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A review of maternal Zika virus infection and its fetal outcomes

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ABSTRACT

The Zika virus was first identified in 2007 with a worldwide outbreak occurring in 2015. Although much is known about the virus, there remains a paucity of information about how it affects fetal growth and development. This paper aims to identify the incidence, risk factors, and fetal growth and development outcomes of the Zika virus. A search of relevant publications was conducted by three independent reviewers. Unpublished data were searched from inception until October 2019, for quantitative studies on pregnant mothers with Zika infection. The findings were summarized and compiled as a systematic review. There is substantial evidence of the effects of Zika virus infection on fetal neurologic outcomes, as well as ophthalmologic, genitourinary, visceral, and femur-protection outcomes in newborns following maternal Zika virus infection. This review hopes to lay the groundwork for future research on preventive measures for maternal Zika virus infection.

INTRODUCTION

The Zika virus is a mosquito-transmitted Flavivirus that was seen to cause epidemics of a mild viral illness for the first time in Brazil and in other countries in Latin America and the Caribbean around 2015 (Musso et al. 2017). The virus is an enveloped, single-stranded RNA that was first isolated from a Rhesus Macaque in 1947 in Uganda (White et al. 2016). It is the reason for earlier outbreaks in 2007 in the Yap Islands (Baud et al. 2017) and in 2013 in the French Polynesia (Musso et al. 2017). Nonhuman hosts, such as sylvatic animals, are considered maintenance hosts, while primates and humans are regarded as amplification hosts (Haddow et al. 2020). The virus can be transmitted via vectors (e.g., mosquitoes), sexually, and through the maternal-fetal route (Novak, Sheffield, and Burd 2017). There has been an observed global spread of Zika virus through an undetermined mechanism; however, possibilities as diverse as adaptive viral evolution contributing to enhanced infectivity to urban *Aedes species* vectors, or adaptive evolution in the human host, leading to exaggerated levels of viremia increasing vector-led and maternal-fetal transmission. The virus also appears to become prominent among new populations as a result of the rise in international travel, the development of tropical urban centers, and the rise in susceptible mosquito populations (Torres, Murillo, and Bofill 2016).

The symptoms of patients infected with the virus are usually mild including low-grade fever, rash, myalgia, and conjunctivitis, which are all typical of nonspecific viral illnesses (Agrawal et al. 2018). Zika infection in pregnant women is associated with miscarriage, fetal abnormalities, and neurological diseases (Shan, Xie, and Shi 2018). Reports have shown that the virus can be isolated from body fluids including urine, saliva, serum, semen, as well as amniotic fluid (Bonaldo et al. 2016). This led to the hypothesis that the virus might cross the placental barrier causing maternal-fetal transmission and the documented abnormalities in several cases (Zanluca, de Noronha, and Duarte Dos Santos 2018).

In February 2016, the World Health Organization (WHO) declared a Public Health Emergency of International Concern and called for research about the causal relationship between the Zika virus and congenital brain abnormalities, including microcephaly and Guillain-Barré Syndrome (Krauer et al. 2017). Moore in 2016 characterized congenital abnormalities due to Zika as a spectrum of fetal neurologic injuries, including cortical malformations, ventriculomegaly, ocular injury, and arthrogryposis. Birth defects usually range from 5-8% but may reach up to 13% (Moore et al. 2017). Studies have reported fetuses with normal head circumference but were later found to

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have abnormal brain structures, as well as late-onset microcephaly (Calvet et al. 2016).

Congenital Zika virus infection or Congenital Zika Syndrome (CZS) has also been associated with other abnormalities, including excessive and redundant scalp skin (CDC 2016a, 2016b). Neurologic findings include hyperreflexia, irritability, tremors, seizures, brainstem dysfunction, and dysphagia (Blázquez and Saiz 2016). Eye abnormalities have also been reported which include, but are not limited to, focal pigmentary mottling and chorioretinal atrophy in the macula, optic nerve hypoplasia, cupping, and atrophy, other retinal lesions, iris colobomas, congenital glaucoma, microphthalmia, lens subluxation, cataracts, and intraocular calcifications (Guevara and Agarwal-Sinha 2018).

