Ref: Ro J Neurol. 2023;22(4)
DOI: 10.37897/RJN.2023.4.8

The long-term neurological consequences of congenital Zika Syndrome to Zika-Infected maternal during pregnancy - A narrative review

Astrit M. Gashi

Department of Obstetrics and Gynaecology, University Clinical Centre of Kosova, Prishtina, Faculty of Medicine, University of Pristine, Pristine, Kosova

ABSTRACT

Background. Congenital Zika Syndrome presents a significant public health concern, particularly due to its association with severe neurological complications in infants born to maternal infected with the Zika virus during pregnancy. This article offers a comprehensive overview of the risks, complications, and preventive measures associated with Zika virus infection during pregnancy.

Methods. A thorough literature search was conducted, encompassing studies, case reports, and clinical observations related to neurological complications in infants with congenital Zika syndrome. The review focuses on elucidating the intricate relationship between maternal Zika virus infection and the subsequent neurological challenges faced by newborns.

Results. The neurological impacts of congenital Zika syndrome are multifaceted, ranging from the well-documented microcephaly to less explored manifestations such as brain abnormalities, ventriculomegaly, intracranial calcifications, seizures, and sensory impairments. Additionally, joint and limb contractures contribute to the complexity of congenital Zika syndrome-related neurological deficits. This narrative review synthesizes current knowledge on the subject, shedding light on the diverse ways in which Zika virus infection during pregnancy can affect the developing fetal nervous system.

Conclusion. Understanding the intricate neurological complications associated with congenital Zika syndrome is crucial for healthcare practitioners, researchers, and policymakers. This review provides a comprehensive overview of the current state of knowledge, emphasizing the need for continued research, surveillance, and public health interventions to mitigate the impact of the Zika virus on maternal and child health.

Keywords: Zika virus, pregnancy, maternal infection, congenital Zika syndrome, neurological complications, risks, global health, preventive measures

INTRODUCTION

The long-term neurological consequences of Congenital Zika Syndrome (CZS) represent a multifaceted and evolving challenge, particularly for infants born to Zika-infected maternal during pregnancy. The Zika virus, primarily transmitted by Aedes mosquitoes, gained global attention for its association with severe neurological outcomes, sparking public health concerns during outbreaks. This review aims to provide an overview of the persistent neurological impacts on children born with congenital Zika syndrome and the broader implications for affected families and healthcare systems. Zika virus, first discovered in 1947 [1], garnered heightened concern when outbreaks occurred in various regions, notably in the Americas. The virus's ability to cross the placental barrier and affect fetal neurodevelopment became a focal point of research and public health efforts. Pregnant women infected with Zika faced an elevated risk of transmitting the virus to the fetus, leading to a spectrum of congenital abnormalities collectively known as congenital Zika syndrome [2]. The Zika virus is a member of the Flaviviridae family and is primarily transmitted to humans through the bite of infected mosquitoes, particularly Aedes mosquitoes [3]. The basic virology: Zika virus belongs to the

