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Maternal mortality due to pandemic influenza A H1N1 2009 virus in Colombia

Abstract

Aims: The 2009 H1N1 pandemic illustrated the higher morbidity and mortality from viral infections in peripartum women. We describe clinical features of women who recently died of H1N1 in Colombia.

Methods: This is a case series study that was gathered through a retrospective record review of all maternal H1N1 deaths in the country. The national mortality database of confirmed mortality from H1N1 in pregnancy and up to 42 days after delivery was reviewed during the H1N1 season in 2009. Women with H1N1 infections were confirmed by the laboratory of virology. Demographic, clinical, and laboratory data were reviewed. Statistical analyses were performed and median values of non-parametric data were reported with inter-quartile range (IQR).

Results: A total of 23 H1N1 maternal deaths were identified. Eighty-three percent occurred in the third trimester. None of the mothers who died had received influenza vaccination. The median time from symptom onset to the initiation of antiviral treatment was 8.8 days (IQR 5.8–9.8). Five fatalities did not receive any anti-viral therapy. Median PaO_2/FiO_2 on day 1 was 80 (IQR, 60–98.5). All patients required inotropic support and mechanical ventilation with barotrauma-related complications of mechanical ventilation occurring in 35% of patients.

Conclusion: In Colombia, none of the women suffering H1N1-related maternal deaths had received vaccination against the disease and most had delayed or had no antiviral therapy. Given the lack of evidence-based clinical predictors to identify women who are prone to die from H1N1 in pregnancy, following international guidelines for vaccination and initiation of antiviral therapy in suspected cases would likely improve outcomes in developing countries.

Keywords: H1N1 subtype; infection; influenza A virus; maternal mortality; pneumonia; pregnancy.

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Introduction

A novel pandemic influenza A virus (H1N1 2009pdm) emerged in Mexico in May 2009 [23]. In June 2009, the World Health Organization (WHO) declared a Phase 6 pandemic due to this novel disease, leading to a global health response that identified over 600,000 laboratory confirmed cases and at least 7826 deaths worldwide during the pandemic period. In the post-pandemic period there were indications that the virus may be more aggressive; however, data supporting this observation are scarce [19].

As previous influenza pandemics have shown [14, 27], pregnant and postpartum women are at an increased risk of death. In pregnant and postpartum women, H1N1 was associated with increased morbidity, high rates of hospitalization and intensive care unit (ICU) admission, and increased mortality [21]. The high mortality rates are thought to be due to the physiologic changes of pregnancy that render pregnant and postpartum women more susceptible to complications from influenza [26].

Nearly all pregnant and postpartum patients who died from this disease in the United States presented with respiratory failure and needed mechanical ventilation [3, 16, 21], with some analyses showing delays in the initiation of antiviral treatment [3, 16, 29]. There is little research describing the general outcomes of pregnant and postpartum women and the different treatment strategies used during their ICU stay. In addition, there is limited information on risk assessment, clinical course and in-hospital

complications of H1N1 2009pdm virus in pregnant and postpartum patients [12].

Approximately 10% of all H1N1 2009pdm-related deaths in Colombia occurred in pregnant and postpartum women [15]. Given that reporting of both maternal deaths and mortality from H1N1 to the Department of Health in Colombia is mandatory, we aimed to describe the epidemiology, clinical features and complications in H1N1 2009pdm-related maternal deaths in 2009. Such evaluation will improve our understanding of the disease in order to enhance preventive and treatment strategies in this vulnerable population.

Methods

This is a case series study gathered through a retrospective record review of all maternal H1N1 deaths in Colombia between July 1, 2009, and November 31, 2009. All H1N1 infections were confirmed by the laboratory of virology of Colombia's National Institute of Health (Instituto Nacional de Salud, INS).

