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ORIGINAL

Clinical expressions in children born from mothers infected by the zika virus during pregnancy Pediatric Hospital Borrás-Marfán. 2016-2018

Expresiones clínicas en niños nacidos de madres infectadas por el virus del Zika durante el embarazo en el Hospital Pediátrico Borrás-Marfán. 2016-2018

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ABSTRACT

Introduction: the infection of the Zika virus that is endemic in Asia and Africa has now been extended to the Americas. This virus is considered teratogenic, producing a new disease that must be studied in depth.
Objetives: this is to identify the clinical expressions found in children from mothers infected with the Zika virus during their pregnancy, and thereby establish the possible association of the time of the prenatal exposure to the Zika virus and the positive clinical findings.
Methods: we carried out a transversal descriptive study, with 86 children from women having had an infection by the Zika virus, which were pregnant between January 2016 and December 2018. For the correlation between the presence of positive findings and the trimester of pregnancy at the detection of the infection by the Zika virus, we used Spearman's correlation with a significance level of $p \leq 0,05$.
Results: out of the total number of patients included in the study, 27 expressed a positive clinical finding. Among the neurological disorders, those related to muscular tone were the most frequent (15,48 %), followed by psychomotor retardation (10,71 %) and microcephaly (9,52 %). An association was observed between the prenatal exposure to the Zika virus during the first trimester of pregnancy and the presence of positive clinical findings.
Conclusions: there was a prevalence of neurological expressions, followed by visual expressions. The evidence proved that the exposure to the Zika virus during the first trimester of pregnancy had a teratogenic effect.
Key words: Zika Virus; Congenital Syndrome due to the Zika Virus; Microcephaly.

RESUMEN

Introducción: la infección del virus del Zika, endémico en Asia y África, se ha extendido a las Américas. Este virus se considera teratógeno, produciendo una nueva enfermedad que debe ser estudiada en profundidad.
Objetivos: identificar las expresiones clínicas encontradas en niños nacidos de madres infectadas con el virus del Zika durante su embarazo, y establecer la posible asociación del momento de la exposición prenatal al virus del Zika y los hallazgos clínicos positivos.
Métodos: realizamos un estudio descriptivo transversal con 86 niños nacidos de mujeres que habían tenido una infección por el virus del Zika durante el embarazo entre enero de 2016 y diciembre de 2018. Para la correlación entre la presencia de hallazgos positivos y el trimestre del embarazo en el que se detectó la infección por el virus del Zika, utilizamos la correlación de Spearman con un nivel de significancia de $p \leq 0,05$.
Resultados: de la cantidad total de pacientes incluidos en el estudio, 27 presentaron hallazgos clínicos positivos. Entre los trastornos neurológicos, los relacionados con el tono muscular fueron los más frecuentes

(15,48 %), seguidos del retraso psicomotor (10,71 %) y la microcefalia (9,52 %). Se observó una asociación entre la exposición prenatal al virus del Zika durante el primer trimestre del embarazo y la presencia de hallazgos clínicos positivos.
Conclusiones: hubo una prevalencia de expresiones neurológicas, seguidas de expresiones visuales. La evidencia demostró que la exposición al virus del Zika durante el primer trimestre del embarazo tuvo un efecto teratógeno.
Palabras clave: Virus del Zika; Síndrome Congénito por el Virus del Zika; Microcefalia.

INTRODUCTION

As of the 1990's congenital malformations were the second cause of death in children under one year of age in Cuba, thereby being of prime importance in the medical and social programs in the country.[1]

The infection by the Zika virus (ZIKV) transmitted by mosquitoes that produces a mild and endemic disease in Africa and Asia, has led to large outbreaks since 2014 in the Americas that have been linked to neurological disorders.[2,3,4,5] After a large number of scientific debates, and through the cooperation of international research institutions, the World Health Organization (WHO) has recognized the possible role of the ZIKV as the cause of microcephaly and other congenital brain defects.[2,3,4,5]

Starting in December 2015 in Cuba, a national epidemiological warning was issued and protocols were established, which were designed to prevent its consequences. In 2016 a national action plan was formulated containing 11 steps against Zika, based on the guidelines of the Pan American Health Organization (PAHO), to control the disease. This plan covered three main objectives, i.e. detection, prevention and response.[2]

At present, we observe the emergence and reemergence of infectious diseases, including Zika. As a part of the epidemiological warning issued by the health authorities worldwide, in relation to the epidemic outbreak by the ZIKV, it is important to study thoroughly and clearly the Zika Congenital Syndrome, which is a newly described disease. This is indispensable for establishing preventive strategies, focused on the early diagnosis of complications that lead to steps for the appropriate training of the family and health workers regarding the treatment and necessary management for comprehensive quality care. Therefore, the objectives of this study were the following: to identify the clinical expressions found in children whose mothers were infected by the ZIKV during their pregnancy, and to establish the possible association between the time of the prenatal exposure to the ZIKV and the positive clinical findings.

