Clinical Expert Series CME

Emerging Infectious Diseases in Pregnancy

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It has been recognized for centuries that pregnant women have unique susceptibilities to many infectious diseases that predispose them to untoward outcomes compared with the general adult population. It is thought a combination of adaptive alterations in immunity to allow for the fetal allograft combined with changes in anatomy and physiology accompanying pregnancy underlie these susceptibilities. Emerging infectious diseases are defined as those whose incidence in humans has increased in the past two decades or threaten to increase in the near future. The past decade alone has witnessed many such outbreaks, each with its own unique implications for pregnant women and their unborn fetuses as well as lessons for the health care community regarding response and mitigation. Examples of such outbreaks include, but are not limited to, severe acute respiratory syndrome, the 2009 H1N1 pandemic influenza, Ebola virus, and, most recently, the Zika virus. Although each emerging pathogen has unique features requiring specific considerations, there are many underlying principles that are shared in the recognition, communication, and mitigation of such infectious outbreaks. Some of these key principles include disease-specific delineation of transmission dynamics, understanding of pathogen-specific effects on both mothers and fetuses, and advance planning and contemporaneous management that prioritize communication among public health experts, clinicians, and patients. The productive and effective working collaboration among the Centers for Disease Control and Prevention, the American College of Obstetricians and Gynecologists, and the Society for Maternal-Fetal Medicine has been a key partnership in the successful communication and management of such outbreaks for women's health care providers and patients alike. Going forward, the knowledge gained over the past decade will undoubtedly continue to inform future responses and will serve to optimize the education and care given to pregnant women in the face of current and future emerging infectious disease outbreaks.

(Obstet Gynecol 2017;129:896–906)
DOI: 10.1097/AOG.0000000000001978

Emerging infectious diseases are defined as pathogenic outbreaks whose incidence in humans has increased in the past two decades or threaten to increase in the near future.[1] The importance of emerging infectious diseases has been recognized for at least 20 years and continues to increase in importance and scope for many societal and ecologic reasons.[2,3] Such outbreaks of novel pathogens frequently cross national and territorial boundaries (in part as a result of the robust travel of modern life) and include recently highlighted and severe pathogens such as severe acute respiratory syndrome (SARS), the 2009 H1N1 pandemic influenza, Ebola virus, and, most recently, the Zika virus. In addition to these highly publicized outbreaks of recent times, emerging pathogen terminology also includes less dramatic, but often no less menacing, considerations such as 1) new infections resulting from changes or evolution of existing organisms, 2) known infections spreading to new geographic areas or populations, 3) previously unrecognized infections appearing in areas undergoing ecologic transformation, and 4) old infections reemerging as a result of the development of antimicrobial resistance to known standard agents or

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Continuing medical education for this article is available at http://links.lww.com/AOG/A942.

The author has indicated that he has met the journal's requirements for authorship.

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Financial Disclosure
The author did not report any potential conflicts of interest.

ISSN: 0029-7844/17

breakdowns in public health measures.[1–3] Commonly cited emerging infectious diseases of interest and some pathogen specifics are compiled in Box 1.

It has been appreciated for centuries that pregnant women have unique immunologic and physiologic characteristics that predispose them to heightened rates of serious and sometimes fatal outcomes from varied infectious diseases. This observation is mostly attributed to the combination of somewhat altered cellular immunity capabilities (presumably to allow for the fetal allograft) combined with changing anatomic specifics that can challenge primarily cardiovascular and respiratory systems with advancing gestational age.[4–9] More recent research has focused on relative concentrations and potencies of various immunoglobulins (immunoglobulin G) during pregnancy as part of the explanation for altered pregnancy immunity.[10] Additionally, ongoing investigations are assessing the role of the placenta and its inherent ability to block some viral pathogens from access to the fetus.[11] Ongoing research will continue to delineate the specifics of the immunology of pregnancy and its effect on disease transmission and pathogenesis.