Case definition and epidemiological surveillance

According to the definition of the Ministry of Social Protection (Ministerio de Protección Social, MPS) established in May 2009, a *suspected* case of H1N1 2009pdm infection refers to an individual with symptoms of acute respiratory infection (temperature >38°C, cough) for no greater than 7 days [20]. A *probable* case is defined as a person with an acute respiratory infection requiring hospitalization or resulting in death without an identifiable cause. A *confirmed* case refers to a suspect or probable case with confirmation of influenza H1N1 2009pdm through real-time reverse-transcriptase (rtRT)-PCR, genetic sequence, or viral culture.

Maternal mortality was defined according to WHO criteria [30] as death during pregnancy or within 42 days of pregnancy termination, independent of the duration and due to any pregnancy-related and/or aggravated conditions, excluding all accidental causes.

Colombia's Epidemiological Surveillance System (Sistema de Vigilancia Epidemiológica, SIVIGILA) mandates immediate notification of maternal deaths and analyzes death certificates of all reported cases. For each probable or confirmed maternal death due to an influenza-like illness, a standard questionnaire was completed by the attending physician during the epidemic. Data collected from the patient's medical record included demographics, gestational age at presentation, vaccination history, diagnosis, treatments, laboratory tests, and clinical data. A national committee further reviewed the medical documentation for the maternal mortality cases confirmed as H1N1 2009pdm virus. Data from this review, which in some cases included home visits to the family for risk assessment, were included as part of the comprehensive review of all collected data for each death.

Data collection and statistical analysis

The extracted data described above were entered into a Microsoft Excel database. The number of live births to establish the maternal mortality ratio in the study period was obtained through data from the National Department of Statistics (Departmento Administrativo Nacional de Estadísticas, DANE) [9, 10].

A descriptive analysis was performed on all baseline characteristics. Because of a non-parametric distribution of the data, continuous data were reported as median, with interquartile range (IQR) as dispersion measure.

Ethical considerations

This study was approved by the Instituto Nacional de Salud and is in compliance with Colombian law, International Sanitary Regulations, and the National Protocol of Maternal and Perinatal Deaths of Colombia. Since the study was deemed beneficial to the public's health and was conducted during the peak of the pandemic as a public health response, no informed consent or review by an institutional Ethics Committee was needed.

Results

From July 1 to November 30, 2009, there were 23 maternal deaths due to H1N1 in Colombia. For the study period, the H1N1-specific maternal mortality ratio (MMR) was 7.8 maternal deaths per 100,000 live births. This ratio represented 5.1% of maternal deaths in Colombia in 2009. Of the 23 deaths, five cases were excluded, due to incomplete data (n=4) and molar pregnancy with lung involvement (n=1). The denominator in various sections below varies based on the number of patients with complete data for the specific outcome being studied.

Median age at the time of death was 26.5 years (IQR, 22.2–36.7). A total of 15 patients (83%) had disease onset during the third semester of gestation, two (11.1%) in the second trimester, and one (5.5%) in the postpartum period. Median gestational age at symptom onset was 33 weeks (IQR, 32–36).

Initial Presentation

In 17 of 18 patients, median duration between symptom onset and hospitalization was four days (IQR, 2–8). One patient was diagnosed during hospitalization for an unrelated condition. Twelve cases (12/17; 64%) were not hospitalized the first time they sought care for influenza-like symptoms. More information is summarized in Table 1.

Table 1 Clinical course of maternal fatal cases during the 2009 H1N1 pandemic in Colombia.

	Median (IQR)[a] (n=18)[a]
Gestational weeks at hospitalization[b]	33 (32–35)
Total number of consultations before hospitalization	1 (0–2)
0	6 (33.3%)
1–2	8 (44.4%)
3–4	4 (22.2%)
Antiviral treatment	12/17 (70.5%)
Oseltamivir and adamantine	12.5%
Oseltamivir alone	87.5%
Time between symptoms onset and hospitalization (days)[c]	4 (2–8)
Length of stay (days)	14.0 (6.5–20.2)
Time between hospitalization and ICU entrance (days)	1.8 (0.7–4.2)
ICU stay (17 cases) (days)	9.3 (3.1–19.4)
Time between hospitalization and antiviral treatment[d] (days)	2.8 (1.6–4.7)
Time between symptoms onset and antiviral treatment[d] (days)	8.8 (5.8–9.8)
Time between antiviral treatment and death[d] (days)	9.2 (3.1–17.9)
Time between hospitalization and beginning of rales (days)	1.3 (0.4–3.1)
Time between respiratory rate >24 and MV[e] (h)	24 (3.6–48)
Time between SO_2<95 and mechanical ventilation (h)[e]	10.2 h (1.8–50.3) Range: 0 h to 15.2 days
Oxygen saturation (SO_2) (n=18)	
SO_2<91% during the disease (%)	100%
SO_2<95% at first determination (%)	88.8%
SO_2<91% at first determination (%)	76.4%

