Journal of Infectious Diseases Advance Access published January 28, 2014

Stillbirth during infection with Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

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Abstract

We conducted an epidemiologic investigation among survivors of a Middle East Respiratory Syndrome coronavirus (MERS-CoV) outbreak in Jordan.

A second trimester stillbirth occurred during the course of an acute respiratory illness which was attributed to MERS-CoV, based on exposure history and positive MERS-CoV serology.

This is the first occurrence of stillbirth during an infection with MERS-CoV and may have bearing upon the surveillance and management of pregnant women in settings of unexplained respiratory illness potentially due to MERS-CoV. Future prospective investigations of MERS-CoV should ascertain pregnancy status and obtain further pregnancy–related data, including biological specimens for confirmatory testing.

Introduction

New cases and clusters of Middle East Respiratory Syndrome coronavirus (MERS-CoV) infections continue to occur sporadically in the Middle East and Europe[1]. MERS-CoV is a novel coronavirus known to cause acute respiratory illness typically associated with fever, which can progress rapidly to respiratory failure and, in some patients, renal failure. There has been no information yet published regarding the impact of MERS-CoV infections on pregnancy outcomes.

Methods

In May 2013, epidemiologists from the U.S. Centers for Disease Control and Prevention (CDC) joined the Jordan Ministry of Health (JMoH) and regional partners to conduct a retrospective investigation of an April 2012 outbreak of respiratory illness using newly developed serologic tests for detection of MERS-CoV antibodies. After the discovery of MERS-CoV, two fatal cases in this outbreak were retrospectively diagnosed with MERS-CoV using stored specimens confirmed by rRT-PCR and reported to World Health Organization (WHO).

Serum specimens were collected and epidemiologic data were obtained from potentially exposed groups, including outbreak survivors and household contacts, through medical chart reviews and interviews. Household members were considered eligible for enrollment if they reported usually sleeping under the same roof as an outbreak member during the outbreak period, February−April 2012. The initial outbreak case definition included, "any case admitted [to the hospital] or their close contacts, who complained of fever and dry cough with radiological evidence of pneumonia during the period from 15 March to 30 April", which identified 13 individuals, including the 2 fatal cases[2].

Interviews focused on a range of topics including the history of illness, detailed contact history (with surviving outbreak group members, the household members of outbreak group members, visiting travelers, and animals), travel history, and occupation.

MERS-CoV antibody positivity was defined as having positive a serologic result from the HKU5.2N Enzyme Immunoassay (EIA) and a correlated test-positive result from either the MERS-CoV Immuno-fluourescent assay (IFA) or MERS-CoV microneutralization titer assay (MNt) developed at CDC.

Results

During the course of the MERS-CoV outbreak investigation in Zarqa, Jordan, we obtained data and specimens from a total of 11 subjects in the initial outbreak group and from another 26 subjects who had resided in those outbreak member households during the outbreak period. One household was lost to follow-up, and one did not consent for participation. Six (16%) of these 37 subjects were women aged 18–45 years old. Three (50%) reported being pregnant during the outbreak period. Two of the pregnancies reportedly resulted in miscarriage, but both of these mothers tested antibody-negative for MERS-CoV.

The third pregnant woman, 39 years of age, had a stillbirth at approximately 5 months of gestation and her laboratory results were antibody positive for MERS-CoV by all three serologic assays: EIA (1:1600), IFA positive, and MNt (80). During the outbreak period, her acute respiratory symptoms (fever, rhinorrhea, fatigue, headache, and cough) occurred concurrently with vaginal bleeding and abdominal pain on the seventh day of illness, and she spontaneously delivered a stillborn infant.

The pregnant subject's onset of respiratory symptoms occurred seven days following the onset of her husband's symptomatic acute respiratory illness; he also tested positive for MERS-CoV antibodies by all three serologic tests [EIA (1:400), IFA positive, and MNt (40)]. Additionally, she had another close relative who died of a MERS-CoV infection, confirmed by real time reverse transcription polymerase chain reaction (rRT-PCR), one day prior to the pregnant subject's date of onset. The pregnant subject reported having unprotected MERS-CoV exposures to both of these family members during their symptomatic illnesses. (**Figure 1**)

The pregnant subject refused medical care during her illness due to stated concerns of receiving chest X-rays and medications during pregnancy. As is common in this region, fetal specimens were not retained and were not available for retrospective evaluation. Prior to her stillbirth, she received regular antenatal care with a physician and had no reported complications during pregnancy. Including the recent stillbirth, she had seven pregnancies resulting in six full-term live births. The surviving six children tested negative for MERS-CoV antibodies.

Discussion

We report a second trimester stillbirth in a pregnant subject occurring concurrently with her acute respiratory illness that met the WHO case definition for probable MERS-CoV infection[3]. Linked to the Jordanian MERS-CoV outbreak, the pregnant subject's illness began within 14 days following unprotected exposures to two MERS-CoV cases during their illnesses (a rRT-PCR-positive relative and a MERS-CoV antibody-positive husband). She was symptomatic but did not seek medical care because she wished to avoid chest X-rays and medications during pregnancy.