The heightened susceptibility to adverse outcomes is most often noted for viral pathogens, with bacterial and parasitic infections occasionally also having this predilection. In addition, pregnant women also have unique characteristics worthy of attention with regard to infectious diseases (and their countermeasures) from clinicians including, but not limited to, the teratogenic potential of an infecting pathogen, differing transmission susceptibilities and specific implications for fetal infection during different stages of pregnancy, and the effect of an in utero infection on subsequent neonatal and infant development. Importantly, despite a predilection for worse outcomes, it does not appear (for the majority of pathogens) that pregnancy makes women more susceptible to acquiring an infection with the possible exceptions of human immunodeficiency virus, malaria, and potentially listeriosis.[12]

In addition to the inherent risks posed by emerging infectious diseases to pregnant women, the concept of the medical establishment's preparedness and response in the face of novel outbreaks has also recently received considerable attention. Much of the early focus toward preparedness was centered on the likelihood of an impending influenza pandemic.[13,14] However, the concepts and collaborations have now matured to include guidance and directives that are simultaneously relevant for a broad range of pathogens as well as specific outbreaks.[15–17] This is most recently evidenced by the appropriate attention received by, and prioritization given to, the ongoing Zika virus outbreak. A robust collaboration among the Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (the College), and the Society for Maternal-Fetal Medicine has also been paramount in highlighting important up-to-date knowledge, thereby enabling practice that is based on the best available data during the evolution of Zika and others. The

Box 1. Commonly Noted Emerging and Reemerging Pathogens of Interest

Pandemic influenza viruses

Novel influenza strains, emerging from antigenic shift in the influenza virus, causing occasional severe influenza pandemics

SARS-associated coronavirus

Highly pathogenic, novel severe respiratory virus that emerged and rapidly spread globally from a small location in China

Ebola virus

Previously recognized serious pathogen associated with modest-sized outbreaks before 2014 (largest outbreak); strikingly high mortality rate

Zika virus

Previously underappreciated pathogen until ongoing outbreak with its association with fetal malformations (most notably microcephaly); its unique characteristics put this outbreak at the intersection of emerging infectious diseases, reproductive rights, and global health security

West Nile virus

The most common mosquito-borne infection in the United States; no documented direct fetal effect

Chikungunya virus

Mosquito-borne virus that was previously found in Asia, Africa, and Europe that has recently been detected in the Americas; no documented direct fetal effect

Methicillin-resistant *Staphylococcus aureus*

Well-known reemerging pathogen given its aggressive clinical nature and relatively limited antimicrobial treatment options

Vancomycin-resistant enterococci

Classic reemerging pathogen that serves as an ongoing reminder of the ever present and evolving epidemic of antimicrobial resistance

SARS, severe acute respiratory syndrome.

women's health field has successfully aligned in response to these recent outbreaks in a manner that will undoubtedly serve pregnant women optimally. This article highlights a series of recent high-profile, specific emerging pathogens of significant maternal–fetal importance given their important lessons to the obstetric and public health community. In addition, the pathogens chosen for discussion have some unique and challenging features and provided unique foundations for progress in the area of health care provider, facility, national, and international preparedness planning and disease mitigation.

SEVERE ACUTE RESPIRATORY SYNDROME

Severe acute respiratory syndrome is a previously unrecognized emerging infectious disease caused by a novel pathogen that challenged the global health community's ability to effectively communicate and cooperate toward a goal of eventual containment. Believed to have originated in China's Guangdong Province late in 2002, it appears to have been spread internationally in the winter of 2003 by a physician who had traveled to the region to provide care against a new mysterious respiratory pathogen. Traveling home from China, he stayed one night at what later came to be referred to as Hotel M (from the epidemiologic perspective) in Hong Kong and was noted to have been ill for approximately 7 days prior with the same respiratory symptoms as his patients. Subsequent to his short, 24-hour stay, approximately 12 additional guests fell ill from this same unknown pathogen (the majority of whom were staying on the same floor as him in the hotel, yet without significant close contact) and then proceeded to travel abroad and perpetuate the global spread of what is now known as SARS. Involved countries included Canada, Vietnam, Singapore, Ireland, and the United States. In total, the World Health Organization (WHO) recognized at least 8,400 associated cases, with more than 800 deaths in greater than 32 countries recorded over roughly 6 months.[5,18] It was accordingly dubbed the first 21st century pandemic.

The infection was characterized by a rapid onset of fever plus other nonspecific symptoms (headache, malaise, and myalgia) followed by a nonproductive cough that progressed to shortness of breath and respiratory failure in a subset of patients. Characteristic laboratory aberrations include lymphopenia and elevated lactate dehydrogenase levels. The causative agent was later noted to be a novel coronavirus likely present in animals being sold in local markets and subsequently infecting those handling the animals (zoonotic spread). Importantly, the subsequent human-to-human spread was through respiratory droplets, yet early on, given the many unknowns, infection control practices included all phases of precautions: respiratory, contact, and droplet.

