

## Review Article

# Zika Virus and Perinatal Outcomes: Beyond the Myth

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## Abstract

The World Health Organization defines the recent outbreak of Zika infection as a *Public Health Emergency of International Concern* (PHEIC). An attempt was made to contribute to a comprehensive screening protocol for Zika in pregnancy, based on systematic assessment of the empirical data. A total of 34 published articles, randomly located in the major scholarship portals (Pubmed, LILACS, SCOPUS) and conferring to the level I-IIA evidence, are sampled to inform clinical, serology, imaging, and histology findings from 8,389 singleton pregnancies. Results of a comparative analysis between the Zika-positive and Zika-negative pregnant women presented with macopapular rash suggest that active Zika virus infection is predictive to the adverse perinatal outcomes: prematurity, fetal growth restriction, microcephaly, and Guillain-Barré syndrome. Temporal analysis between the viral peak lags, the first acute rash in women, and perinatal outcomes, support such associations.

**Keywords:** Zika virus; Flavivirus; Microcephaly; Guillain-Barre syndrome; White brain damage

## Introduction

Outbreaks of a mosquito-borne flavivirus, known as Zika Virus (ZIKV), are consistently described in South America [1-5], Puerto Rico [6], French Polynesia [7-9], Southeast Asia [10-12], Federated States of Micronesia [13,14], and other parts of the Oceania [15,16]. Present in Africa and Asia decades ago, the ZIKV infection is currently moving to South and Central America [17,18]. It is anticipated, that Zika virus will spread to all other countries in the Americas that have dengue carrying *Aedes* mosquitoes—that is, all except Canada and Chile [15,17].

Based on the reported clusters of microcephaly, cerebellar hypoplasia, and Guillain-Barré syndrome in neonates born to the ZIKV-affected mothers [18-23], the World Health Organization defines Zika infection as a *Public Health Emergency of International Concern* (PHEIC) [24-26].

Yet, vertical transmission of ZIKV remains ambiguous. Unlike other arboviral or tourism-infections such as Dengue (DEN), Chikungunya (CHIK), West Nile Virus (WNV), St. Louis Encephalitis (SLE), or La Crosse Encephalitis (LAS), Zika infection causes a fairly mild fever, headache, arthralgia, myalgia, and rarely it manifests in maculopapular rash, acute exanthematous illness, or conjunctivitis. About the 80% of persons infected with ZIKV are asymptomatic and the fatality is thought to be rare [27-31]. Evolving findings suggest a presence of Zika virus in the semen, a significant challenge to be addressed for better understanding of teratogenicity and congenital anomalies [32].

## Aim

To contribute to a comprehensive screening and diagnostic protocol for ZIKV in pregnancy, based on a systematic assessment of published empirical data.

## Sampling

A total of 34 published articles, conferring to the level I-IIA

evidence, are randomly identified in the major research portals (Pubmed, SCOPUS, LILACS) to inform clinical (obstetrical, neurological), serology, imaging, and histology findings from 8,389 Zika-affected pregnancies.

**Inclusion criteria:** rash, and singleton pregnancies.

## Exclusion criteria:

1. Pregnancies with twins or multitons
2. Pregnancies with the uterine fibroids;
3. Severe preeclampsia;
4. Familial history of congenital anomalies;
5. Prior infections with cytomegalovirus, rubella, dengue, toxoplasma gondii, parvovirus B19;
6. History of habitual miscarriages, stillbirth, and perinatal death;
7. Familial history of microcephaly;
8. Alcohol or illicit drug use during pregnancy.

Clinical (observational) data include: miscarriage, stillbirth, Fetal Growth Restriction (FGR), oligohydramnios, preeclampsia, preterm birth, Small for Gestational Age (SGA) newborns, placentation defects (premature detachment, accreta, increta, percreta), neonatal conjunctivitis, neonatal pneumonia, microcephaly, splenomegaly, Guillain-Barré syndrome, congenital birth defects, and perinatal death. Serology data are generated from the reported results of Reverse Transcription-Polymerase Chain Reaction (RT-PCR), Immunoglobulin M (IgM) quantitative testing, and Enzyme-Linked Immunosorbent Assay (ELISA). Imaging data include the results of ultrasound, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) from the abdominal, thoracic, and cranial screenings of the newborns. Pathological data include placental histology and neonatal autopsy results.

