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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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
Este artigo teve como objetivo revisar sistematicamente a literatura sobre a cognição de crianças expostas à infecção pelo vírus Zika (ZIKV) durante a gestação. Após buscas nas principais bases de dados eletrônicas, PubMed, Capes, Web of Science, Scopus, Cochrane e BVS, as palavras-chave "Zika vírus", "ZIKV infecção", "gravidez", "congênita", "síndrome congênita", "desenvolvimento", "Cognição", "neurodesenvolvimento", "criança", "lactentes", "neuropsicologia", "transtornos do desenvolvimento", "Bayley", "Denver" foram utilizados para a busca sistemática de dados. Após a aplicação dos critérios de elegibilidade para inclusão, foram selecionados 20 artigos relacionados à avaliação cognitiva de crianças expostas ao ZIKV intrauterino publicados até novembro de 2019. A revisão sistemática identificou como principais resultados: atraso na cognição, habilidades motoras, linguagem e domínio social pessoal, com pior desempenho em crianças com microcefalia ou outras lesões cerebrais graves. A maioria das crianças normocefálicas expostas ao ZIKV apresentou desempenho compatível com a idade. No entanto, um número menor de crianças normocefálicas apresentou escore baixo em pelo menos um domínio cognitivo avaliado, caracterizando déficits específicos de desenvolvimento. Esta revisão destaca o alto risco de exposição intrauterina ao ZIKV para o neurodesenvolvimento e sugere investigar o desenvolvimento cognitivo de todas as crianças expostas ao ZIKV para perfis cognitivos de longo prazo, permitindo acesso precoce a programas de reabilitação multidisciplinares.

Palavras-chave: síndrome congênita do zika, cognição, desenvolvimento infantil

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 mosquitos, 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

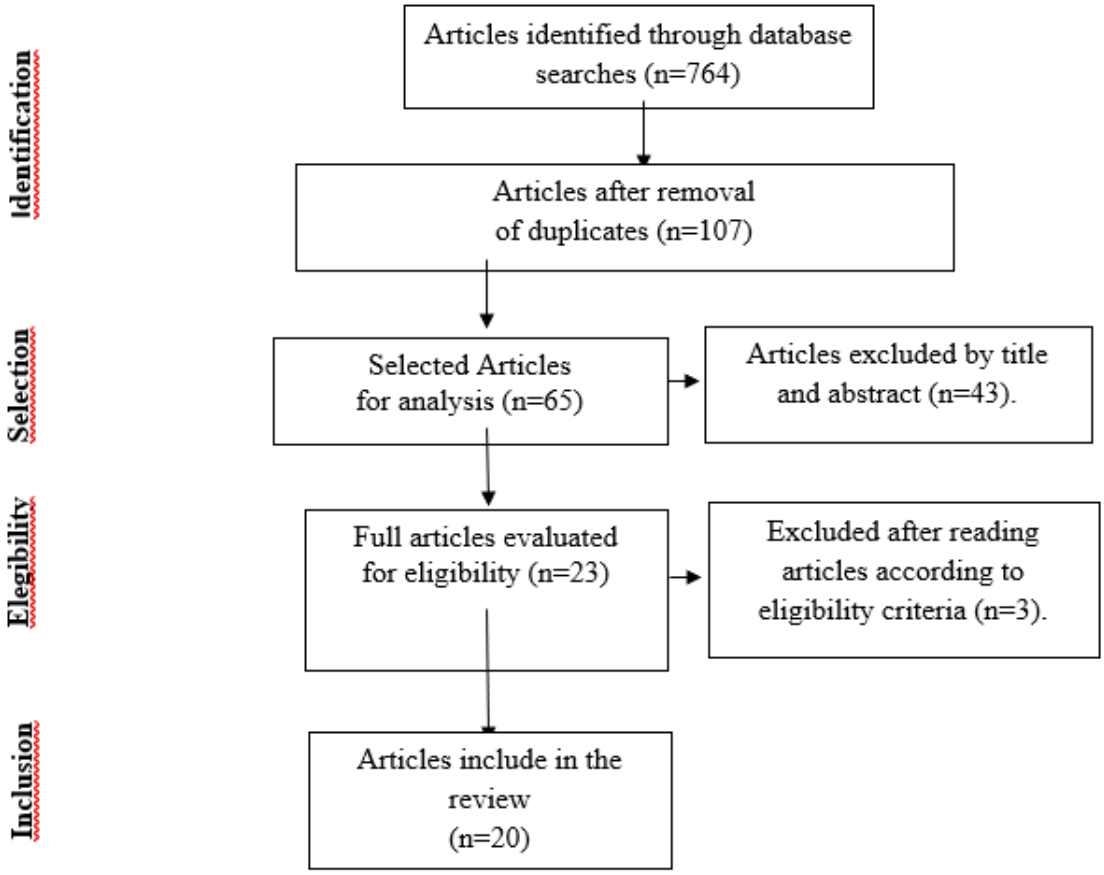
2.1 LITERATURE SEARCH

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).