Cohorting (grouping of persons [patients or health care workers] who have been exposed to a disease, a form of isolating groups to minimize disease spread within in a location) and isolating of patients in facilities as well as widespread public education, contact tracing, quarantine practices, border surveillance, and travel advisories were instituted and successfully contributed to the eventual global control within approximately 5 months of first notification.[5,18] In the few affected obstetric hospitals, close attention was paid to minimizing exposure to unaffected patients and staff by way of cohorting exposed and infected patients, visitor limitations, vigilance toward the use of personal protective equipment (such as masks and gowns), clinical flexibility, facility temporary closure, working collectively to establish coordinated and regionalized care, and a willingness to consider and establish care models that minimized mixing of patients and obstetric health care providers.[18,19] All of these nonpharmaceutical interventions are important for all facilities providing care to pregnant women to consider and plan for in advance. This is a key lesson from the SARS epidemic; traditional nonpharmaceutical countermeasures are very effective for curbing disease spread, even in the absence of pharmaceutical interventions.

Understanding the effects of SARS on pregnancy is more challenging given the relatively low numbers of women infected. The few small available case series suggest that pregnant women had at least equal, and likely higher, rates of severe illness, intensive care unit admission, and death (similar to other serious respiratory pathogens in pregnancy).[18,20] As noted in other severe respiratory infections, some women underwent preterm cesarean delivery presumably for maternal respiratory benefit. No documented cases of perinatal transmission were noted despite relatively rigorous methods of investigation for viral particles, serologic responses, or both in neonates born to infected mothers. The low numbers of infected pregnant women were also attributable in part to the critically important and rigorous infection control practices noted (cohorting, regionalization of care, minimizing patient and health care worker mixing, use of personal protective equipment) used in hospitals that were successful in interrupting disease transmission.[18–20] The importance of the traditional infection control measures in and of themselves cannot be overemphasized. Important lessons for obstetric health care providers,

Box 2. Important Lessons Learned for Health Care Providers and Facilities From Select Recent Emerging Infectious Disease Outbreaks

SARS virus

- Novel emerging pathogens originating abroad can become local problems quickly given international travel patterns and methods of transmission
- Globally coordinated nonpharmaceutical responses to infectious disease outbreaks are critically important for disease mitigation and control
- Nonpharmaceutical efforts to minimize nosocomial spread of infectious diseases are critically important, especially in busy labor and delivery units with its inherent risks of exposure to numerous body fluids
- Clinical flexibility for facilities management is an important principle when dealing with a serious infectious disease with high potential for local spread among patients and health care providers

Influenza virus

- Even when predicted, expected, or both, emerging and reemerging infectious diseases (pandemic influenza) can cause significant morbidity and mortality in pregnancy
- Timely availability and use of influenza vaccine in pregnancy is a major priority for obstetric providers to recommend both in seasonal and pandemic outbreaks
- Influenza can be a severe respiratory disease that can be transmitted person to person before symptom onset, complicating mitigation efforts
- Early use of anti-influenza antivirals are very important and may lessen the severity of infection for mothers and their offspring
- Immediately postpartum women (2 weeks) are at similar heightened risk of morbidity and mortality as pregnant women from influenza

Ebola virus

- Pregnant women are susceptible to serious illness and death from Ebola infection
- Very high associated pregnancy wastage rates, and no infant has survived long-term after being born to an Ebola-infected mother
- Transmission of Ebola is very permissive making screening, recognition, and sequestering or cohorting* critically important interventions to undertake in the management of this infection to minimize spread
- Numerous body fluids have been found to carry Ebola infectious particles challenging infection control practices, including amniotic fluid
- Labor and delivery with its high risk of exposure to bodily fluids is a highly vulnerable area for inadvertent transmission and should be managed accordingly

Zika virus

- Unexpected new or reemerging infections can arise at any time, from any location, and can threaten the entire global health community
- The combination of the exact nature of transmission and the effect of an emerging infectious disease drives the societal attention and medical establishment's response in real time
- When little substantiated data are available at the onset of outbreaks, more conservative public health guidance is appropriately delivered
- Public health guidance must be appropriately updated, altered, or both as the nature and understanding of a novel outbreak evolves
- The true and full effect of outbreaks with teratogenic potential is not known for many years after the outbreak ensues

SARS, severe acute respiratory syndrome.
*Cohorting is grouping of persons (patients or health care workers) who have been exposed to a disease—a form of isolating groups to minimize disease spread within in location.

patients, and health care facilities from this particular outbreak are highlighted in Box 2.