**Table 1:** Assessments of clinical properties in reported studies are in compliance with the following definitions.

Term	Definition	Source
Asymmetric fetal growth restriction	Fetus with an estimated weight below the 10 <sup>th</sup> percentile for gestation age, with Femur-Length (FL)/Abdominal-Circumference(AC) greater than 23.5, with restriction of the fetal weight followed by length, while the head continues to grow at normal rates (head sparing).	American College Of Obstetrics & Gynecology (ACOG); Royal College Of Obstetricians & Gynecologists (RCOG)
Symmetric fetal growth restriction	Fetus with an estimated weight below the 10 <sup>th</sup> percentile for gestation age, with FL/AC greater than 23.5, and with the cranial circumference in proportion to the rest of the body.	ACOG, RCOG
Growth-Adjusted Sonographic Age (GASA)	Estimated by ultrasound measurements of crown-rump length, BPD, FL, and AC.	ACOG, RCOG
Ponderal Index (PI)	A ratio of the fetal body weight to the length. $PI = [weight \times 100] \div [length]$ .	The World Health Organiz. (WHO)
Doppler-Shifted Frequency (Fd)	Depends on the angle of the ultrasound beam relative to the direction/angle of the blood flow ( $\Theta$ ), frequency of the initial sound ( $F_0$ ), velocity of the flow ( $V$ ), and speed of the sound in the tissue (commonly, 1540 m/sec). $Fd = V (2F_0 \cos \Theta) \div C$	Lams et al (1990) <sup>35</sup>
Amniotic fluid index	A pocket of amniotic fluid that measures at least 1 cm in two perpendicular planes. Scores 0-10.	ibid
Biparietal Diameter (BPD)	The transverse distance between the eminences of the two parietal bones of fetal skull.	WHO
Occipito-Frontal Diameter (OFD)	The diameter of the fetal head from the external occipital protuberance to the most prominent point of the frontal bone in the midline.	WHO
Microcephaly	Fetal/neonate head circumference at least 2SD below the average circumference size for age, sex, race, and gestation week.	Mayo Clinic Foundation
Guillain-Barré syndrome	An acute form of polyneuritis, often preceded by a respiratory infection, causing weakness and often paralysis of the limbs.	WHO, Mayo Clinic Foundation
Preeclampsia	Diastolic blood pressure increased to 15 mmHg, on two occasions at least 6 hours apart—with a difference > 5 mmHg between the arms; proteinuria (presence of 0.3 g protein in 24-h urine specimen on two random samples collected at least 4 hours apart), and HELLP syndrome—all occurring after 20 gestation weeks.	ACOG
Preterm birth	Delivery of an infant from 23rd to 37th weeks of gestation, which approximates an average fetal weight from 500 to 2500 g, and height from 28 to 48 cm.	WHO
Perinatal death	Death of fetus (or neonate) weighing 500 grams or more and with height of 28cm and more in the period between the 22 <sup>nd</sup> gestation week to the 7 <sup>th</sup> neonatal day.	ACOG, RCOG, WHO
Odds	The ratio of probability of the outcome to the probability of not having the outcome: $p/(1 - p)$ .	Fletcher et al (2005) <sup>36</sup>
Odds Ratio (OR)	A comparison of event rates between exposed and unexposed groups, calculated using odds instead of probabilities.	ibid
Relative Risk Reduction (RR)	The percentage of diseases prevented by a treatment: $RRR = (risk\ in\ unexposed - risk\ in\ exposed) / risk\ in\ unexposed$	ibid

## Definitions

Assessments of clinical properties in reported studies are in compliance with the following definitions: Table 1.

## Data extraction

Frequencies and means extracted from the studies are combined to present weighted mean difference statistic and are modeled as measurable outcomes. Odds of the numerical variables, Biparietal Diameter [BPD], Femur Length [FL], Occipito-Mental Diameter [OMD], Occipito-Frontal Diameter [OFD], Sub-Occipito-Bregmatic Diameter [SOBD], Sub-Mento-Bregmatic Diameter [SMBD], Amniotic Fluid Index [AFI], and Apgar scores are used as linear functions exposed to the factors. Temporal correlations and time lags are tested to distinguish the primary and recurrent infections, also to identify the proximity between the epidemic curves and reported clinical and parametric outcomes.

## Data analysis

Calculations use births as units of analysis. One-Way Analysis Of Variance (ANOVA) is used for the continuous data. Kruskal-Wallis ANOVA is used for the ranked ordinal data. For binary variables Relative Risk (RR) and its 95% Confidence Interval (CI) are computed to treat the basis. For multivariate outcome-score models generalized estimating equations are used with a canonical correlation structure (for continuous variables), recursive partitioning (for dichotomous variables), and discriminant analysis (for both).