METHODS

A descriptive transversal study was carried out at the National Center of Medical Genetics in Cuba. We applied non-probabilistic sampling, the method used for the selection of the population that will be analyzed. The study included the children of mothers diagnosed (either having a presumptive or confirmed diagnosis) with the ZIKV infection during pregnancy. The data collected covered the period from January 2016 to December 2018 in Havana, Cuba. The follow-up of the children was carried out during their first year of life at the Clinical Genetics Service of the Borrás-Marfán Pediatric Hospital. The children excluded were those with clinical signs that were characteristic of other known nosological entities.

The population of cases was of 84 patients that formed three groups depending on the presence or absence of clinical signs and the results of the identification of ZIKV during pregnancy, using polymerase chain reaction (PCR) in any of the fluids tested (serum, urine, amniotic fluid, etc.). The groups of cases were:

- ***Group 1:*** Those whose mothers showed clinical signs of infection by ZIKV during pregnancy, with a positive confirmation through PCR.
- ***Group 2:*** Those from mothers showing clinical signs of ZIKV infection, but without a positive confirmation through PCR (either because there was no result, the result was negative, or the test was not made).
- ***Group 3:*** Patients whose mother showed no clinical signs of Zika during pregnancy, but because they lived within a radius of 300 meters of a case with a presumptive or positive diagnosis, they were studied and PCR confirmed the ZIKV infection.

Collecting the information

- The source of information were the clinical data collected, according to the standardized methodology of the National Medical Genetics Network.[3]
- The individual clinical record of each pregnant woman diagnosed was consulted (whether with a presumptive or confirmed diagnosis) for the infection by ZIKV during pregnancy.

The variables were: sex, group, trimester of pregnancy of the mother at the diagnosis of ZIKV infection; as well as the signs recorded during the physical examination, of which we considered as variables the

morphological alterations of the central nervous system (whether they were identified before birth through imaging, or after birth), the presence or absence of microcephaly (according to the curves suggested by PAHO/WHO for age and sex),[4] other neurological signs, disorders of the musculoskeletal system (MSS), visual and ocular fundus signs during the first year of life, and signs derived from the hearing evaluation.

Information processing and analysis

The data was stored in a Microsoft Office Access 2016 database and processed through SPSS 20,0; and GraphPad Prism. Statistical techniques were applied to describe, compare and show relationships between the above variables. For qualitative variables, we determined the absolute and relative frequencies, and used bar graphs for their representation.

Pearson's Chi square (X^2) or the Fisher test were used to study the existence of an association between nominal qualitative variables. Spearman's correlation was applied to determine the correlation between the ordinal qualitative variables and the quantitative variables. We calculated the Odds Ratio to measure the size of the association between the presence of clinical signs in children and the evidence of the exposure of their mothers to the disease during pregnancy.

In all cases, statistical significance was considered when $p<0,05$.

Ethical aspects

The study was approved by the Ethics and Research Committee of the National Center of Medical Genetics of Cuba, according to legally established by the Ministry of Public Health (Agreement number 25, 2016);[5] the legal guardian of all the children gave written informed consent for their participation in this research.

RESULTS

Out of 84 cases included in the study, 44, i.e. 52 %, corresponded to females. There was a prevalence of patients belonging to group 1, with mothers showing clinical signs that were presumed to be due to the Zika virus infection, as well as having a positive PCR test (in any of the fluids used). Group 1 had 64 cases, representing approximately 76 % of those of the study, while groups 2 and 3 were represented in 13 cases (15,5 %) and 7 cases (8,3 %) respectively.

On analyzing the distribution of the cases, considering the trimester of pregnancy at which the Zika virus infection diagnosis was carried out in the mothers, it is noteworthy that there was a prevalence of the second trimester (40 cases, i.e. 47,6 %), while in the first and third trimesters there were 11 (13,1 %) and 33 (39,29 %) cases, respectively.

As shown in figure 1, positive findings were observed in 27 patients included in the study. The highest proportion was found in group 1 with 21,42 % (18 patients). There was an association between the groups and the presence of positive findings in the patients, and although this was statistically significant for the three groups, the magnitude was greater for groups one and two.

