Cognition of infants exposed to Zika virus in pregnancy: a systematic review

Cognição de bebês expostos ao vírus zika na gestação: revisão sistemática

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Samantha Nunes Santos
Doctor in Interactive Processes of Organs and Systems
Instituição: Federal University of Bahia
Endereço: Av. Reitor Miguel Calmon, s/n, Vale do Canela, CEP: 40110-902 Salvador BA Brazil
E-mail: saminunes@gmail.com

Denise Miranda
Postgraduate in Psychopedagogy
Instituição: Federal University of Bahia
Endereço: Rua Augusto Viana, s/n, CEP: 40110-060, Salvador, BA, Brazil
E-mail: deniselm@gmail.com

Gúbio Soares Campos
Doctor in Virology
Instituição: Federal University of Bahia
Endereço: Av. Reitor Miguel Calmon s/n, Vale do Canela, CEP: 40110-100, Salvador BA, Brazil
E-mail: gubiosoares@gmail.com

Silvia Inês Sardi
Doctor in Virology
Instituição: Federal University of Bahia
Endereço: Av. Reitor Miguel Calmon s/n, Vale do Canela, CEP: 40110-100, Salvador BA, Brazil
E-mail: sissardi@yahoo.com

Marina Martorelli Pinho
Doctor in Psychology
Instituição: Pontifical Catholic University of Rio de Janeiro
Endereço: Rua Marquês de São Vicente, 225, Gávea, Rio de Janeiro-RJ, Brazil
E-mail: marinamartorelli2@gmail.com

Nayara Argollo
Doctor in Medicine and Health
Instituição: Federal University of Bahia
Endereço: Rua Augusto Viana, s/n, CEP: 40110-060, Salvador-BA, Brazil
E-mail: nayaraargollo@me.com
ABSTRACT
This article aimed to systematically review the literature on the cognition of children exposed to Zika virus infection (ZIKV) during pregnancy. After searching the main electronic databases, PubMed, Capes, Web of Science, Scopus, Cochrane and BVS, the keywords “Zika virus”, “ZIKV infection”, “pregnancy”, “congenital”, “congenital syndrome”, “development”, “Cognition”, “neurodevelopment”, “child”, “infants”, “neuropsychology”, “developmental disorders”, “Bayley”, “Denver” were used for systematic data search. After applying the eligibility criteria for inclusion, 20 articles related to the cognitive assessment of children exposed to intrauterine ZIKV published until 2019 November, were selected. The systematic review identified the following as the main results: delayed cognition, motor skills, language and personal social domain, with worse performance in children with microcephaly or other severe brain injuries. Most normocephalic children exposed to ZIKV showed performance compatible with age. However, a smaller number of normocephalic children had a low score in at least one evaluated cognitive domain, characterizing specific developmental deficits. This review highlights the high risk of intrauterine ZIKV exposure to neurodevelopment and suggests investigating the cognitive development of all children exposed to ZIKV for long-term cognitive profiling, allowing early access to multidisciplinary rehabilitation programs.

Keywords: zika congenital syndrome, cognition, child development.

RESUMO
1 INTRODUCTION

Zika Virus (ZIKV) has caught the world’s attention (CDCP, 2016; PETERSEN et al., 2016; MUSSO; STRAMER; BUSCH, 2016). ZIKV emerged in recent years as a significant human pathogen mainly because of the impact it has on the neonate. ZIKV is a Flavivirus most often transmitted via mosquitoes, however it can be transmitted sexually also (PANCHAUD et al., 2016). The focal point of scientific damage has been congenital ZIKV infection and microcephaly (CDCP, 2016; PETERSEN et al., 2016; MUSSO; STRAMER; BUSCH, 2016). Congenital Zika syndrome (CZS) comprehends the spectrum of symptoms detected in infants who have been exposed to the Zika virus in utero (COSTA et al., 2016).

