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Impact of Zika Virus on Pregnancy and Neonatal Health- A Review

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ABSTRACT

The Zika virus, mainly spread by day-active Aedes mosquitoes, often leaves many infected individuals' symptom-free. However, those showing symptoms may experience a rash, fever, conjunctivitis, muscle and joint pain, malaise and headaches for 2 to 7 days. In pregnancy, Zika can cause severe outcomes like microcephaly and other congenital malformations, preterm birth and miscarriage. It's also linked to Guillain-Barré syndrome, neuropathy and myelitis in both adults and children. Outbreak management relies on vector control and personal care since a Zika vaccine is still under development. Traditionally found in Africa and Asia, the virus has caused major outbreaks as it spreads, including the significant 2013 Oceania outbreak that first reported neurological issues, and the massive 2015-2016 Americas outbreak, which saw a surge in microcephaly cases. This led the WHO to declare Zika-associated microcephaly a public health emergency. Managing outbreaks largely depends on public health measures, given the current lack of effective vaccines or antiviral treatments, highlighting significant gaps in research and response strategies.

Keywords: *Aedes mosquitoes, conjunctivitis, malaise, Guillain-Barré syndrome, neuropathy and myelitis.*

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INTRODUCTION

This review summarizes the complications of Zika virus infection in pregnancy and Zika syndrome in newborn, making it a public health concern. It also addresses recent outbreaks and their public health implications, discussing transmission, contributing factors, health consequences, clinical symptoms, diagnosis, treatment and the challenges in containing the virus transmission.

History and Discovery:

The Zika virus, first discovered in Uganda in 1947, is a mosquito-borne flavivirus mainly spread by Aedes mosquitoes. The first significant outbreak took place in Yap in 2007, after which the virus spread to regions such as Asia, India, several Pacific islands, Central and South America, the Caribbean, and the U.S. Virgin Islands. Major outbreaks were also documented in Africa and Southeast Asia in 2007, 2013 and 2015. Although global cases have declined since 2017, low-level transmission persists in several countries and endemic regions. To date, 89 countries and territories have reported evidence of mosquito-borne Zika virus infections.

Virology and Molecular Biology:

A research team led by Dr. Richard Kuhn and Michael Rossmann from Purdue University studied the structure of the mature Zika virus using cryo-electron microscopy. This technique involves freezing virus particles and using high-energy electrons to produce a detailed 3-D visualization. Their findings showed that the Zika virus shares structural similarities with other flaviviruses, but with a unique region in the envelope glycoprotein.

Systematic Classification of Zika Virus Structure:

Group: Group IV ((+)ssRNA)
Family: Flaviviridae
Genus: Flavivirus
Species: Zika virus

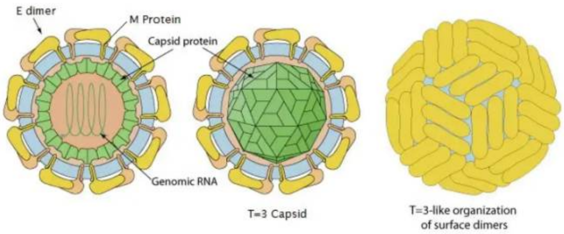

Fig 1: Structure of Zika virus

Virion Shape: Zika virions are generally icosahedral-shaped, enveloped particles, with diameters ranging from 18 to 45 nanometers.

Genome: The Zika virus genome is composed of a positive-sense, single-stranded RNA, enclosed within a capsid and surrounded by a lipid membrane. The RNA genome contains 10,794 nucleotides and encodes 3,419 amino acids.[1].

Envelope Glycoprotein: The surface of the Zika virus is made up of envelope glycoproteins, which play a critical role in facilitating the virus's attachment to and entry into human cells.

Reservoirs of Zika Virus include:

- Mosquitoes (gut, blood, saliva)
- Humans(blood, prostate, semen, testes)
- Unknown reservoirs, such as saliva, urine, and breast milk [2].

1. Origin of Zika virus infection (Pathogenesis):

Zika virus is transmitted through mosquito bites, blood transfusions, perinatal transmission, and sexual contact. It primarily inhabits mosquitoes of the Aedes genus. The disease cycle involves a mosquito and a reservoir host, with viremia in the mosquito lasting 5-7 days. Although the exact incubation period for Zika virus disease is uncertain, it is estimated to range from 3 to 12 days.