MV=Mechanical ventilation, ICU=intensive care unit, SO_2=oxygen saturation.
[a]Unless otherwise specified.
[b]One patient was postpartum at hospitalization.
[c]Symptom onset. One patient was already hospitalized when first symptom presented.
[d]In 13 patients who received antiviral treatment.
[e]Duration of time between SO_2<95 or respiratory rate >24 and mechanical ventilation (14 of 16 cases with available data).

Prevention and antiviral treatment

None of the patients in this study had received influenza vaccination during the influenza season.

Five fatalities did not receive any antiviral treatment. Of the remaining patients, 87.5% received oseltamivir alone and 12.5% received both oseltamivir and amantadine. The median time from symptom onset to the initiation of antiviral treatment was 8.8 days (IQR, 5.8–9.8), and the median time from hospitalization to initiation of antiviral treatment was 2.8 days (IQR, 1.6–4.7).

Maternal clinical course

The timeline of all maternal deaths and their clinical course is illustrated in Figure 1. Median time from hospital admission to ICU admission was 1.8 days (IQR, 0.7–4.2). Among the 18 cases, one died prior to ICU admission. The remaining 17 patients developed symptoms of severe pneumonia, received antibiotics, and needed mechanical ventilation. Ampicillin/sulbactam was the most common first-line antibiotic used for treatment (9 of 15 cases) in addition to antiviral therapy.

From 15 cases with adequate data, 11 had a chest X-ray suggestive of multi-lobar pneumonia prior to ICU admission (73.3%).

ICU stay

Seventeen of the eighteen patients required ICU services during their H1N1 hospital-related admission. One patient died before ICU admission. All patients developed multiple organ dysfunction syndrome. Of the 16 patients with adequate ICU data, eight required inotropic support on the first day of ICU admission (50%), and all patients required ventilatory and inotropic support during their ICU stay. Three cases required renal replacement therapy during their ICU stay (16.6%). Of 12 patients with available data, ten received neuromuscular blockers (83%) during mechanical ventilation; five required lung recruitment

