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Oral alterations among children with congenital zika virus syndrome: A systematic review and meta-analysis

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***Abstract*---**Background and aim: the aim of present study was evaluating the oral alterations in children with congenital Zika syndrome -associated microcephaly compared to the group of children without this problem. Method: all international databases, PubMed, Scopus, Science Direct, ISI, and Embase were examined, searching between 2015 to March 2023 based on keywords related to the objectives of the study. Stata/MP v.17 software was used to conduct the meta-analysis. Result: After reviewing the abstracts of 177 articles, 21 articles were selected for full text review, of which 5 articles were included in the meta-analysis. Odds ratio of delayed tooth eruption between children with congenital Zika syndrome group and control group was 1.79 (OR, 1.79 95% CI 1.33, 2.25; p<0.001). Children with congenital Zika syndrome -associated microcephaly, compared to healthy children, had 2.15 (OR, 2.15 95% CI 1.62, 2.67; p<0.001) times chance of palate alteration. Conclusion: chance of delay in deciduous dental eruption, difficulty in lip sealing, palate alteration and ankyloglossia in children with CZS-associated microcephaly was significantly more than the control group.

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***Keywords*---**Children, Zika Virus, Congenital Zika Virus Syndrome, Oral Alterations, dental care.

Introduction

During the outbreak of Zika virus (ZIKV) infection in France, it was reported that this virus can endanger the human central nervous system(1). ZIKV is an RNA Flavivirus which was first isolated in 1947 in Uganda, Africa(2). There were also reports of ZIKV infection in Latin American countries in 2015. Between 2015 and 2020, an estimated 300,000 cases of ZIKV infection were reported(3, 4). The dramatic consequences of ZIKV on public health since 2015, have highlighted the threat that ZIKV represents. Although the pandemic has waned since that time, the virus is still circulating, and areas with competent vectors are at risk of ZIKV re-emergence. An estimated 3.6 billion people live in at-risk areas(5). According to reports, ZIKV infection during pregnancy, especially in the first trimester of pregnancy, can increase the incidence of microcephaly in children(6). congenital Zika syndrome (CZS) is characterized by congenital anomalies resulting from ZIKV infection during pregnancy(7). WHO and Pan American health Organization (PAHO) have issued clinical diagnostic criteria for Zika. The WHO case definition of Zika includes rash or fever and at least one of the following: arthralgia, arthritis, conjunctivitis. PAHO criteria include rash and at least 2 of: fever, conjunctivitis, arthralgias, myalgia and periarticular edema(5). Based on evaluation of 556 ZIKV-positive children aged 2 to 14 years old, children tend to show mild clinical findings compared to adults. Indeed, only 32% of them met the WHO clinical diagnostic criteria, and 20% of them met the PAHO clinical diagnostic criteria. Children are also less frequently affected by arthralgia, regardless of their ability to communicate the presence of this symptom(8). Indeed, most children resented with only a rash or a rash with leucopenia, which is a clinical presentation that does not meet the WHO or PAHO criteria(2, 9). Based on the findings of studies that investigated oral changes in children born with CZS, it was observed that the disorder of tooth formation, change in jaw formation, and delay in tooth eruption are common in these children. On the other hand, these oral changes endanger oral and dental health and are seen with an increase in the number of oral biofilms, periodontal and tooth decay(10-16). More comprehensive studies that examine the results of the studies and can provide strong evidence so that the treatment can be started faster and prevent further complications are very important. Therefore, the present study was conducted with the aim of investigating oral alterations among children with congenital Zika Virus syndrome.

Method

Search strategy

In the current study, all international databases, PubMed, Scopus, Science Direct, ISI and Embase were examined, searching between 2015 to March 2023 based on keywords related to the objectives of the study. The current study was conducted based on the PRISMA 2020 checklist(17).