Signs and Symptoms:

Only 20-25% of individuals infected with the Zika virus show symptoms. The most frequently reported symptoms include:

- Conjunctivitis (red eyes)
- Fever
- Muscle ache
- Joint pain (arthritis, arthralgia)
- Maculopapular rashes

Zika infection poses significant risks due to its association with two neurological conditions:

1. Microcephaly: A serious birth defect characterized by a smaller head size and incomplete brain development, often resulting from maternal infection during the first trimester of pregnancy.
2. Guillain-Barré Syndrome (GBS): A rare disorder in which the immune system attacks nerve cells, leading to muscle weakness and, in some cases, paralysis.[3]

CLINICAL MANIFESTATIONS OF ZIKA VIRUS INFECTION:

Common Symptoms: Common and rare symptoms, including the spectrum of disease from mild to severe. Exanthema (89% cases), Arthralgia (63% cases), Fever (62% cases), Conjunctivitis (45% cases), Myalgia (48% cases), Headache(46% cases), Diarrhea(13% cases).

Neurological Complications:

Neurological Complications includes i). Guillain-Barré Syndrome (GBS 0.3% cases) attacks the nerves, leading to muscle weakness and sometimes paralysis[4], ii). Neuropathy and Myelitis, iii). Encephalopathy and Encephalitis[5]. Pregnancy-Related Complications includes microcephaly, fetal Loss, stillbirth and preterm birth[6].

Other Complications:

Other complications includes thrombocytopenia and hospitalization associated with co-morbidities or severe complications like GBS[7].

DIAGNOSIS **OF ZIKA VIRUS INFECTION:**

Molecular Testing (Nucleic Acid Amplification Test, NAAT): NAAT assays detect viral genomic material, confirming the presence of infection. Despite their high specificity, false positive results have been reported.

Zika Virus Immunoglobulin (IgM) Antibody Testing: IgM antibodies can be detected starting in the first week after the onset of symptoms and may persist for months to years. However, the presence of cross-reactive antibodies from other flaviviruses can complicate the conclusive identification of the infecting virus. False positives are more common with IgM testing compared to NAAT[8].

Plaque Reduction Neutralization Tests (PRNT): PRNTs evaluate virus-specific neutralizing antibody titers and can help clarify false-positive IgM results due to non-specific reactivity. However, PRNT may struggle to effectively differentiate between infections, particularly after secondary flavivirus infections.

Polymerase Chain Reaction (PCR): Reverse transcriptase-polymerase chain reaction (RT-PCR) targeting the non-structural protein 5 genomic region is the primary diagnostic method for detecting viral nucleic acids. It is most effective during the first 3-5 days after the onset of symptoms [9].

Serological Tests: An ELISA has been developed to detect IgM antibodies to Zika virus, but it can only do so after five days post-infection. Due to the close relationship of Zika with dengue and yellow fever, this test may cross-react with antibodies from those viruses.

Nucleic Acid Amplification Test (NAT): NAT can also be employed to detect viral RNA[10].

Plaque Reduction Neutralization Assay (PRNT): The plaque reduction neutralization assay typically offers better specificity compared to immunoassays, but it may still produce cross-reactive results in cases of secondary flavivirus infections.

Distinguishing Zika virus from other similar illnesses (e.g., dengue, chikungunya, west nile virus, japanese encephalitis and bacterial infections like leptospirosis, rickettsial infections, malaria, measles and rubella)[11, 12, 13, 14].

TREATMENT AND MANAGEMENT

Current Treatment Options: There are currently no specific vaccines or medications available to prevent or treat Zika virus infections. The symptoms associated with the virus are generally mild.[15].