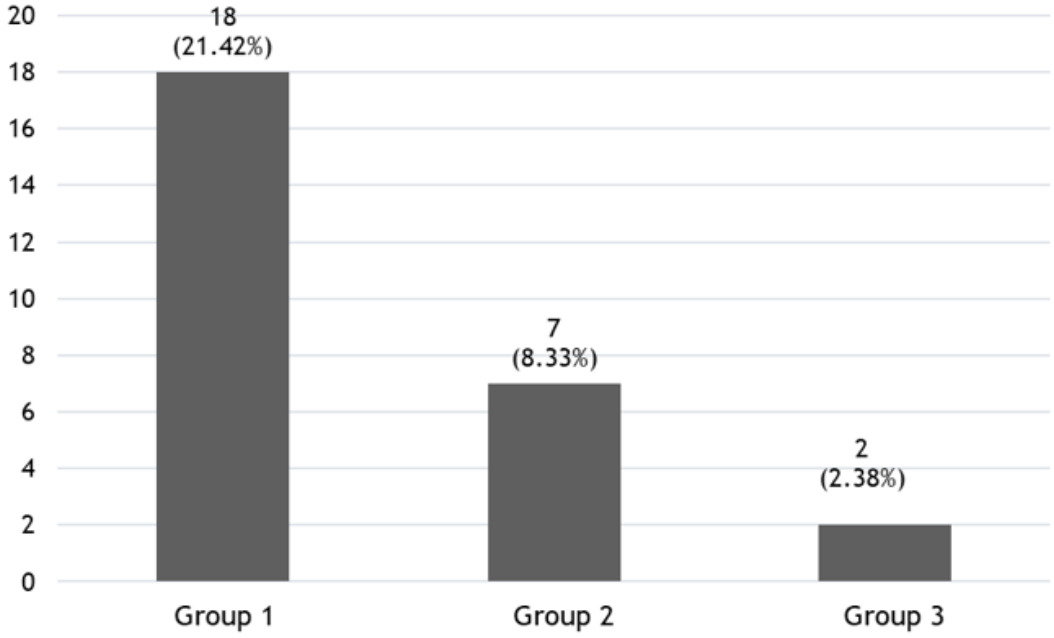
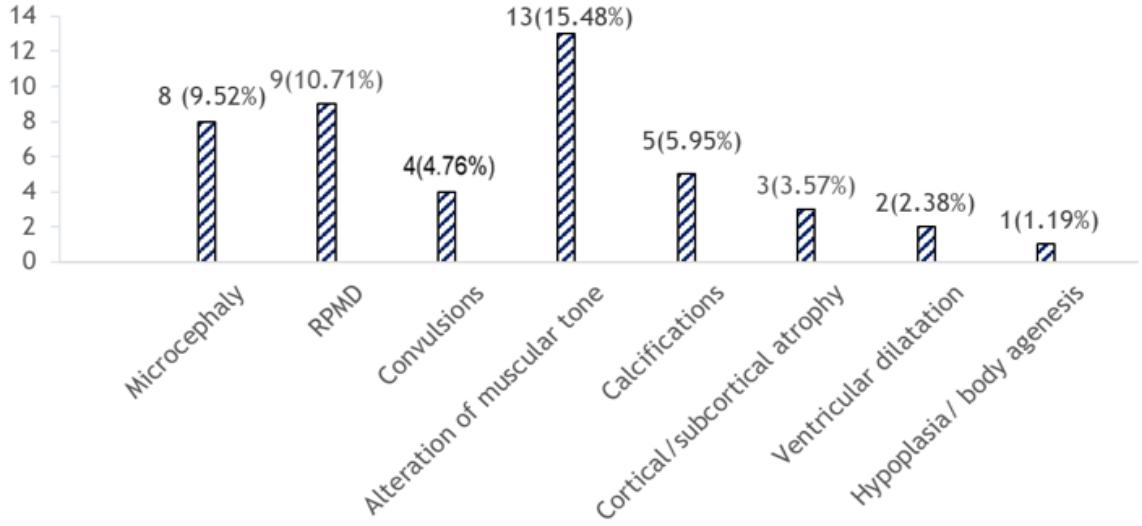


Figure 1. Distribution of the cases according to the presence of clinical findings. Borras-Marfán Pediatric Hospital. Havana 2016 - 2018

Group 1: X2= 17,99 p<0,0001 OR= 10,57 IC (2,952 – 37,81).
Fisher test: p<0,0001.
Group 2: X2= 30,77 p<0,0001 OR= 31,50 IC (6,444 – 154,0).
Fisher test: p<0,0001.
Group 3: X2= 8,120 p< 0,0044 OR= 11,20 IC (1,509 – 83,11).
Fisher test: p< 0,0430.

