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Neurodevelopment in the first year of children exposed to SARS-CoV-2 during intrauterine period: systematic review

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Neurodesenvolvimento no primeiro ano de crianças expostas ao SARS-CoV-2 durante período intrauterino: revisão sistemática

Neurodesarrollo en el primer año de niños expuestos al SARS-CoV-2 durante el período intrauterino: revisión sistemática

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ABSTRACT

Objective: To identify, in the literature, the implications of gestational exposure to SARS-CoV-2 on neurodevelopment in the first postnatal year, focusing on changes in the motor, personal-social, socio-emotional, and communication and language domains.
Method: Systematic review with narrative synthesis, considering neurodevelopmental outcomes, categorized according to gross and fine motor skills, personal-social interaction, socio-emotional aspects, and communication and language. Searches were conducted in PubMed, LILACS/BIREME, and EMBASE databases between January 2020 and June 2023. Two independent researchers performed selection by reading the title and abstract and applying the inclusion and exclusion criteria. Cohort studies that evaluated children up to one year old, exposed to SARS-CoV-2 in utero, were included. The Newcastle-Ottawa scale was used to assess methodological quality.
Results: Seventeen articles were included, with methodological quality ranging from intermediate to good. The most frequently used instrument to characterize neurodevelopment was the Ages & Stages Questionnaires. Infants aged 0 to 3 months had lower scores for fine and gross motor skills. Infants aged 3 to 12 months had more fine motor, social and communication and language impairments.
Conclusion: Most infants exposed to SARS-CoV-2 showed development as expected, however delays were identified in the motor, personal-social, socio-emotional and communication and language domains according to the age group.
Descriptors: SARS-CoV-2. Pregnancy. Child development. Neurodevelopmental Disorders.

RESUMO

Objetivo: Identificar, na literatura, implicações da exposição gestacional ao *SARS-CoV-2* sobre o neurodesenvolvimento no primeiro ano pós-natal, com foco nos domínios motor, pessoal-social, socioemocional e de comunicação e linguagem.
Método: Revisão sistemática com síntese narrativa, considerando desfechos do neurodesenvolvimento, categorizados quanto à motricidade grossa e fina, interação pessoal-social, aspectos socioemocionais e de comunicação e linguagem. As buscas nas bases de dados PubMed, LILACS/BIREME e EMBASE ocorreram entre janeiro/2020 e junho/2023. Dois pesquisadores independentes realizaram seleção pela leitura do título e resumo e a aplicação dos critérios de inclusão e exclusão. Foram incluídas coortes com crianças de até um ano, expostas ao *SARS-CoV-2* in utero. Adotou-se a escala *Newcastle-Ottawa* para avaliar qualidade metodológica.
Resultados: Foram inclusos 17 artigos cuja qualidade metodológica apresentou-se de intermediária a boa. O instrumento mais utilizado para caracterização do neurodesenvolvimento foi o *Ages & Stages Questionnaires.* Bebês de 0 a 3 meses apresentaram menores pontuações para motricidade fina e grossa. Bebês de 3 a 12 meses apresentaram mais alterações motoras finas, sociais e na comunicação e linguagem.
Conclusão: A maioria dos bebês expostos ao *SARS-CoV-2* apresentou desenvolvimento de acordo com o esperado, porém puderam ser identificados atrasos nos domínios motor, pessoal-social, socioemocional e comunicação e linguagem conforme faixa etária.
Descritores: SARS-CoV-2. Gravidez. Desenvolvimento Infantil. Transtornos do Neurodesenvolvimento.

