]number of methicillin-resistant *Staphylococcus aureus*; no. of methicillin-sensitive *Staphylococcus aureus*; no. of *Streptococcus pneumoniae*.

strongly, with Acute Physiology and Chronic Health Evaluation II (OR per unit increase: 1.15; 95% CI: 1.07–1.24). The estimates using Sequential Organ Failure Assessment were approximately the same. Pregnancy shows a trend toward higher ICU mortality among ICU-admitted women (OR: 1.86; 95% CI: 0.61–5.73) (Table 3).

Mechanical ventilation was applied in 78% of pregnant and in 70% of nonpregnant women ($p = .396$). Invasive mechanical ventilation was used in 73% of pregnant and 59% of nonpregnant women ($p = .116$). Noninvasive ventilation was applied in 23% of pregnant and 26% of nonpregnant women ($p = .894$). Empirical administration of antiviral treatment was less frequent in pregnant women and only 14% of them received antiviral therapy within the first 48 hrs of symptoms onset.

Thirteen pregnant patients (26%) received early corticosteroid therapy at ICU admission. Patients surviving the ICU stay and receiving corticosteroids early after ICU admission had a mean duration of corticosteroid therapy of six days (in-

Table 2. Results of the logistic multivariate analysis in women aged 15–44 yrs admitted to the intensive care unit for A/H1N1v influenza, in relation to primary pneumonia and death

Diagnosis or Outcome	Odds Ratio (95% Confidence Interval)[a]	*p*
Primary pneumonia (n = 231)		
Variables in the model		
Pregnancy	4,90 (1.40–17.19)	.013
Obesity	2.03 (.93–4.41)	.076
Time from onset influenza symptoms to hospital admission (days)	1.30 (1.08–1.56)	.005
Asthma	0.34 (.16–.74)	.007
Death (n = 155)		
Variables in the model		
Acute Physiology and Chronic Health Evaluation II	1.15 (1.07–1.24)	<.001
Obesity	2.78 (1.04–7.44)	.042
Pregnancy	1.86 (.61–5.73)	.279
Variables in the model		
Sepsis–Related Organ Failure Assessment	1.34 (1.15–1.56)	<.001
Obesity	2.88 (.91–9.15)	.073
Pregnancy	1.64 (.45–6.02)	.454

[a]Odds ratio and confidence interval to 95%.

Table 3. Treatment of pregnant and nonpregnant women (age ≥15 and ≤44 yrs), with A/H1N1v influenza, admitted to Spanish intensive care units, from June 2009 to February 15, 2010

Therapy	Pregnant (n = 50)	Nonpregnant (n = 184)	*p*
Artificial ventilation: no./total (%)	38 of 49 (78)	129 of 184 (70)	.396
Invasive MV: no./no. total (%)	35 of 48 (73)	109 of 184 (59)	.116
MV in prone: no./total (%)	12 of 50 (24)	33 of 183 (18)	.456
Median time of MV (range) (days)	7.50 (0–49)	3.50 (0–60)	.569
Noninvasive ventilation: no./total (%)	11 of 47 (23)	47 of 183 (26)	.894
Failure noninvasive ventilation: no./total (%)	9 of 47 (19)	26 of 183 (14)	.539
Pneumonia associated with MV: no./total (%)	4 of 26 (15)	7 of 105 (7)	.227[c]
Associated treatment: amine pressure (noradrenaline, dopamine)	26 of 50 (52)	70 of 183 (38)	.112
Dialysis: no./total (%)	0 of 50 (0)	7 of 183 (4)	.351[c]
Continuous venovenous hemofiltration: no./total (%)	5 of 50 (10)	7 of 183 (4)	.139[b]
Immunomodulatory antibiotic: macrolide no./total (%)	18 of 49 (37)	25 of 179 (14)	.001
Antiviral treatment after symptom onset			
Median no. days until beginning treatment (range)	5 (1–10)	4 (1–14)	.081[a]
Treatment within 48 hr of symptom onset: no./total (%)	5 of 36 (14)	28 of 118 (24)	.304
Treatment 4 or more days since symptom onset	14 of 36 (39)	67 of 118 (57)	.091
Oseltamivir empirical: no./total (%)	22 of 32 (69)	99 of 116 (85)	.030
Oseltamivir in monotherapy: no./total (%)	35 of 35 (100)	123 of 123 (100)	1.000
Oseltamivir: 75 mg/12 h: no./total (%)	10 of 35 (29)	38 of 123 (31)	.956
Oseltamivir: 150 mg/12 h: no./total (%)	25 of 35 (71)	85 of 122 (70)	1.000
Days on oseltamivir: median (range)	10 (1–15)	10 (1–20)	.835
Zanamivir: no./total (%)	1 of 5 (20)	0 of 2 (0)	1.000[b]
Associated treatment: steroids no./total (%)	13 of 34 (38)	49 of 123 (40)	1.000
Associated treatment: steroids in pneumonia no./total (%)	9 of 12 (75)	41 of 50 (82)	.686[b]

MV, mechanical ventilation.

[a]Mann-Whitney *U* test; [b]Fisher's exact test; [c]number of days until the beginning of antiviral treatment, consisting of monotherapy with oseltamivir and occasionally zanamivir (in four patients). Test tendencies in proportions. If not marked as Mann-Whitney *U* test or Fisher's exact test, results are from a two-tailed chi-square test, with correction of continuity.

terquartile range 5–10). Pregnant patients who received early corticosteroid therapy on ICU admission had a nonsignificantly higher ICU mortality than those who did not (15.4% vs. 13.5%, *p* value: 0.86).

