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Emerging Infections and Pregnancy: West Nile Virus, Monkeypox, Severe Acute Respiratory Syndrome, and Bioterrorism

Denise J. Jamieson, MD, MPH[a,*],
Daniel B. Jernigan, MD, MPH[b], Jane E. Ellis, MD, PhD[c],
Tracee A. Treadwell, DVM, MPH[b]

[a]*Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 4770 Buford Highway, Atlanta, GA 30341, USA*
[b]*National Center for Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, USA*
[c]*Department of Gynecology and Obstetrics, Emory University School of Medicine, 69 Jesse Hill Jr. Drive, S.E., Atlanta, GA 30303, USA*

In 1991, the National Academy of Science's Institute of Medicine convened a 19-member multidisciplinary panel to study the emergence of infectious disease threats. This expert panel issued a landmark report, entitled *Emerging Infections—Microbial Threats to Health in the United States* [1], which described a host of factors that contribute to the introduction and spread of novel infectious diseases. In 2003, a follow-up report was issued, entitled *Microbial Threats To Health: Emergence, Detection, and Response* [2]. These two reports emphasize the urgent threat posed by the introduction and spread of novel infectious disease agents in the United States. Furthermore, they describe the critical role that globalization plays in the rapid and efficient spread of these infectious diseases. As global borders blur, and people, animals, food, and other products are rapidly transported, the infectious diseases that they harbor may also be

* Corresponding author.
E-mail address: djamieson@cdc.gov (D.J. Jamieson).

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efficiently transported to new locations. In addition to the unintentional spread of disease, we also now face the possibility of intentional disease spread by bioterrorist attacks.

As new infectious diseases, such as West Nile virus, monkeypox, and severe acute respiratory syndrome (SARS) are recognized in the United States, there are critical questions about how these infectious diseases will affect pregnant women and their infants. In addition, the implications of bioterrorist attacks for exposed pregnant women need to be considered. In this article, the authors address the following questions for a number of infectious disease threats: (1) Does pregnancy affect the clinical course of these novel infectious diseases? (2) What are the implications for prophylaxis and treatment of exposed or infected pregnant women? (3) Are these novel infectious diseases transmitted during pregnancy, labor and delivery, or breastfeeding?

West Nile virus

West Nile virus is a mosquito-borne flavivirus that is transmitted to humans primarily through the bite of infected mosquitoes [3]. Infection in humans is varied: it can be asymptomatic; it can result in a mild illness with fever, rash, and headache; or it can be severe, with meningoencephalitis and other neurologic sequelae, because the virus has a predilection for the human nervous system [4]. Information about West Nile virus in pregnancy is fairly limited, with only six cases of West Nile virus in pregnancy having been reported to date [5–10], although the Centers for Disease Control and Prevention (CDC) has been tracking more than 70 pregnant women infected with West Nile virus since 2003 [6].

There has been only one documented case of probable intrauterine infection with West Nile virus [5,7]. A 20-year-old woman at 27 weeks gestation presented with fever, severe headache, blurred vision, abdominal and back pain, and vomiting. She was treated with intravenous antibiotics. On the fourth day of hospitalization, the patient was afebrile, but had pain and symmetric weakness in her legs. After more than 2 weeks of hospitalization, the patient left against medical advice and was readmitted 2 days later after having fallen. Electromyelography (EMG) indicated widespread involvement of the lower motor neurons. Serologic testing revealed West Nile virus-specific (WNV-specific) IgM antibodies in the serum and in cerebrospinal fluid, consistent with the diagnosis of meningoencephalitis. At 38 weeks of gestation, the patient had a spontaneous vaginal delivery of a viable infant. At delivery, WNV-specific IgM was detected in maternal serum, cord blood, infant serum, and infant cerebrospinal fluid. The infant also had WNV-specific IgM antibody in the serum. The placenta was polymerase chain reaction (PCR)-positive for West Nile virus at one of two reference laboratories. In addition, the infant had evidence of bilateral chorioretinitis and cerebral tissue destruction. This is the only reported case of documented intrauterine transmission of West Nile virus. The infant ocular and

neurologic abnormalities that were noted at birth likely resulted from the infection with West Nile virus.