Corresponding author:
Astrit M Gashi
E-mail: astritgashi772@gmail.com

Article History:
Received: 20 December 2023
Accepted: 29 December 2023

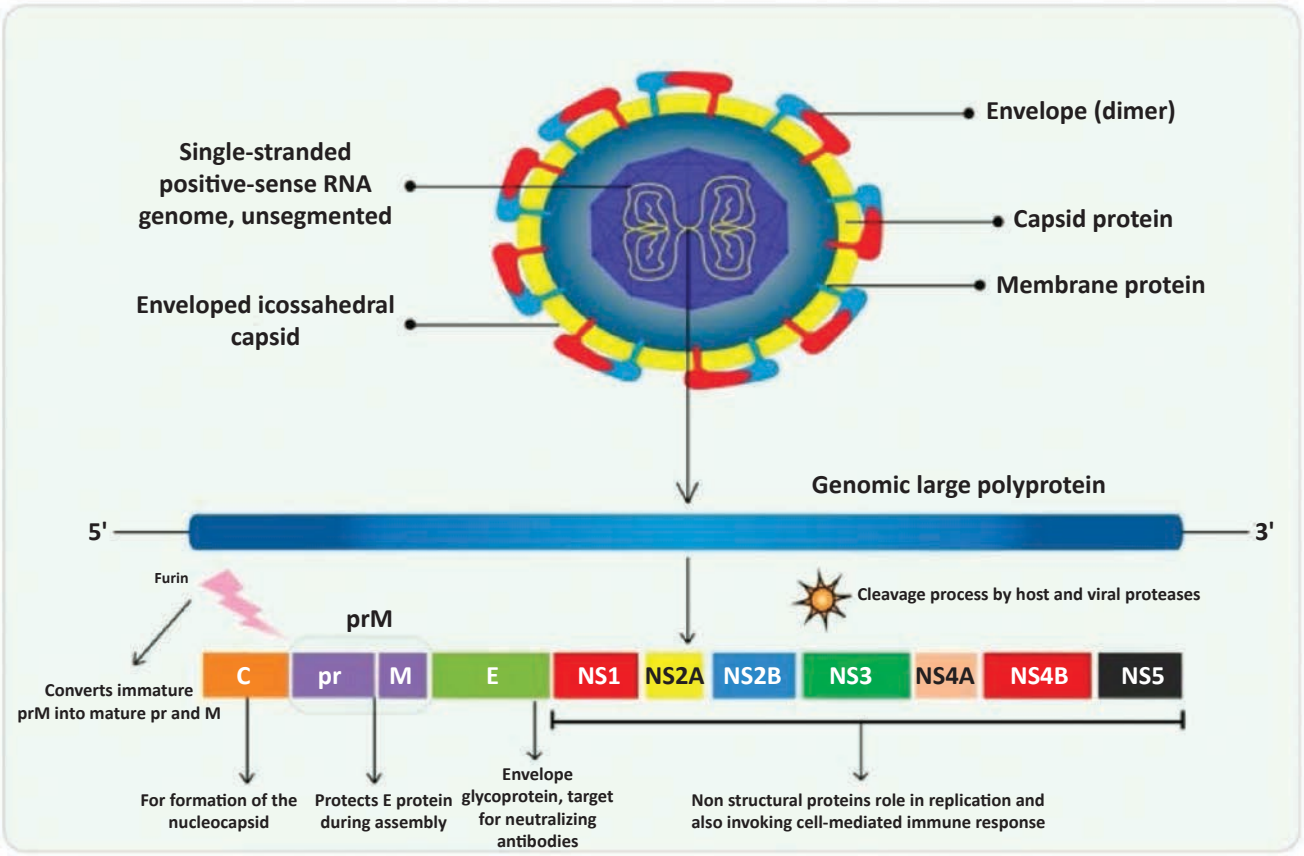

FIGURE 1. Zika virus structure and genome [4]

Flavivirus genus, and it has a single-stranded, positive-sense RNA genome. The virus has an envelope and a spherical structure with a diameter of about 50 nanometers. Its surface is covered with protein spikes [4].

Perinatal transmission: Zika virus can be transmitted from an infected maternal to her fetus during pregnancy or at the time of delivery [5].

Sexual transmission: Zika virus can be sexually transmitted from an infected person to their partner.

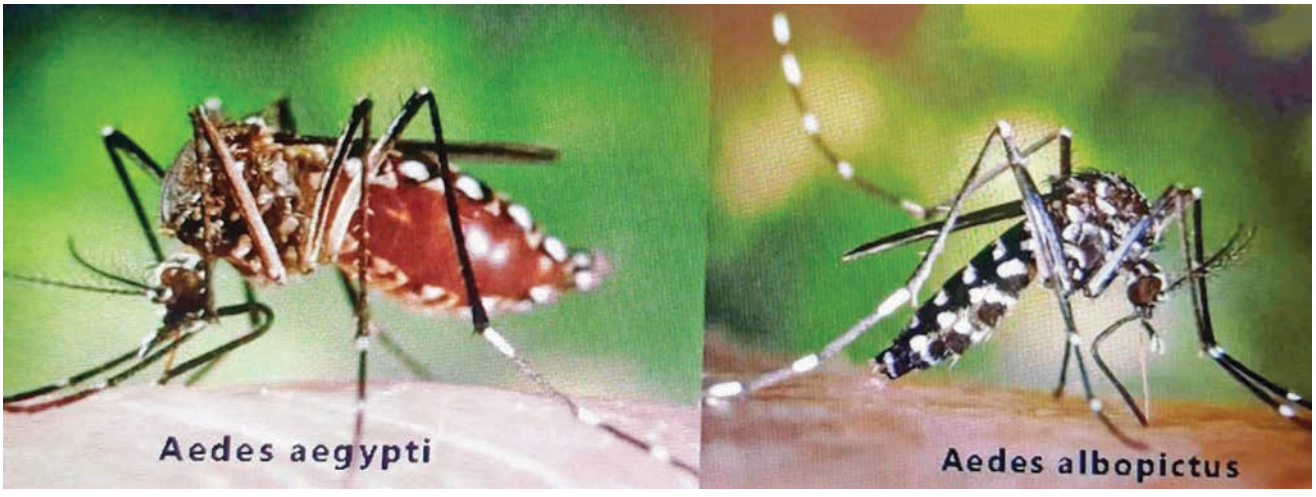

FIGURE 2. Two Zika virus mosquitoes: *Aedes aegypti* and *Aedes albopictus*, photos by Centers for Disease Control and Prevention (.gov)

The primary mode of transmission is through the bite of infected Aedes mosquitoes, particularly *Aedes aegypti* and *Aedes albopictus*. These mosquitoes are also vectors for other viruses like dengue and chikungunya.