INFLUENZA VIRUS

Influenza is a well-recognized cause of recurrent yearly global epidemics of febrile respiratory disease and has been documented as such for at least the previous four centuries. During this time, records suggest that the global community has experienced at least 30 influenza pandemics. The most severe recorded influenza pandemic was the 1918–1919 Spanish flu with estimates of global mortality of at least 20 million.[6,7] More recently the global community endured the 2009 H1N1 influenza pandemic and its associated morbidity and mortality, mostly noted in adults younger than 50 years of age, including disproportionate numbers of pregnant and puerperal women. The natural history of influenza mutation combined with the inevitability of antigenic shift (producing pandemic strains) makes influenza an emerging pathogen of interest.[6,7]

Influenza infection is primarily transmitted person to person through large droplets generated by coughing and sneezing from an already infected (and often asymptomatically incubating) person. In addition to respiratory droplets, transmission is also possible by contact, either directly to a susceptible host or by passive transfer through an intermediate object (ie, contaminated hands or objects). The incubation period for influenza is approximately 1–4 days followed by acute onset of fever, chills, nonproductive cough, nasal

congestion, headache, sore throat, malaise, and fatigue. Most patients have a combination of systemic symptoms and respiratory symptoms, and this finding can help differentiate influenza from other common respiratory pathogens. However, influenza is primarily a respiratory disease and most associated serious morbidity and mortality are attributable to respiratory compromise. Importantly, patients are infectious and transmit the virus during the short incubation period before symptom onset. This fact explains some of the challenges with prevention of spread in the population and in facilities.[6]

The occurrence of an upcoming influenza pandemic was well-predicted and expected (based mostly on the time lapse since the last flu pandemic). However, the source, timing, and location of the outbreak were not predicted and provided some early challenges for a global response.[13,14,21,22] Previous 20th century influenza pandemics consistently demonstrated that pregnant women suffered from disproportionate morbidity, high rates of pregnancy wastage, and higher rates maternal mortality (when compared with the general adult population).[6,13,14] This same phenomenon was again noted during the 2009 H1N1 pandemic. Multiple publications demonstrate higher rates of morbidity, critical care admission, preterm labor and birth, and higher rates of death (approximately 5-fold to 20-fold higher than expected from population-based data) among pregnant and early postpartum women.[21–27] Although this experience was not surprising, it provides a sober reminder of the uniquely susceptible nature of pregnant and early postpartum women to severe respiratory viral infections. Moreover, this recent experience clearly reinforced the importance of influenza vaccines and the use of other therapeutic measures during pregnancy.

In this author's opinion, a beneficial and long-lasting effect of the 2009 H1N1 influenza pandemic (notwithstanding its occasionally devastating effects on pregnant women) was that the unique nature of pregnant women was elevated to an international level of recognition never noted before. Coincidental to the 2009 H1N1 pandemic was a contemporaneous publication demonstrating in a randomized controlled fashion that immunization of pregnant mothers against influenza can also provide neonatal protection against influenza for up to 6 months of life.[28] This key finding, which has been replicated in subsequent investigations coupled with additional publications highlighting the higher rates of untoward outcomes from 2009 H1N1 among pregnant women, provided a renewed scientific and policy focus on the potential for disease prevention for mothers and infants through maternal immunization.[29] This focus continues today and provides novel opportunities with new vaccine products designed specifically for use in pregnancy to minimize the maternal and neonatal infectious disease burden.