In another reported case of West Nile virus infection in pregnancy complicated by meningoencephalitis, there was no evidence of fetal infection, although the work-up of the infant for infection was incomplete [8]. A 28-year-old having a history of chronic hypertension and sickle cell trait presented at 16 weeks gestation with headache, neck pain, fever, nausea, and vomiting. She reported recently being bitten by mosquitoes, and WNV-specific IgM was detected in her cerebrospinal fluid, consistent with the diagnosis of West Nile virus meningoencephalitis. She was treated with antibiotics and antivirals, and required mechanical ventilation. At 32 weeks, she was induced for superimposed preeclampsia and fetal growth restriction. The infant appeared normal and did well, although a serologic evaluation for possible West Nile virus infection in the infant was not undertaken. In this case, it is likely that the maternal hypertensive disease contributed substantively to the fetal growth restriction. What is unclear is whether infection with West Nile virus could have also contributed to the fetal growth restriction.

In four other cases of West Nile virus infection in pregnancy that have been reported in the literature [9,10], there has been no evidence of fetal infection or fetal effects from maternal infection. In each of these cases, infant serologic testing for WNV-specific IGM was negative. In addition to the cases during pregnancy, there has also been one reported case of probable West Nile virus infection to an infant through breastfeeding [11].

Based on the limited information reported to date, it is not clear whether pregnant women are more susceptible to infection to West Nile virus, or if they have a more severe clinical course. With the CDC now actively collecting information on cases in pregnancy, we hope that there will be additional information addressing these issues in the near future. The fetal effects of maternal infection are also unclear, with one probable case of congenital anomalies associated with intrauterine infection and one possible case of fetal growth restriction, although the growth restriction could also easily be attributed to the maternal hypertensive disease. West Nile virus is a flavivirus with antigenic similarities to Japanese encephalitis and St. Louis encephalitis [3]. Other flaviviruses have been associated with spontaneous abortion and neonatal illness, but they have not been known to cause birth defects [6]. In terms of preventing illness, pregnant women should be advised to use protective clothing, avoid outdoor exposure during times of the day when mosquitoes are most active (ie, dawn and dusk), and use insect repellants containing N,N-diethl-m-tolumide (DEET) [6].

Monkeypox

Monkeypox, which belongs to the orthopoxvirus group of viruses [12], was so-called because it was discovered in laboratory monkeys in 1958 [13].

Monkeypox was first identified as the cause of a smallpox-like illness in humans in Africa in 1970 [13], and subsequent outbreaks were reported, including one large series of 88 cases reported from the Democratic Republic of the Congo [14]. Information about monkeypox infection among pregnant women is extremely limited, because most prior descriptions of monkeypox outbreaks in Africa do not include a description of the natural history of outbreaks among pregnant woman. One probable case of perinatal infection has been reported from Zaire. At approximately 24 weeks gestation, a pregnant woman developed a febrile illness with a rash, and monkeypox virus was subsequently isolated from a vesicular lesion. Six weeks later she delivered a 1500 g infant who had a generalized skin rash resembling monkeypox [13].

In June 2003, the first evidence of community-acquired monkeypox infection was reported in the United States [12]. By July 8, 2003, a total of 71 monkeypox cases had been reported from six states [15]. This outbreak resulted from contact with infected pet prairie dogs, who acquired monkeypox after being housed or transported with infected African rodents. Because some of these infected pets were in households with pregnant mothers, there was concern about how to advise pregnant women [16].

Because smallpox (vaccinia) vaccine had been reported to reduce the risk of monkeypox among previously vaccinated persons in Africa, the CDC recommended that persons exposed to a sick prairie dog or an infected person be vaccinated, regardless of their pregnancy status [16].

Severe acute respiratory syndrome

SARS is an acute viral infection with a novel coronavirus [17,18], which in 2003 caused outbreaks of more than 50 cases in 6 countries, but affected 25 countries [19]. The largest case series of pregnant women comes from Hong Kong, where 12 pregnant women who had SARS were hospitalized in 2003 [20–23]. Three of the 12 pregnant patients who had SARS died, for a case-fatality rate of 25%. Among the 7 women who presented in their first trimester of pregnancy, 4 had spontaneous abortions between 2 and 5 weeks after onset of illness, and 2 electively terminated their pregnancies after recovery from SARS. Among the 5 women who presented in the late second or third trimesters, 4 had preterm deliveries, with 3 patients delivered by emergency cesarean section due to inadequate maternal oxygenation and 1 due to fetal distress. Two patients had evidence of intrauterine growth restriction and oligohydramnios. Six patients were admitted to the intensive care unit [22]. Among the five newborn infants, there was no evidence of clinical or serologic evidence of perinatal transmission, as assessed by SARS-associated coronavirus reverse-transcriptase PCR and viral culture on cord blood, placenta tissue, and amniotic fluid [21]. A matched study in Hong Kong [20] comparing the clinical course and outcomes of 10 pregnant SARS patients with 40 nonpregnant controls found that pregnant and non-

pregnant patients had similar clinical symptoms and presentation, but that pregnant patients had evidence of more severe illness. Pregnant patients were more likely to require endotracheal intubation and admission to the intensive care unit, and they were more likely to develop renal failure and disseminated intravascular coagulopathy compared with nonpregnant patients. There were three deaths among the pregnant patients compared, with no deaths in the nonpregnant group.