Intrauterine growth retardation with femur sparing was also reported by Walker and colleagues in 2018. They reported this pattern of fetal growth restriction among fetuses with congenital Zika virus exposure using Intergrowth-21st Project fetal body ratios comparing head or abdominal circumference to femur length (Walker et al. 2018).

Studies have determined a causal link between Zika virus infection and neurologic abnormalities seen in human fetuses (Gladwyn-Ng et al. 2018). Although the pathophysiology of the Zika virus is well described, less is known about the various effects it has on fetal growth and development (Garcez et al. 2016). To improve the understanding of the incidence, predictors, and complications of the Zika virus, the authors conducted a review to identify the risk factors, epidemiology, and outcomes of Zika virus exposure or infection on fetal growth and development.

MATERIALS AND METHODS

This review was conducted from February 2021 to December 2023. The authors adapted Arksey and O'Malley's framework to determine the presence of significant new developments in fetal growth and development outcomes from mothers infected with the Zika virus (Daudt, van Mossel, and Scott 2013). The following steps were done: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; and (5) collating, summarizing, and reporting results **(Figure 1)**.

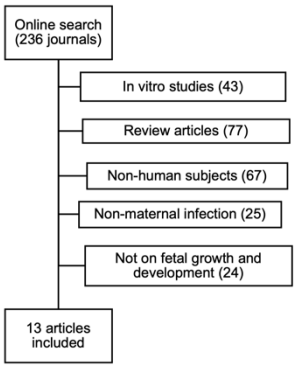

Figure 1: Outline of the search and inclusion of articles

The databases PubMed and Herdin were searched from inception to December 2023 using a combination of search terms "Zika", "Zika virus", "Zika infection", "fet* growth", "fet* development", "fet* outcome" and were filtered for human subjects. Searches were limited to studies on humans and published in the English language. Authors of identified studies were contacted and consulted regarding clarification, if necessary.

Two reviewers independently screened titles and abstracts of all identified studies using a priori selection criteria. Studies were included if the main subjects were human fetuses of confirmed Zika virus-infected mothers and reported at least one fetal growth and development outcome. Review articles, studies done on cell cultures and non-human subjects, proceedings, interviews, and commentaries were excluded from this paper.

The authors provided a preliminary assessment of the potential size and scope of the available research literature on the Zika virus.

A total of 236 articles resulted after an online PubMed search using the following terms: Zika virus, infection, maternal, prognosis (prognosis, prediction, course), fetal growth, fetal development, and outcomes. From these, the following were excluded: review articles (77); in vitro studies (43); non-human subjects (67); studies not dealing with maternal infection (25) and those not reporting on fetal growth and development (24). Only 13 articles were included for review in this study **(Table 1)**.

Table 1: Articles included in the review

Title	Authors
Adverse fetal and neonatal outcomes in pregnancies with confirmed Zika virus infection in Rio de Janeiro, Brazil: A cohort study	Souza et al (Souza et al. 2021)
Zika virus infection in pregnancy and adverse fetal outcomes in São Paulo State, Brazil: a prospective cohort study	Sanchez Clemente et al (Sanchez Clemente et al. 2020)
Urinary bladder agenesis and renal hypoplasia potentially related to in utero Zika virus infection.	Villamil-Gomez et al (Villamil-Gómez et al. 2019)
The challenge of the laboratory diagnosis in a confirmed congenital Zika virus syndrome in utero	Sulleiro et al (Sulleiro et al. 2019)
Sequential neuroimaging of the fetus and newborn with in utero Zika virus exposure	Mulkey et al (Mulkey et al. 2019)
A clinical and histopathological study of malformations observed in fetuses infected by the Zika virus	Beaufrère et al (Beaufrère et al. 2019)
Femur-sparing pattern of abnormal fetal growth in pregnant women from New York City after maternal Zika virus infection	Walker et al (Walker et al. 2018)
Serial head and brain imaging of 17 fetuses with confirmed Zika virus infection in Colombia, South America	Parra-Saavedra et al (Parra-Saavedra et al. 2017)
Zika virus infects human fetal brain microglia and induces inflammation	Lum et al (Lum et al. 2017)
Fetal magnetic resonance imaging findings in prenatal Zika virus infection	Sanín-Blair et al (Sanín-Blair et al. 2017)
Placental pathology of Zika virus: viral infection of the placenta induces villous stromal macrophage (Hofbauer cell) proliferation and hyperplasia	Rosenberg et al (Rosenberg et al. 2017)

