International Journal of Gynecology and Obstetrics 116 (2012) 148–152

Contents lists available at SciVerse ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

www.figo.org

CLINICAL ARTICLE

Perinatal outcomes and congenital abnormalities in the newborns of women affected by the 2009 pandemic influenza A (H1N1) in Beijing, China

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ARTICLE INFO

Article history:
Received 11 May 2011
Received in revised form 31 August 2011
Accepted 18 October 2011

Keywords:
Congenital abnormalities
Pandemic influenza
Perinatal outcomes

ABSTRACT

Objective: To investigate the pregnancy complications, perinatal outcomes, and congenital abnormalities (CAs) that occurred in Beijing, China, when pregnant women became infected with the 2009 pandemic influenza A (H1N1) (H1N1pdm). *Methods:* Pregnancy complications, perinatal outcomes, and CAs were compared among 3 groups of pregnant women. The 23 women in group 1 were confirmed to harbor viral RNA; the 23 in group 2 had serum levels of virus-specific antibodies against H1N1pdm, meaning that they were suspected of being infected with the virus; and the 93 in group 3 had no detectable virus-specific antibodies. *Results:* Perinatal outcomes and pregnancy complications were not significantly different in groups 1 and 3. Higher percentages of stillbirths (12.0%) and placental disorders (13.0%) were observed in group 2 than in group 3. Many women in group 2 (62.5%) experienced symptoms of having a cold during pregnancy and most took no medication. Two cases of CA occurred in group 1, in the offspring of women infected in the second trimester. *Conclusion:* When left untreated, infection with the 2009 H1N1pdm virus during pregnancy appears to have increased fetal mortality and morbidity. Because CAs are traumatic for all concerned, their possible association with the virus should be further evaluated.

1. Introduction

An outbreak of H1N1 influenza A that began in April 2009 in Mexico rapidly spread worldwide and was declared a pandemic by the WHO on June 11, 2009 [1]. Pregnant women were particularly severely affected by the 2009 H1N1 pandemic (H1N1pdm) virus [2–7] but their early treatment with antiviral agents seemed to be associated with fewer intensive care admissions and deaths [5]. Perinatal outcomes have been less investigated than maternal outcomes, however, in part because delivery had not yet occurred when earlier reports were published. To understand fully the risks that the 2009 H1N1pdm posed for pregnant women and their offspring, the pregnancy complications, perinatal outcomes, and congenital abnormalities (CAs) possibly due to viral infection should be properly assessed.

Although an H1N1pdm vaccine became available at the end of September 2009, only approximately1400 pregnant women in China had been vaccinated by the end of 2009 (publication by the Ministry of Health of China) [8], in part because pregnant Chinese women tend to favor traditional Chinese medicine over Western treatments [9]. To understand better the risks that the 2009 H1N1pdm posed for the offspring of affected pregnant women, a cross-sectional study was conducted to compare perinatal outcomes and numbers of CAs, as well as the pregnancy complications among 3 groups.

2. Materials and methods

The study took place at Chinese People's Liberation Army General Hospital, Beijing, China—a large, comprehensive tertiary-care center with a well-established record-keeping system. The study protocol was approved by the Institutional Review Board of the China Center for Disease Control and Prevention. All participants were explained the purpose of the study and gave informed consent.

From June 2, 2009, to April 30, 2010, all pregnant women with a temperature higher than 37.5 °C were screened for H1N1pdm infection at the hospital's fever clinic by means of reverse-transcription polymerase chain reaction (RT-PCR), the WHO-recommended assay [10]. These assays were performed at a reference laboratory in the hospital. In the present study, group 1 consisted of the women who tested positive for H1N1pdm RNA.

Additionally, from January 6 to August 27, 2010, 15–20 randomly selected hospitalized pregnant women were enrolled each month. Their serum samples were sent to the Beijing Institute of Microbiology and Epidemiology, Beijing, China, to be tested for virus-specific

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0020-7292/$ – see front matter
doi:10.1016/j.ijgo.2011.08.024

antibodies against H1N1pdm. Microneutralization (MN) and hemagglutination inhibition (HI) assays were performed, as in previous reports [11,12]. The virus strain used for the assays, A/California/07/2009 (H1N1), was provided by the Chinese National Influenza Center, Beijing, China. Results were considered positive when MN and HI titers were 1:40 or higher and 1:20 or higher, respectively. Negative results were also actively looked for, but only after January 31, 2010, to allow for antibodies against the H1N1pdm virus to develop following the pandemic wave of January 2010 [13]. For H1N1pdm infection to be ruled out, the participants had to have no influenza-like symptoms (e.g. temperature higher than normal and/or respiratory signs such as cough and sore throat) within 7 days of admission to the hospital. Moreover, their MN and HI titers had to be undetectable. Group 2 consisted of the women who tested positive and group 3 of the women who tested negative for virus-specific antibodies against H1N1pdm. Of the 136 serum samples tested, 20 were excluded because the results were indeterminate.

Demographic information was collected from the participants, as well as date of last menstruation, whether any illnesses other than possible H1N1pdm influenza occurred during the pregnancy, whether fetal loss occurred before the 20th week of gestation, whether any medical or obstetric problems occurred during the pregnancy or labor, whether delivery took place at the hospital, and if so date of delivery. For each delivery, the following information was recorded: whether delivery was vaginal or cesarean; duration of gestation; whether the fetus was delivered live and, if not, the number of completed weeks of gestation; birth weight; Apgar scores at 1 and 5 minutes; whether the newborn was admitted to the neonatal intensive care unit or the pediatric department; and the occurrence of any complications at the time of hospital discharge. Clinical reports were retrieved from the fever clinic for participants confirmed by RT-PCR to harbor the H1N1pdm virus; the reports included the antiviral treatment received (if any) and the gestational age of the fetus at delivery. These data were collected retrospectively and updated on January 22, 2011.