Considering all positive findings (N=69), approximately 66 % (N=46) showed neurologic signs, as observed in figure 2; those related to muscular tone were found in 13 patients (15,48 %). It is important to point out that two cases had axial hypotonia combined with that of the limbs. In second place, we found retardation of psychomotor development (RPMD) in nine cases (10,71 %) and microcephaly in eight cases (9,52 %). In four patients with microcephaly, the diagnosis was carried out during the prenatal stage. On applying Spearman's correlation (trimester of pregnancy and microcephaly) the result was – 0,396 (a significant correlation at p ≤ 0,01 [bilateral]).



*RPDM: retardation of psychomotor development

Figure 2. Distribution of neurological signs in the cases studied. Borras-Marfán Pediatric Hospital. Havana 2016 - 2018

Figure 3 shows the distribution of the cases according to the trimester of pregnancy at the diagnosis of the ZIKV infection, and the presence of positive findings. Through Spearman's rank correlations we determined the relationship between the presence of positive findings (total amount), and the trimester of pregnancy at which the diagnosis of the ZIKV infection was made. This was statistically significant when the exposure to the infection by ZIKV occurred during the first trimester of pregnancy.

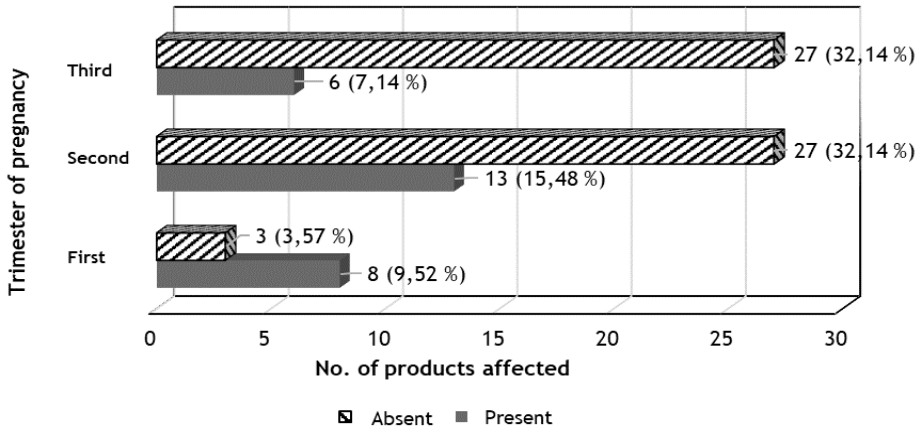


Figure 3. Distribution of the cases according to the trimester of pregnancy at the diagnosis of ZIKV infection and the presence of positive findings. Borras-Marfán Pediatric Hospital. Havana 2016 - 2018

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Spearman's correlation = - 0,374 (significant correlation at p ≤ 0,01 [bilateral]).

In an independent manner, we also analyzed the clinical signs according to specific systems, and the possible relationship with the trimester of pregnancy at the exposure to ZIKV. Hence, it is important to point out that 100 % of the cases presenting neurological involvement showed evidence of the prenatal exposure to the virus occurring in the first two trimesters of pregnancy. Furthermore, in the specific case of microcephaly, out of the eight cases found, five showed that prenatal infection by ZIKV occurred in the first trimester of pregnancy, and the other three were at the second trimester. The specific time of prenatal exposure to ZIKV in this case was at 14 weeks of pregnancy (figure 4).