Figure 1. Flowchart indicating the number of records that were identified, screened, eligible, and included in the review



Source: Own authorship

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

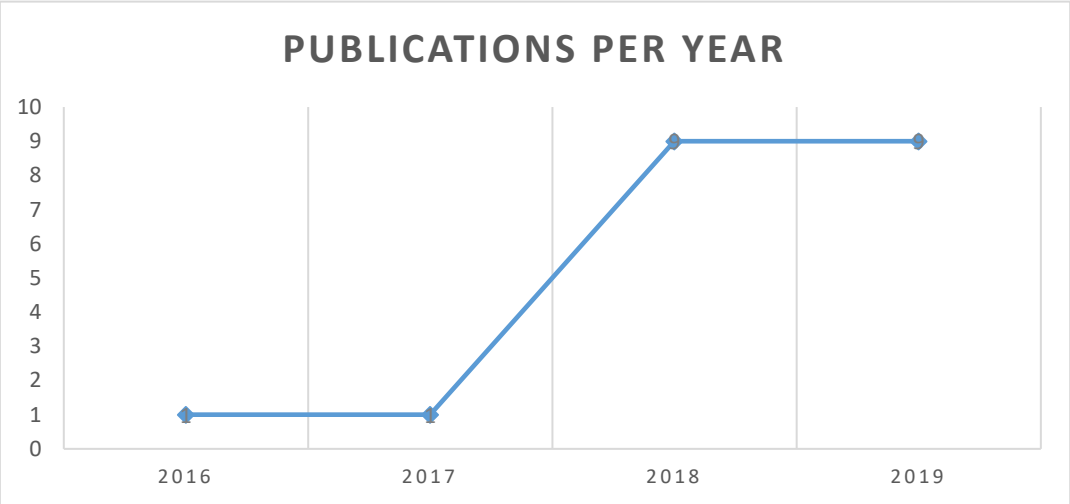
The following information was extracted independently: year of publication, first author, article title, cognitive tests or scales, sample size, cognitive profiles (cognitive deficits), study methodology. In the articles that presented incomplete data, contact with the corresponding author was performed.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



Source: Own authorship

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

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

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

				auditory and joint changes.			fine and gross motor.
3	França et al., 2018, Rio Grande do Norte, Brazil	8	Average 20,5	Growth and development retardation	Reduction in brain volume, changes in the ventricles and calcifications, olymphalmological changes in the macula and optic nerve.	Bayley III	Extremely poor performance in motor and cognitive domains.
4	Subissi et al., 2018, French Polynesia	21	Uninformed	Microcephaly, arthrogryposis	Ventriculomegaly brainstem dysfunction	CDAS	Typical development of children without birth defects.
5	Alves et al., 2018 Pernambuco, Brazil	24	Average 19,9	Microcephaly, epilepsy, pneumonia, urinary tract infection, diarrhea, ventriculoperitoneal shunt	Severe brain injuries	Denver II	Developmental delay in language, gross motor, fine motor, personal / social. Severe neuropsychomotor impairment.
6	Cabral et al, 2018 Bahia, Brazil	18	Average 19	Normocephalic	Not performed	Bayley III, MDI	Delay in language, cognition and motor skills.
7	Wheeler et al., 2018, Pernambuco, Brazil	47	13 – 22	Microcephaly, prematurity, arthrogryposis, hypertonia	Severe brain injuries	ASQ-3, BISQ	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.
8	Soares-Marangoni et al., 2018,Mato Grosso, Brazil	2	Uninformed	Microcephaly	Severe brain in one case	AIMS, PGMA	Motor disorders and severe neurodevelopmental impairment.
9	Ferreira et al., 2018, Paraíba e Rio Grande do Norte, Brazil	34	21	Microcephaly	Severe brain injuries	GMFM-88	Complete disability in most categories of body function, impaired mobility. Intellectual and language delay.
10	Lopes Moreira et al., 2018, Rio de Janeiro, Brazil	104	12-18	Microcephaly, normocephalic	Abnormal neuroimaging findings (39 children)	Bayley III	59 children without Bayley III findings; 11 had one or more lower language and motor scores