The virus can persist in semen for an extended period, and sexual transmission has been documented.

Blood transfusion and organ transplantation: There have been cases of Zika virus transmission through blood transfusion and organ transplantation.

Laboratory exposure: There have been rare cases of Zika virus transmission through laboratory exposure.

Zika virus infection in adults is often mild or asymptomatic, with symptoms including fever, rash, arthralgia and nonpurulent conjunctivitis.

The Zika virus gained attention due to its association with fetal central nervous system (CNS) abnormalities, such as intracranial calcification, ventriculomegaly and microcephaly, as well as other neurological complications in infants born to maternal infected during pregnancy, especially in the first and second trimesters [6].

A neurological consequence of congenital Zika syndrome is microcephaly, marked by an abnormally small head circumference, indicative of underlying brain malformations. However, the neurological impact extends far beyond microcephaly, encompassing a range of structural and functional abnormalities that unfold throughout an infant's development [7].

Infants born with congenital Zika syndrome often face challenges in neurodevelopment, experiencing delays in motor skills, speech, and cognitive functions. The consequences are not confined to infancy but persist into childhood and adolescence, revealing a spectrum of cognitive and behavioral implications. These may include difficulties in learning, memory, and attention, as well as behavioral disorders, necessitating ongoing support and intervention [8].

In addition to challenges in neurodevelopment, congenital Zika syndrome manifests in ocular and auditory complications. Vision impairment, chorioretinal atrophy, and optic nerve abnormalities are common ocular findings while varying degrees of hearing loss underscore the virus's impact on the auditory system. These sensory deficits further contribute to the complex landscape of long-term neurological consequences [9,10].

Despite advances in diagnostic techniques, accurately identifying congenital Zika syndrome during pregnancy remains a challenge. Prenatal diagnosis relies on a combination of ultrasound findings and serological tests, each with its own set of limitations. This presents a dilemma for healthcare providers in delivering timely and accurate information to expectant parents, highlighting the need for improved diagnostic tools and counselling strategies [11].

Addressing the long-term neurological consequences of congenital Zika syndrome demands a holistic and multidisciplinary approach to care [12].

As affected children transition into adolescence and adulthood, ongoing research is essential to monitor the evolving nature of neurological challenges and to identify effective interventions. Moreover, the broader public health implications underscore the importance of preventive strategies, including robust vector control measures and public awareness campaigns, to mitigate the impact of Zika virus transmission.

This comprehensive review framework can provide valuable insights into the neurological complications associated with congenital Zika syndrome, enhancing our understanding of the long-term effects and potential interventions.

METHODS

Identification of research

In the Web of Science, PubMed, and Scopus databases, the literature related to neurological complications associated with Zika virus infection during pregnancy was searched. Search keywords: Zika virus; pregnancy; global health; risks; neurological complications; preventive measures

Keywords are combined with Boolean operators (AND/OR): ("Zika virus" AND "Pregnancy" AND "Zika virus" OR "Neurological complications" AND "Zika virus" OR "Global health" OR "Zika virus" AND "Preventive measures" OR "Zika virus" AND "Risks".

Inclusion criteria: Studies published in the English language from medicine, original quantitative studies and full-text studies on the neurological complications associated with Zika virus infection during pregnancy.

Exclusion criteria: Studies published in multidisciplinary journals, studies published in languages other than English, and studies with limited access were excluded.

Selected research

The studies were selected by the criteria for the literature review. Thirty-two studies were included in the current review. To prevent and reduce prejudices in the process of selecting studies, a professor in the field of Obstetrics and Gynaecology. Disagreements were discussed and resolved with full agreement by both researchers.

RESULTS

Zika virus infection during pregnancy

Zika virus infection during pregnancy is a significant concern due to the potential for adverse outcomes in the developing fetus. Zika virus during pregnancy is primarily transmitted through sexual contact between partners and from the maternal to the fetus during pregnancy or childbirth. The timing of Zika virus infection during pregnancy is crucial. The risk of birth defects is believed to be highest when infection occurs during the first trimester, but adverse outcomes can occur even if the infection

happens later in pregnancy. When a pregnant woman is infected with the Zika virus, the virus can cross the placenta and infect the developing fetus. Zika virus infection during pregnancy can lead to serious neurological complications in newborns.

The most well-known and severe consequence is a condition called congenital Zika syndrome (CZS). Congenital Zika Syndrome (CZS) is associated with a range of birth defects, including intracranial calcifications, ventriculomegaly, microcephaly, and other neurological complications such as seizures, developmental delays, impaired growth, hearing and vision problems, and difficulties with balance and coordination.

