Chapter 74

Orofacial alterations of Congenital Syndrome by Zika Virus in different periods of infection in pregnancy

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ABSTRACT
Objective: To estimate and compare the prevalence of orofacial changes in children with Congenital Zika Virus Syndrome (SCVZ) with different periods of infection in pregnancy, according to social, demographic, and clinical characteristics. Method: Cross-sectional study nested to a cohort of 108 children with SCVZ seen in a reference center for this disorder in Maranhão in the period from October 2016 and July 2019. The orofacial changes (face, lips, palate, tongue, oral mucosa and teeth) were assessed through clinical examination under artificial light in knee-knee position, while the social and clinical characteristics, through medical records and interviews. The children were divided into two groups according to the trimester of pregnancy in which the mother was infected: 1st trimester (n=56) and 2nd/3rd trimester (n=52). To compare if there was a difference in orofacial changes between the two groups chi-square and Fisher's exact test was performed at 5% significance level ($p<0.05$). Results: The prevalence of orofacial changes in children with SCVZ was 90.7% (n=97), with no statistically significant difference (p=0.38) between those infected in the 1st trimester 76.8% (n=43) and in the 2nd/3rd trimesters 69.2% (n=36). Atresia of the palate was the most prevalent type of alteration 67.6% (n=73). Two children had cleft lip and palate (1.8%), both infected in the 1st trimester. Lingual frenum alteration was observed in 17.9% (n=10) in the 1st trimester infected group and 11.6% (n=6) in the other group (p=0.35). Conclusion: Regardless of the time of infection, orofacial changes in children with SCVZ were similar in both groups of pregnant women infected in the 1st trimester and in those in the 2nd/3rd trimesters.

Keywords: Congenital Zika Virus Syndrome, Orofacial alterations, Dental alterations.

1 INTRODUCTION

In Brazil, the average annual number of microcephaly cases between 2000 and 2014 was 164. In 2015, this number increased ninefold, totaling 1,608 cases[1,2] . Subsequently, a causal relationship was established between this increase and the outbreak of Zika virus (ZIKV) infection, which occurred months earlier .[3-9]

However, microcephaly is only one of several congenital anomalies resulting from ZIKV infection *in utero*, called Congenital Zika Virus Syndrome (SCVZ)[3,6,7] . The main features of SCVZ include:

parenchymal calcifications, ventriculomegaly, central nervous system hypoplasia or atrophy, ophthalmologic changes, arthrogryposis, and low birth weight[1,3,6,7] .

Although the SCVZ has a varied phenotype[1,7,8,10-12] , research on facial and dental aspects is concentrated in children with microcephaly[13-19] . Among these structures, the presence of cleft palate or abnormal formation of the palate, inadequate lingual posture at rest (poorly positioned lingual bridle), micrognathia, changes in the shape and/or number of teeth, changes in the sequence of tooth eruption, and muscle spasms have already been observed[13-18] .

The orofacial morphology develops in the first trimester of gestation (fourth gestational week)[20,21,24] and disturbances during this phase can result in cleft lip and palate[25,26] , narrowing of the palate[27] , changes in the tongue[28] , dental changes (in shape, size and number)[25,29] , and in dental enamel deformations such as opacity and hypoplasia[30] .

However, although some orofacial alterations have already been described, little is known about the relationship between them and the period of Zika virus infection during pregnancy. Therefore, the aim of this study was to estimate and compare the prevalence of orofacial changes in children with SCVZ in different periods of infection during pregnancy.

2 METHODS

Cross-sectional study nested in a cohort of children with SCVZ seen at a reference center for this condition in Maranhão.

This cohort study collected data from 134 children referred to the Reference Center for Neurodevelopment, Child Care and Rehabilitation (NINAR/Government of the State of Maranhão/Brazil) for investigation of congenital zika syndrome (SCZ). The children were born between October 2015 and September 2018 in different municipalities of the state of Maranhão

Population

The selection occurred from suspected cases of SCVZ (n=134) referred to the Reference Center for Neurodevelopment, Child Care and Rehabilitation (NINAR/Government of the State of Maranhão/Brazil), located in the capital, São Luís. The children were born in the period from October 2015 to September 2018.