Two of the eight people who had laboratory-confirmed SARS in the United States in 2003 were pregnant women [24–26]. Both had traveled to Hong Kong and stayed in the same hotel as the physician who is thought to be the source of infection for index case-patients in a variety of countries. A 36-year-old woman traveled to Hong Kong at 19 weeks gestation. Upon her return to the United States she was hospitalized for pneumonia, and subsequently required mechanical ventilation. Serum specimens were tested at the CDC and found to be positive for SARS-coronavirus antibody. She recovered and did well until 38 weeks gestation, when she underwent cesarean delivery for a complete placenta previa. The infant was normal-appearing and had no evidence of infection; however, clinical specimens from the infant were not tested for SARS coronavirus [24,25]. The second patient in the United States was a 38-year-old who traveled to Hong Kong at 7 weeks gestation. She and her husband also stayed at the Hong Kong hotel implicated in the spread of SARS to a number of countries. Both the pregnant woman and her husband were diagnosed with SARS upon their return to the United States. The pregnant woman was hospitalized for 9 days and recovered fully from her illness. At 36 weeks gestation, she had preterm premature rupture of membranes and delivered a healthy infant without evidence of infection [26].

Although not confirmed by the two cases in the United States, the cases reported from Hong Kong suggest that pregnant women who have SARS may have a more severe clinical course compared with nonpregnant women. In addition, SARS during pregnancy may be associated with increased rates of spontaneous abortion, preterm delivery, and intrauterine growth restriction. There has been no evidence, however, of perinatal transmission of SARS. In terms of treatment, although ribavirin has been used empirically to treat SARS, it has not been studied systematically to determine whether it is effective treatment [27]. There are concerns about using ribavirin early in pregnancy; embryocidal and teratogenic effects of ribavirin have been noted in animal studies and ribavirin is designated as pregnancy category X, indicating that it should not be used in pregnancy [28]. Although there are few data regarding use early in pregnancy, in the few women given ribavirin later in pregnancy for measles or influenza, no fetal adverse effects have been noted [29,30]. Eleven of the 12 pregnant SARS patients in Hong Kong received ribavirin, including 6 of the 7 patients diagnosed in the first trimester [23]. It is possible that the high rates of spontaneous abortion observed in Hong Kong could be due to treatment with ribavirin rather than the SARS infection.

Bioterrorism

In this new age of heightened concern about terrorist attacks, the possibility of intentional attacks in the United States using biologic weapons has been of increased concern recently, particularly after the anthrax attacks of 2001 [31]. The Working Group on Civilian Biodefense, which is an expert panel composed of representatives from academic, government, military, public health, and emergency management agencies and institutions, has identified a limited number of biologic agents that are of particular concern. These include anthrax, smallpox, botulism, tularemia, plague, and the viral hemorrhagic fevers [32–38]. Physicians and public health officials have been developing strategies for how to respond to potential bioterrorist attacks, including identifying that an attack has occurred, prophylaxing those exposed, diagnosing and treating cases, and implementing containment measures to minimize the number of people exposed. It is critical that these comprehensive response plans include specific guidance for pregnant women, so that pregnant women who are exposed or who are cases can be treated appropriately. For some of these bioterrorist agents, such as smallpox, we have some information about infection in pregnancy; however, for many of these potential bioterrorist agents there is limited information about these infections in pregnancy.