## Results

All recruited studies are observational - with longitudinal cohort (87.5%), cross-section (9.4%), and retrospective case-control (3.1%) designs. The mean age of ZIKV-positive women is 28.3 years (with a range of 19-41 years) and the median age is 26 years. The mean age of ZIKV-negative women is 27.8 years with the median age of 25 years. Timing for the acute ZIKV ranges from 11<sup>th</sup> to 32<sup>nd</sup> gestation weeks. Table 2 presents the descriptive data stratified for ZIKV-positive and ZIKV negative women.

As seen from Table 2, a total of 8389 enrollments of the ZIKV-exposed pregnant women are reported in studies published from September 2014 through April 2016; of these 6275 (74.8%) test ZIKV positive by RT-PCR or IgM ELISA. Those who are ZIKV IgM negative form the comparative group of 2114 women (25.2%). The Cronbach's alpha inter-item coefficient, ranging from 0.425 to 0.872, proves the clusters as comparable. All pregnant women have rash as part of their clinical presentation, since rash is an inclusion criterion.

As shown in Table 2, some of the continuous variables (gestation week at preterm birth, microcephaly, oligohydramnios, Ig titers for ZIKV) are presented in prevalence rates based on already established parameters and clinical observations in the reviewed studies. The presented rates refer to the prevalence, not to the incidence, as a traditional meta-assessment cannot capture the temporal order of the events.

The first-impression descriptive data suggest that the ZIKV-

**Table 2:** Clinical and Parametric Properties of the Sample.

Several properties of singleton pregnancies	ZIKA-positive women	ZIKA-negative women	OR or RR (95% CI)	t test T (P) or test for trend x2 (P)
Sample size	6275	2114		
Tobacco smoking in pregnancy (%)	0	1.2	-	-
History (or presence) of dengue (%)	31.4	56.2	0.5	0.08
Gestation age of ZIKV-exposure [M (range)]	20 (11-37)	17 (14-41)	1.2	0.3
Fever (%)	28	23.4	1.2	0.5
Headache (%)	62.5	58.1	1.1	0.3
Myalgia (%)	74	38.4	1.9	0.05
Arthralgia (%)	65	41	1.6	0.16
Conjunctivitis in women (%)	58	19	3.1	0.002
Retro-orbital pain (%)	49.3	31.4	1.6	0.25
Photophobia (%)	23.7	32.5	0.7	0.5
Descending macular rash (%)	51.4	50	1.02	0.8
Macopapular rash (%)	44	12	3.7	0.005
Pruritis (%)	94	72	1.3	0.04
Lymphadenopathy (%)	40.5	6.5	6.2	0.02
Paresthesia (%)	46.6	40	1.2	0.8
Asymmetric fetal growth restriction (%)	5.8	4.9	1.2	0.01
Symmetric fetal growth restriction (%)	17.5	3.4	5.1	0.005
Fetal anomalies detected by Doppler scan (%)	27.2	5	5.4	0.02
Neonate anomalies confirmed after birth (%)	13.6	4	3.3	0.005
Oligohydramnios (%)	8	2.35	3.4	0.01
Amniotic fluid index (AFI) (M/SD)	4.4 (2.1-7.34)	6.2 (2.8-9.1)	0.7	0.8
Preeclampsia (%)	35.9	25	1.4	0.03
Trombocytopenia (%)	1.3	0	-	-
Premature birth (%)	48.5	12.9	3.8	0.5
Perinatal death (%)	2.3 +1	0	-	-
Conjunctivitis in newborns (%)	7.9	2.3	3.4	0.02
Rash in newborns (%)	7.9	3.4	2.3	0.02
Guillain-Barré syndrome (%)	11.5	2.3	5	0.01
Microcephaly (%)	8.75	1.2	7.3	0.02
Ventricular calcification in the brain (%)	8.6	2.1	4.1	0.05
Chronic placentitis (%)	89.3	46.7	1.9	0.002