Progressive lesions of central nervous system in microcephalic fetuses with suspected congenital Zika virus syndrome	Sarno et al (Sarno et al. 2017)
Autopsy and postmortem studies are concordant: pathology of Zika virus infection is neurotropic in fetuses and infants with microcephaly following transplacental transmission	Schwartz (Schwartz 2017)
Zika virus infection and stillbirths: A case of hydrops fetalis, hydranencephaly and fetal demise	Sarno et al (Sarno et al. 2016)
Clinical and imaging findings in an infant with Zika embryopathy	Culjat et al (Culjat et al. 2016)

RESULTS AND DISCUSSION

A total of 1,067 infected mothers were covered in the 13 papers that were included in the study. Of these, 863 fetuses were affected with various outcomes: neurologic (99%), ophthalmologic (1%), renal (2%), visceral (3%), reproductive (1%), and femur-sparing growth retardation (25%) being the systems of involvement. Of the 863 affected pregnancies, 49 were terminated. The main modes of the study were prenatal ultrasonograms (8/13), cranial magnetic resonance imaging studies (2/13), histopathology (6/13), and immunologic studies (3/13). The most common outcomes in each of these papers have been outlined below (Table 2).

Table 2: Summary of outcomes per study included

Authors	Outcomes	
Souza et al (Souza et al. 2021)	microcephaly/cerebral atrophy	SGA
Sanchez Clemente et al (Sanchez Clemente et al. 2020)	microcephaly	
Villamil-Gomez et al (Villamil-Gómez et al. 2019)	oligohydramnios	IUGR
Sulleiro et al (Sulleiro et al. 2019)	IUGR	microcephaly
Mulkey et al (Mulkey et al. 2019)	microencephaly	Chiari abnormality
Beaufrère et al (Beaufrère et al. 2019)	meningoencephalitis	lymphocytes in testes
Walker et al (Walker et al. 2018)	IUGR	intraventricular hemorrhage 1
Parra-Saavedra et al (Parra-Saavedra et al. 2017)	microcephaly	ventriculomegaly
Lum et al (Lum et al. 2017)	Zika virus in microglial cells	
Sanín-Blair et al (Sanín-Blair et al. 2017)	agyria	hydrocephalus
Rosenberg et al (Rosenberg et al. 2017)	cerebral mantle atrophy	diffuse cerebral cortical thinning
Sarno et al (Sarno et al. 2017)	microcephaly	ventriculomegaly
Sarno et al (Sarno et al. 2016)	hydrops fetalis	anencephaly
Culjat et al (Culjat et al. 2016)	ZIKV IgM antibody titers in serum and cerebrospinal fluid.	impaired brain development in the second half of gestation

IgM, immunoglobulin M; IUGR, intrauterine growth retardation; SGA, small for gestational age

Diagnosis of Zika Virus

CZS has been documented in a recent epidemic largely attributed to mother-to-child transmission of the Zika virus (Del Campo et al. 2017; Moore et al. 2017). Maternal symptoms are typically mild and these include fever, generalized body malaise, or rash, all characteristics of nonspecific viral infections (Moore et al. 2017). Zika virus IgG in the serum is an important marker and is used to detect acute infection (Laengin et al. 2020). Notably, seroconversion only typically occurs from 21 to 24 weeks age of gestation (Sulleiro et al. 2019).