Anthrax

Anthrax infections can be cutaneous, inhalational, or gastrointestinal, and are caused by *Bacillus anthracis*, an aerobic, gram-positive, spore-forming bacillus species [36,38]. Although anthrax has been around since the time of ancient Rome [39], information about anthrax in pregnancy is limited. There were two recent cases of anthrax infection in pregnancy reported from Turkey in 2003 [40]. In one case, a 33-year old woman at 32 weeks gestation presented with a submandibular eschar and extensive edema of the face, neck, and upper thorax. Her report of flaying a dead cow 7 days earlier was consistent with exposure, because herbivores are often infected after ingesting anthrax spores from the soil. She was treated with penicillin and prednisolone, recovered 10 days later, and delivered prematurely at 34 weeks gestation. The second case was a 29-year-old woman at 33 weeks of gestation who had a lesion on her elbow, was treated with penicillin, and delivered at 34 weeks gestation. In both cases, *B anthracis* was isolated from their lesions, they recovered quickly without sequelae, and their neonates did not have any evidence of infection.

There have been several other cases of anthrax infection in pregnancy from Iran and India [41,42]. In two cases, pregnant women presented with gastrointestinal anthrax after ingesting contaminated meat. In both cases the women died from peritonitis. Of over 140 maternal death autopsies performed at a hospital in Iran, four women had anthrax [41]. There are no reported cases of perinatal transmission of anthrax in the literature, and no cases of inhalational anthrax in pregnancy.

During the anthrax attacks of 2001, which resulted in 22 cases and five deaths [38], guidelines were rapidly developed and disseminated to address prophylaxis for exposed persons as well as recommendations for treatment. Both the American College of Obstetricians and Gynecologists (ACOG) and the CDC recommend that pregnant women who have a high-risk environmental exposure should receive prophylaxis [43,44]; however, decisions about whether an exposure is risky enough to merit prophylaxis for a pregnant woman should be made by public health officials, not by the woman's obstetrician-gynecologist or other care provider [44]. The first-line regimen for prophylaxis of pregnant women should be a 60-day course of ciprofloxacin. If the specific strain of *B anthracis* is found to be penicillin-sensitive, then a switch to amoxicillin may be considered. Due to effects on fetal bone and dental enamel, doxycycline, the other first-line agent for anthrax prophylaxis among nonpregnant adults, should be used with caution in asymptomatic pregnant women, and only when contraindications proscribe use of other drugs. If doxycycline is used in pregnant women, periodic liver function testing should be performed because of the small increased risk of maternal hepatic necrosis. Although anthrax vaccine supplies are currently limited, anthrax vaccination has been proposed as an adjunct to microbial prophylaxis for optimal postexposure prophylaxis [38]; however, there are no animal or human safely studies of the anthrax vaccine during pregnancy, and the vaccine is not recommended for use in pregnancy [45]. For initial therapy of inhalational anthrax among nonpregnant adults, intravenous ciprofloxacin or doxycycline, along with one or two additional agents, is recommended [38]. For pregnant women, the recommendations for treatment are similar to those of nonpregnant adults, although ciprofloxacin would be generally preferable to doxycycline.

Smallpox

Due to its high fatality rate and its ease of transmission, as well as the general lack of immunity currently in the US population, smallpox is one of the most feared potential agents of bioterror. Smallpox is caused by variola virus, a DNA virus of the genus *Orthopoxvirus*, the same genus as monkeypox, cowpox, and vaccinia. Variola differs from the other orthopox viruses in that it is readily transmitted from person-to-person [35].

Smallpox is generally more severe in pregnant women than in nonpregnant women or in men [46]. In several reports from India, pregnant women had a higher case-fatality rate and a sevenfold increased risk of a severe hemorrhagic type of smallpox compared with nonpregnant adults [47]. Rates of spontaneous abortion, stillbirth, and preterm delivery are very high among women who have smallpox [46]. In addition, congenital cases of smallpox have been reported [46]. Therefore, the potential impact that an intentional attack with smallpox in the United States would have specifically on pregnant women is particularly concerning.

Vaccinia vaccine, the highly effective vaccine against smallpox, was recommended for all US children until 1972. Currently, only those laboratory workers and health care workers at high risk of exposure are being offered vaccinia vaccination [48]; however, vaccination during pregnancy is generally contraindicated because of documented cases of fetal vaccinia following maternal vaccination. Although pregnancy is a contraindication to routine nonemergency vaccination, in the case of an intentional attack, pregnancy should not be a contraindication to postexposure vaccination [48]. Vaccinia immune globulin (VIG) is recommended for persons who have severe, life-threatening complications from vaccinia vaccination. VIG is not contraindicated in pregnancy if severe adverse vaccine reactions occur [48].

