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Contemporary Understanding of Ebola and Zika Virus in Pregnancy



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KEYWORDS

• Emerging infectious diseases • Ebola virus • Zika virus

KEY POINTS

- Pregnancy represents a unique challenge for understanding the emergence of infectious diseases such as Ebola and Zika virus.
- Pregnant women are not at greater risk of acquiring Ebola virus; however, the effects of hypovolemia and hemorrhage are more profound in this population, and pregnancy loss or neonatal demise occurs in nearly 100% of cases.
- Zika virus, typically spread by mosquito vectors, is associated with vertical transmission, resulting in significant congenital defects, namely microcephaly.

INTRODUCTION

The past decade has yielded the emergence of several infectious diseases of critical importance in pregnancy. In particular, the Ebola resurgence of 2013 to 2016 resulted in infection of at least 5000 women of reproductive age and a pregnancy loss rate of nearly 100%.¹ The 2015 to 2016 outbreak of Zika virus captured widespread media attention as 100,000 women of childbearing age became infected, and the significant associated teratogenicity became apparent.² Both diseases were determined to be public health emergencies of international concern by the World Health Organization (WHO).³

This article seeks to review the epidemiology, transmission, pathogenicity, and management of Ebola and Zika viruses as among the most important emerging infectious diseases in modern history. Our objective is to provide clinically relevant background information and guide best practices for obstetricians as they approach these novel infections.

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EBOLA VIRUS

Epidemiology

The genus *Ebolavirus* is comprised of Ebola virus, Bundibugyo virus, Sudan virus, Taï Forest virus, Bombali virus, and Reston virus.⁴ *Ebolavirus* belongs to the family *Filoviridae*, which also contains Marburg virus. Ebola virus disease is caused by infection with any of the *ebolaviruses*, although Bombali and Reston viruses are not known to cause disease in people. Ebola virus was discovered in 1976 in the Democratic Republic of the Congo (formerly Zaire).⁵ Ebola virus is associated with an unprecedented high case fatality rate. To date, 17 outbreaks across middle and western Africa have been reported. These outbreaks have led to 15,000 deaths and 34,000 cases, of which at least 5000 cases were among women of childbearing age.⁶ The pregnancy-specific mortality rate has been difficult to discern based on published findings but is suspected to be between 74% and 93%.^{1,7} The fetal loss rate is nearly 100% for pregnant women with Ebola virus disease.^{8,9} Furthermore, of 14 live neonates born to mothers infected with Ebola virus as of 2016, 100% died within 3 weeks of life.¹⁰

Transmission

The natural reservoir of Ebola virus is unknown, although evidence is accumulating to implicate bats as the most likely source.¹¹ Most outbreaks in people have been traced back to single spillover events from an infected source. Human-to-human spread of the virus is via direct contact with infected blood and bodily fluids including urine, saliva, stool, vomit, and semen, or from surfaces that have been contaminated with infected fluids.¹² Ebola virus has specifically been identified in amniotic fluid, placental and fetal tissue, and breastmilk.^{13–15} Pregnant women are not thought to be at greater risk of acquiring Ebola virus.¹⁶

Pathogenicity

Ebola virus effectively targets host immune cells, which allows reproduction and dissemination of the virus.¹⁷ The virus inhibits both the innate and adaptive immune responses via inhibition of interferons, impairment of antigen presentation, and neutralization of antibodies against viral glycoproteins. The viral glycoproteins then induce cytopathic effects by damaging endothelial cells and disrupting coagulation pathways, while the activated immune mediators induce cellular apoptosis or necrosis. In particular, these effects result in hepatic, renal, and gastrointestinal injury and coagulopathy. Clinical findings are initially nonspecific and include malaise, myalgia, and fever. As the viral RNA load rises, progression to asthenia, vomiting, secretory diarrhea, and hemorrhage occurs, which without adequate resuscitation can result in hypovolemic shock, multiorgan dysfunction, and death.