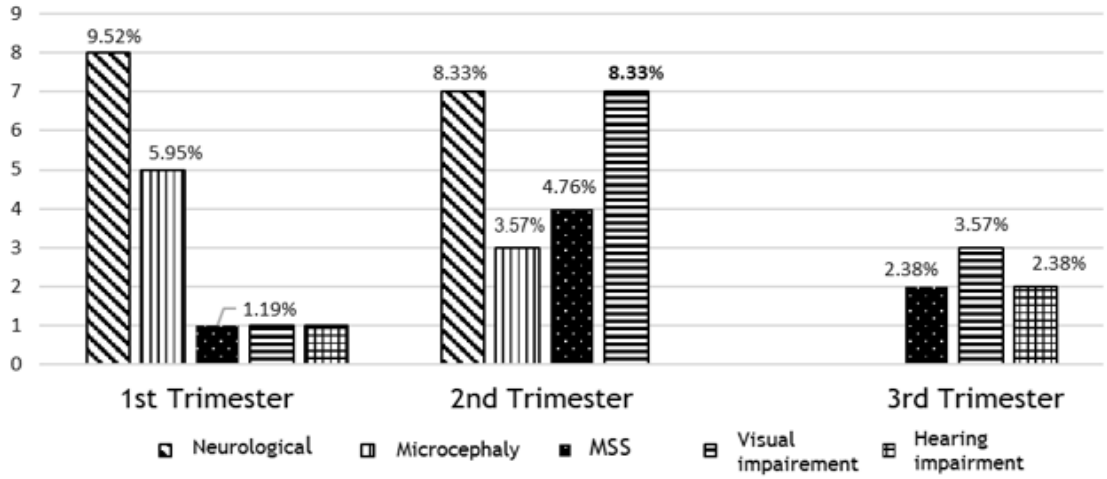

Figure 4. Distribution of the cases with positive findings according to the system of the body and trimester of pregnancy at which the exposure to ZIKV occurred

Spearman's correlation (trimester and microcephaly): - 0,396 (significant correlation at p ≤ 0,01 [bilateral]).

Positive findings in the neurological system were predominant in children exposed to the prenatal ZIKV infection in the first trimester of pregnancy (60,9 % of the cases) (figure 5).

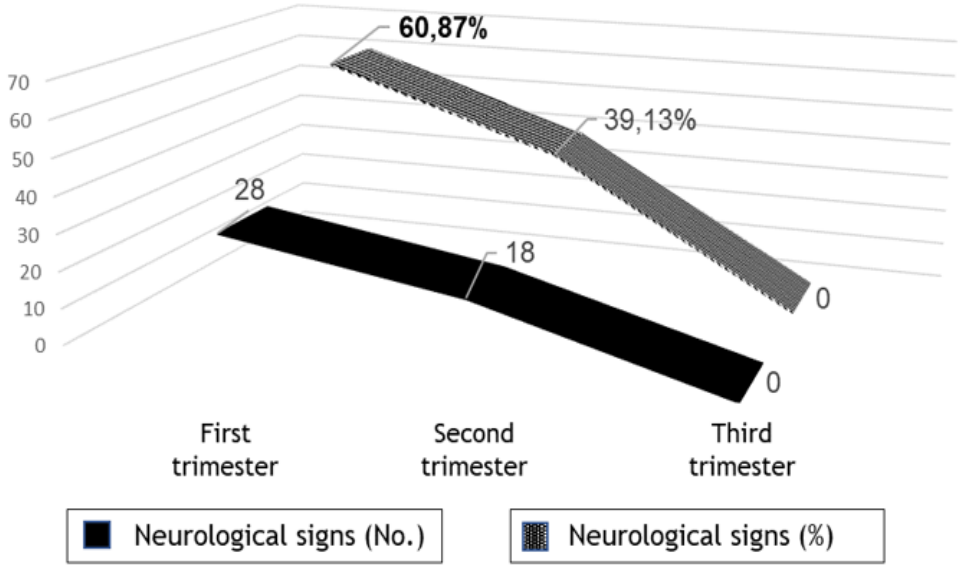

Figure 5. Correlation between the presence of neurological signs and the trimester of pregnancy at the diagnosis of ZIKV infection. Borras-Marfán Pediatric

Borras-Marfán Pediatric Hospital. Havana 2016 - 2018.
Source: Clinical Record.
Neurological signs: X^2= 29,76 p < 0,0001
Spearman's correlation: - 0,521 (significant correlation at p ≤ 0,01 [bilateral]).
The second most frequent clinical signs were visual disabilities (13 %), including myopia with the largest

number, i.e. 10 patients, of which two had the combination of myopia and astigmatism. They were followed by the MSS disorders in general, with seven cases. In relation to the congenital dislocation of the hip, we found a bilateral presentation in two cases. Concerning hearing, we only found conduction hearing loss, which was bilateral in two cases and unilateral in the other case (figure 6).

We carried out the analysis between the prenatal exposure to ZIKV and its possible association with each one of the clinical hearing and eyesight signs and those of the MSS separately. The results obtained were statistically significant for refraction disorders and the MSS disorders as a whole.