Only children who had a clinical-laboratory diagnosis for ZIKV (n=108) were included, according to the criteria of França et al., 2016 described by Ribeiro et al., 2020 with the same cohort of children. Unconfirmed, inconclusive cases, and children without dental examination (n=26) were excluded.

The final sample of 108 children was divided into two groups: children whose mothers had been infected in the 1st trimester (n=56), and those infected in the 2nd or 3rd trimesters (n=52). The choice to

leave the first trimester of gestation in a separate category is justified by the higher probability of congenital anomalies, in general, resulting from maternal ZIKV infection .[1,14-18]

Data collection and variables

Dental examinations occurred from October 2016 to July 2019. Orofacial changes were considered to be those found in the structures of the face, lips, palate, tongue, oral mucosa, and teeth.

The examinations were performed by a trained dental surgeon, under artificial light, in the knee-knee position (the child was in dorsal decubitus, with the head and part of the trunk on the examiner's lap, and the rest on the parent's lap). The soft tissue structures were inspected through visualization and palpation, with the aid of a plastic spatula. For the dental structures, the tooth surfaces present in the oral cavity were checked, duly dried, using a plane mirror nº 5, periodontal probe and sterile gauze.

Through medical records and complemented by interviews with mothers, fathers, and guardians, the following characteristics were described: (1) sociodemographic (maternal age and child's age at the time of the examination, sex, mother's education, and city of birth of the child); (2) clinical (trimester of infection, number of prenatal visits, type of delivery, prematurity and low weight, microcephaly). Prematurity was considered as gestational age less than 37 weeks and low weight, less than 2,500g[33] , cephalic perimeter <2 standard deviations below the mean for each gestational age and sex[34] ; and (3) dental (first erupted tooth, mean age of eruption and mean number of teeth present at the time of examination).

Statistical Analysis

The information obtained from the children with SCVZ was stored in a database of REDCap software (Vanderbilt University, Nashville, USA). The STATA program® (version 14.0) was used for statistical analysis. Mean, standard deviation for continuous variables and absolute and relative frequencies for categorical variables were used to describe the characteristics of children with SCVZ. To test the statistical differences in orofacial changes between children infected in the 1st trimester and those infected in the 2nd/3rd trimester, the chi-square and Fisher's exact test was used, adopting a significance value of 5% (p= 0.05).

Ethical Aspects

This study was approved by the Research Ethics Committee (CEP) of HU/UFMA under opinion no. 1,510,305 from June 9, 2017. Those responsible for the children were informed about the research and signed the Informed Consent Form.

3 RESULTS

Most children with orofacial alterations (92.5%) were born in the interior of Maranhão and had a mean age of 32 months. Most mothers (84.3%) were aged between 20 and 35 years and had high school or technical schooling (74.8%) (Table 1).

The mean age of eruption of the first tooth of the children was 9 months. Children infected in the 1st trimester had, on average, 16 (±3.3) teeth present at the time of examination, while those infected in the 2nd/3rd trimester had, on average, 17 (±4.0) teeth present, and only one child had no teeth present at the time of examination. The first teeth to erupt were the left lower central incisor (tooth 81), with 61.7% in the 1st trimester and 47.9% in the 2nd/3rd trimester, and the right upper central incisor (tooth 51) with 31.9% and 33.3%, respectively. Lingual frenum alterations were observed in 14.8% of the children, 13% being the short frenum type and 1.8% the submucosal frenum type.

Table 1. Social and clinical characteristics of children with Congenital Syndrome by Zika Virus. Maranhão, 2016-2019.