There is poor understanding of the specific mechanisms of Ebola pathogenicity in pregnancy. In pregnancy, the effects of hypovolemia and immune dysregulation become exaggerated because of a need for expanded blood volume and an already-altered immune state, respectively.¹⁸ Hypoperfusion of the placenta may represent the mechanism by which miscarriage or intrauterine fetal demise occur. Furthermore, transplacental viral transmission to the amniotic fluid and fetus can result in fetal infection and therefore interruption of normal development and growth.^{1,19}

Diagnosis

Diagnosis of Ebola virus can be made presumptively based on symptoms and history of exposure and should be confirmed with molecular testing. Testing typically includes reverse transcriptase polymerase chain reaction (RT PCR) for the detection of viral

RNA in serum, although it is important to note that such tests can be negative for up to 72 hours after symptom onset.⁷ Alternatively, enzyme-linked immunoassay (ELISA) testing for immunoglobulin M (IgM) specific to the virus is available, although it is less commonly used, because positive results can be delayed up to 3 weeks in acutely symptomatic patients.²⁰ Novel rapid diagnostic tests are currently under study but not yet available. Testing strategies remain the same for pregnant women, although rapid testing should be even more imperative given the overlap of the presentation of pregnancy-related conditions and Ebola virus and the potential need for acute obstetric intervention.⁷

Management

The mainstay in management of individuals infected with Ebola virus is supportive management, namely massive fluid resuscitation.²⁰ Additional measures include frequent monitoring for and correction of electrolyte, glucose, and acid-base imbalances, antiemetic and antidiarrheal therapy, nutritional support, vasopressor support, intubation and ventilation, and continuous renal replacement therapy in the setting of renal dysfunction. Additionally, broad-spectrum antibiotics may be necessary for concomitant infections such as gastroenteritis secondary to bacterial translocation in the setting of gut inflammation or malaria, a frequent coinfection.

There has not been significant research as to the specific care for Ebola virus infections among pregnant women.²¹ In 2020, the WHO released guidelines for the management of pregnant women with Ebola virus, which represent the first comprehensive guidelines on specific strategies for their care.¹⁶ When possible, specifically trained providers should be available to care for pregnant women and their neonates, and care should be provided at a private, high-risk facility. Shared decision making for women infected by or recovering from Ebola virus is of necessity.

Generally, maternal rather than fetal indications should take precedent in management decisions. Aggressive fluid resuscitation of up to 10 L per day is particularly important among pregnant women given their significantly increased volume of distribution.⁷ There is no strong evidence to suggest that induced abortion, labor induction, or invasive procedures for fetal indications are of benefit to pregnant women with Ebola virus. In fact, fetal monitoring is generally not recommended.¹⁸ There may be benefit to delaying delivery when possible because of the risk of coagulopathy in the setting of high viral load. A decision for surgical delivery should be made on a case-by-case basis, as there is unlikely to be fetal benefit, and women with severe disease may not survive an operation. Fundal massage and administration of uterotonic medications should be strongly prioritized over surgical management of postpartum hemorrhage.¹⁶

For survivors of Ebola virus who plan pregnancy continuation, comprehensive counseling regarding the risks of fetal or neonatal demise and risk of transmission from pregnancy tissues should be performed.¹⁶ Regular prenatal care with a high-risk obstetrician is recommended for pregnant women who recover from Ebola virus. Expectant management is considered most appropriate.

There is no current approved treatment for Ebola virus. Several therapeutics are undergoing phase I and II clinical trials; these include ZMapp, REGN-EB3, and mAb114 (chimeric monoclonal antibodies) and remdesivir (a broad-spectrum antiviral). Additional antivirals, some of which were designed to target other viruses, are under investigation for use with Ebola virus but have not held as much promise as the aforementioned agents. Convalescent plasma treatment has also demonstrated possible benefit in treatment. The Monitored Emergency Use of Unregistered and Investigational Interventions ethical framework recommends that vulnerable

populations including pregnant women be offered similar treatments to the nonpregnant population when potential benefits can outweigh risks. To date, 2 reports describe use of investigational therapeutics in pregnant women with Ebola virus. A 25% mortality rate was noted among 8 women who received convalescent plasma.²² Additionally, a report details 1 pregnant woman who received favipiravir, a broad-spectrum antiviral, but subsequently died of hemorrhagic shock during labor. However, her newborn is the first reported survivor of congenitally acquired Ebola after receiving ZMapp and remdesivir as well as a buffy coat transfusion from an Ebola virus survivor.^{23,24}