No less important was novel clinical observational data demonstrating that the use of oseltamivir in pregnancy appears to mitigate to some extent the severity of infection. These data that had previously been noted in the general population were now validated in pregnancy and justify the use of antivirals early in cases of suspected or proven influenza infection. Creanga et al showed that severity of illness among pregnant women in New York City and timing of antiviral treatment are correlated. Pregnant patients who started therapy beyond the 48-hour (after symptom onset) recommended window of treatment were more likely to have severe influenza illness (3% compared with as high as 44% having severe illness, comparing less than 48-hour to greater than 5-day treatment onset, respectively, $P=.002$).[26] Similarly, a separate larger domestic investigation of 788 pregnant women with 2009 H1N1 demonstrated a significantly elevated relative risk of 6.0 (95% confidence interval 3.5–10.6) for admission to the intensive care unit for women treated more than 4 days after symptom onset (compared with less than 48 hours).[22] Combining the limited ability to predict which pregnant women will rapidly decompensate with the fact that severe outcomes are more likely, universal early oseltamivir treatment should be given by obstetric health care providers in all clinical settings as recommended.[30]

The other important phenomenon that the 2009 H1N1 influenza pandemic demonstrated was that despite significant efforts toward preparedness, the production and distribution capabilities of the vaccine industry did not optimally match the timeline of need (ie, early in the outbreak). Optimal protection from a mass vaccination program occurs when the vaccine is given at least 2 weeks before peak population exposure risk. Despite progress made in terms of vaccine manufacturing and timeliness in the lead-up to the pandemic, the majority of vaccines became available during or after the most significant wave of infection in the fall of 2009.[31] This situation continues to stimulate alternative methods for mass vaccine production and administration that may mitigate the supply–demand mismatch in future influenza pandemics. Important lessons learned from the 2009 H1N1 experience are highlighted in Box 2.

EBOLA VIRUS

Ebola virus has been recognized as a severe viral pathogen responsible for viral hemorrhagic fever for

approximately 40 years. The strain responsible for the most recent outbreak was first identified in 1976 along the Ebola River in what is now the Democratic Republic of Congo during a local outbreak of viral hemorrhagic fever. It is another zoonotic infection that humans most commonly initially contract from the natural reservoir of fruit bats. Once established in humans, subsequent infection is transmitted very efficiently from person to person by direct contact of mucous membranes or skin with bodily fluids or contaminated objects. Sexual transmission may occur. Incubation is typically 7–10 days and humans become infectious once fever and other nonspecific symptoms ensue. After the onset of generalized manifestations, severe gastrointestinal symptoms become apparent. Given the viruses' predilection for cytokine dysregulation, progression to multiorgan failure and hemorrhagic shock commonly occurs. Case fatality rates range from 55–90%, demonstrating its aggressive nature. This is also partly the result of the lack of Ebola-specific therapy, leaving supportive care as the option.[15]

The recent Ebola virus outbreak in regions of West Africa that started in 2014 and continued into 2015 was the largest ever recorded with a total of 28,652 cases, 15,261 of which were laboratory-confirmed, and a total of 11,325 deaths (40–75% case fatality rate).[32] The WHO declared this outbreak an International Public Health Emergency on August 8, 2014, and the outbreak continued for many months thereafter. It is worth noting that few pathogens have the ability to undergo widespread dissemination like Ebola and also carry such a high mortality rate. The overwhelming majority of cases were in the West African countries of Guinea, Sierra Leone, Liberia, and Nigeria. However, there were health care worker-associated cases (as a result of travel from Western Africa) in a handful of Western countries, including the United States, which prompted significant domestic efforts toward management of the potential for exposed and infected patients arriving in Western health care facilities. Many will remember significant domestic efforts in the fall of 2014 in response to a missed opportunity for identification and containment. Although the outbreak situation has mostly resolved, the CDC keeps a small force of roughly 75 workers in affected regions to have capabilities to detect and mitigate any potential new or smoldering outbreaks.