Neurologic

Neurologic abnormalities are the most common fetal effects of the Zika virus. As documented through neurologic imaging, the time frame from infection to the development of abnormalities ranges from 15 to 24 weeks (Parra-Saavedra et al. 2017; Sulleiro et al. 2019). It is presumed that damage occurs to the fetal brain and other organs before birth through direct injury by the Zika virus. Active infection ends during intrauterine life, and as a consequence, the immune system of the infant is unable to build up a consistent immune response enough to neutralize the virus (Sulleiro et al. 2019).

Of the collected data, 99% of the fetal effects of Zika are neurologic in nature. These include microcephaly, delayed neurologic development, Chiari abnormalities, cerebral and cortical dysplasia, intraventricular hemorrhage, choroid cysts, corpus callosum abnormalities, cerebral malformations, cerebral hypoplasia, ventriculomegaly, and even anencephaly (Driggers et al. 2016; Moore et al. 2017; Sanchez Clemente et al. 2020; Schwartz 2017; Souza et al. 2021). The finding of heterotopias has been described at autopsy findings of a microcephalic fetus with Zika virus. Heterotopias are a form of neuronal migration defect. It remains unclear if encephalocele and other neural tube defects have causal associations with Zika (Štrafela et al. 2017). Higher rates of fetal brain abnormalities are expected in the first trimester of pregnancy because this is the period when the brain actively develops (Hoen et al. 2018; Moore et al. 2017; Pacheco et al. 2020).

Additionally, a review of postnatal brain neuroimaging scans reveals the development of brain infarcts (Mulkey et al. 2019). It is unclear whether these lesions are the result of a direct destructive viral insult or vaso-occlusive ischemia. However, cerebral vasculopathy has been described in studies on subjects with Zika infection (Landais et al. 2017). Placental thromboembolism secondary to placental inflammation is likely the mechanism involved in other congenital infections (Chabrier et al. 2011). Hydrocehphalus ex vacuo, in addition to a diffuse neuronal loss resulting from an endoplasmic reticulum (ER)

stress caused by the Zika virus infection, has been reported in three cases (Beaufrère et al. 2019). There were also findings of meningoencephalitis associated with diffuse arachnoiditis, ependymitis, and vasculitis. Diffuse vasculitis is characterized by endothelial cell swelling, surrounded by active astrocytosis (glial fibrillary acidic protein-positive) and a macrophagic reaction (CD68-positive) in the cerebral hemispheres, namely in the subcortical and intermediary zones. The presence of actively replicating Zika virus RNA in the neurons was also present. The authors of the study also observed extensive neuronal loss, along with numerous Zika virus-infected neurons showing chromatin changes, surrounded by apoptotic residues. Finally, another study concluded that Zika virus-associated ER stress, leading to decreased cortical progenitor cell proliferation and increased mature neuron cell death in the cerebral cortex, is fully consistent with data documented previously in animal models (Gladwyn-Ng et al. 2018). Remarkably, accumulation of chop1 mRNAs has been observed in the subventricular zone, suggesting that Zika virus attacks intermediary cortical progenitor cells, causing apoptosis. Overall, it appears that brain malformations observed in the fetal Zika virus infection result from a series of pathological mechanisms involving the progenitor neural cells, the cortical neurons, and endothelial cells (Chavali et al. 2017; Mladinich, Schwedes, and Mackow 2017).

Microglia represent an important component in the neural defects associated with Zika virus infections. Data suggest that microglia are highly susceptible to Zika virus infection as they are directly exposed to the pathogen through the direct contact of their processes with blood vessels. Local neuroinflammation is thought to occur together with viral dissemination into the brain parenchyma, which may result in cell death of developing neurons, in particular in the cortex, and lead to neurological alterations and microcephaly. These findings highlight the need for comprehensive studies to determine the molecular mechanisms that could be harnessed for targeted therapeutic interventions (Miner et al. 2016; Mlakar et al. 2016).