Between 2015 and 2016, the ZIKV spread to ten Brazilian states, with the highest incidence of infections in the Northeast and Southeast of the country. The Brazilian Ministry of Health (MS) published an epidemiological report in 2016, describing 216,207-suspected cases of the disease. In 2017, there was a reduction to 16,616 cases and to 7,544 in 2018. In 2019, so far, 10,441 probable cases of Zika have been recorded in the country. Of these, 1,649 probable cases of Zika were reported in pregnant women, 447 of which were confirmed (BRAZIL a, 2019). Regarding to microcephaly cases, from November 2015 to December 2018, the MS was notified of 17,041 suspected cases of changes in neonatal growth and development, possibly related to ZIKV infection and other infectious etiologies (BRAZIL b, 2019).

ZIKV infection can be considered a new clinical neuropathological condition (MUSSO; STRAMER; BUSCH, 2016). Therefore, research into the repercussions of ZIKV infection on the development of children, whose mothers were infected during pregnancy, even among those without obvious malformations, is of utmost importance. Identifying cognitive impairments infants exposed to intrauterine ZIKV may potentially allow early the adoption of therapeutic interventions. Until May 2020, there was no systematic review on the subject. Thus, the aim of this study was to systematically review and analyze the cognitive profiles of infants exposed to intrauterine ZIKV up to the first two years of life.
2 METHOD

2.1 LITERATURE SEARCH

In November 2019 a systematic literature search was conducted to identify studies that assessed the cognition of children exposed to intrauterine ZIKV infection. The main electronic databases on the subject were systematically searched: Pubmed, Capes Journals, Web of Science, Scopus, Cochrane and "Biblioteca Virtual de Saúde". The descriptors “Zika virus”, “ZIKV infection”, “pregnancy”, “congenital”, “Congenital syndrome”, “development”, “cognition”, “neurodevelopment”, “child”, “infants”, “neuropsychology”, “developmental disorders”, “Bayley”, “Denver” were used for systematic search, combined with Boolean operators "And" and /" Or". No limits were placed for date of publication, language, or field. Other sources of information, such as “annals of scientific events, thesis banks and academic google”, were included to identify unpublished data. The guidelines established by Prisma Statement were used in this systematic review.

2.2 SELECTION OF STUDIES

Three authors (SN, DM, MMP) independently searched the literature. The eligibility criteria of this review were: 1) articles that performed cognitive assessment of children exposed to intrauterine ZIKV infection; 2) publications that clarified the outcome used in the assessment. On the other hand, articles were excluded if (1) they did not describe in detail the procedures and cognitive instruments used; (2) publications that consisted only of systematic or literature reviews on the subject; (3) publications with sample dropout rates greater than 50%. Disagreements about the inclusion criteria of the articles were decided by consensus among the researchers. A flowchart with the article selection steps was elaborated (Figure 1).
2.3 METHODOLOGICAL QUALITY ASSESSMENT

The quality of the studies was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology - STROBE (EBRAHIM; CLARKE, 2007). All included studies followed the criteria required by the STROBE (EBRAHIM; CLARKE, 2007).

2.4 DATA EXTRACTION

The following information was extracted independently: year of publication, first author, article title, cognitive tests or scales, sample size, cognitive profiles (cognitive deficits), study methodology. In the articles that presented incomplete data, contact with the corresponding author was performed. In case of failure, after two contact attempts, the articles were excluded.
3 RESULTS

A total of 764 studies were found, but only 20 articles met the eligibility criteria for this review. The detailed description of article selection is depicted below (Figure 1).

The articles referred to publications in the English language and only one manuscript in the Portuguese language was found (FLOR; GUERREIRO; ANJOS, 2017). The period of publication was from 2016 to 2019 (Figure 2).

Figure 2. Yearly growth in the number of publications of Cognition and ZIKV from 2016 to 2019

![PUBLICATIONS PER YEAR](chart)

Source: Own authorship

The countries of origin of the studies were Brazil, with most publications, French Polynesia and Puerto Rico (Table 1).