Management of Complications:

Managing complications involves addressing both acute and long-term health issues. Acute Management mainly includes symptomatic Treatment can be managed with rest, hydration, and pain relief (e.g., acetaminophen) and by avoiding NSAIDs to reduce the risk of hemorrhage[16]. Other prominent complication is Guillain-Barré Syndrome (GBS) can be managed with supportive care, including plasmapheresis or intravenous immunoglobulin (IVIG) therapy [17]. But in case of Congenital Zika Syndrome have to perform regular monitoring of pregnant women to detect fetal abnormalities [18]. Postnatal Care: Infants with congenital Zika syndrome require multidisciplinary care involving neurology, ophthalmology and physical therapy. Long-term Management: Patients with Guillain-Barré syndrome (GBS) or other neurological issues may need ongoing rehabilitation and physical therapy. Additionally, counseling and support for families affected by congenital Zika syndrome are crucial[19].

Prevention and Control:

Vector control strategies are essential for preventing Zika virus infection. Key preventive measures include:

1. Vector Control: Reduce mosquito populations through insecticide use, eliminate standing water, and use mosquito nets.
2. Public Health Education: Inform communities about protective measures such as using insect repellents and wearing long-sleeved clothing [20]
3. Source Reduction: Eliminate standing water where mosquitoes breed (e.g., in flower pots, buckets, and discarded tires) and regularly clean containers that can hold water.
4. Chemical Control: Apply insecticides to kill adult mosquitoes, especially during outbreaks [21].
5. Biological Control: Use bacteria like Wolbachia to reduce mosquito populations.
6. Personal Protective Measures:
    a) Wear long-sleeved clothing to reduce skin exposure.
    b) Use insect repellents that contain DEET, IR3535, or icaridin.
    c) Sleep under mosquito nets to provide additional protection from bites [22].

Vector Control Strategies for Zika Virus Prevention:

The various methods for controlling mosquito populations includes:

Chemical Control: This involves using insecticides such as pyrethroids to eliminate adult mosquitoes and larvicides like temephos and methoprene to target mosquito larvae in their breeding sites. Indoor Residual Spraying (IRS) is also employed to kill mosquitoes that come into contact with treated surfaces.

Biological Control: This method is often preferred and involves introducing fish species that feed on mosquito larvae in water bodies or utilizing bacteria like *Bacillus thuringiensis israelensis* (Bti) to infect and kill mosquito larvae.

Genetic Control: This strategy can be implemented through the Sterile Insect Technique (SIT), which involves releasing sterilized male mosquitoes to mate with wild females, leading to no offspring. Alternatively, genetically engineered mosquitoes that produce non-viable offspring may also be released.

Environmental Management: This is a crucial strategy that focuses on eliminating standing water and improving drainage and water management to reduce mosquito breeding sites.

Personal Protection Measures: To prevent Zika virus infection, individuals can take precautions such as:

- *Using insect repellents containing DEET, picaridin, or oil of lemon eucalyptus.*
- *Wearing long-sleeved shirts and long pants to minimize mosquito bites.*
- *Utilizing bed nets in areas with high mosquito activity.*

Public Health Impact:

Impact on Affected Populations:

Zika virus infection during pregnancy can result in congenital Zika syndrome (CZS), as well as neurological complications, preterm birth, and stillbirth. The outbreak in Brazil from 2015 to 2016 was notably severe, resulting in a significant number of cases of microcephaly and other neurological disorders. Caring for children with CZS and addressing related neurological issues can place a considerable burden on families and healthcare resources.

Zika is primarily transmitted by Aedes mosquitoes, particularly Aedes aegypti, and there are documented cases of both sexual transmission and vertical transmission (from mother to fetus) [26]. International collaboration is crucial for Zika management, involving partnerships with organizations like WHO to coordinate responses, share information, and secure funding for outbreak activities.

Epidemiological Surveillance: Continuous monitoring is conducted through national and international health agencies to track Zika virus cases. Surveillance systems, such as The European Surveillance System (TESSy), collect and analyze data related to Zika virus infections. This ongoing surveillance helps identify trends, outbreaks, and the effectiveness of control measures.[27]. Countries report Zika cases to organizations such as the World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC). Recent data show a global decline in cases since the peak outbreak in 2015-2016; however, low-level transmission persists in some regions. Ongoing surveillance has highlighted the long-term impacts of congenital Zika syndrome, including microcephaly and various developmental issues.[28].