Features	No orofacial changes (n=10)	With orofacial alterations (n=97)	Total (n=107)	p value
SOCIODEMOGRAPHIC	**n (%)**	**n (%)**	**n (%)**	
Sex				0,19
Female	2 (4,5)	42 (95,5)	44 (41,1)	
Male	8 (12,7)	55 (87,3)	63 (58,9)	
City where you were born				0,37
Capital	5 (12,5)	35 (87,5)	40 (37,4)	
Interior	5 (7,5)	62 (92,5)	67 (62,6)	
Maternal Age				0,45
≤ 19 years old	3 (13,6)	19 (86,4)	22 (20,6)	
20-24 years old	4 (12,5)	28 (87,5)	32 (29,9)	
>25 years old	3 (5,7)	50 (94,3)	53 (49,5)	
Maternal education*				0,63
Didn't study/Fundamental	2 (12,5)	14 (87,5)	16 (15,1)	
Middle/Technical	8 (10,1)	71 (89,9)	79 (74,5)	
College/ Post-graduation	0 (0,0)	11 (100,0)	11 (10,4)	
Family income				0,79
Up to 1 minimum wage	5 (12,5)	35 (87,5)	40 (37,4)	
Up to 2 minimum wages	2 (6,9)	27 (93,1)	29 (27,1)	
Up to 3 minimum wages	0 (0,0)	11 (100,0)	11 (10,3)	
Up to 4 minimum wages	3 (11,1)	24 (88,9)	27 (25,2)	
CLINICS				
Number of prenatal visits*				0,65
< 6	5 (6,4)	73 (93,6)	78 (78,0)	
≥ 6	2 (9,1)	20 (90,9)	22 (22,0)	
Type of delivery				0,51
Vaginal	6 (12,2)	43 (87,8)	49 (45,8)	
Cesarean section	4 (6,9)	54 (93,1)	58 (54,2)	
Prematurity*				0,60
Term/Post Term	9 (10,0)	81 (90,0)	90 (87,4)	
Preterm	0 (0,0)	13 (100,0)	13 (12,6)	
Low birth weight*				0,45
>2.500g	7 (8,5)	75 (91,5)	82 (78,1)	
<2.500g	3 (13,0)	20 (87,0)	23 (21,9)	
Microcephaly*				0,70
Yes	3 (8,8)	31 (91,2)	34 (35,8)	
No	4 (6,6)	57 (93,4)	61 (64,2)	

*The variable presented losses

The occurrence of cleft lip and palate was observed in two children (1.8%), both infected in the 1st trimester.

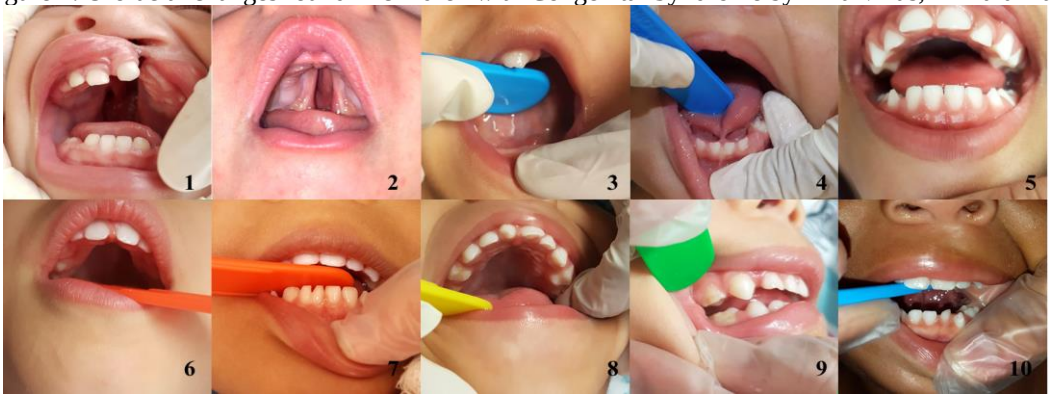
The prevalence of orofacial alterations in children was 73.2% (n=79), with palate atresia being the most prevalent 67.6% (n=73). Lingual frenulum alterations were observed in 14.8% (n=16) of the children. Of the children who had teeth present at the time of the examination (n=107), dental enamel changes (opacity and hypoplasia) occurred in 45.8% (n=49) and odontogenic changes in 49.5% (n=53) (Table 2 and Figure 2).

Table 2. Comparison of orofacial changes found in children with Congenital Syndrome by Zika Virus according to trimesters of infection during pregnancy. Maranhão, 2016-2019.