positive women present significantly higher rates of conjunctivitis (RR 3.1; at 95% CI and  $p < 0.002$ ), macopapular rash (RR 3.7;  $p < 0.005$ ), local or regional lymphadenopathy (RR 6.2;  $p < 0.02$ ), symmetric and asymmetric types of fetal growth restriction (RR 5.1 and 5.4 correspondingly,  $p < 0.02$ ), and oligohydramnios (RR 3.4;  $p < 0.01$ ). Among the noted adverse perinatal outcomes associated with active ZIKV are premature birth (RR 3.8;  $p < 0.5$ ), neonatal conjunctivitis (RR 3.4;  $p < 0.02$ ), Guillain-Barré syndrome (RR 5.0,  $p < 0.01$ ), microcephaly (RR 7.3;  $p < 0.02$ ), with ventricular calcification of the white brain matter (RR 4.1;  $p < 0.05$ ). Neonatal anomalies, confirmed after birth, are more evident in ZIKV-positive group (RR 3.3;  $p < 0.005$ ). Interestingly, the chronic placentitis has almost similar presentation in both ZIKV-positive and ZIKV-negative women with descending macular or maculopapular rash.

Pearson queue reveals substantial associations between the oligohydramnios and ventricular calcification of the white brain matter (0.422, CI 95%), as well as between the macopapular rash and Guillain-Barré syndrome (0.538, CI 95%). Weak associations are established between the paresthesia in women and Guillain-Barré syndrome in newborns (0.189) with reliable Cohen's Kappa ( $> 0.80$ ). For other clinical and parametric components (retro-orbital pain, fever, arthro-myalgia, pruritis, chronic placentitis, preeclampsia, premature birth), correlations fail to produce convincing associations.

Unlike other studies [16,19,22], our findings do not prioritize pruritus and athromyalgia as predominating symptoms of the active ZIKV (RR 1.3-1.9), nor see them as strongly associated with the most described adverse perinatal outcome, such as microcephaly ( $r = 0.246$ ,  $p < 0.01$ ).

Temporal associations between the microcephaly and ZIKV counts are described in a few studies that explore transplacental transmission of ZIKV [33,34]. For each model variant, maximum likelihood estimates of model parameters are obtained with a simulated annealing algorithm. The likelihood ratio method is used to compare different peak models. For the small size clusters, the Akaike information criterion is utilized [35-37]. In sensitivity analysis, scenarios are explored in which the final attack rate is 50%, 60%, 70%, or 80% and the weekly number of births is 60 or 100, and the relative changes in estimates ranges from -20% to 33%.

The viral proteins and viral RNA are identified in placenta, Hofbauer cells, intervillous spaces, as well in scattered foci of microcalcifications in the brain tissue of the newborns to mothers infected at different weeks of pregnancy. Number of Guillain-Barré syndrome cases peaked after a lag of 5-9 weeks from the first acute rash, and number of suspected cases of microcephaly peaked after a lag of 30-33 weeks from the onset of the acute rash; correspond to time of potential infections during the first trimester. Such findings support the association of Guillain-Barré syndrome and microcephaly with Zika virus infection, providing with evidence of a temporal relationship between the arboviral infection during the first trimester and poor perinatal outcomes.

## Discussions

The massive outbreak of the mosquito-borne Zika infection enables quantifying and prioritizing associations between Zika virus in pregnancy and adverse perinatal outcomes (microcephaly, Guillain-Barré syndrome, white brain damage in the newborn). Given the challenges in ZIKV testing of pregnant women and neonates, more case control studies (with exclusion of other viral infections) are required for sensitive and specific diagnostics. Among other study-limitations, RT-PCR tests may not detect ZIKV RNA in a newborn who acquired ZIKV infection *in utero* if the period of viremia has passed.

Still controversial, the risk of microcephaly from Zika infection seems lower compared to that from other viral infections associated to birth defects (cytomegalovirus, rubella, parvovirus B19) [37-39]. However, the incidence of Zika virus in general population can be higher during the outbreaks (so too the risk to pregnant women) compared to that in cytomegalovirus [40], rubella or parvovirus B19 [40,41]. The mosquito vector, as the vulnerable point for Zika virus transmission, is a possible explanation. The high risk of symmetric fetal growth restriction with microcephaly, identified in our study, reconfirms that Zika virus is a captious public health concern.

## Conclusions

The comparative analysis between ZIKV -positive and ZIKV-negative pregnant women exposed to the Zika virus outbreak and presenting with macopapular rash supports that the active Zika virus infection is predictive to the adverse perinatal outcomes such as prematurity, fetal growth restriction, microcephaly, and Guillain-Barré syndrome. Temporal analysis between the viral peak lags, the first acute rash in women, and perinatal outcomes, support such associations.

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