Prevention

Critical to the prevention of Ebola virus is interruption of community and healthcare-associated spread.²⁰ This includes isolation and contact tracing of infected individuals, appropriate containment of infectious material, and protection for those in contact with infected individual.⁷ Even if an individual recovers from Ebola virus, a person's bodily fluids may be infectious for 6 months or longer.²⁵ In particular, pregnancy-related tissue including amniotic fluid, placenta, and fetus are highly infectious even if the pregnant woman has recovered from acute illness. Handling of tissues should be avoided when possible, and potentially infectious waste should undergo proper disposal. Autopsies should be avoided. Personal protective equipment should include a face mask with head cover and eye protection, a gown, double gloves, and boots.²⁶ Minimization of sharps and invasive procedures can mitigate risk to health care providers.

Multiple trials are underway to study candidate vaccines against Ebola virus.⁷ The most promising is the live replicating rVSV-ZEBOV-GP vaccine, which is manufactured by Merck under the trade name Ervebo and has been prequalified by the WHO.^{27,28} Although no vaccine, including rVSV-ZEBOV-GP, has been specifically evaluated in pregnant women, an analysis of available data on women who became pregnant during the rVSV-ZEBOV-GP study time frame suggests there to be no significant increase in pregnancy loss or congenital anomalies among vaccinated women.²⁹ It has been strongly recommended by multiple international public health and humanitarian organizations that pregnant women be included in vaccine clinical trials and compassionate use protocols.^{16,30} After years of exclusion from vaccination, pregnant women in the Democratic Republic of the Congo, the location of a widespread Ebola outbreak, were able to start receiving the vaccine in 2019.

ZIKA VIRUS

Epidemiology

Zika virus is a member of the family Flaviviridae, which also includes dengue, West Nile, yellow fever, and Japanese encephalitis viruses.³¹ Zika virus was first isolated in 1947 in a Rhesus macaque in the Zika forest of Uganda.³² Human infection was identified in 1953.³³ There were only 13 cases identified over the next 57 years, until an outbreak affecting 5000 people occurred in Micronesia in 2007.³⁴ Subsequent outbreaks occurred in Pacific islands, with sporadic cases occurring across Southeast Asia.^{35,36} Most recently, a pandemic occurred in Brazil, with virus spreading across the Americas to affect greater than 1 million individuals between 2015 and 2017.³⁷

Recognition of the more serious complications of Zika virus began to emerge during the pandemic in Brazil. In particular, approximately 4000 cases of microcephaly were detected in infants of women infected with Zika virus.³⁸ It has been estimated that 20% to 40% of infected pregnant women will transmit Zika virus to their fetus.^{39,40}

Approximately 5% to 10% of cases of vertical transmission will result in fetal loss, and 10% to 15% will result in congenital Zika syndrome including microcephaly. Vertical transmission can occur in any trimester and regardless of maternal symptomatology.

Transmission

Zika virus is spread by multiple species of *Aedes* mosquito to mammalian hosts, including people.³¹ The geographic distribution of these mosquito species is expanding secondary to climate change. More recently, it has been discovered that in addition to vectorborne transmission, Zika virus can be spread via sexual contact, perinatal transmission (both during pregnancy and delivery), blood transfusion, and bone marrow and organ transplantation.⁴¹ Although breastmilk has been shown to contain Zika virus, there is no conclusive evidence that the virus can be transmitted by breastfeeding.⁴²

Pathogenicity

Zika virus exhibits broad tropism in human cells, undergoing replication and widespread distribution after cell entry by endocytosis.⁴³ Zika virus preferentially targets neural stem cells and progenitor cells.⁴⁴ Zika inhibits the ability of interferons and other cellular signaling pathways to produce an innate immune response to the virus. In pregnancy, Hofbauer macrophages and other immune cells of the placenta that usually serve as a maternal-fetal barrier provide a mechanism for the virus to infect fetal cells.⁴⁵