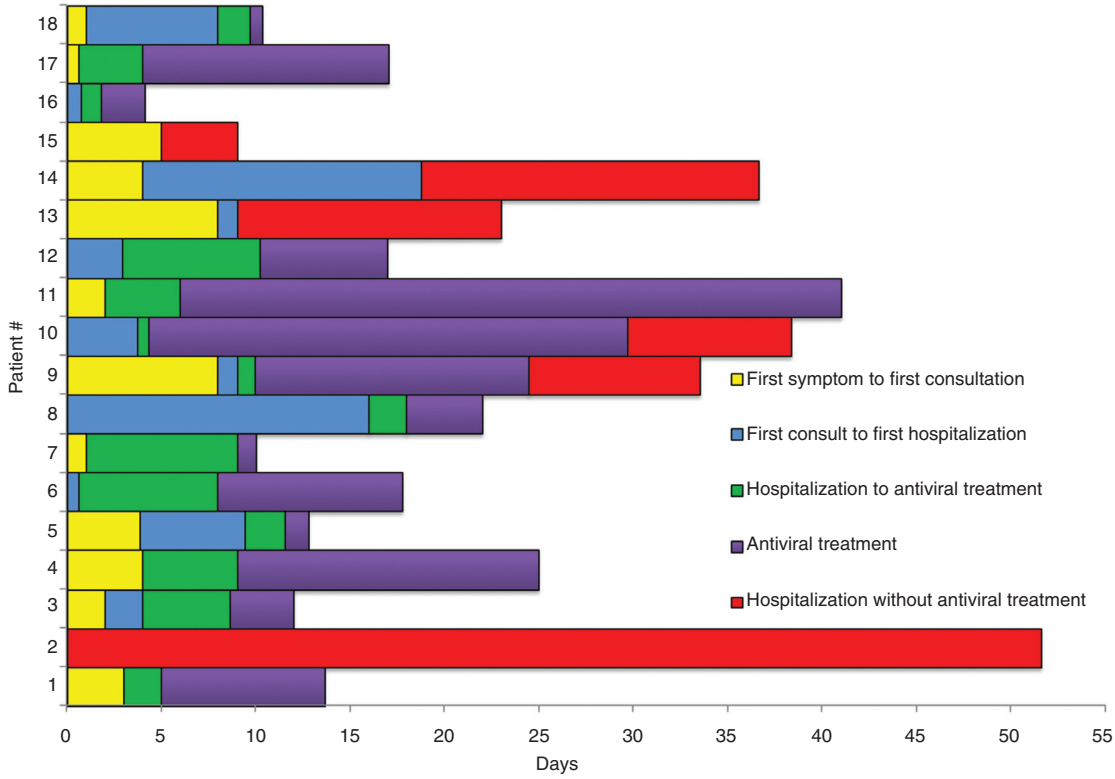

Figure 1 Clinical course of maternal deaths from pandemic H1N1 in 2009 in 18 Colombian patients.

maneuvers; three (17.6%) required prone positioning (after delivery); three (17.6%) patients were ventilated with airway pressure release ventilation (APRV); two patients needed invasive bi-level ventilation (11.7%); and one patient received nitric oxide (5.8%). The average positive end expiratory pressure (PEEP) levels on day one were 12.3 cm H_2O. On day seven the average PEEP was 18.2 cm H_2O (see Figure 2). Tracheotomy was performed in 3/17 patients (17.6%). Complications resulting from mechanical ventilation included pneumothorax in 3/17 (17.6%) of patients, pneumomediastinum (2/17), and pneumothorax and pneumo-peritoneum (1/17).

In addition, 2/17 (11.7%) patients were diagnosed with pulmonary hypertension, 2/17 developed intracranial hypertension, and 1/17 had intracerebral bleeding and subarachnoid hemorrhage.

Oxygen-saturation levels of the disease

Most patients (16/18 patients; 89%) had an initial SaO_2 of <95% at first determination and median value of the first recorded SaO_2 was 88.5% (IQR, 76.7–89.7). Median time between admission and first determination of SaO_2 was 17.3 h (IQR, 0.7–97.7). Oxygenation data are shown in Figure 2.

Fetal and pregnancy-specific outcomes

Of 18 confirmed cases, four (22.2%) were identified as having pre-eclampsia and two cases (11.1%) developed HELLP syndrome after the onset of H1N1 infection. One case (1/18) had pre-eclampsia before H1N1 onset. Of 18 maternal deaths, most (15 patients) had preterm deliveries; of these, one occurred before fetal viability (23–24 weeks). Preterm birth resulted from emergency cesarean deliveries performed as a result of maternal or fetal compromise. Of the other patients, 3/17 were at term, and 16/17 cases had cesarean delivery. Among these, 8/16 (50%) delivered after ICU admission. None of the C-sections were perimortem.

Out of 15 cases with available neonatal information, twelve resulted in live newborns requiring resuscitation at birth and 3/15 were stillbirths. Median birth weight was 2299 g (IQR, 1844–2965).