Pregnant women with possible Zika virus exposure or symptoms should be tested for Zika virus. Ultrasound examinations may be performed to monitor fetal development.

Obstetricians play a crucial role in counselling and supporting pregnant women at risk of Zika virus exposure. This includes providing information on preventive measures, monitoring for symptoms, and discussing potential risks and outcomes.

Pregnant women or those planning pregnancy should consult with their Obstetricians for personalized advice based on their circumstances and potential exposure to Zika virus. Staying informed about travel advisories and taking appropriate preventive measures are essential components of managing the risk associated with the Zika virus during pregnancy.

Neurological complications associated with Zika virus infection during pregnancy

Zika virus infection during pregnancy is associated with a range of neurological complications in the developing fetus [13], collectively known as Congenital Zika Syndrome (CZS). The severity of these complications can vary, and they are most commonly observed when the infection occurs during the early stages of pregnancy. Some of the neurological complications associated with Zika virus infection during pregnancy:

- *Microcephaly:* Microcephaly is one of the most recognized and severe neurological complications linked to Zika virus infection during pregnancy. It involves an abnormally small head size and can result from incomplete brain development. Microcephaly is associated with intellectual disabilities, developmental delays, and other neurological issues.
- *Brain abnormalities:* Zika virus can lead to various abnormalities in the structure and function of the brain. These abnormalities may include calcifications (calcium deposits) in the brain, decreased brain tissue volume, and malformations in different parts of the brain.
- *Ventriculomegaly:* This refers to the enlargement of the fluid-filled ventricles within the brain. Ventriculomegaly is often associated with impaired brain development and can contribute to neurological problems.
- *Intracranial calcifications:* Zika-infected fetuses may develop calcium deposits in the brain, which can be visualized through imaging studies. These calcifications are indicative of abnormal brain development and can contribute to neurological impairment.
- *Seizures:* Some infants born to mothers infected with the Zika virus during pregnancy may experience seizures. Seizures are abnormal electrical activities in the brain that can lead to various neurological symptoms.
- *Hearing loss:* Hearing abnormalities, including sensorineural hearing loss, have been reported in infants with congenital Zika syndrome. These issues can contribute to developmental challenges.
- *Vision problems:* Zika virus infection during pregnancy has been linked to eye abnormalities and vision problems in affected infants. These issues may range from mild to severe and can impact visual development.
- *Joint and limb contractures:* Infants with congenital Zika syndrome may experience joint and limb contractures, which involve the abnormal shortening or tightening of muscles, tendons, or other tissues. This can affect mobility and coordination.

It's important to note that the full spectrum of neurological complications associated with Zika virus infection during pregnancy is still being studied, and ongoing research aims to better understand the long-term outcomes for affected infants.

Diagnoses of ZIKA virus during pregnancy

Zika virus infection during pregnancy can have severe consequences for the developing fetus, so a quick and correct diagnosis is required. Diagnosis of Zika virus infection during pregnancy involves a combination of clinical evaluation, laboratory testing, and imaging studies,[14-16].

- *Clinical evaluation:* A pregnant woman with Zika virus infection may experience symptoms such as fever, rash, joint pain, and red eyes.
- *Travel history:* Obtaining a thorough travel history is crucial, as the Zika virus is primarily transmitted through the bite of infected mosquitoes. If a pregnant woman has travelled to an area with active Zika virus transmission, there may be an increased risk of infection.

- *Laboratory testing:* Testing for Zika virus can be done using molecular and serologic methods. Molecular tests, such as reverse transcription-polymerase chain reaction (RT-PCR), can detect the virus's genetic material. Serologic tests, such as enzyme-linked immunosorbent assay (ELISA), detect antibodies produced by the body in response to the infection. *Placental tissue testing:* In some cases, testing of placental tissues may be recommended to confirm Zika virus infection and assess the impact on the fetus.
- *Ultrasound and imaging studies:* In cases where Zika virus infection is confirmed or suspected, ultrasound examinations may be performed to assess fetal anatomy and identify any abnormalities associated with congenital Zika syndrome.
- *Amniocentesis:* In certain situations, amniocentesis may be recommended to test the amniotic fluid for Zika virus RNA.

Treatment of ZIKA virus during pregnancy

There is no specific antiviral treatment for Zika virus infection, and management primarily involves supportive care. For pregnant women who are infected with Zika virus or are at risk of Zika virus exposure, the focus is on monitoring the health of both the mother and the developing fetus.