Other agents

Several other agents, such as botulism, tularemia, plague, and hemorrhagic fever viruses, have been highlighted by the Working Group on Civilian Biodefense as potential biologic weapons. Botulism is an extremely potent biological toxin that comes from *Clostridium botulinum*. Once absorbed, botulism toxin binds irreversibly to peripheral cholinergic synapses and blocks acetylcholine release, causing paralysis. Recovery may take weeks to months to complete, and results from reinnervation of paralyzed muscle fibers [32]. There have been several cases of botulism in pregnancy reported in the literature. In the most dramatic case [49], a 37-year-old woman at 23 weeks gestation who had consumed home-produced green beans was hospitalized for progressive weakness and eventual paralysis, requiring assisted ventilation for 2 months. Botulism antitoxin was administered. Although she became increasingly paralyzed, fetal growth was normal and fetal movement was apparent. She recovered fully and delivered a healthy infant at term. In another case, an Alaskan native was hospitalized at 16 weeks gestation with botulism after ingesting contaminated whitefish. After receiving antibotulism toxin, she was discharged home on the tenth hospital day. She delivered a healthy infant at term [50]. There has been no evidence to date of transplacental transport of botulism toxin to the fetus, nor have there been any reports of adverse fetal effects of maternal treatment with botulism antitoxin [49–51]. Based on limited information, pregnant women should receive the same treatment for botulism as nonpregnant adults, which consists of supportive care and passive immunization with equine antitoxin [32].

Tularemia is a plaguelike disease of rodents caused by *Francisella tularensis*. For prophylaxis of tularemia after an intentional attack, ciprofloxacin, one of the two preferred regimens for nonpregnant adults, is recommended for pregnant women,. For treatment of tularemia, gentamicin, also one of the two preferred choices for nonpregnant adults, is recommended [34].

Yersinia pestis, the causative agent of plague, is an enzootic infection of rodents that most commonly causes bubonic plague. In an intentional attack using *Y pestis*, the recommendation for pregnant women is to use gentamicin for prophylaxis [37].

The viral hemorrhagic fevers, which are caused by several families of viruses, are a clinical illness associated with fever and a bleeding diathesis. Several of these such as Ebola, Marburg, Lassa, and yellow fever have been identified by the Working Group on Civilian Biodefense as potential biologic weapons [33]. There is some evidence that the mortality of some viral hemorrhagic fevers appears to be higher in pregnancy. Although there are no antiviral drugs approved by the US Food and Drug Administration for treatment of viral hemorrhagic fevers, ribavirin may reduce mortality of several of them, including Lassa fever. As previously mentioned, ribavirin is designated as pregnancy category X and is contraindicated in pregnancy; however, given the severity of the hemorrhagic fevers, the Working Group on Civilian Biodefense feels that the benefits appear likely to outweigh the risks and recommends ribavirin use for severely ill pregnant women [33].

Summary

As we face emerging and re-emerging health threats, we will need to understand how these novel diseases will affect pregnant women. In some cases, such as SARS, the hemorrhagic fevers, and smallpox, it appears that pregnant women may have more severe clinical courses compared with nonpregnant adults. In some cases, it appears that the rapid diagnosis of the disease may be delayed due to pregnancy. For example, in one of the reported anthrax cases, there was probably a delay in diagnosis of anthrax peritonitis because the pregnancy complicated the presenting clinical picture [41]. In terms of prophylaxis and treatment of emerging diseases, in many cases, such as anthrax, tularemia, and plague, first-line therapies and postexposure prophylaxis is similar in pregnant and nonpregnant adults. Although vaccinations such as those for smallpox and anthrax are not generally recommended for pregnant women, in some cases they may be used for postexposure prophylaxis. For example, for pregnant women exposed to monkeypox or smallpox, use of the vaccinia vaccine is recommended. In some cases, such as with ribavirin, which is generally contraindicated in pregnancy due to its teratogenic and embyrocidal effects, decisions about use in pregnancy need to be carefully weighed. In the case of SARS, where treatment is generally supportive and the effectiveness of ribavirin has not been convincingly demonstrated, use of ribavirin may not be indicated. By contrast, ribavirin has been shown to be effective treatment for some of the viral hemorrhagic fevers, such as Lassa fever, and despite the risks, treatment of pregnant women may be warranted given the severity of illness. In terms of perinatal transmission, there are cases of intrauterine transmission of West Nile virus, monkeypox, and smallpox virus reported in the literature.

There are a growing number of new or newly recognized pathogens in the United States that threaten our health. As new disease threats emerge, it will be critical to evaluate and understand how these diseases affect pregnant women, so

that reasonable response plans for diagnosis and treatment of pregnant women can be rapidly developed.

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