Pathology

Of the 23 demises due to H1N1 that occurred during pregnancy, only four autopsies were authorized by family members. Pathology revealed changes ranging from

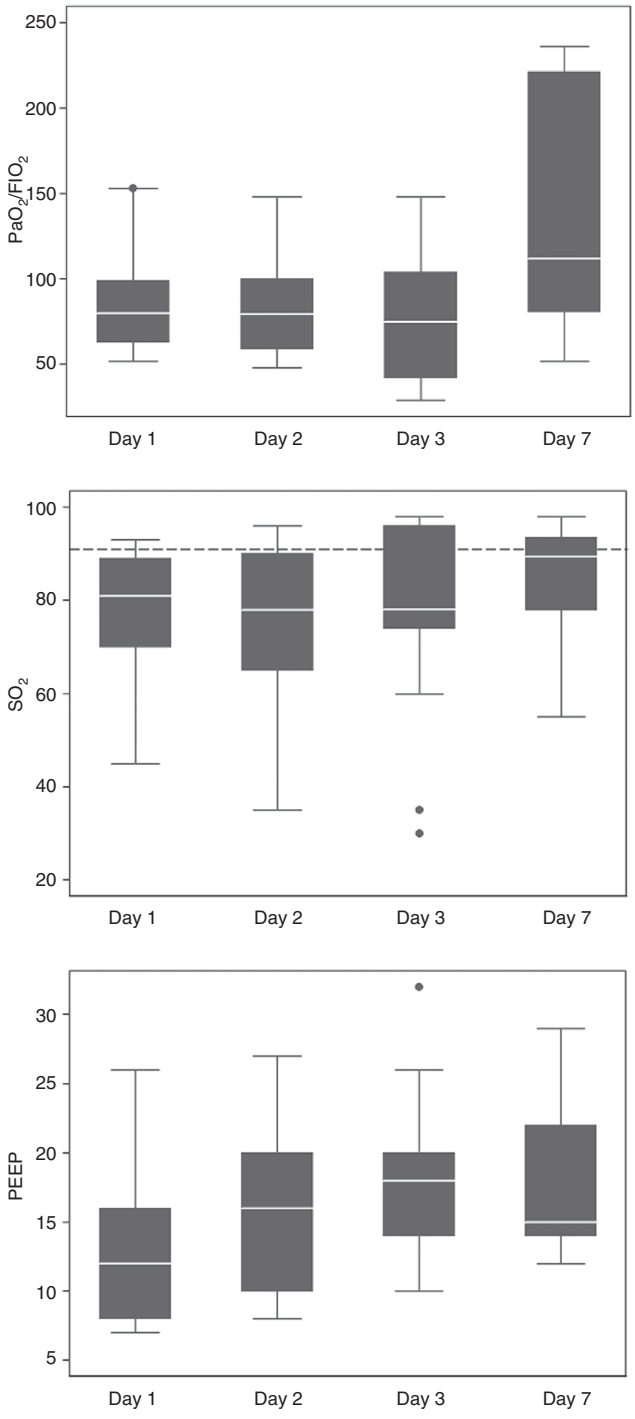

Figure 2 Graph of oxygenation index (PaO_2/FiO_2), arterial oxygen saturation (SaO_2), and positive end expiratory pressure (PEEP) in 17 fatal H1N1pdm/2009 patients admitted to ICU in Colombia.

severe acute exudative fibrinous pneumonia with lymphocytic infiltration in the interstitium (see Image 1) to necrotizing alveolitis and alveolar hemorrhage and edema (see Images 2–4). There was no evidence of intracytoplasmatic inclusions in any of the cases.

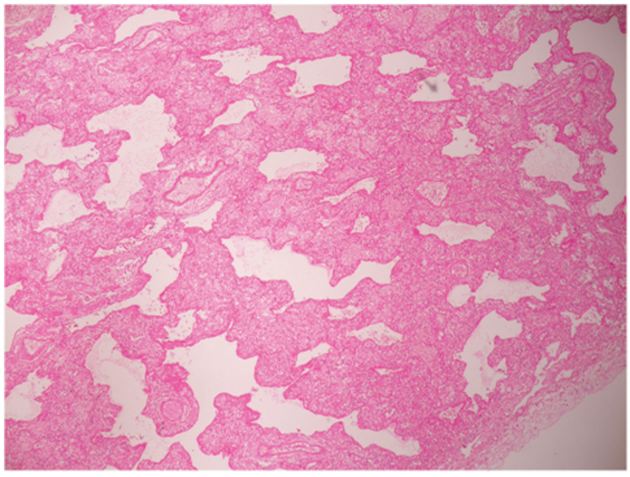

Image 1 Exudative fibrinous pneumonia with hyaline membrane-like changes (H&E 10×).