From October 21, 2010, to January 22, 2011, the parents or guardians of living infants were followed-up via telephone questionnaire by a trained physician. The questionnaire included items regarding CAs in the infant and any hospitalization after neonatal discharge. The questionnaire also inquired from the women in groups 2 and 3 whether they experienced any symptoms of having a cold or flu, such as headache, stuffy or runny nose, sneezing, coughing, and/or fever during their pregnancy, as well as the fetal age when fever was present and what (if any) anti-fever treatment they received.

Statistical analysis was performed using SPSS version 11.5 (SPSS, Chicago, IL, USA). Basic medians and percentages were calculated. Percentages were compared among the groups using the Fisher exact test. $P<0.05$ was considered statistically significant.

3. Results

The flowchart of the study is shown in Fig. 1. The RT-PCR assays detected H1N1pdm RNA in 26 participants (group 1), and the results of the randomly administered tests for antibodies against H1N1pdm virus were positive for 23 participants (group 2). Of the 26 original participants in group 1, 3 were lost to follow-up. The median age was lower in group 1 than in groups 2 or 3 ($P<0.001$) (Table 1). Most of the participants in groups 1 and 2 had no coexisting chronic illnesses. However, there were pregnancy-related, obstetric, and/or gynecologic disorders in these groups. In group 1 (n = 10 for this information) and group 2 combined (n = 33), 11 (33.3%) participants experienced an obstetric problem during their pregnancy, with 5 (15.2%) developing pregnancy-induced hypertension or preeclampsia, 5 (15.2%) developing anemia, and 3 (9.1%) developing gestational diabetes; moreover, hysteromyomas were detected in 3 (9.1%) participants in group 2 (Table 1).

Of the 26 original participants in group 1, 4 were infected in the first trimester and 11 in the second trimester. Among the remaining 11, who were infected in the third trimester, 2 were diagnosed when they were hospitalized for labor. Twenty-three of the original participants in group 1 were admitted to the fever clinic with an influenza-like illness, and 2 of them developed acute respiratory distress syndrome (ARDS), 1 in the third trimester; this participant was transferred to a designated hospital. Seven days after onset of fever, the other participant with ARDS was hospitalized at the study hospital with critical signs. The median temperature of the 23 participants admitted with an influenza-like illness was 38 °C, and common clinical features in the least severe cases were headache, sore throat, and rhinorrhea. The median hematologic values in group 1 were 174×10^9 cells/L for platelets and 7.7×10^9 cells/L for white blood cells (of which 78.0% were neutrophils, 13.0% were lymphocytes, and 8.0% were monocytes). Twenty-two of the original participants in group

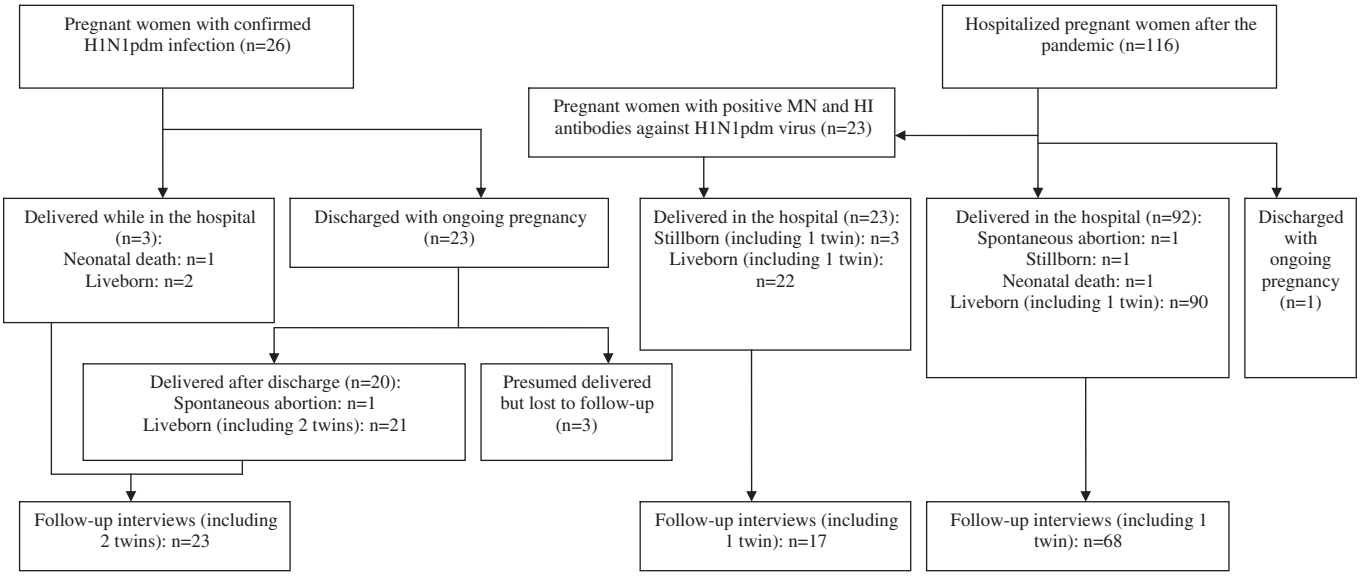

Fig. 1. Flowchart of a study on pregnancy complications, perinatal outcomes, and congenital abnormalities (CAs) in Beijing, China, when pregnant women became infected with the 2009 pandemic influenza A (H1N1) (H1N1pdm). Abbreviations: HI, hemagglutination inhibition; MN, microneutralization.