Placenta

Placental findings in Zika-infected patients include prominently enlarged, hydropic chorionic villi with hyperplasia and focal proliferation of Hofbauer cells. The degree of Hofbauer cell hyperplasia gives an exaggerated immature appearance to the villi. Additionally, no acute or chronic villitis, villous necrosis, remote necroinflammatory abnormalities, chorioamnionitis, funisitis, or hemorrhages were detected. An RNA probe to the Zika virus was positive in villous stromal cells, which are apparently Hofbauer cells (Rosenberg et al. 2017). Zika virus placental infection appears to induce proliferation and hyperplasia of Hofbauer cells in the chorionic villi, which does not appear to elicit villous necrosis or a maternal or fetal lymphoplasmacellular or acute inflammatory cell reaction (Rosenberg et al. 2017).

Renal and Bladder Agenesis

A case study by Villamil-Gonzales showed urinary bladder agenesis and renal hypoplasia in a subject. The renal cortex was found to have decreased thickness of the nephroblast layer, with an arrest in the glomerular migration towards the deepest zones of the cortex. There was paucity in the renal papilla with a noticeable reduction in the migration and maturation of the tubular collecting system, with an exaggerated expansion of the interstitial matrix at the expense of immature mesenchymal tissue (Villamil-Gómez et al. 2019). Given that the full teratogenic potential of Zika virus was not originally known (Nazer et al. 2018; Rodriguez-Morales et al. 2018; Valdespino-Vázquez et al. 2019), damage to the lower and upper urinary tract is likely related to this flavivirus infection. More studies are needed to confirm these findings. Besides, complete agenesis of the urinary bladder is a particularly rare anomaly seen in only a few live cases (Villamil-Gómez et al. 2019).

The kidneys are an active site of Zika virus replication in the fetus, as evidenced by the presence of viral-like particles in the renal tissues and the isolation of infectious Zika virus from the renal tissues (Valdespino-Vázquez et al. 2019). This impairment in the development of the kidney of the fetus is believed to lead to renal hypoplasia. Additionally, the renal tubular epithelium is a site of Zika virus infection (Valdespino-Vázquez et al. 2019). Zika virus replication in the kidneys is likely why there is continuous viral shedding seen in the urine of some CZS patients (Valdespino-Vázquez et al. 2019). Urinary bladder agenesis has been reported among the rarest urinary tract anomalies, with a reported incidence of 1 in 600,000 patients and only 64 cases reported worldwide (Nazer et al. 2018). Urinary bladder agenesis is usually associated with other severe malformations that are incompatible with life. It has been linked with urogenital sinus injury at weeks 5-7 of embryogenesis (Villamil-Gómez et al. 2019), which is likely caused by Zika virus infection during the first weeks of pregnancy without other apparent infectious and non-infectious teratogenic factors.

Visceral Findings

In a study by Beaufrère et al, there was a note of several other visceral involvements due to Zika (Beaufrère et al. 2019). Three terminated pregnancies were studied, with the following findings in their visceral examination of the fetus: hepatomegaly (liver weight of 63 g, which falls >95th percentile for term), splenomegaly (spleen weight: 11.6 g, which was >95th percentile for term), and thymus hypertrophy (thymus weight: 6 g, falling in the >95th percentile for term fetuses). Adrenal gland hypoplasia (adrenal weight: 0.4 g, seen in <5th percentile for term) was observed in another case. Microscopic examination showed no major visceral changes, except an interstitial lymphocytic infiltrate (established by anti-CD45 immunohistochemistry) when testing both of these male fetuses (Beaufrère et al. 2019).

Testis interstitial lymphocytic infiltrate was also consistent with data observed previously in experimentally infected mice. Zika viral particles were detected in the testis and epididymis of male mice, and the infiltrating inflammatory cells associated with the infection appeared to worsen tissue injury (Govero et al. 2016). In humans, Joguet and colleagues showed that replication-competent Zika virus can be isolated from motile spermatozoa, and semen alterations were seen (Joguet et al. 2017).