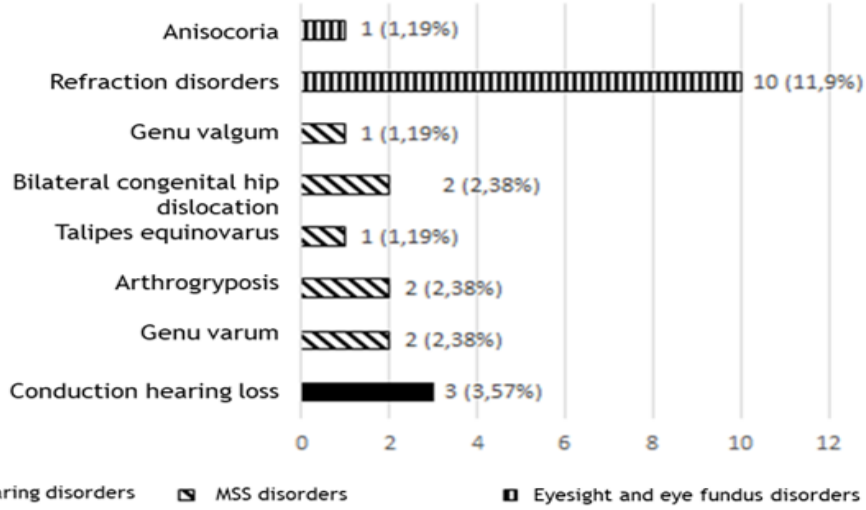

Figure 6. Distribution of the cases according to the presence of clinical signs in hearing and eyesight and signs of MSS. Borras-Marfán Pediatric Hospital. Havana 2016 - 2018

DISCUSSION

ZIKV is a neurotropic virus that interacts with the receptors and specific routes, thus producing neurological damage. Its geographic expansion has currently turned it into a true epidemiological threat for the world health system.[6]

The congenital Zika virus syndrome (CZVS) has not been completely defined. Observations show that many of its components are common to other congenital infections. There is a consensus between its clinical signs that may include: microcephaly, which can sometimes be severe (with a partially collapsed skull), a thin brain cortex having subcortical calcifications, macular scars and dotted focal pigment of the retina, congenital contractures, early marked hypertonia, and extrapyramidal symptoms.[7,8] Since it is important to know the signs of any disease for its diagnosis, it is indispensable to define those of CZVS by combining the observations of clinical descriptions of patients where there is evidence of a prenatal infection by ZIKV.[9]

In this study, there was a predominance of patients whose mothers had clinical conditions that could presumably be an infection by ZIKV, which was later confirmed with a positive PCR test. This favors the reliability of the analysis that is carried out through the data obtained. There was a prevalence of neurologic disorders. These include muscular tone, with the highest incidence, followed by psychomotor development retardation and microcephaly, respectively. Reports show that the clinical signs of CZVS are a consequence of the direct neurological disorder and the loss of intracranial volume, producing structural and functional changes. It was proven that the structural disorders include those of cranial morphology, brain and ocular anomalies, and congenital contractures, while the functional disorders are exclusively related to neurological deterioration.[10] Microcephaly was the first birth defect known, which was reported in association with the congenital infection of the Zika virus.[11] In this study we found through Spearman's correlation that there was an inverse relationship between the trimester of pregnancy and the presence of microcephaly. This indicates that an infection at a shorter time of pregnancy will produce a higher incidence of microcephaly. These results differ from those obtained by Del Campo et al.[12], who found microcephaly in 57,4 % of the cases (N=35), mostly identified at birth. These authors also observed that there was a prevalence of muscular tone disorders, specifically hypertonia (74,7 %).[12] This is in agreement with the results of this study, where it was the sign with the highest prevalence, not only within the disorders of the nervous system, but in general. Other studies show similar results, such as decrease in muscular force, hypertonia and hyperreflexia.[13]

In relation to the rest of the clinical signs found in the patients of this study, the hearing disorders were only found in three patients. Two of the patients had been exposed to ZIKV at the third trimester of pregnancy, and the other case at the first trimester. All three patients were diagnosed as having conduction hearing loss. This does not correspond with the observations of the majority of the studies in that the main type of hearing loss

reported in children whose mothers had been exposed to the ZIKV during pregnancy was the neurosensory loss of hearing, which was explained by the damage produced in the nervous fibers of the inner ear. In most of these studies, however, the prenatal exposure to ZIKV occurred in the second trimester, specifically during week 20 of pregnancy.[14] In the cases included in this study with loss of hearing, the exposure to ZIKV did not occur during the second trimester of pregnancy. It is well known that infections can also lead to conduction hearing loss by producing lesions in the external ear canal, the eardrum membrane or the middle ear.[14] Furthermore, different authors sustain that, although there is no type of hearing loss detected at birth, it is essential to systematically evaluate all patients,[14] and it is possible that a sequel of a prenatal infection producing conduction hearing loss may be observed in a larger number of patients.