Changes	1st Quarter (n=56)	2nd/3rd Quarter (n=52)	Total	p-value
	n (%)	n (%)	n (%)	
Orofacial alteration				0,38
No	13 (23,2)	16 (30,8)	29 (26,8)	
Yes	43 (76,8)	36 (69,2)	79 (73,2)	
Atresia of the Palate				0,38
No	16 (28,6)	19 (36,5)	35 (32,4)	
Yes	40 (71,4)	33 (63,5)	73 (67,6)	
Lingual Brake				0,35
No	46 (82,1)	46 (88,4)	92 (85,2)	
Yes	10 (17,9)	6 (11,6)	16 (14,8)	
Odontogenesis alteration*				0,92
No	28 (50,0)	26 (51,0)	54 (50,5)	
Yes	28 (50,0)	25 (49,0)	53 (49,5)	
Dental alteration*				0,51
No change	28 (50,0)	26 (51,0)	54 (50,5)	
Enamel[1]	27 (48,2)	22 (43,1)	49 (45,8)	
Shape/size[2]	1 (1,8)	3 (5,9)	4 (3,7)	

[1]Opacity and Hypoplasia
[2] Microdontia and Twinning/Fusion
*The variable presented losses

Figure 1. Orofacial changes found in children with Congenital Syndrome by Zika Virus, in Maranhão.



1)Complete unilateral transforamen cleft; 2) Complete incisive post-foramen cleft; 3) Submucosal lingual fret; 4) Short lingual fret; 5 and 6) Atresic palate; 7) Twinning/fusion; 8) Microdontia; 2); 3) Hypoplasia; 4) Opacity.

4 DISCUSSION

In the present study, no difference was observed in the prevalence of orofacial alterations between the periods of ZIKV infection during pregnancy; however, children infected in the 1st trimester presented more severe alterations, such as cleft lip and palate, the most common congenital facial malformation at birth, which impact phonation, chewing, and swallowing, important functions in the stomatognathic system[20,23,24] .

Considering that ZIKV has a special tropism for nerve cells[1], which have an embryological origin similar to the orofacial structures[24,25] it was expected that changes in the morphology of these structures would be associated with infection in the 1st gestational trimester.

The orofacial morphology develops in the first trimester of gestation (fourth gestational week)[21,24] and disturbances during this phase may result in cleft lip and palate[25,26] , narrowing of the palate[27] , changes in the tongue[28] , dental changes (in shape, size and number)[25,29] , and in dental enamel deformities such as opacity and hypoplasia[30] . However, little is known about the relationship between orofacial changes in children with SCVZ and the period of infection in pregnancy.

The orofacial region plays an important role in child development, and alterations can compromise primordial functions such as chewing and speech, and teeth with alterations can become more susceptible to caries lesions, generating a potential focus of infection for these children whose systemic health is already compromised[20,23,24] .

After birth, physical and behavioral limitations of individuals with SCVZ that present microcephaly and muscular hypotonia may cause changes in the palate[9,14,15] . Hypotonia of the facial muscles is associated with incompetent lip seal, malocclusion, and mouth breathing[14,16,18] , impacting the formation of the palate. The presence of atrophic palate was also observed in other studies, with similar population[13,17] . Microcephaly and short lingual frenum favor incorrect tongue positioning, and hinder palate development . [15]

Some aspects that make up the SCVZ phenotype, such as microcephaly, arthrogryposis, dysphagia, muscle hypotonia, among others, also have a direct and indirect impact on the development of the stomatognathic apparatus[1,7,8,10-12] .

The main strength of this study was the use of robust criteria with clinical-laboratory diagnosis, confirmed from RT-PCR for the syndrome.

One of the limitations of the study, includes the size of the population of children referred to the NINAR Referral Center, partly explained by the dependence of health services for the notification and referral of cases to the referral center, which may underestimate the cases with SCVZ and the possibility of memory bias of the information collected retrospectively, but minimized by the complementation of data through medical records.

Most of the children with SCVZ showed some orofacial alteration, regardless of whether they were infected in the 1st trimester or in the 2nd/3rd trimester.

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