- *Prenatal care:* Pregnant women with confirmed or suspected Zika virus infection should receive regular prenatal care to monitor the progress of the pregnancy. This includes routine ultrasounds to assess fetal development.
- *Symptomatic treatment:* Treatment for Zika virus infection is generally supportive and includes rest, hydration, and the use of medications (acetaminophen) to alleviate symptoms such as fever and pain.
- *Avoiding further exposure:* Pregnant women should take measures to avoid further exposure to the Zika virus, including preventing mosquito bites. This may involve using insect repellent, wearing long-sleeved clothing, and staying in air-conditioned or screened-in accommodations in areas with active Zika transmission.
- *Specialized care:* In cases where the Zika virus infection is confirmed, specialist treatment is necessary, from maternal-fetal medicine specialists or infectious disease experts, to provide specialized care and guidance.
- *Monitoring fetal development:* Ultrasound examinations are essential for monitoring fetal development and detecting any abnormalities associated with congenital Zika syndrome. The timing and frequency of ultrasounds may be adjusted based on the specific circumstances of the pregnancy. Pregnant women must communicate openly with their Obstetrician/Gynecologist about any potential Zika virus exposure, travel history, and symptoms.

Since the information in the medical field is subject to updates, it's recommended to consult with an Obstetrician/Gynaecologist or consult the latest guidelines from health organizations, such as the Centers for Disease Control and Prevention (CDC) or the World Health Organization (WHO), for the most current information on the management of Zika virus during pregnancy.

Diagnosis of neurological complications of the ZIKA virus during pregnancy

The diagnosis of neurological complications of Zika virus during pregnancy involves a combination of clinical evaluation, laboratory testing, and imaging studies. Neurological complications in the context of the Zika virus during pregnancy may include abnormalities in the developing fetus's brain, a condition referred to as congenital Zika syndrome.

Clinical Evaluation:

- Prenatal ultrasound: Routine prenatal ultrasounds are essential for monitoring fetal development, including the development of the brain.

Ultrasound examinations may reveal structural abnormalities in the brain, such as microcephaly (small head size) or other brain malformations.

Neurological examination: Specialized prenatal assessments may be conducted to evaluate the fetal nervous system and identify any signs of neurological abnormalities.

Laboratory testing:

Testing for Zika virus in the mother may be conducted using molecular and serologic methods.

- Amniotic fluid testing through amniocentesis may also be considered to detect Zika virus RNA.
- Placental and fetal tissue testing: In some cases, testing of placental and fetal tissues may be recommended to confirm Zika virus infection and assess the impact on the developing fetus.

Imaging studies:

Magnetic Resonance Imaging (MRI): MRI may be used to provide detailed images of the fetal brain and identify any structural abnormalities. MRI is particularly useful for assessing brain structures that may not be visualized on ultrasound.

- Follow-up and monitoring: Regular prenatal care, including continued monitoring through

ultrasounds, is crucial to assess the progression of neurological complications and other potential issues.

- Genetic counseling: Genetic counselling may be recommended to help parents understand the implications of neurological abnormalities identified during pregnancy.

Consultation with specialists: In cases where neurological complications are detected, consultation with specialists such as maternal-fetal medicine experts, pediatric neurologists, and genetic counsellors may be recommended.

It's important to note that the Zika virus can cause a range of neurological complications in developing fetuses, and the severity can vary. Not all pregnancies affected by the Zika virus will result in congenital Zika syndrome. Obstetrician/Gynecologist will tailor the diagnostic approach based on the specific circumstances of each case.

Treatment of neurological complications of the ZIKA virus during pregnancy

There is no specific antiviral treatment for Zika virus or direct treatment for congenital Zika syndrome, which encompasses the neurological complications that may arise in a developing fetus during pregnancy, [17]. The management of neurological complications associated with the Zika virus during pregnancy is focused on supportive care, monitoring, and addressing specific symptoms or complications.

Some general aspects of managing neurological complications during pregnancy include:

1. *Multidisciplinary care:* The care of pregnant women with Zika virus-related neurological complications involves a multidisciplinary approach. Specialists such as maternal-fetal medicine experts, neonatologists, pediatric neurologists, and genetic counsellors may be involved.
2. *Monitoring and imaging:* Regular monitoring of fetal development through ultrasounds and, in some cases, magnetic resonance imaging (MRI) can help assess the extent of neurological abnormalities. Monitoring may continue after birth to assess the baby's neurodevelopmental progress.
3. *Supportive care for the mother:* Pregnant women infected with the Zika virus should receive appropriate prenatal care and support. Symptomatic treatment for the mother, such as pain management and rest, may be recommended.
4. *Delivery planning:* Timing and mode of delivery may be carefully considered based on the severity of neurological complications and other factors.
5. *Postnatal care for the infant:* Infants born to mothers with Zika virus-related neurological complications may require specialized care, including monitoring for developmental delays and neurological issues. Early intervention services and rehabilitation may be recommended to address developmental challenges.
6. *Genetic counseling:* Genetic counselling can help parents understand the implications of neurological abnormalities detected during pregnancy. It provides information about the potential long-term effects and supports parents in making informed decisions.
7. Clinical trials and research: Participation in clinical trials or research studies may be considered, as ongoing research aims to better understand the Zika virus and identify potential treatments.