With the currently limited knowledge of MERS-CoV epidemiology and patho–physiology, it is prudent to review observed associations between pregnancy outcomes and other severe respiratory pathogens. Complications including maternal mortality and stillbirth have been reported among pregnant women with severe respiratory infections caused by the SARS-CoV[4] , H1N1 influenza[5,6], and other viruses causing pneumonia[7]. Uncomplicated pregnancies lead to physiologic changes resulting in altered pulmonary and immunologic function[8,9], including a 20% increase in maternal oxygen consumption, 10-25% decrease in functional residual capacity, and significantly increased forced vital capacity after 14-16 weeks gestation. Severe respiratory illness during pregnancy may further disrupt maternal tolerance to hypoxemia and reduce oxygen flow to the fetus. Of twelve pregnant women infected with SARS-CoV in South China during January 1-July 31, 2003, spontaneous miscarriages were reported from over half (59%) of those infected during their first trimesters[10]. Premature deliveries, thought to be related to poor fetal oxygenation, were experienced among 80% of those infected during their second to third trimesters and were associated with intrauterine growth restriction.

Further investigations in other MERS-CoV outbreak settings may shed light on factors related to the risk of infection and adverse birth outcomes in pregnant women, including any temporal relationship between maternal infection and period of gestation, biomarkers of immune hyperactivity, decreased respiratory function, and evidence of tissue necrosis upon hospitalization, as was observed during the SARS-CoV epidemic to indicate negative prognoses[11,12]. Further information regarding the risk of adverse consequences to mother and fetus due to MERS-CoV during pregnancy, as well as benefits and risks of possible therapies, is needed to better inform treatment decisions in pregnant women.

While it is unclear whether cultural sensitivities restricted the full capture of information during our interviews, this was a joint investigation with CDC and the Jordan MoH and the interviewers included females from the region. All interviewers demonstrated an understanding of cultural sensitivities and spoke Arabic. A limitation of our report is that confirmation from sero-epidemiological evidence is difficult with any retrospective investigation, and associating serologic evidence to a particular outcome can appear spurious. Indeed, the fetal loss rate for a 20-week gestation is estimated to be 0.5% (95% confidence interval 0.3-0.8%)[13] from non-chromosomal and non-structural causes in a developed country population, and other biological explanations for our observations are possible. Nonetheless, no other MERS-CoV infections have been confirmed in Jordan outside of this brief outbreak period despite hundreds of specimens being tested via active surveillance[14]. Based on the exclusivity of the timing of the pregnant subject's unprotected MERS-CoV exposure history, concurrent respiratory illness and stillbirth, and her subsequently positive MERS-CoV serologic results, we describe a possible association between MERS-CoV infection and stillbirth.

We conclude that adverse maternal and birth outcomes observed during the SARS-CoV epidemic and H1N1 influenza pandemic are consistent with the possibility that MERS-CoV infection during pregnancy may pose serious health risks to both mother and fetus. The Kingdom of Saudi Arabia, where the majority of MERS-CoV cases have occurred, included pregnant women in its 2013 recommendation of groups that should, "…postpone the performance of Umrah and Hajj this year [2013]"[15]. Neither CDC nor WHO has issued evaluation or management strategy recommendations specifically for MERS-CoV among pregnant women. As indicated by our investigation, MERS-CoV infections could potentially remain undetected among pregnant women due to barriers to receiving appropriate diagnostic

care. Future prospective investigations of MERS-CoV should ascertain pregnancy status and further pregnancy–related data should be obtained, including biological specimens for confirmatory testing.

Acknowledgements

Members of the Jordan MERS-CoV Investigation Team:

Dr. Nabil Sabri, Dr. Mohammad Al Azhari, Dr. Hala Khazali, Dr. Mohammad Al Maayah, Dr. Adel Bilbeisi, Dr. Naim Dawood, Dr. Bilal Al Zubi (Jordan Ministry of Health), Dr. Jawad Meflih (Eastern Mediterranean Public Health Network (EMPHNET)), Dr. Tony Mounts, Dr. Julia Fitzner, Dr. Akram Eltom, Dr. Ali Mafi, (World Health Organization), Congrong Miao, Dr. Hayat Caidi, Suvang Trivedi, Shifaq Kamili, Dr. Aron J. Hall, Aaron Curns, Jessica Moore, Huong Pham, Dr. Chris Zimmerman (National Center for Immunization and Respiratory Diseases, US Centers for Disease Control and Prevention), Dr. Eileen Farnon, Dr. Genessa Giorgi, Dr. Russell Gerber (Center for Global Health, US Centers for Disease Control and Prevention**)**, Dr. David Kuhar (National Center for Emerging and Zoonotic Infectious Diseases, US Centers for Disease Control and Prevention).

Conflicts of Interest:

All co-authors have submitted their ICMJE conflict of interest forms and none report any conflicts of interest relevant to this manuscript.

Funding Source:

This work was supported by the US Global Disease Detection Operations Center Outbreak Response Contingency Fund.

Footnote Page

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I, Daniel C. Payne, confirm that I had full access to all the data in the study and had final responsibility for the decision to submit for publication. No external assistance in drafting this manuscript was obtained. The manuscript is not under consideration at another journal, and findings have not been presented at a public meeting.

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Timeline of events: MERS-CoV-associated stillbirth, April 1 – 30, 2012