Keywords and the MeSH terms:

(((((("Zika Virus"[Mesh]) OR "Zika Virus Infection"[Mesh]) OR ("Zika Virus Infection/classification"[Mesh] OR "Zika Virus Infection/complications"[Mesh] OR "Zika Virus Infection/prevention and control"[Mesh])) AND ("Child"[Mesh] OR "Adult Children"[Mesh] OR "Dental Care for Children"[Mesh] OR "Only Child"[Mesh])) AND ("Mouth"[Mesh] OR "Oral Health"[Mesh])) OR "Salivation"[Mesh]) OR "Biofilms"[Mesh]) OR ("Bruxism"[Mesh] OR "Sleep Bruxism"[Mesh])

Eligibility criteria

Inclusion criteria: Only articles published in English, randomized clinical trials, prospective and retrospective studies, case-control studies, cross-sectional studies, no limit on sample size, only children, age group less than 18 years and complete data.
Exclusion criteria: studies without control group, case series, case reports, in-vitro and reviews papers; studies without full text access.
The Google Scholar search engine was used to search for articles and the PECO strategy to answer the research questions (Table 1).

Table1. PICO strategy

PECO strategy	Description
P	Population: children
E	Exposure: CZS-associated microcephaly
C	Comparison: without CZS
O	Outcome: oral alteration

Data collection

Two reviewers independently screened each record and each report was retrieved. All studies were selected based on inclusion and exclusion criteria. The specifications of samples of the selected studies were extracted based on a checklist that included 4 items, the items were: author's name, publication year, study design, sample size, and age.

Risk assessment

The quality of studies was measured using Joanna Briggs Institute Critical Appraisal Checklist (18).

Data analysis

Meta-analysis was performed using STATA/MP. V17 software. Mantel-Haenszel methods are fixed-effect meta-analysis methods using a different weighting scheme that depends on which effect measure. 95% confidence interval for odds ratio with fixed effect model and Mantel-Haenszel method were calculated. Potential heterogeneity between studies was reported with the I^2 coefficient (low:50%<; moderate: 50%-75%; high:>50%).

Result

Study selection

In the initial search using keywords, 239 articles were found, and all references were entered into EndNote X8 software. Among these articles, 32 articles were duplicated, 15 articles were due to Records marked as ineligible by automation tools, and 15 articles were due to other reasons were removed and finally the abstracts of 177 articles were reviewed and 156 articles that did not meet the inclusion criteria were removed at this stage. The full text of 21 articles was fully reviewed by two blinded observers. Incomplete articles, without data, inconsistency with the objectives of the study were excluded (16 articles) and finally five articles were selected (Figure 1).