Important consideration

Given the dynamic nature of medical research and guidelines, it's essential to consult with an Obstetrician/Gynaecologist who can provide the most up-to-date information. Local health authorities and the World Health Organization (WHO) can also offer guidance specific to the geographic region. Healthcare providers can offer personalized guidance based on the specific circumstances of each case.

DISCUSSION

One of the most well-documented neurological impacts of congenital Zika syndrome is microcephaly, characterized by a smaller-than-average head size. This results from the virus's ability to target neural progenitor cells during fetal brain development. Beyond microcephaly, congenital Zika syndrome often leads to various structural brain abnormalities, such as cortical malformations, ventriculomegaly, and cerebellar hypoplasia [18]. Understanding the range and severity of these structural alterations is crucial for predicting long-term neurological outcomes. Infants born with congenital Zika syndrome commonly experience neurodevelopmental delays, affecting milestones like motor skills, speech, and cognitive functions[19]. These delays can manifest early in infancy and continue throughout childhood. Research indicates that the extent of neurodevelopmental impairment varies, emphasizing the need for individualized care and intervention strategies. As affected children grow, cognitive and behavioral challenges become more apparent. Cognitive impairments may include difficulties with attention, memory, and executive functions. Behavioral issues such as hyperactivity and irritability are also observed. Understanding the nature of these challenges is essential for developing

targeted interventions and support systems for affected individuals and their families [20,21].

Congenital Zika syndrome is associated with a spectrum of ocular complications, ranging from mild to severe. These include chorioretinal atrophy, optic nerve abnormalities, and vision impairment [22]. Ophthalmological assessments are crucial in the comprehensive evaluation of congenital Zika syndrome-affected infants, and early intervention is crucial to managing and mitigating the impact of these ocular complications.

Hearing loss is another significant neurological consequence of congenital Zika syndrome. The virus can affect the development of the auditory system, leading to varying degrees of hearing impairment. Audiological assessments and early interventions, such as hearing aids or cochlear implants, are vital in addressing this aspect of congenital Zika syndrome-related neurological impact [23,24].

Despite advances in diagnostic techniques, congenital Zika syndrome poses challenges for prenatal diagnosis. Ultrasound findings, while indicative of potential issues, may not be definitive, and serological tests have limitations in terms of sensitivity and specificity. Improving the accuracy and accessibility of prenatal diagnostic tools is crucial for early identification and appropriate counselling for affected families [25].

Given the multifaceted nature of neurological impacts in congenital Zika syndrome, a multidisciplinary approach to care is imperative. Neurologists, pediatricians, ophthalmologists, audiologists, and rehabilitation specialists must collaborate to provide comprehensive care tailored to the individual needs of each congenital Zika syndrome-affected child. Early intervention services, including physical therapy, speech therapy, and educational support, optimize outcomes.

On a broader scale, the neurological impacts of congenital Zika syndrome highlight the importance of public health strategies in preventing Zika virus transmission. Efforts should focus on effective vector control, public awareness campaigns, and support for pregnant women in Zika-endemic regions. Investing in research for vaccines and antiviral treatments is also essential to mitigate the impact of congenital Zika syndrome on neurological outcomes [26,27].

In perspective, ongoing research is necessary to deepen our understanding of the long-term neurological consequences of congenital Zika syndrome. Longitudinal studies tracking the development of affected children into adolescence and adulthood will provide valuable insights into the evolving nature of neurological challenges. Additionally, advancements in treatment modalities and neuroprotective strategies merit further exploration [28].

CONCLUSION

In conclusion, the neurological impacts of Congenital Zika Syndrome encompass a spectrum of challenges that extend from structural brain abnormalities to cognitive, behavioral, ocular, and auditory complications. A holistic and multidisciplinary approach, coupled with ongoing research and public health initiatives, is essential for addressing the complex needs of infants affected by congenital Zika syndrome and their families. Understanding the basic virology and modes of transmission is crucial for implementing effective public health strategies and preventive measures to control the spread of the Zika virus and minimize its impact, especially on vulnerable populations such as pregnant women and their infants.

Ethics approval and consent to participate:
This study is a literature review. It was conducted using only aggregated data in the literature. Institutional review board approval was not required.

Conflict of interest:
The author declares that there is no financial interest or conflict of interest.