Zika virus has an incubation period of 3 to 14 days. Most infected individuals are asymptomatic or display mild symptoms such as fever, rash, and myalgias lasting up to 1 week. However, a minority of people will suffer severe neurologic symptoms including meningoencephalitis or Guillain-Barré syndrome because of neurotropism or postinfectious immune response.⁴⁶ Given this predilection for neural cells, congenital Zika syndrome is primarily a constellation of central nervous system abnormalities.⁴⁷ In particular, fetal brain disruption sequence results in microcephaly and cortical atrophy, intracranial calcifications, other neural and ocular abnormalities, and growth restriction.^{48,49} In infants, this manifests with developmental delay, visual or hearing impairment, seizures, and movement and behavioral disorders.⁵⁰ It is important to note that asymptomatic pregnant women can still vertically transmit Zika virus to their neonates.

Diagnosis

Zika virus infection is typically detected by serum and urine RT PCR nucleic acid molecular screening and/or serologic IgM ELISA screening.³⁸ Molecular testing should be performed within 2 weeks of onset of symptoms, whereas serologic testing can be accurately used up to 12 weeks after symptom onset. Of note, serologic testing is subject to significant cross-reactivity with antibodies to other flaviviruses, in particular Dengue virus, and to persistence of antibodies for many months after the resolution of the acute infection.

In nonpregnant individuals with a possible exposure to Zika virus yet without severe symptoms, serum and urine molecular testing are recommended.⁵¹ In the setting of concern for Guillain-Barré, molecular testing of the serum and urine as well the cerebrospinal fluid is recommended as soon as possible. If the index of suspicion for Zika virus infection is high but molecular testing is negative, serum testing for IgM should be performed within 2 to 12 weeks to evaluate for seroconversion.

For pregnant women, the screening paradigm shifts.^{52,53} For those with symptoms, serum and urine molecular testing and serologic testing are recommended as soon as

possible. If there is a discrepancy with a negative molecular result and positive serologic result, a plaque reduction neutralization serologic test is recommended to confirm infection.⁵⁴ Pregnant women with ongoing exposure but no symptoms should be screened with molecular testing every trimester. Dedicated Zika virus testing is not routinely recommended as a routine part of preconception screening or in the setting of a single asymptomatic exposure for pregnant women.

Detailed anatomy ultrasound is recommended at 18 to 22 weeks of gestation for women with symptoms or recurrent exposure, and serial scans should be performed every 3 to 4 weeks thereafter to evaluate for development of evidence of congenital infection.⁵⁵ Should there be evidence of fetal anomalies consistent with congenital Zika syndrome on ultrasound, amniotic fluid should be sent for nucleic acid testing if amniocentesis is already being performed for diagnostic purposes. However, amniocentesis is not universally recommended, as a negative result cannot rule out congenital infection caused by the transient and sometimes delayed nature of shedding of the virus into amniotic fluid.⁵⁶ If microcephaly or other complex central nervous system abnormalities are noted on routine ultrasound in the absence of alternate explanation and with possible Zika exposure, molecular and serologic testing should be undertaken.

In the setting of suspected congenital Zika infection, newborn or fetus and placenta should be tested after delivery.

Management

Treatment of Zika virus consists of supportive management including antipyretics, analgesics, and rehydration, typically with good response.³⁸ Severe cases involving Guillain-Barré syndrome may require plasma exchange or immunoglobulin.