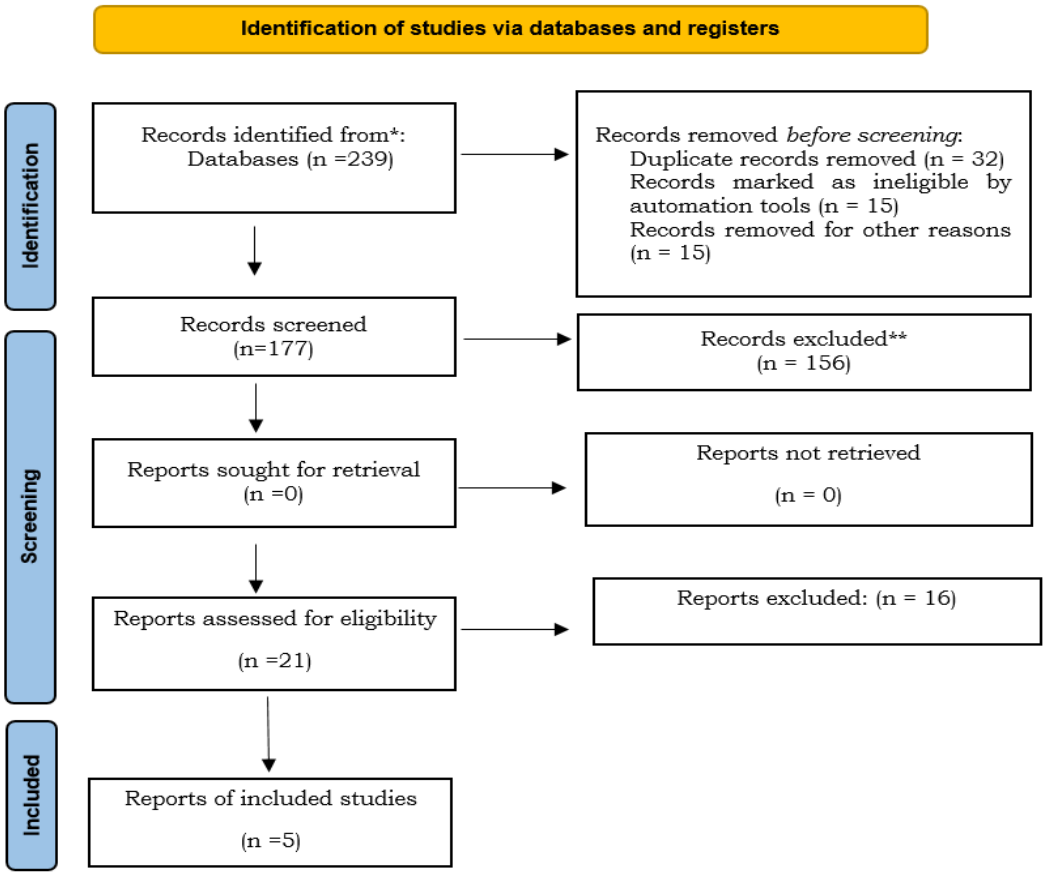

Figure 1. PRISMA 2020 Checklist

Study characteristics

Four cross-sectional studies, one case-control study was selected and included in present meta-analysis. A total of 388 patients (CZS group: 193; control group:

195) included. The range of age in CZS group and control group was 17-36 months. Table 2 shows a summary of Data extracted.

Risk assessment

According to Joanna Briggs Institute Critical Appraisal Checklist, all studies had high quality (low risk of bias).

Table 2. Summary of demographic data of studies selected for meta-analysis

n	Study. Years	Study design	Number of patients				Age (Month)	
			CZS		control			
			boy	girl	boy	girl		
1	Gomes et al., 2022 (19)	Case-control	15	17	15	17	30-36	30-36
2	Ribeiro et al., 2021 (20)	Cross-sectional	29	32	25	33	22.8±4.7	23.8±6.1
3	do Amaral et al., 2021 (21)	Cross-sectional	22	18	22	18	30-36	30-36
4	de Oliveira et al., 2020 (13)	Cross-sectional	21	24	20	30	17±6.1	17±6.2
5	Carvalho et al., 2019 (11)	Cross-sectional	8	7	8	7	25±5.1	25±5.1

Delayed tooth eruption

Odds ratio of delayed tooth eruption between CZS group and control group was 1.79 (OR, 1.79 95% CI 1.33, 2.25; p<0.001) with high heterogeneity (I^2=75.33%; P =0.00) (Fig.2). There was significant difference between CZS group and control group in terms of delayed tooth eruption (p=0.00). According to this result, children with CZS-associated microcephaly, compared to healthy children, had 1.79 times chance of delayed tooth eruption.

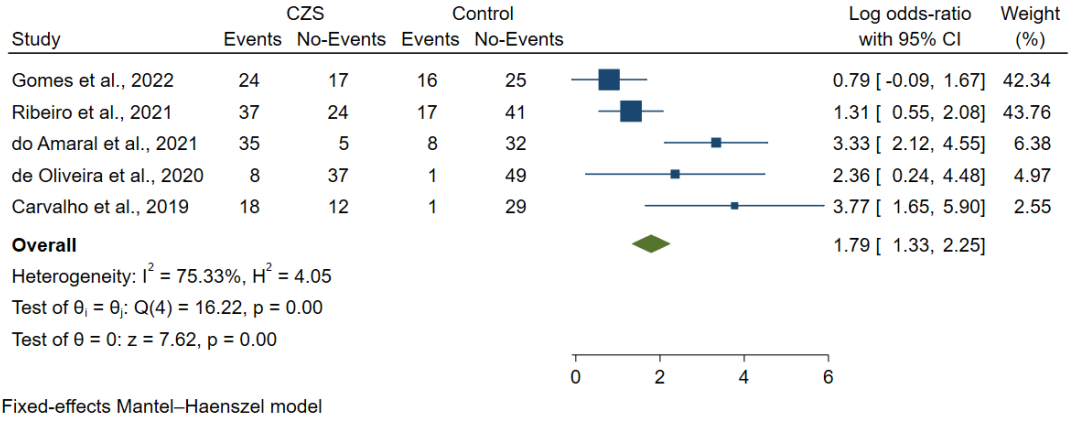

Figure 2. Forest plot showed odds ratio of delayed tooth eruption

Difficulty in lip sealing

Odds ratio of difficulty in lip sealing between CZS group and control group was 2.63 (OR, 2.63 95% CI 1.77, 3.48; p<0.001) with moderate heterogeneity (I^2=68.24%; P =0.08) (Fig.3). There was significant difference between CZS group and control group in terms of difficulty in lip sealing (p=0.00). According to this

result, children with CZS-associated microcephaly, compared to healthy children, had 2.63 times chance of difficulty in lip sealing.