REFERENCES

1. Sampathkumar P, Sanchez JL. Zika Virus in the Americas: A Review for Clinicians. *Mayo Clin Proc.* 2016 Apr;91(4):514-21. doi: 10.1016/j.mayocp.2016.02.017. PMID: 27046524.
2. Crisanto-López IE, Jesús PL, López-Quecho J, Flores-Alonso JC. Congenital Zika syndrome. *Bol Med Hosp Infant Mex*. 2023;80(1):3-14. English. doi: 10.24875/BMHIM.22000110. PMID: 36867568.
3. Dahiya N, Yadav M, Yadav A, Sehrawat N. Zika virus vertical transmission in mosquitoes: A less understood mechanism. *J Vector Borne Dis.* 2022 Jan-Mar;59(1):37-44. doi: 10.4103/0972-9062.331411. PMID: 35708402.
4. Almeida RDN, Braz-de-Melo HA, Santos IO, Corrêa R, Kobinger GP, Magalhaes KG. The Cellular Impact of the ZIKA Virus on Male Reproductive Tract Immunology and Physiology. *Cells*. 2020 Apr 18;9(4):1006. doi: 10.3390/cells9041006. PMID: 32325652; PMCID: PMC7226248.
5. Auriti C, De Rose DU, Santisi A, Martini L, Piersigilli F, Bersani I, et al. Pregnancy and viral infections: Mechanisms of fetal damage, diagnosis and prevention of neonatal adverse outcomes from cytomegalovirus to SARS-CoV-2 and Zika virus. *Biochim Biophys Acta Mol Basis Dis.* 2021 Oct 1;1867(10):166198. doi: 10.1016/j.bbadis.2021.166198. Epub 2021 Jun 10. PMID: 34118406; PMCID: PMC8883330.
6. Muñoz LS, Parra B, Pardo CA; Neuroviruses Emerging in the Americas Study. Neurological Implications of Zika Virus Infection in Adults. *J Infect Dis.* 2017 Dec 16;216(suppl_10):S897-S905. doi: 10.1093/infdis/jix511. Erratum in: *J Infect Dis*. 2018 Mar 28;217(8):1334. PMID: 29267923; PMCID: PMC5853915.
7. van der Linden H Jr, Pessoa A, van der Linden A, Florêncio RN, Carvalho MDCG, van der Linden V. Epilepsy and EEG Abnormalities in Congenital Zika Syndrome. *J Clin Neurophysiol.* 2022 May 1;39(4):248-252. doi: 10.1097/WNP.0000000000000878. Epub 2022 Jan 6. PMID: 34999638.
8. Alves LV, Paredes CE, Silva GC, Mello JG, Alves JG. Neurodevelopment of 24 children born in Brazil with congenital Zika syndrome in 2015: a case