Molecular Mechanisms of Zika Virus Pathogenesis

The cellular entry of Zika virus (ZIKV) primarily occurs through receptor-mediated endocytosis. The virus binds to specific receptors on the host cell surface, including TIM-1, AXL and TYRO3. This interaction facilitates the virus's uptake into the cell, initiating the infection process[29]. Once inside the host cell, the Zika virus releases its RNA genome into the cytoplasm. The viral RNA is then translated into a single polyprotein, which is crucial for the virus's replication process.

Immune Evasion:

The non-structural proteins of Zika virus (ZIKV), especially NS5, play a significant role in inhibiting the host's interferon response. This inhibition allows the virus to effectively evade the immune system, facilitating its persistence and replication within the host[30]. ZIKV infection alters the host’s microRNA expression, which can suppress antiviral responses and promote viral replication. ZIKV shows a strong preference for infecting neural precursor cells, leading to cell death and impaired neurogenesis [31].

Cellular pathways affected by Zika Virus mainly Toll-Like Receptor (TLR) signaling pathway especially TLR-3 which is crucial for initiating antiviral responses. The virus also manipulates autophagy pathways to enhance its replication and induces apoptosis in infected cells, leading to tissue damage[32].

Recent Research and Developments:

Congenital Zika Syndrome (CZS) is a condition marked by severe microcephaly, brain calcifications, retinal abnormalities, and joint contractures. These symptoms result from maternal Zika virus infection during pregnancy, leading to significant developmental issues in affected infants [33]. Recent studies have indicated that the Zika virus can impact brain development during any trimester of pregnancy, with the highest risk occurring in the first and second trimesters. This highlights the critical importance of monitoring and preventive measures during these early stages of pregnancy [34]. The Zika virus can cross the placental barrier, resulting in direct infection of the fetal brain. This transmission can lead to serious neurological complications and developmental issues in the fetus, underscoring the risks associated with maternal infection during pregnancy [35]. Children exposed to the Zika virus in utero may experience a range of outcomes, from mild learning disabilities to severe neurological impairments. The severity of these effects can vary significantly, depending on factors such as the timing of the maternal infection and individual susceptibility[36]. As per literature, the maternal immune response to Zika virus infection can contribute to fetal brain damage and inflammatory cytokines may exacerbate neural damage[37].

Advancements in diagnosis now include prenatal screening techniques like advanced ultrasound and MRI for early detection of fetal abnormalities linked to Zika virus infection. Research continues to identify biomarkers for predicting adverse outcomes in affected pregnancies, enabling early intervention and management. To assess long-term health effects, neurodevelopmental follow-ups are necessary to understand the full spectrum of outcomes. Early intervention programs are vital for improving these outcomes. Additionally, families affected by congenital Zika syndrome often face significant psychological and social challenges, making counselling essential for their support[38].

Emerging Therapies:

Antiviral Therapies includes:

1. Favipiravir - an antiviral drug inhibiting Zika virus replication in preclinical studies and evaluated for safety and efficacy in pregnant women.
2. Sofosbuvir developed for hepatitis C.

Immunotherapies include:

1. Monoclonal Antibodies that specifically target the Zika virus, providing passive immunity to pregnant women and their fetuses.
2. Convalescent Plasma from recovered Zika patients, which contains antibodies to treat active infections and is still under investigation [39].

Vaccines under development:

1. DNA Vaccines, aimed at inducing a strong immune response.
2. mRNA Vaccines, similar to COVID-19 vaccines, offering rapid and effective protection [40].

Currently, there is no approved vaccine for Zika virus infection, although several candidates are under development. DNA-based vaccines from the National Institute of Allergy and Infectious Diseases (NIAID) have shown promise in early clinical trials by inducing neutralizing antibody responses. Another candidate, the Purified Inactivated Vaccine (ZPIV), developed by the Walter Reed Army Institute of Research, employs techniques similar to those used for Japanese encephalitis and dengue vaccines. Additionally, live attenuated vaccines are in experimental stages. Despite these advancements, none of the vaccines have been approved for public use yet.

Advancements in prenatal screening techniques, such as high-resolution ultrasound and MRI, facilitate the early detection of fetal abnormalities caused by Zika virus infection. Furthermore, biomarkers have been developed to predict adverse outcomes in affected pregnancies, allowing for timely intervention and management.

Collaborative international research programs are currently underway to address the impact of Zika virus infection on pregnancy and neonates.