The interface between Ebola virus infection and pregnancy was partially appreciated at the outset of the recent outbreak. Historically women have been more likely to contract Ebola infection compared with men, likely related to cultural practices and caregiver roles. No data exist to suggest that pregnancy affects susceptibility to infection. However, historical reports suggest that pregnant women are more likely to suffer worse clinical disease and succumb to illness. The two largest case series reported before the recent epidemic note a cumulative mortality in excess of 90% during pregnancy from Ebola.[33,34] Affected pregnant women were equally represented across all gestational ages and presented with similar symptoms as the nonpregnant population with the notable exception of near universal reports of hemorrhage (mostly genital tract). No differences in clinical presentation or course of disease based on age or parity were documented. Additionally, very high rates of spontaneous miscarriage (approximately 60–70%) and pregnancy-related hemorrhage (both during delivery and abortion) were noted as well as the fact that no neonates born to infected mothers have survived longer than 3 weeks.[15,34,35] Interestingly, recent data demonstrate the presence of Ebola virus RNA in amniotic fluid, cord blood, and the placenta after delivery with associated implications.[35] Overall, the recent epidemic substantiates the earlier findings of higher risk for morbidity and mortality in pregnancy. An additional trend recently noted suggests that the overall decline in regional health care workers during the 2014–2015 Ebola outbreak plus a reluctance to care for infected pregnant women (presumably as a result of gravid women's high infectivity at the delivery) may have disproportionately predisposed pregnant women to receive less overall supportive care, leading to worse outcomes.[36,37] The full extent to which these trends may have affected outcomes remains to be fully realized.

Data from the most recent 2014 outbreak also provide additional relevant information for perinatal health for obstetric health care providers to understand. The recent outbreak verifies that vertical transmission of maternal Ebola virus infection to the fetus can occur during an acute Ebola infection, subsequently leading to intrauterine fetal death, stillbirth, or neonatal death.[37] Importantly, Ebola virus has been found in the breast milk during acute disease and may have led to infection in one infant, suggesting vertical transmissibility during lactation. Ebola also persists in many body sites for months, including semen, raising concerns about persistent vertical and sexual transmission months after clinical recovery.[37] This has large implications for proper infection control practices during future outbreaks. Additional take-home concepts from the recent Ebola virus outbreak are elaborated in Box 2.

ZIKA VIRUS

The ongoing Zika virus pandemic, with its documented association with fetal anomalies and other adverse neonatal and adult neurologic morbidities, has captured the world's attention over the past 12–18 months. Modern society has not experienced a teratogenic viral outbreak since the Rubella epidemic in the 1960s.[38] A vague, poorly appreciated and understood single-stranded RNA virus, Zika was first recognized in the 1940s in Africa and has until recently been associated with sporadic small regional outbreaks of minimal global importance.[39] This most recent epidemic with its epicenter in Brazil and associated effects on fetuses has awoken the global public health community to potential devastation from a novel emerging infectious disease. Attention must not fade as we learn more about the specific implications of Zika infection in pregnancy and the virus establishes natural endemicity.[40]

Zika is primarily a mosquito-borne infection and is a member of the same family of Flaviviruses as Dengue, Chikungunya, and Yellow fever. The most common vector for transmission is the *Aedes aegypti* mosquito (similar to other flaviviruses) with *Aedes albopictus* also able to transmit. Most patients infected with Zika are unaware of the infection (asymptomatic in approximately 75% of cases); if they are symptomatic, the clinical illness is invariably mild and self-limited. Clinical reports suggest a nonspecific constellation of fever, conjunctivitis, arthralgias, and maculopapular rash with the illness typically lasting 1 week or less. Associated nonspecific symptoms such as headache, myalgias, pruritus, and vomiting are also reported and share a self-limited nature. Additionally, Zika virus has been associated with Guillain-Barré syndrome and it appears previous infection confers lifelong immunity.[39]

In addition to the primary mode of vector-borne transmission, additional forms of transmission include sexual, laboratory, and likely bloodborne (through transfusion). The combination of vector-borne and sexual transmission makes this scenario unprecedented; never before has a documented teratogen been noted to be transmitted in this combined fashion. Furthermore, this combination generates a multitude of public and sexual health issues and questions. In April 2016, then-director of the CDC Dr. Thomas Frieden noted, "Never before in history has there been a situation where a bite from a mosquito could result in a devastating malformation."[41] This situation has generated much discussion about outbreak management, containment, and improved fetal outcomes. Additionally, considerations around how to appropriately design investigations and expeditiously license pharmaceuticals and vaccinations for mitigation against this outbreak have received significant attention.[41,42]

The most striking congenital finding garnering global attention is the atypically high numbers of neonates born with microcephaly across regions in Brazil noted to have had high numbers of cases of Zika. The disease outbreak was originally noted in the spring of 2015, and early reports of higher numbers of microcephalic neonates began to accumulate late in the fall of 2015. In February 2016, the WHO declared the Zika outbreak a public health emergency of international concern.[39,41] The constellation of findings that is now being coalesced into being referred to as the "congenital Zika syndrome" includes, but is not limited to, severe microcephaly with a partially collapsed skull; thin cerebral cortices; macular scarring and retinal mottling; congenital contractures; and marked early hypertonia with associated symptoms of extrapyramidal involvement.[43] Additionally, given Zika's predilection for neural tissue, some have postulated the high potential for adverse neurodevelopmental outcomes among neonates with both overt and unrecognized Zika exposure throughout gestation.[39,43]