DISCUSSION

Our results confirm that >20% of women of reproductive age admitted to ICU for pH1N1 infection were pregnant. In our series, primary viral pneumonia was more frequent in pregnant women and 14% died. However, only a minority of pregnant women received oseltamivir within 48 hrs of influenza onset. It predisposed these patients to more complications, particularly primary viral pneumonia.

The ICU mortality risk in pregnant women was associated with an increased severity of illness at ICU admission and obesity. Among women of childbearing age admitted to Spanish ICUs, we did not find differences in severity on admission between the pregnant group and the nonpregnant group. Among our patients admitted to ICUs, 5.4% were pregnant women, a rate similar to that recorded in Australia and New Zealand (9.1%) (22). Patients admitted to an ICU in Salt Lake City, UT (23) were also young, and 8.5% were pregnant. In Canada, Kumar et al (24), reported that 67.3% of ICU admissions were women, mostly young, and 7.7% were pregnant.

In addition, pregnancy is characterized by a state of immunotolerance to avoid rejection of the fetus. Although humoral immunity during pregnancy remains unchanged, a marked depression in cell-mediated immunity has been suggested (25). A recent report by Gordon et al (26) suggested that patients with severe influenza A/H1N1 were significantly more likely to be deficient in immunoglobulin G2 than patients with moderate H1N1 infection. In addition, pregnancy-related reductions in immunoglobulin G2 level may explain the increased severity of influenza A/H1N1 in pregnant patients. Furthermore, pregnant women are prone to secrete increased levels of proinflammatory mediators such as adipokines (27).

Findings coming from cell culture models confirm that influenza virus can induce proinflammatory cytokine gene expression in human chorion cells (28).We have observed increased levels compared to nonpregnant healthy controls of the Th17 cytokines (interleukin-6, interleukin-9), of the proinflammatory chemokines (interleukin-8, IP-10, MCP-1), and also of the immunomodulatory mediator interleukin-1ra in two pregnant women included in a cohort of critically ill patients with severe pandemic influenza and impaired adaptive immunity response (29).

As described using *in vitro* models, increased levels of cytokines could impair the development of appropriated antiviral response. In consequence, the proinflam-

matory conditions induced by influenza virus infection in pregnant women, who show in addition altered levels of cytokines and chemokines due to pregnancy itself, could impair the development of the specific host response against the virus (30).

Pregnant women did not present differences in comorbidities compared with nonpregnant women, except for obesity in which the prevalence was lower than in nonpregnant women, thus corroborating previous reports (33, 34). Several studies of pandemic influenza A/H1N1 (31) have reported the use of empirical corticosteroid therapy in more than half of these patients, both as primary therapy and as rescue therapy for patients with severe acute respiratory distress syndrome. Recent guidelines for the management of human infection with pandemic influenza A/H1N1 warned against routine corticosteroid use, although low doses may be considered for patients in septic shock who require vasopressors and have suspected adrenal insufficiency (32, 33). In our cohort, the number of patients treated with steroids was quite high (75–82% of patients with primary pneumonia) and may be due to the pressure to start steroids in very sick pregnant patients in the last stages of the process, to increase the maturation of the fetal lung and to allow safe delivery. Theoretically, corticosteroid therapy suppresses inflammatory reactions and prevents migration of inflammatory cells from the circulation to tissues by suppressing the synthesis of chemokines and cytokines. Bermejo-Martin et al (34) recently reported that severe influenza A/H1N1 with respiratory involvement is characterized by an early secretion of a group of T-helper 1 and T-helper 17 chemokines and cytokines which mediate migration of inflammatory cells to the infected tissue. Finally, there is clear data to suggest that corticosteroid use was associated with a longer duration of viral shedding (35, 36). Furthermore, lack of benefit on survival with higher risk of superinfections has been recently reported by Martin-Loeches et al (37) in ICU patients affected by influenza A/H1N1 in the European Society for Intensive Care Medicine registry. Therefore, the prescription of steroids has to be balanced with the specific goals of steroids in this unique population, which was often to help the fetus and improve infant survival if delivered prematurely.

Mortality in pregnant women affected by an influenza A/H1N1v infection is unexpectedly high, from 20% (40, 41) to 45% (34). However, in our study, mortality in pregnant women admitted to ICU (14%) for influenza A/H1N1 was lower than in previous reports and similar to the rates recorded by other authors (11–13). Some subjects might not have been captured by the present registry, and this represents a potential limitation, however, according to data of the Spanish Ministry of Health (38). In the present study, 98% of severe pregnant women were recorded.

Finally, the negative impact of the following factors in the severity and evolution of influenza A/H1N1 in pregnancy is clear: obesity, the delay in the diagnosis of viral infection (10, 39, 40) ICU admission and the onset of antiviral treatment (5, 30). Our study also confirms the findings of other authors (5, 9, 12, 33, 41) regarding the severity of primary viral pneumonia in pregnant women with the highest need of mechanical ventilation and factors that are associated with risk of death, especially in women. However, no significant differences were found between delayed treatment with oseltamivir, the frequency of pneumonia and mortality, or dosing of oseltamivir. Our findings confirm that prompt treatment with oseltamivir within 48 hrs of the onset of symptoms should be provided for pregnant women. In addition to this, triage algorithms are needed to optimize maternal health outcomes and to equitably allocate limited resources in a population affected by a pandemic influenza outbreak (42).

CONCLUSION

Rate of ICU admission and primary viral pneumonia are high in pregnant *women of childbearing age* with influenza A/H1N1. Pregnant women should receive prompt treatment with oseltamivir within 48 hrs of the onset of influenza symptoms.

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APPENDIX

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