series study. BMJ Open. 2018 Jul 16;8(7):e021304. doi: 10.1136/bmjopen-2017-021304. PMID: 30012787; PMCID: PMC6082469.
9. Ventura CV, Ventura Filho MC, Ventura LO. Ocular Manifestations and Visual Outcome in Children With Congenital Zika Syndrome. *Top Magn Reson Imaging.* 2019 Feb;28(1):23-7. doi: 10.1097/RMR.0000000000000192. PMID: 30817677.
10. Thawani A, Sammudin NH, Reygaerts HS, Wozniak AN, Munnamalai V, Kuhn RJ, Fekete DM. Zika virus can directly infect and damage the auditory and vestibular components of the embryonic chicken inner ear. *Dev Dyn.* 2020 Jul;249(7):867-883. doi: 10.1002/dvdy.176. Epub 2020 May 8. PMID: 32384225; PMCID: PMC7753925.
11. Eppes C, Rac M, Dunn J, Versalovic J, Murray KO, Suter MA, et al. Testing for Zika virus infection in pregnancy: key concepts to deal with an emerging epidemic. *Am J Obstet Gynecol.* 2017 Mar;216(3):209-25. doi: 10.1016/j.ajog.2017.01.020. Epub 2017 Jan 23. PMID: 28126366.
12. Gama G, Conceição Matias MD, de Luiz Vânia M, de Sales Regis T, Peregrino-Filho A, de Sales Tavares J, et al. Motor and cognitive response to intensive multidisciplinary therapy: the first reported case of congenital Zika virus syndrome. *Physiother Theory Pract.* 2023 Jan 10:1-10. doi: 10.1080/09593985.2023.2165887. Epub ahead of print. PMID: 36625893.
13. Marbán-Castro E, Goncé A, Fumadó V, Romero-Acevedo L, Bardají A. Zika virus infection in pregnant women and their children: A review. *Eur J Obstet Gynecol Reprod Biol.* 2021 Oct;265:162-8. doi: 10.1016/j.ejogrb.2021.07.012. Epub 2021 Jul 9. PMID: 34508989.
14. Mulkey SB, Ansusinha E, Cristante C, Russo SM, Biddle C, Kousa YA, et al. Complexities of Zika Diagnosis and Evaluation in a U.S. Congenital Zika Program. *Am J Trop Med Hyg.* 2021 Apr 19;104(6):2210-19. doi: 10.4269/ajtmh.20-1256. PMID: 33872214; PMCID: PMC8176469.
15. Santana EFM, Casati MFM, Geraldo MSP, Werner H, Araujo Júnior E. Intrauterine Zika virus infection: review of the current findings with emphasis in the prenatal and postnatal brain imaging diagnostic methods. *J Matern Fetal Neonatal Med.* 2022 Dec;35(25):6062-8. doi: 10.1080/14767058.2021.1904874.
16. Cordeiro MT. Laboratory diagnosis of Zika virus. *Top Magn Reson Imaging*. 2019 Feb;28(1):15-17. doi: 10.1097/RMR.0000000000000190. Erratum in: *Top Magn Reson Imaging.* 2019 Apr;28(2):97. Title corrected. PMID: 30817675.
17. Citil Dogan A, Wayne S, Bauer S, Ogunyemi D, Kulkharni SK, Maulik D, et al. The Zika virus and pregnancy: evidence, management, and prevention. *J Matern Fetal Neonatal Med.* 2017 Feb;30(4):386-96. doi:
18. Soares de Oliveira-Szejnfeld P, Levine D, Melo AS, Amorim MM, Batista AG, Chimelli L, et al. Congenital Brain Abnormalities and Zika Virus: What the Radiologist Can Expect to See Prenatally and Postnatally. *Radiology*. 2016 Oct;281(1):203-18. doi: 10.1148/radiol.2016161584.
19. Wheeler AC, Toth D, Ridenour T, Lima Nóbrega L, Borba Firmino R, Marques da Silva C, et al. Developmental Outcomes Among Young Children With Congenital Zika Syndrome in Brazil. *JAMA Netw Open.* 2020 May 1;3(5):e204096. doi: 10.1001/jamanetworkopen.2020.4096.
20. Wheeler AC, Ventura CV, Ridenour T, Toth D, Nobrega LL, Silva de Souza Dantas LC, et al. Skills attained by infants with congenital Zika syndrome: Pilot data from Brazil. *PLoS One.* 2018 Jul 26;13(7):e0201495. doi: 10.1371/journal.pone.0201495.
21. Sato JR, Junior CEB, de Araújo ELM, de Souza Rodrigues J, Andrade SM. A guide for the use of fNIRS in microcephaly associated to congenital Zika virus infection. *Sci Rep.* 2021 Sep 29;11(1):19270. doi: 10.1038/s41598-021-97450-w.
22. Costa CBDC, Freitas D. Ocular findings of congenital Zika virus infection with microcephaly. *Int Ophthalmol.* 2022 Oct;42(10):3117-27. doi: 10.1007/s10792-022-02311-8.
23. Almeida LC, Muniz LF, Maciel RJ, Ramos DS, Albuquerque KMG, Leão ÂMC, et al. Hearing and communicative skills in the first years of life in children with congenital Zika syndrome. *Braz J Otorhinolaryngol.* 2022 Jan-Feb;88(1):112-17. doi: 10.1016/j.bjorl.2020.05.007. Epub 2020 Jun 11.
24. Muniz LF, Maciel RJF, Ramos DS, Albuquerque KMG, Leão ÂC, Van Der Linden V, Pet al. Audiological follow-up of children with congenital Zika syndrome. *Heliyon*. 2022 Jan 7;8(1):e08720. doi: 10.1016/j.heliyon.2022.e08720.
25. Viens LJ, Fleck-Derderian S, Baez-Santiago MA, Oduyebo T, Broussard CS, Khan S, et al. Role of Prenatal Ultrasonography and Amniocentesis in the Diagnosis of Congenital Zika Syndrome: A Systematic Review. *Obstet Gynecol.* 2020 May;135(5):1185-1197. doi: 10.1097/AOG.0000000000003829.
26. Broussard CS, Shapiro-Mendoza CK, Peacock G, Rasmussen SA, Mai CT, Petersen EE, et al. Public Health Approach to Addressing the Needs of Children Affected by Congenital Zika Syndrome. *Pediatrics*. 2018 Feb;141(Suppl 2):S146-S153. doi: 10.1542/peds.2017-2038C.
27. Gashi AM, Ismajli J, Sherifi A, Sopa G, Ismajli D. The susceptibility of pregnant women during viral pandemics–A mini-review. Ro J Infect Dis. 2020 Oct 1;23(4):261-5. doi: 10.37897/RJID.2020.4.2.
28. Xu M, Lee EM, Wen Z, Cheng Y, Huang WK, Qian X, et al. Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen. *Nat Med.* 2016 Oct;22(10):1101-7. doi: 10.1038/nm.4184.