<table>
<thead>
<tr>
<th>Authors, region, country</th>
<th>Subjects</th>
<th>Age (months)</th>
<th>Clinical findings</th>
<th>Neuroimaging Findings</th>
<th>Development Assessment Battery</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botelho et al., 2016, Pernambuco, Brazil</td>
<td>4</td>
<td>4</td>
<td>Microcephaly, motor disorders and functional vision, delayed phonologicalarticulatory functions</td>
<td>Calcifications at cortico-subcortical junction, cortico-subcortical atrophy in frontal lobe, ventriculomegaly and cerebellar hypoplasia</td>
<td>TIMP, NFDS</td>
<td>Atypical motor development, muscle tone and altered spontaneous motor skills, impaired functional vision that can cause learning disruption and performance of functional activities. Delay in language, personal social interaction,</td>
</tr>
<tr>
<td>Flor et al., 2017, Bahia, Brazil</td>
<td>22</td>
<td>8, 9</td>
<td>Microcephaly, seizures, visual,</td>
<td>Severe brain injuries</td>
<td>Denver II</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Scientific articles that evaluated cognition of children exposed to ZIKV during pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Methods/Findings/Regarding Developmental Delay</th>
<th>Bayley/CDAS/MDI</th>
<th>Additional Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>França et al., 2018, Rio Grande do Norte, Brazil</td>
<td>8, Average 20.5</td>
<td>Growth and development retardation</td>
<td>Reduction in brain volume, changes in the ventricles and calcifications, ophthalmological changes in the macula and optic nerve</td>
<td>Extreme poor performance in motor and cognitive domains.</td>
</tr>
<tr>
<td>Subissi et al., 2018, French Polynesia</td>
<td>21, Uninformed</td>
<td>Microcephaly, arthrogryposis</td>
<td>Ventriculomegal brainstem dysfunction</td>
<td>Typical development of children without birth defects.</td>
</tr>
<tr>
<td>Alves et al., 2018, Pernambuco, Brazil</td>
<td>24, Average 19.9</td>
<td>Microcephaly, epilepsy, pneumonia, urinary tract infection, diarrhea, ventriculoperitoneal shunt</td>
<td>Severe brain injuries</td>
<td>Developmental delay in language, gross motor, fine motor, personal/social. Severe neuropsychomotor impairment.</td>
</tr>
<tr>
<td>Cabral et al., 2018, Bahia, Brazil</td>
<td>18, Average 19</td>
<td>Normocephaly</td>
<td>Not performed</td>
<td>Delay in language, cognition and motor skills. Up to 16 months all with developmental delay. Communication and gross motor skills with better performance. Problem solving and fine motor skills, worse results. Sleep disorders.</td>
</tr>
<tr>
<td>Wheeler et al., 2018, Pernambuco, Brazil</td>
<td>47, 13–22</td>
<td>Microcephaly, prematurity, arthrogryposis, hypertonia</td>
<td>Severe brain injuries</td>
<td>Motor disorders and severe neurodevelopmental impairment. Complete disability in most categories of body function, impaired mobility, intellectual and language delay.</td>
</tr>
<tr>
<td>Soares-Marangoni et al., 2018, Mato Grosso, Brazil</td>
<td>2, Uninformed</td>
<td>Microcephaly</td>
<td>Severe brain injury in one case</td>
<td>59 children without Bayley III findings; 11 had one or more lower language and motor scores.</td>
</tr>
<tr>
<td>Ferreira et al., 2018, Paraíba e Rio Grande do Norte, Brazil</td>
<td>34, 21</td>
<td>Microcephaly</td>
<td>Severe brain injuries</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Location</td>
<td>Sample Size</td>
<td>Duration</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Zancanelli et al., 2018</td>
<td>Minas Gerais, Brazil</td>
<td>5</td>
<td>0 a 20</td>
<td>Normocephalic and postnatal microcephaly</td>
</tr>
<tr>
<td>Faiçal et al., 2019</td>
<td>Bahia, Brazil</td>
<td>29</td>
<td>Average 18,2</td>
<td>Normocephalic</td>
</tr>
<tr>
<td>Prata-Barbosa et al., 2019</td>
<td>Rio de Janeiro, Brazil</td>
<td>29</td>
<td>0 – 29</td>
<td>Microcephaly, normocephalic</td>
</tr>
<tr>
<td>Carvalho, et al., 2019, Bahia, Brazil</td>
<td>82</td>
<td>Average 4,8</td>
<td>Severe brain injuries</td>
<td>Bayley III</td>
</tr>
<tr>
<td>Marques et al., 2019</td>
<td>Rio de Janeiro, Brazil</td>
<td>25</td>
<td>12</td>
<td>Microcephaly and cerebral palsy</td>
</tr>
<tr>
<td>Cardoso et al., 2019, Rio de Janeiro, Brazil</td>
<td>19</td>
<td>1 -7</td>
<td>Normocephalic</td>
<td>Not performed</td>
</tr>
<tr>
<td>Einspieler et al., 2019</td>
<td>Minas Gerais, Brazil</td>
<td>91</td>
<td>12</td>
<td>35 Microcephaly not tested</td>
</tr>
<tr>
<td>Nielsen-Saines et al., 2019</td>
<td></td>
<td>146</td>
<td>0-24</td>
<td>Microcephaly</td>
</tr>
</tbody>
</table>
3.1 SAMPLE

