Factors associated with the development of Congenital Zika Syndrome in infants born to mothers with probable gestational infection: a case-control study

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BACKGROUND

- On March 31, 2016, the World Health Organization published a statement on the evidence for a causal link between Zika virus infection during pregnancy and the occurrence of congenital brain abnormalities, including microcephaly. With further observational studies, a whole set of congenital abnormalities was identified and linked to *in utero* Zika virus infection. This set of abnormalities was termed the Congenital Zika Syndrome (CZS) and may include microcephaly, craniofacial disproportion, irritability, spasticity, seizures, feeding difficulties, ocular abnormalities, and hearing loss on examination, as well as calcifications, cortical disorders, and ventriculomegaly on neuroimaging..
- We aim to investigate possible maternal- and pregnancy-related factors associated with the development of Congenital Zika Syndrome (CZS) in children of mothers with probable gestational infection

MATERIALS AND METHODS

This case-control study, we recruited mother-infant pairs between May 2015 and October 2017 in a pediatric infectious disease clinic in Rio de Janeiro. Inclusion criteria required either that the mother reported Zika infection symptoms during pregnancy or that the infant presented with clinical or imaging features of the CZS. Exclusion criteria included detection of an alternative cause for the patient's presentation or negative polymerase chain reaction assays for Zika in all specimens tested within 12 days from the beginning of maternal symptoms. Infants with CZS (CDC definition) were selected as cases and infants without CZS, but with probable maternal Zika virus infection during pregnancy, were selected as controls. Maternal and pregnancy-related informations were collected and their relationship to the presence of congenital anomalies due to CZS was assessed by Fisher exact or Mann-Whitney test

RESULTS

Out of the 42 included neonates, 24 (57.1%) were diagnosed with CZS (cases). The mean maternal age at the birth was 21 years old. The early occurrence of maternal symptoms during pregnancy was the only variable associated with CZS (odds ratio = 0.87, 95% CI: 0.78-0.97).

Case's mothers presented symptoms until the 25th week of gestational age (GA) (Figure), while control's mothers presented until 36th weeks of GA. Income; illicit drug, alcohol, or tobacco use during pregnancy; other infections during pregnancy (including previous dengue infection) were not associated with CZS (Table)

Table: Factors associated with SCZ:

Maternal demographic and gestational variables		Total population (n=42)	Controls (n=18)	Cases (n=24)	P-value
Week of gestation at time of symptoms, median (IQR ¹)		13 (8.25-24.25)	20	10	< 0,01
Maternal age at delivery in years, median (IQR)		21 (19.75-29)	26.5	23	0.95
Week of gestation at delivery, median (IQR) (missing data: 1)		38 (37-39)	39	38	< 0.02
Household income per capita ² , median (IQR) (missing data: 15)		0.43 (0.25-0.71)	0.33	0.46	0.60
No. of previous gestations, median (IQR)		1 (0-3)	1	2	0.89
Week of gestation at first prenatal visit, median (IQR) (missing data: 14)		7 (6-15.25)	6.5	7.5	0.96
Substance use during pregnancy (%)					
	Tobacco	6/40 (15.00%)	2/18 (11.11%)	4/22 (18.18%)	0.67
	Alcohol	10/41 (24.39%)	4/18 (22.22%)	6/23 (26.09%)	1
	Illicit drugs	2/40 (5.00%)	0/18 (0%)	2/22 (9.09%)	0.49
Maternal coinfections during pregnancy ³ (%)					
	Syphilis	3/34 (8.10%)	2/16 (12.50%)	1/21 (4.76%)	0.57
	Human Immunodeficiency Virus	4/37 (10.81%)	3/16 (18.75%)	1/21 (4.76%)	0.30
Maternal dengue virus IgG reactivity at initial evaluation (%)		9/24 (37.50%)	5/12 (41.67%)	4/12 (33.33%)	1

Figure: Gestational age at symptoms

CONCLUSIONS

Our study corroborates the hypothesis that Zika virus infection earlier in pregnancy is a risk factor to the occurrence of congenital anomalies in their fetuses