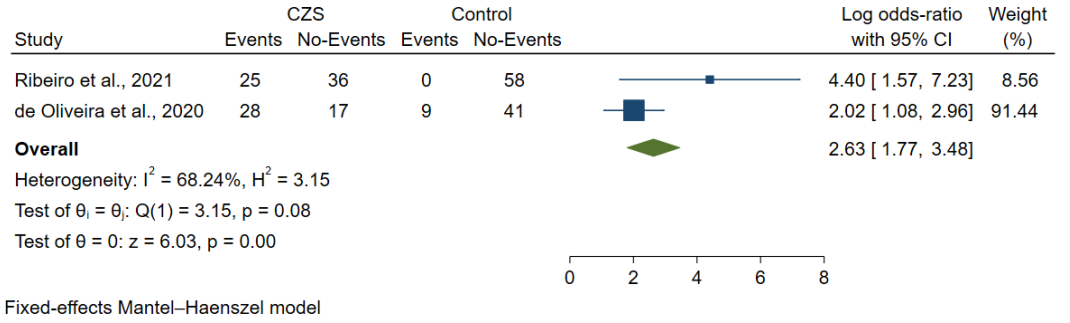

Figure 3. Forest plot showed odds ratio of difficulty in lip sealing

Palate alteration

Odds ratio of palate alteration between CZS group and control group was 2.15 (OR, 2.15 95% CI 1.62, 2.67; p<0.001) with moderate heterogeneity (I^2=68.19%; P =0.02) (Fig.4). There was significant difference between CZS group and control group in terms of palate alteration (p=0.00). According to this result, children with CZS-associated microcephaly, compared to healthy children, had 2.15 times chance of palate alteration.

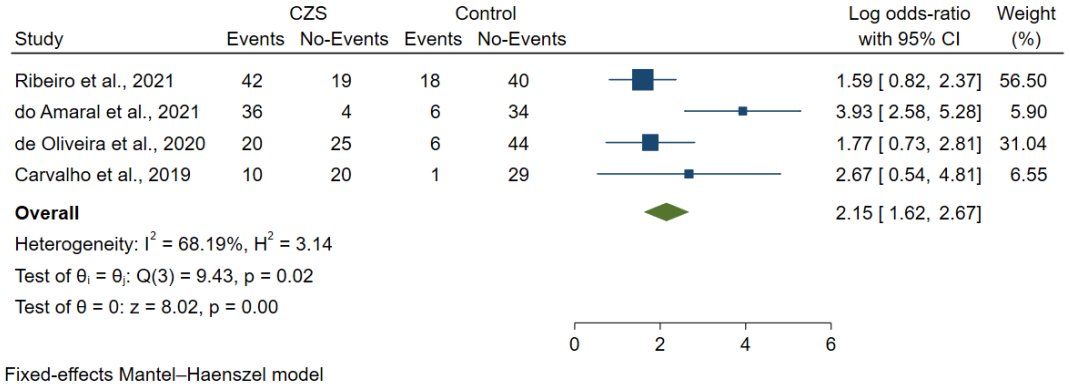

Figure 4. Forest plot showed odds ratio of palate alteration

Ankyloglossia

Odds ratio of ankyloglossia between CZS group and control group was 0.86 (OR, 0.86 95% CI 0.28, 1.43; p<0.001) with low heterogeneity (I^2=53.60%; P =0.12) (Fig.5). There was significant difference between CZS group and control group in terms of ankyloglossia (p=0.00). According to this result, children with CZS-associated microcephaly, compared to healthy children, had 0.86 times chance of ankyloglossia.