11	Zancanelli et al., 2018 Minas Gerais, Brazil	5	0 a 20	Normocephalic and postnatal microcephaly	Not performed	Bayley III, AHEMID-IS AHEMID-SR	Motor, cognitive and language delay.
12	Faiçal et al, 2019 Bahia, Brazil	29	Average 18,2	Normocephalic	Not performed	Bayley III	10 children had developmental delay, mainly in language.
13	Prata-Barbosa et al., 2019 Rio de Janeiro, Brazil	29	0 – 29	Microcephaly, normocephalic	Severe brain injuries	EDCGA	Global delay in the development of children with microcephaly (5); specific language delays, adaptive behavior, personal-social behavior, fine motor skills in 7 normocephalic children and normal development in 17 normocephalic children.
14	Carvalho, et al., 2019, Bahia, Brazil	82	Average 4,8	Microcephaly, cerebral palsy epilepsy, persistence of primitive reflexes, lack of postural reactions	Severe brain injuries	Bayley III	Extremely low cognitive performance, language and motor. Poor prognosis for independent walking
15	Marques et al., 2019 Rio de Janeiro, Brazil	25	12	Microcephaly and cerebral palsy	Severe brain injuries	AIMS, Bayley III	Severe delay in gross motor development.
16	Cardoso et al., 2019, Rio de Janeiro, Brazil	19	1 -7	Normocephalic	Not performed	AIMS,Denver II	18 with developmental delay, hypotonia, hypertonia, ataxia, asymmetry, irritability, dyskinesia, epilepsy, dysphagia, chorea, tremors 1 typical child.
17	Einspieler et al., 2019 Minas Gerais, Brazil	91	12	35 Microcephaly not tested 56 Normocephalic	Brain atrophy, calcifications, hydrocephalus	Bayley III, PGMA	10 normocephalic children presented developmental delay; 46 normocephalic children with normal development until 12 months
18	Nielsen-Saines et al., 2019,	146	0-24	Microcephaly	Severe brain injuries	Bayley III	35% had below average rates on Bayley III, with worse

	Rio de Janeiro, Brazil						language performance
19	Carvalho, et al., 2019, Bahia, Brazil	69	24	Microcephaly and cerebral palsy	Severe brain injuries	Bayley III	Children with cerebral palsy secondary to congenital Zika had severe impairment in cognition, language and motor skills
20	Valdes, et al., 2019 Puerto Rico	65	Average 8,98	Normocephalic	Not performed	MSEL	Prenatal maternal ZIKV infection is associated with lower receptive language scores during the first year of life. Expressive language, fine and gross motor and visual reception development normal at a first year.

Denver II - Denver Developmental Screening Test II, Bayley III - Scales of Infant and Toddler Development Third Edition; AIMS - Alberta Infant Motor Scale; ASQ-3 - Ages and Stages Questionnaire, 3rd edition; BISQ - Brief Infant Sleep Questionnaire; CDAS - Child Development Assessment Scale; MDI – Mental Development Index; TIMP - Test of Infant Motor Performance; NFDS - Neural Function Development Scale.; AHEMD – IS -Affordances in the Home Environment for Motor Development – Infant Scale; AHEMD – SR -Affordances in the Home Environment for Motor Development – Self Report; PGMA – Prechtl General Movmente Assessment; EDCGA -*Escala* de Desenvolvimento Comportamental de *Gesell* e Amatruda; GMFM-88 - Gross Motor Function Measure; MSEL – Mullen Scales of Early Learning
Source: Own authorship

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

Eligible research from this systematic review consisted of 20 articles ranging from case studies to longitudinal research. Botelho et al. (2016) evaluated four cases, while Soares-Marangoni et al. (2018) evaluated two cases with intrauterine ZIKV infection. oth (BOTELHO et al, 2016; SOARES-MARANGONI et al., 2018) articles include cases with and without microcephaly. On the other hand, Alves et al (2018) performed multiple case studies, all with microcephaly. Longitudinal surveys comprised 11 (55%) of the included studies: Cabral et al (2018), Einspieler et al (2019), Nielsen-Saines et al (2019), Wheeler et al (2018), Cardoso et al (2019), Marques et al (2019), Carvalho et al (2019a), Prata-Barbosa et al (2019), Zancanelli et al (2018), Lopes-Moreira et al (2018) and Carvalho et

al (2019b). The cross-sectional surveys comprised five (25%) included studies: Valdes et al (2019), Flor; Guerreiro; Anjos (2017), Ferreira et al (2018), Faiçal et al (2019) and França et al (2018). Finally, Subissi et al (2018) evaluated child development related to intrauterine ZIKV infection through a case-control study.

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;

ALVES et al 2018; CABRAL et al 2018; FERREIRA et al 2018; LOPES MOREIRA et al 2018; CARDOSO et al 2019; CARVALHO et al 2019a; CARVALHO et al 2019b; NIELSEN-SAINES et al 2019; PRATA-BARBOSA et al 2019). Finally, Valdes et al (2019) found differences only in the development of receptive language in infants with positive and negative prenatal tests for ZIKV and other preserved cognitive functions.

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[18]. 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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