The publications included in this review comprised 844 subjects ranging in age from (ZANCANELLI, 2018; NIELSEN-SAINES et al., 2019) to 29 months (PRATA-BARBOSA et al., 2019).

3.2 ELIGIBLE RESEARCH DESIGNS


3.3 INSTRUMENTS FOR THE ASSESSMENT OF NEUROPSYCHOMOTOR DEVELOPMENT

The outcome assessment in the 20 studies included in this review was also not homogeneous. The Bayley III Scales of Infant and Toddler Development: was used in nine (45%) of the included studies Zancanelli (2018); Cabral et al (2018); França et al (2018); Lopes Moreira et al (2018); Cardoso et al (2019); Carvalho et al (2019a); Carvalho et al (2019b); Einspieler et al (2019); Faiçal et al (2019); Nielsen-Saines et al (2019). In addition to Bayley-III, Cabral et al (2018) employed the Mental Development Index (MDI). The Denver Developmental Screening Test (Denver-II) was used in 3 selected studies Flor; Guerreiro; Anjos (2017); Alves et al (2018); Cardoso et al (2019). Valdes et al (2019) applied to Mullen Scales of Early Learning (MSEL), while Subissi et al (2018), the French version of the Child Development Scale (CDAS) and Wheeler et al (2018) used the Brazilian version of the Ages and Stages questionnaire in its third edition (ASQ-3). The outcome of motor development was also performed by the Alberta Infant Motor Scale (AIMS) for 4 included studies Cardoso et al (2019); Einspieler et al (2019); Marques et al (2019); Soares-Marangoni et al (2019). Finally, Einspieler et al (2019) and Soares-Marangoni et al (2019) applied the General Movement Assessment Scale (GMA), while Botelho et al (2016), the Test of Infant Motor Performance (TIMP).

3.4 NEUROPSYCHOMOTOR PROFILES

Studies that evaluated case series or case reports found deficits in gross, fine motor development and / or manual function (BOTELHO et al 2016; ALVES et al 2018; SOARES-MARANGONI et al 2019), as well as atypical cognitive and language development (ALVES et al 2018). In addition, specific deficits in motor development (fine and gross motor skill, manual function) were also found in 4 additional included studies (WHEELER et al 2018; ZANCANELLI, 2018; EINSPIELER et al 2019; MARQUES et al 2019). Deficits in neuropsychomotor development more generally were found in 55% of the included studies (11 studies), thus impairing cognitive, motor and language development (FRANÇA et al 2016; FLOR; GUERREIRO; ANJOS, 2017;
4 DISCUSSION

The results of this systematic review identified 20 articles that performed cognitive assessment in infants exposed to ZIKV during intrauterine life. The main findings of the selected studies were deficits in neuropsychomotor development, specifically: cognitive, motor and language development. The number of publications on Zika topics in Brazil has increased substantially over the last five years, coinciding with the ZIKV infection outbreak. This phenomenon could be verified by the increasing number of Brazilian international papers as shown by our present systematic review. Microcephaly and CZS are likely outcomes of intrauterine exposure to Zika virus, which led the Brazilian scenario to generate WHO international alert. Scientific communications on the subject are of prominent importance, especially in Brazil, as the consequences of this exposure are not fully elucidated. In addition, the scarcity of systematic reviews in the specialized literature that can synthesize the different clinical outcomes points to the relevance of this review.