The visual disorders were also frequent in patients included in this study, with a prevalence of refraction disorders, specifically myopia. However, reports from the literature show higher frequencies, when there is a prenatal exposure to ZIKV, in chorioretinal atrophy, changes in retinal pigmentation, hypoplasia of the optic nerve, paleness of the optic disk, a more curved optic disk, hemorrhagic retinopathy and abnormal retinal vasculature.[15] However, these findings were not observed in this study.

The alterations of MSS, observed in these cases, are consistent with the results of Marín et al.[16]. Nonetheless, we also found two cases with congenital bilateral hip dysplasia that were not observed by the above authors, which could be related to the poor position that are secondary to the neurological alterations.

Hence, in the current study, the main clinical signs observed in children under one year of age, with a history of an exposure to ZIKV during the prenatal stage, are shown as follows. Neurological disorders, where those of muscular tone have the highest incidence; this was followed by a delay in psychomotor development and microcephaly, respectively; while convulsions, intracranial calcifications, cortical/subcortical atrophy, ventricular dilatation, hydrocephaly and agenesis of the corpus callosum, showed a lower incidence. In relation to the disorders in the visual organs, there was a prevalence of refraction disorders, mainly myopia. The alterations of the skeletomuscular system included genu varum/valgum, arthrogryposis, talipes equinovarus and congenital hip dislocation. Effects in the hearing system (hearing loss) were observed with a lower frequency.

It has been stated that the fetal disorder may be produced regardless of the presence of maternal symptoms, or the trimester of pregnancy of the infection. In this study, we found a greater risk for the development of microcephaly and other disorders when the exposure period to ZIKV was in the first trimester of pregnancy. Through the Spearman correlation (with statistical significance), it was demonstrated that there was an inverse correlation between the trimester of pregnancy at the exposure to the ZIKV and the neurological findings. In other words, the shorter the time of pregnancy, the greater the presence of neurological findings. There was a prevalence of these disorders in the first trimester of pregnancy, both in the number of disorders, and in their severity. These results agree with the reports of Araneda-Sazo[17] and Ospina et al.[18].

It is true that the vertical transmission does not occur in all infected pregnant women, as well as the fact that the congenital infection is not observed in all fetuses exposed to ZIKV. Some infected neonates will remain asymptomatic or with minor symptoms, while others will present major structural and functional disorders. The absence of microcephaly, as well as other clinical or imaging abnormalities does not rule-out the risk of the appearance of disorders at a medium or long term.[19]

The ruling principles of teratology must be highlighted. These include the fact that the genetic susceptibility to the action of the teratogenic agent depends on the genotype (both the maternal and fetal genotypes) and the way in which it interacts with the environmental conditions; the stage of development of the fetus during which the teratogenic agent appears; the characteristics of the teratogenic agent that acts in specific ways on different tissues; as well as the exposure time or dose.[20] These elements provide for the differences in the clinical expressions between pregnant women, as well as the diverse complications appearing in pediatric patients having a prenatal exposure to ZIKV.

Considering the behavior or the prenatal exposure to ZIKV (according to the trimester of pregnancy at which the woman had evidence of the infection) and the presence of positive findings in children from mothers with this infection, it was found that there was a risk at all three trimesters of pregnancy. Although we found that the largest number of cases was at the second trimester, the statistical significance of the correlation was observed between the prenatal exposure to ZIKV at the first trimester of pregnancy, and the presence of positive findings.

Through the different statistical methods used in this study, we were able to establish a significant association between the presence of positive findings in pediatric patients and the prenatal exposure to ZIKV, thus establishing a causal relationship.

Limitations to the study

The clinical record was the source of information for the cases. We made only one evaluation of how the children evolved in all cases.

CONCLUSIONS

There was a prevalence of neurological signs followed by visual signs. The evidence proved that the exposure to ZIKV in the first trimester of pregnancy had a teratogenic effect.

REFERENCES

1. Valdés Silva Y, Sánchez Ramírez E, Fuentes Arencibia S. Malformaciones congénitas relacionadas con los agentes teratógenos. Correo Científico Médico 2018;22:652–66.

2. Gorry C. Cuba Confronts Zika: All Hands on Deck. MEDICC Rev 2016;18:6. https://doi.org/10.37757/MR2016.V18.N1-2.2.

3. Roblejo Balbuena H. Manual de normas y procedimientos. Servicios de genética médica en Cuba. Havana: Editorial Ciencias Médicas; 2017.