Femur-sparing Intrauterine Growth Restriction

Zika virus was also found to demonstrate a femur-sparing pattern in Intrauterine Growth Restriction (IUGR) in late gestation (Walker et al. 2018). Fetuses that were either small for gestational age or growth-restricted were observed in 9% of pregnancies likely infected by the Zika virus in a Brazilian study (Brasil et al. 2016). There were four cases of microcephaly in their cohort labeled as either “proportionate” (2/4, 50%) or “disproportionate” (2/4, 50%), relative to the size of the infant. The authors defined “disproportionate” microcephaly as a grossly differential growth of the head with respect to other body parts in at least half of their index cases. IUGR has also been described as a hallmark feature of several murine models of Zika virus infection in pregnancy and is associated with spontaneous abortion and stillbirth in these models (Mysorekar and Diamond 2016; Uraki et al. 2017; Yockey et al. 2018). This femur-sparing pattern of growth restriction was seen in 52% of pregnancies with either head circumference:femur length or (HC:FL) or abdominal circumference:femur length (AC:FL) fetal body ratio <10th percentile (2014 International Fetal and Newborn Growth Consortium for the 21st Century Project Z-score e1.3 or IG-21) (Walker et al. 2018). This study suggested that infants born

following a possible maternal Zika virus infection may have abnormal growth patterns of the fetal head and abdomen with respect to the femur. Hence, IG-21 fetal body ratios may provide an early indication of aberrant fetal growth before a clinical or sonographic diagnosis of IUGR or microcephaly is detected. Alerting clinicians to deviations in symmetric growth of a nonmicrocephalic fetus with congenital Zika virus exposure, may aid in the identification of cases at risk for a greater spectrum of Zika virus-associated morbidity (e.g., postnatal microcephaly, optical abnormalities). More intensive neonatal follow-up in low-resource settings for earlier interventions after delivery may be warranted (Walker et al. 2018).

The Zika virus infection poses an emerging threat to maternal and fetal health around the globe. The authors have determined that fetal manifestations were multi-systemic, affecting mostly neurologic outcomes. However, there is growing evidence that it affects the development of various other organs and organ systems, such as the placenta, the urogenital, the gastrointestinal, immune, and musculoskeletal systems.

The Philippines remains vulnerable to the onslaught of the Zika virus as a result of its lingering challenges in the healthcare system. Global travel to and from Zika-affected countries remains a viable risk factor, along with the overall change in global climate and unreliable vector control initiatives in the country. Various challenges in surveillance, clinical management, screening, and health promotion exist. Co-circulation of Zika, along with Dengue and Chikungunya, has been highlighted as a diagnostic challenge; hence, an intensified community awareness campaign zeroing in on these viral infections continues to be recommended by specialists (Lonogan et al. 2020).

This review brings to light the need for awareness of the potentially catastrophic effects of Zika virus infection in pregnant women. Identifying risk factors, primary prevention and early identification of signs and symptoms, should be included in the care of at-risk populations in the country. The comprehensive nature of this review provides physicians and allied healthcare professionals the armamentarium for content and evidence synthesis in educational campaigns to combat the conceivable detrimental effects of the virus in the community. However, the authors acknowledge that limitations exist, such as the timeframe covered by the review and the intrinsic broad nature of this study, which requires additional steps to draw verifiable conclusions.

It is the hope of the authors that further studies involving other organs and/or organ systems, as well as management strategies to prevent and control Zika virus infection, materialize soon. Public health strategies include incorporating these into national programs that are implementable and measurable in various healthcare settings in the Philippines.

CONCLUSION

We have reviewed the literature available on the effects of maternal and/or congenital Zika virus infection on fetal growth and development. There is substantial evidence of the effect on neurologic outcomes, and emerging effects on the ophthalmologic, genitourinary, visceral, and femur-protection outcomes. The need for additional research on emerging types of effects of the Zika virus has been identified. Nonetheless, this study provides the groundwork for informing other stakeholders of the effects of the Zika virus on vulnerable populations.

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FINANCIAL AND COMPETING INTEREST DISCLOSURE

The authors have self-funded this study and declare no competing interests.

CONTRIBUTIONS OF INDIVIDUAL AUTHORS

Marissa Elizabeth L. Lim, Arlene I. Afaga, and Jon Timothy Rivero contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript.

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