Global developmental delay is an expected outcome recognized as secondary to microcephaly, as found in other congenital infections or syndromes, as reported by most studies in this review (BOTELHO et al 2016; FLOR; GUERREIRO; ANJOS, 2017; ALVES et al 2018; FERREIRA et al 2018; LOPES MOREIRA et al 2018; WHEELER et al 2018; ZANCANELLI, 2018; CARVALHO et al 2019; EINSPIELER et al 2019; MARQUES et al 2019; NIELSEN-SAINES et al 2019; PRATA-BARBOSA et al 2019; SOARES-MARANGONI et al 2019; VALDES et al 2019). Other severe brain injuries are also related to impaired overall performance, with severe intellectual disability, associated learning disability, and consequently, poor prognosis regarding functional independence and social adaptation. Furthermore, ZIKV-associated neurological changes have recently been known, and it is important to use batteries that involve global assessment of development, as performed in ten studies França et al (2016); Alves et al (2018); Cabral et al (2018); Lopes Moreira et al (2018); Zancanelli, (2018); Cardoso et al (2019); Carvalho et al (2019a); Carvalho et al (2019b); Einspieler et al (2019); Faiçal et
al (2019); Nielsen-Saines et al (2019); Valdes et al (2019), since they allow deeper knowledge in this context of unraveling new avenues for understanding this complex issue.

Some studies Subissi et al (2018); Cardoso et al (2019); Marques et al (2019) have shown results compatible with healthy peers in normocephalic children exposed to ZIKV, suggesting typical development up to the age group evaluated. However, studies Lopes Moreira et al (2018); Einspieler et al (2019); Faiçal et al (2019); Marques et al (2019); Prata-Barbosa et al (2019) reported normocephalic children with poor performance in specific areas, suggesting that they have less cognitive impairment. At the time of regular schooling, formal learning may become a time to highlight different levels of difficulty, when children will in fact be more cognitively and problem-solving required.

Only one study Alves et al (2018) reported results associated with the personal-social domain, which is related to autonomy and social interaction. Behavioral problems and psychiatric conditions, secondary to neurological impairment, are commonly comorbidities found in children with neurodevelopmental disorders that affect cognitive development and learning. Therefore, they deserve more attention. Thus, early evaluation, when still a baby, is necessary and allows anticipating possible cognitive profiles for more severe cases and insertion into early stimulation programs. On the other hand, underperforming children, or changes in specific areas, are at risk of receiving less attention from public policies aimed at rehabilitation.

The strength of our review lies in an attempt for understanding the prognosis and developmental deficits of ZIKV-exposed children. Especially, cases with mild developmental disorders are not yet clear and this review may contribute to the knowledge of expert practitioners. In addition, this study reinforces the growing need for public policy planning and intervention strategies for these children. However, the limiting factors of this review should be highlighted: heterogeneity in the instruments used to assess outcomes, sample size of publications and studies encompassing preliminary result.

The prognosis of cases with severe cognitive impairment can be expected. However, the evolution of cases with mild alterations is still unknown, which indicates the need for cognitive assessment of all children exposed to ZIKV during pregnancy. Among the follow-up measures of children exposed to intrauterine ZIKV, one suggestion is that pediatricians be trained to conduct cognitive screening batteries and refer suspicious cases for comprehensive assessment.
5 CONCLUSION

This systematic review allowed identifying as main results: delayed cognition, motor skills, language and social domain, with worse performance in children with microcephaly or other severe brain injuries. Most normocephalic children exposed to ZIKV showed age-compatible performance; however, a smaller number of these children scored low on at least one assessed cognitive domain, characterizing specific developmental deficits.

ETHICAL ASPECTS

Do not apply.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTIONS

All authors read and approved the final manuscript. SN, DM and MMP worked equally. EPS, NA, GSC and SIS collaborated in the discussion of the results.
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