4. Villar J, Ismail LC, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. The Lancet 2014;384:857–68. https://doi.org/10.1016/S0140-6736(14)60932-6.

5. Castro Chávez NC, García Estupiñán S. Principios éticos rectores de las investigaciones de tercer nivel o grado académico en Ciencias Médicas. Educ Med Super 2018;32:1–12.

6. Ortega Pérez M, González González J, Maragoto Rizo C, Galvizu Sanchez R, Zaldivar Bermúdez M, Pubillones E. Características clínicas del síndrome congénito asociado a la infección por el virus Zika. Invest Medicoquir 2021;13.

7. de Araújo TVB, Ximenes RA de A, Miranda-Filho D de B, Souza WV, Montarroyos UR, de Melo APL, et al. Association between microcephaly, Zika virus infection, and other risk factors in Brazil: final report of a case-control study. Lancet Infect Dis 2018;18:328–36. https://doi.org/10.1016/S1473-3099(17)30727-2.

8. Freitas DA, Souza-Santos R, Carvalho LMA, Barros WB, Neves LM, Brasil P, et al. Congenital Zika syndrome: A systematic review. PLoS One 2020;15:e0242367. https://doi.org/10.1371/journal.pone.0242367.

9. Counotte MJ, Meili KW, Taghavi K, Calvet G, Sejvar J, Low N. Zika virus infection as a cause of congenital brain abnormalities and Guillain-Barré syndrome: A living systematic review. F1000Res 2019;8:1433. https://doi.org/10.12688/f1000research.19918.1.

10. 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;265:162–8. https://doi.org/10.1016/j.ejogrb.2021.07.012.

11. Krauer F, Riesen M, Reveiz L, Oladapo OT, Martínez-Vega R, Porgo TV, et al. Zika Virus Infection as a Cause of Congenital Brain Abnormalities and Guillain-Barré Syndrome: Systematic Review. PLoS Med 2017;14:e1002203. https://doi.org/10.1371/journal.pmed.1002203.

12. Del Campo M, Feitosa IML, Ribeiro EM, Horovitz DDG, Pessoa ALS, França GVA, et al. The phenotypic spectrum of congenital Zika syndrome. Am J Med Genet A 2017;173:841–57. https://doi.org/10.1002/ajmg.a.38170.

13. Quilião ME, Venancio FA, Mareto LK, Metzker S de A, Nascimento AI do, Vitorelli-Venancio DC, et al. Neurological Development, Epilepsy, and the Pharmacotherapy Approach in Children with Congenital Zika Syndrome: Results from a Two-Year Follow-up Study. Viruses 2020;12. https://doi.org/10.3390/v12101083.

14. Almeida LC de, Muniz LF, Maciel RJ, Ramos DS, Albuquerque KMG de, Leão ÂMC, et al. Hearing and communicative skills in the first years of life in children with congenital Zika syndrome. Braz J Otorhinolaryngol 2022;88:112–7. https://doi.org/10.1016/j.bjorl.2020.05.007.

15. Pomar L, Musso D, Malinger G, Vouga M, Panchaud A, Baud D. Zika virus during pregnancy: From maternal exposure to congenital Zika virus syndrome. Prenat Diagn 2019;39:420–30. https://doi.org/10.1002/pd.5446.

16. Marín I, Sánchez A, Reyes M, García J, Torrealba R, Rodríguez B. Síndrome congénito asociado a virus Zika. Bol venez infectol 2019;30:72–8.

17. Araneda Sazo D. Zika en embarazo y resultado perinatal. Rev Méd (Col Méd Cir Guatem) 2019;158:7–10. https://doi.org/10.36109/rmg.v158i1.113.

18. Ospina ML, Tong VT, Gonzalez M, Valencia D, Mercado M, Gilboa SM, et al. Zika Virus Disease and Pre gnancy Outcomes in Colombia. N Engl J Med 2020;383:537–45. https://doi.org/10.1056/NEJMoa1911023.

19. Gine F. Virus Zika: ¿Qué sabemos sobre las causas del síndrome congénito y las complicaciones neurológicas que ocasiona? Master Thesis. Universidad de La Laguna, 2021.

20. Motta I. La importancia de conocer los factores teratogénicos que afectan el SN. Rev Dig Pros Psicol 2019;3.

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CONFLICTS OF INTEREST

The authors state that there was no conflict of interest related to this study.

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