Notable initiatives:

European Union Efforts:

1. ZIKAlliance: A multinational research consortium focused on the clinical, epidemiological, and virological aspects of Zika virus infection.

2. ZikaPLAN: A network aimed at improving preparedness and response to Zika outbreaks, including studies on its impact on pregnancy and neonatal health.

United States Initiatives:

1. National Institutes of Health (NIH): Funding is being directed toward multiple studies to investigate the effects of Zika virus on pregnancy and neonatal health, including prospective cohort studies. These studies aim to enhance understanding of the virus's impact and to develop strategies for prevention and intervention.

2. Centers for Disease Control and Prevention (CDC): The US Zika Pregnancy and Infant Registry has been established to monitor pregnancies and infants affected by the Zika virus. This registry collects data to assess the virus's full impact on maternal and infant health, helping to inform public health strategies and interventions.

International collaborations are essential in addressing the Zika virus, with the World Health Organization (WHO) coordinating global research efforts and providing guidelines for managing Zika in pregnant women. The WHO also supports the development of diagnostic tools and vaccines. Another significant initiative is the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R), which facilitates rapid research responses to infectious disease outbreaks.

Studies have demonstrated that the Zika virus can be transmitted from mother to fetus, resulting in severe congenital abnormalities such as microcephaly. Ongoing research is focused on developing safe and effective vaccines to protect pregnant women and their infants from Zika virus infection [41].

FUTURE DIRECTIONS

Research underscores the necessity for longitudinal studies to evaluate the long-term neurodevelopmental impacts of in utero Zika virus exposure. Understanding the mechanisms by which Zika crosses the placental barrier, as well as the immune responses in pregnant versus non-pregnant individuals, could significantly enhance treatment strategies. Furthermore, the effects of co-infections with dengue or chikungunya on pregnancy outcomes warrant additional investigation, highlighting the urgent need for effective vaccines for pregnant women utilizing both traditional and novel platforms.

Research into antiviral drugs may also help reduce the severity of Zika infections and prevent fetal transmission. Identifying biomarkers associated with adverse pregnancy outcomes will facilitate timely interventions. Additionally, it is crucial to implement public health strategies aimed at preventing Zika transmission in endemic regions while strengthening global surveillance systems for prompt outbreak detection and data sharing [42].

Implementing comprehensive public health education campaigns is crucial to inform communities about Zika virus transmission, prevention, and the importance of prenatal care. Expanding vector control programs, such as using insecticides, biological methods, and community engagement, can help reduce mosquito populations and eliminate breeding sites. Increasing funding for Zika virus research is essential for progress, focusing on understanding vertical transmission mechanisms, long-term neurodevelopmental outcomes, and developing vaccines and antiviral therapies [43].

Developing guidelines for routine prenatal screening for Zika virus in endemic areas, along with providing access to high-quality prenatal care and diagnostics, can mitigate infection impacts [44].

CONCLUSION

The Zika virus is primarily transmitted by Aedes mosquitoes, which are most active during the day. While most individuals infected with the virus do not develop symptoms, those who do may experience a range of symptoms including rash, fever, conjunctivitis, muscle and joint pain, malaise, and headache, typically lasting for 2 to 7 days. Zika virus infection during pregnancy can result in infants being born with microcephaly and other congenital malformations, as well as preterm birth and miscarriage. Additionally, Zika virus infection is linked to Guillain-Barré syndrome, neuropathy, and myelitis in both adults and children.

Strategies for managing outbreaks include vector control and personal care measures, though a vaccine for Zika is still under development. The virus, which has historically been present in regions of Africa and Asia and can cause mild febrile illness or asymptomatic cases, has expanded its reach, leading to significant outbreaks.

The Oceania outbreak in 2013 marked the first time neurological manifestations were reported. The subsequent outbreak in the Americas (2015-2016) is considered the largest Zika epidemic to date, resulting in a notable increase in microcephaly cases and prompting the World Health Organization (WHO) to declare Zika-associated microcephaly a public health emergency of international concern.

The responsibility for controlling outbreaks primarily falls on public health interventions, given the lack of effective vaccines or antiviral treatments, leaving substantial gaps in research and response strategies.

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