There is no approved targeted treatment for Zika virus infection, although several agents are being investigated. These include both host- and virus-targeting antivirals or antibodies, either repurposed from drugs in use for other diseases or screened from compound libraries.^{57,58} For example, drugs that upregulate the interferon innate immune pathway or suppress viral replication have shown therapeutic promise.⁵⁷ As of yet, no medication has completed phase II clinical trials.^{59,60} Additionally, although there is no drug that is proven to mitigate the effects of Zika infection during pregnancy, studies of neutrally active compounds such as NMDA blockers can potentially modulate the fetal neuronal damage that occurs with vertical transmission.⁶¹

Prevention

Primary prevention strategies against Zika virus include vector control.⁶² To prevent mosquito bites, high-risk outdoor areas and in particular bodies of standing water should be avoided. Long sleeves and pants, mosquito repellent, and mosquito netting should be used in endemic regions.⁶³ Insect repellents, when used per manufacturers' guidelines, are safe for use among pregnant women.⁶⁴ Individuals who may have a Zika virus exposure or have a known infection should also undertake measures to avoid mosquito bites and therefore reduce spread. Standard precautions to prevent nosocomial transmission of Zika virus are also important, although as of 2016, no cases of occupational infection have been documented.⁶⁵

Travel guidelines have evolved as the Zika virus epidemic progressed, and additional research is needed to appropriately inform travel restriction policy.⁶⁶ General recommendations have been to avoid travel to high-risk regions during pregnancy or while attempting conception.^{67,68} Couples residing in affected areas are advised to delay pregnancy.⁶⁹ Those with a known exposure or infection should delay

attempts at conception for 2 months for female partners and 3 months for male partners.⁵² A pregnant woman whose partner has had an exposure or infection with Zika virus should practice abstinence or consistent condom use for the remainder of the pregnancy.

Efforts are underway to develop a vaccine against Zika virus, although none has yet been approved for use. The most promising vaccine candidates have been shown to induce effective antibodies in mice, and phase I and II clinical trials are in process.^{70–72} Among the 20 candidates are DNA vaccines, synthetic peptide vaccines, nanoparticles, and live recombinant and purified inactivated viruses.⁷³

DISCUSSION

As one faces emerging infectious diseases such as the novel coronavirus first identified in late 2019, the details of the recent Ebola and Zika virus outbreaks can provide a framework for an approach to new diseases.⁷⁴ Understanding of the transmission, maternal and fetal effects, and effective treatment, vaccination, and containment methods are imperative to achieving a successful response from the public health and scientific research communities. Specifically addressing emerging infections in pregnancy is important because of the potential differential impact of infections among pregnant women, the possible effects on the fetus, and the unique prophylaxis and treatment strategies necessary for efficacy and acceptability among pregnant women.⁷⁵ Attention must be paid to the successes and failures of the response to the Ebola and Zika outbreaks as physicians strive to provide excellent care for pregnant women who are affected by or at risk for emerging infectious diseases.

Best practices

What is current practice?

- Molecular testing is standard of care for both Ebola and Zika viruses.
- Supportive care including rehydration and antipyretics is necessary for individuals infected with Ebola and Zika virus; there are no targeted therapeutics.
- No vaccines are available. Prevention of Ebola virus includes containment of infected substances and personal protection equipment use, and prevention of Zika virus entails protection against mosquito bites, avoidance of high-risk regions, and delay of childbearing.

What changes in current practice are likely to improve outcomes?

- Development of targeted therapeutics and vaccines can decrease the burden of disease and in particular reduce risk for pregnant women and their offspring.

Major recommendations

- Test individuals who have traveled to endemic areas or have been in contact with individuals infected with Ebola or Zika virus who display associated symptoms. There is a role for testing of asymptomatic individuals with recurrent Zika virus exposure also.
- Successful management of Ebola virus includes aggressive rehydration and intensive care. Delivery timing should be based on maternal rather than fetal indications. Properly dispose of all infected substances and use necessary personal protective equipment to prevent nosocomial and community transmission.
- Pregnant women with Zika virus should undergo serial ultrasounds to evaluate for congenital Zika syndrome, although vertical transmission cannot be prevented once a woman has been infected.
- Uninfected women who are pregnant or considering childbearing should avoid travel to Zika virus endemic areas or unprotected intercourse with infected or exposed partners.

Summary statement

Ebola virus is associated with high mortality and a very high pregnancy or neonatal loss rate. Zika virus carries a risk of congenital Zika syndrome. Treatment of both is limited to management of symptoms; therefore prevention of transmission is critical to avoid adverse outcomes.

Data from Refs.^{1,2}

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