Discussion

This study reviews the clinical course of pregnant patients who died in Colombia from complications of confirmed 2009 H1N1. Findings from this study suggest that none of the non-survivors of H1N1 disease had received prenatal influenza vaccine and most had a delay in the initiation of antiviral therapy after the development of symptoms and profound hypoxemia with challenges related to mechanical ventilation in all cases. Despite the known epidemic (after mid-2009), one-third of patients failed to receive antiviral therapy. Women who were pregnant at the time of H1N1 diagnosis and died from the disease had high rates of stillbirths and preterm births.

Most of the fatalities were among women in the third trimester. This is consistent with prior studies from other

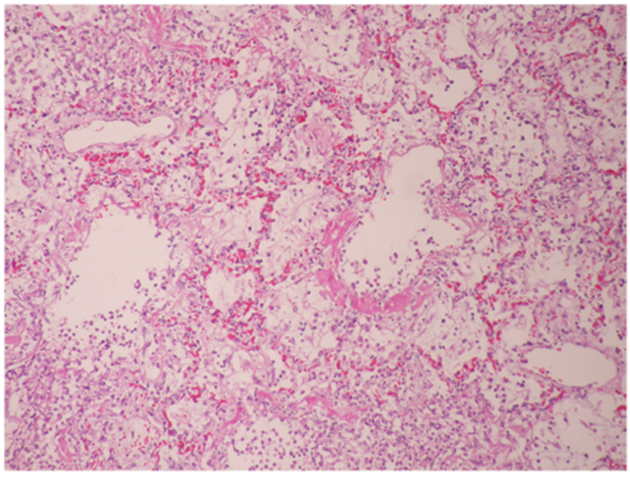

Image 2 Necrotizing alveolitis, prominent exudation of cell and damage of alveolar wall (H&E 40×).

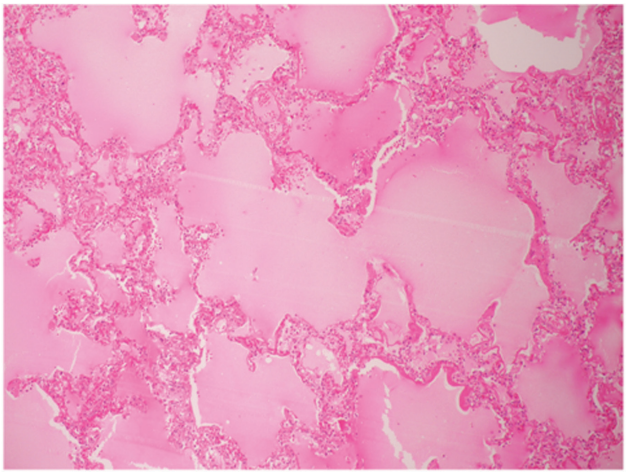

Image 3 Alveolar edema (H&E 10×).

countries [8, 16, 18, 19]. This timing coincides with alterations in T-cell immunity that occurs in late pregnancy and predisposes women to contracting certain infections and to developing more severe disease from these infections.

With regards to antiviral treatment, almost all of the women had an evident delay in the initiation of antiviral therapy after the development of influenza symptoms compared to what has been described in prior studies in critically ill patients who survived [3, 4, 17]. Our experience during the pandemic is in accordance with the empiric treatment of pregnant women with suspected influenza [26, 28]. In addition, almost all of our patients who died were seen in consultation prior to hospitalization and are therefore presumed to have had access to care.