Currently there are no medical countermeasures available to prevent, mitigate, or manage active Zika infection. Indeed, numerous trials of various vaccine candidates are underway within academia, the pharmaceutical industry, and the National Institutes of Health.[44] Although there are promising candidates in early-stage trials, it is unlikely that a vaccine product will be available on a wide-scale basis for use among reproductive-aged women (likely target population for first use) in the near future, even with the accelerated efforts underway. Until such a product exists, the bulk of the management centers on education of prospective patients as well as obstetric health care providers about 1) the specific recommendations surrounding travel restrictions to Zika-affected areas (an ever-increasing geographic list), 2) sexual activity considerations to minimize or eliminate the possibility of exposure of both men and women, and 3) minimizing risks for mosquito bites occurring in areas with active Zika transmission. These specific recommendations, areas with travel advisories, and specifics in regard to methodology of testing for Zika infection are well delineated on both the CDC's and the College's websites, and the reader is referred to these locations for a comprehensive discussion.[45,46] A brief summary of high-level recommendations for the obstetric community is detailed in Box 3. Importantly, the CDC has also developed two pregnancy registries for women

Box 3. Zika Virus–Specific Obstetric Guidance

Identification of areas with active Zika transmission (ie, risk for mosquito-borne acquisition)

- Centers for Disease Control and Prevention website: https://www.cdc.gov/zika/geo/active-countries.html
- World Health Organization website: http://www.who.int/emergencies/zika-virus/situation-report/en/
  - The precise locations of risk for traveler-associated (or endemic or both) Zika acquisition continue to evolve
  - When possible, avoid travel to these areas when pregnant or contemplating conception

Sexual activity after travel to Zika-affected areas

- Women should avoid conception for 2 mo after returning from area with active Zika transmission
- Men should abstain from sex, practice safe sex, or both for 6 mo after returning from an area with active Zika transmission
- More information can be found at: https://www.cdc.gov/zika/prevention/protect-yourself-during-sex.html

Prevention of mosquito-borne acquisition in areas with local transmission

- Use all available measures to avoid mosquito bites
  - Use insect repellent (DEET or other U.S. Food and Drug Administration–approved repellent)—safe in pregnancy at recommended levels
  - Stay in facilities with air conditioning or that have screens on windows
  - Wear clothes that cover limbs thoroughly when outside
  - Empty all areas of standing water nearby
  - More information found at: https://www.cdc.gov/zika/prevention/prevent-mosquito-bites.html

Sexual transmission prevention

- Guidance for prevention:
  - Abstinence while pregnant if partner potentially or confirmed to be infected
  - Consistent and correct use of condoms with each sex act
  - No sex toy sharing with someone with or at risk for Zika virus
  - If the clinical scenario is consistent with Zika infection, abstain from sexual activity
  - More information can be found at: https://www.cdc.gov/zika/transmission/sexual-transmission.html

Testing specifics

- Current guidance:
  - Test those at epidemiologic risk (travel, sexual, occupational), with symptoms, or both consistent with Zika infection
  - Currently available tests are serology (antibody) as well as molecular (RNA)-based—algorithm-based, depending on time since exposure, presence, or both of symptoms
  - Consultation with local, regional, and state health departments currently recommended for testing guidance, standardization, and epidemiologic purposes
  - Commercial laboratory options currently under development
  - Further information can be found at: https://www.cdc.gov/zika/symptoms/diagnosis.html, http://www.acog.org/About-ACOG/ACOG-Departments/Zika-Virus, and http://www.who.int/csr/resources/publications/zika/laboratory-testing/en/

Obstetric management of suspected or confirmed Zika virus infection in pregnancy

- If Zika infection confirmed or strongly presumed in pregnancy:
  - Serial ultrasonogram (every 3–4 wk) in second and third trimesters to detect Zika-specific findings
  - Amniocentesis should be considered on a case-by-case basis
  - Extensive guidance with confirmed algorithms available at: http://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Interim-Guidance-for-Care-of-Obstetric-Patients-During-a-Zika-Virus-Outbreak#clinicalmanagement
  - Postnatal management should be coordinated with pediatricians; further guidance available at: https://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm?s_cid=mm6533e2_w

infected with Zika in the United States and in Puerto Rico.[47,48] As these valuable registries prospectively collect data, they will continue to inform the obstetric and neonatal communities on evolving Zika specifics. This outbreak continues to unfold and reminds the medical and global communities of the persistent threat of emerging infectious diseases and the unpredictable effects and human toll they can impart.