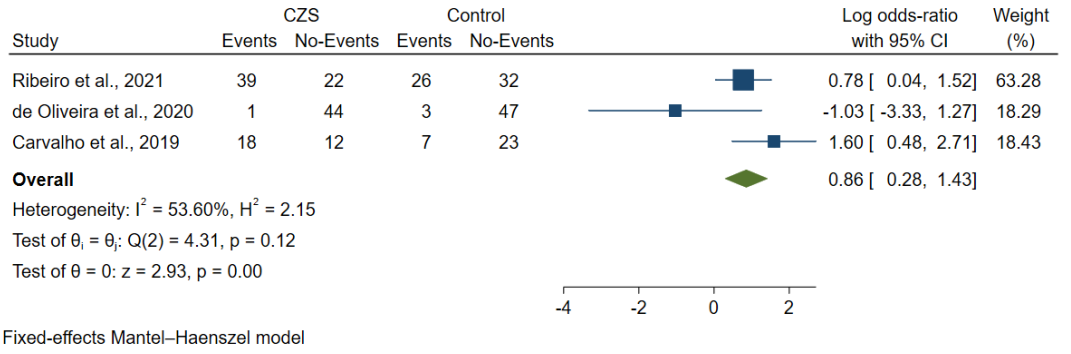

Figure 4. Forest plot showed odds ratio of ankyloglossia

Discussion

Children who are congenitally affected by neurological changes may also have neurological, eye, hearing, dental and craniofacial abnormalities(22). Based on the results of studies, it has been determined that ZIKV infection during pregnancy is a risk factor for dental changes. However, a laboratory study that proves the relationship between ZIKV and oral disorders has not been done(23). Based on the findings of the selected studies, compared to the control group, children in the CZS-associated microcephaly group had improper language posture at rest, difficulty in sealing the lips; These findings were not included in the meta-analysis because the study data were sparse. The present meta-analysis showed that the delay in deciduous dental eruption in children of CZS-associated microcephaly group was significantly more than the control group. Based on the present meta-analysis, Difficulty in lip sealing, Palate alteration and Ankyloglossia in children of CZS-associated microcephaly group were significantly more than the control group. The delay in the growth of milk teeth can be related to the changes in the cephalic neural crest cells(24). Changing the shape of the palate can be related to improper language position and low tone of the oral facial muscles(25). Based on meta-analysis and Figure 4, one study showed that the chance of ankyloglossia was similar for both groups, and the chance of ankyloglossia in the CZS-associated microcephaly group of children compared to the control group was lower than other parameters; However, this difference was statistically significant. More studies are needed in this regard. Some oral changes in children with CZS-associated microcephaly can be caused by caregivers' actions. Because these children depend on other people to maintain oral and dental hygiene, and if the oral and dental hygiene is not performed well by the caregiver, an increase in the accumulation of biofilm and tooth decay will appear. As a result, children with CZS-associated microcephaly are more vulnerable than other children to oral diseases such as gingivitis and tooth decay (26-29). In the current study, a high heterogeneity was observed between the studies, which could be related to the cognitive methodology of the studies or geographical regions; Therefore, the interpretation of the results of the present study should be done with caution and more studies are needed to confirm the present evidence. Most of the studies in this field were without a control group, which were excluded from the present study, and only 5 studies were found that had a control group; Therefore, it is necessary to conduct future studies with the

control group to provide better results. One of the limitations of the current study was that the sample size of the articles was small and their methodology was considered weak, however, the quality of the studies was high. Also, the parameters examined in the articles were very scattered. Most of the studies were done in Brazil, which needs to be done in other places as well. Prospective studies and RCTs are needed to provide sufficient evidence by determining the incidence of oral lesions in children with microcephaly associated with CZS.

Conclusion

In the present study, by examining the oral alterations in children with CZS-associated microcephaly compared to the group of children without this problem, it was observed that the chance of delay in deciduous dental eruption, difficulty in lip sealing, palate alteration and ankyloglossia in children with CZS-associated microcephaly was significantly more than the control group. Accordingly, veterinarians should be aware that children with CZS-associated microcephaly are at higher risk for oral and dental changes that can have systemic effects. Caregivers of these children should also be given comprehensive training regarding oral and dental hygiene; because lack of oral and dental hygiene can increase the risk of tooth decay.

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