In terms of the natural course of the illness among the 18 deaths, all but one had symptoms 3–5 days prior to ICU admission and subsequent mechanical ventilation. The development of symptoms many days prior to becoming critically ill is consistent with similar experiences in many other countries, including the United States, Turkey, and Canada [4, 8, 18, 24]. Based on lessons learned from 2009 H1N1, earlier recognition during the time period prior to the development of severe hypoxemia and multiple organ dysfunction will result in more rapid initiation of life-saving antiviral therapy [31].

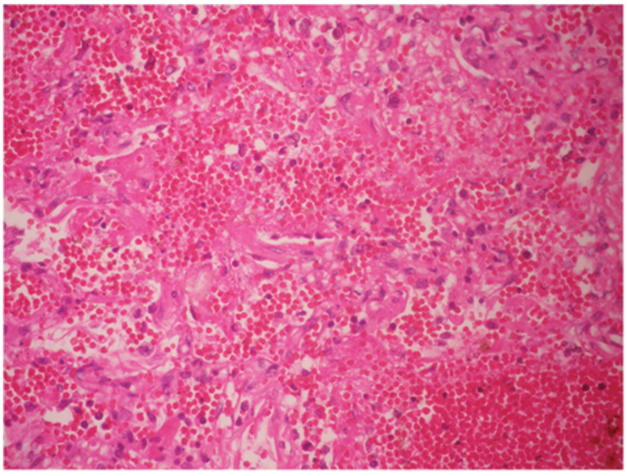

Image 4 Alveolar hemorrhage (H&E 40×).

Consistent with the experiences of other countries, the oxygenation and mechanical ventilation of the patients with 2009 H1N1 who died posed real technical and logistical challenges [1]. At the time of ICU admission, the vast majority were already profoundly hypoxic and met criteria for acute lung injury or acute respiratory distress syndrome (ARDS). Despite the lack of a control group in this series, the presence of hypoxemia (oxygen saturation <91%) on admission in 76.4% of cases deserves some emphasis and additional clinical scrutiny. Though the study design is not such that it would allow the identification of this or other markers as predictors of mortality, based on available literature in the non-pregnant population, women with hypoxemia in the setting of an acute respiratory illness during a pandemic may be more likely to have a more complicated course. More than half of our patients who died were administered some form of rescue therapy, such as airway pressure release ventilation (APRV) or prone ventilation in the hopes of improving oxygenation. In addition, there was a very high rate of barotrauma-related complications from mechanical ventilation, such as pneumothorax that has not been described in many prior studies [8, 11, 18, 27]. While there was no access to extracorpeal membrane oxygenation (ECMO) in Colombia at the time of this pandemic, this intervention has been hypothesized to offer a survival benefit by improving oxygenation early in the course of ARDS from 2009 H1N1 by facilitating a low-tidal volume strategy. So far, there is still limited rigorous data to support its use [1, 6, 13, 22]. Vaccination and early initiation of anti-viral therapy both for prophylaxis and treatment may be the most effective means of reducing maternal mortality of women infected with influenza [7, 26]. The findings in our study raise significant questions about triage and resource allocation that need to be better addressed prior to the next outbreak [2] and make the recommendation of such extensive measures as ECMO almost irrelevant for this country and similar socioeconomic settings.

In terms of fetal outcomes, 80% of the patients with available neonatal data (12/15) had live births, which is consistent with data in the USA but lower than that

reported in the United Kingdom [5, 25]. Many of the surviving babies had low birth weight, however, consistent with previous studies [5, 21, 25].

Strengths of our study include the use of national data, given the fact that all maternal mortality including mortality from H1N1 requires mandatory reporting. Despite limitations, our study points to several valuable lessons that can be used to guide therapy and prevention for the care of pregnant women in future influenza pandemics in developing countries. A limitation of our study is that data was not readily accessible to compare the clinical courses of survivors vs. non-survivors in the country. For that reason, predictors of poor outcomes could not be ascertained.

In summary, in preparation for the next influenza pandemic, the findings of this study suggest that it is important to implement clinical and public health strategies for timely immunization, and educate health care providers regarding the importance of early administration of antiviral therapy according to available guidelines.

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