PREPAREDNESS FOR EMERGING INFECTIOUS DISEASE OUTBREAKS

The certainty of future emerging outbreaks combined with the uncertainty of the specific nature of the outbreak

makes broad preparedness measures appropriate to undertake at all levels (international, domestic, regional, and facility-specific). Much attention was noted in this regard in preparation for the last influenza pandemic for both the general population and pregnant women.[13,14,49] Many efforts were influenza-specific because the natural history of influenza evolution predicts that pandemic strains will continue to emerge.[6] However, much of the preparatory efforts also apply to other less predictable outbreaks of variable nature.[50] After the World Trade Center and Anthrax attacks in 2001, the SARS epidemic in 2003 combined with the lead-up to an impending influenza pandemic, the Pandemic and All Hazards Preparedness Act was passed in 2006 by the U.S. Congress to allow for wide-scale preparedness activities across the Department of Health and Human Services. The stated purpose of the act is "to improve the Nation's public health and medical preparedness and response capabilities for emergencies, whether deliberate, accidental, or natural."[51] In addition to other activities, the act also established a new Assistant Secretary for Preparedness and Response; provides new authorities for a number of programs, including the advanced development of medical countermeasures; and also calls for a quadrennial National Health Security Strategy.[51] The U.S. Congress reauthorized this act most recently in 2013, given the certainty of emerging infectious disease outbreaks and other unpredictable disasters and the need for preparedness planning.[51,52]

In a similar fashion, all health care facilities are encouraged (and in some respects compelled) to continually prepare for impending disasters, either manmade or natural. Facilities are obligated to have regularly updated guides to disaster management with plans for topics including (but not limited to) surge capacity management, supply chain management, evacuation planning, utilities limitations and outage management, staffing plans for use during disasters, and financial sustenance considerations. Many facilities (both general medical and maternity-specific) as well as the College and the CDC also have considered plans and issued guidance for the ethical delineation of care and triage of limited resources.[53–56] These are necessary measures for all facilities to undertake in advance of future emerging disaster scenarios given the challenge of real-time management. Proactive considerations are especially important for facilities providing obstetric care given the nuanced specifics of maternal–newborn care and because these populations are often not considered in national preparedness deliberations. Individual institutions are strongly encouraged to consider the specific challenges and solutions to assure safe and effective operations during outbreaks. Box 4 lists some maternity-specific considerations for health care providers and facilities in preparation for future emerging infectious disease outbreaks.

Box 4. Specific Measures to Consider for Obstetric Hospital Preparedness

First-order priorities

- Comprehensive and realistic planning for surge capacity
- Cohorting* plan to minimize nosocomial disease spread
- Plans for maintaining and augmenting the workforce, assuming workforce absenteeism
- Planning for continued integrity of internal and external communications
- Coordination with neonatal service for maternal–infant dyad care postpartum—consideration of alternative locations

Second-order priorities

- Improving hospital surveillance capabilities to enable appropriate patient cohorting
- Delineate schema for the ethical allocation of limited health care resources
- Preparedness education and training and drilling activities
- Expansion of on-site occupational health capabilities
- System to proactively stock necessary supplies

*Cohorting is grouping of persons (patients or health care workers) who have been exposed to a disease, a form of isolating groups to minimize disease spread within a location.

DISCUSSION

Emerging infectious diseases present constant and nuanced threats to maternal and child health internationally. Given the predisposition for many infectious diseases to place pregnant women and their offspring at higher risk for untoward outcomes, the obstetric community has specific responsibilities to optimize maternal–fetal health. Much has been learned from recent outbreaks and their implications for maternal–child health. These lessons will continue to be relevant for all current and future emerging outbreaks, wherever they may originate and whatever toll they may impart.

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