RESUMEN

Objetivo: Identificar en la literatura las implicaciones de la exposición gestacional al *SARS-CoV-2* sobre el neurodesarrollo en el primer año postnatal, enfocándose en los cambios en los dominios motor, personal-social, socioemocional y de comunicación y lenguaje.
Método: Revisión sistemática con síntesis narrativa, considerando los resultados del neurodesarrollo, categorizados en desarrollo de la motricidad gruesa y fina, interacción personal-social, aspectos socioemocionales y de comunicación y lenguaje. Las bases de datos utilizadas fueron PubMed, LILACS/BIREME y EMBASE entre enero de 2020 y junio de 2023. Dos investigadores independientes realizaron la selección inicial mediante la lectura del título y el resumen y la aplicación de los criterios de inclusión y exclusión. Se incluyeron estudios de cohortes prospectivos y retrospectivos que evaluaron a niños de hasta un año, expuestos al *SARS-CoV-2* in utero. Se adoptó la escala Newcastle-Ottawa para evaluar la calidad metodológica.
Resultados: Se incluyeron 17 artículos cuya calidad metodológica fue intermedia a buena. El instrumento más utilizado para caracterizar el neurodesarrollo fue el *Ages & Stages Questionnaires*. Los bebés de 0 a 3 meses obtuvieron puntuaciones más bajas en habilidades motoras finas y gruesas. Los bebés de 3 a 12 meses mostraron más cambios motores finos, sociales y de comunicación y lenguaje.
Conclusión: La mayoría de los bebés expuestos al *SARS-CoV-2* se desarrollaron como se esperaba, pero se pudieron identificar retrasos en los dominios motor, personal-social, socioemocional y de comunicación y lenguaje según el grupo de edad.
Descriptores: *SARS-CoV-2.* El embarazo. Desarrollo infantil. Trastornos del neurodesarrollo

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INTRODUCTION

Fetal brain development begins during the first trimester and occurs throughout gestation, being highly influenced by maternal and environmental humoral factors, due to the vulnerability of developing nerve cells[1]. This process is influenced by a series of epigenetic factors that may be involved in the origin of neurological developmental disorders in children[2]. Neurodevelopmental disorders comprise a spectrum of alterations resulting from the abnormal development of the nervous system, such as motor, socio-emotional, communication and language development disorders[3].

The Severe Acute Respiratory Syndrome coronavirus, SARS-CoV-2, is the infectious agent responsible for COVID-1[4]. SARS-CoV-2 shows, in astrocytes, a strong tropism in developing human cortical tissue, as evidenced by the high rate of infection and viral replication in these cells. After exposure to the virus, it was found that 90% of astrocytes located in the external subventricular zone exhibited infection markers. Astrocytes are essential for neurotransmitters regulation, maintenance of the blood-brain barrier, and neural metabolism control, which can significantly impact brain development[5].

Maternal infections during pregnancy can alter the structure and function of the fetal brain by inducing an inflammatory cytokine cascade[6]. SARS-CoV-2 infection during pregnancy causes dysfunction in the renin-angiotensin (RA) system and vasoconstriction, due to the binding of the virus to angiotensin-converting enzyme 2 receptors, present in the placenta and uterus, which predisposes to preeclampsia and poor placental perfusion. For the fetus, epigenetic changes occur in organs, including the brain, mitochondrial dysfunction, and reactivity of macrophages and brain microglia. Increased pro-inflammatory cytokines implies adversities in neurodevelopment, including early cognitive and behavioral changes[7,8].

Children represent a minority in lethal SARS-CoV-2 infections: 23 deaths per 1,000,000 children in Brazil in 2020[9,10]. However, this group is indirectly affected when considering infection among pregnant women[11]. Gestational infection by SARS-CoV-2, as with other viral pathogens such as Chikungunya, Herpes simplex and Varicella Zoster, can cause encephalopathy, meningopathies and postnatal sequelae[12].

Although maternal SARS-CoV-2 infection presents low neonatal mortality, it cannot be concluded that the infection does not bring complications to pregnancy and the child[13]. This is because changes in child development occur within complex systems, with many components that interact over time. Complex physical systems comprise interacting elements that span several levels, from the molecular (e.g., genes) to the neural, behavioral and social[14]. Therefore, motor development, by facilitating knowledge acquisition about the world, triggers cascades of changes in perceptual, cognitive, and social domains[15]. Genetic and environmental factors provide continuous modification of brain capacity through experience and stimuli, which favors learning and growth, but also highlights the sensitivity of the nervous system to pathological changes, as well as its capacity for recovery through neuronal plasticity[16].

Due to the neurotropic potential of the SARS-CoV-2 virus and considering the intense process of neurodevelopment and neuroplasticity in the first year of extrauterine life, continuous monitoring of infants exposed to this pathogen in the prenatal period is necessary[16]. Thus, the objective of this study was to identify in the literature the implications of gestational exposure to SARS-CoV-2 on neurodevelopment in the first postnatal year, focusing on the motor, personal-social, socio-emotional, and communication and language domains.

METHOD

This is a systematic literature review, registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identification CRD42023408029. The review was developed in compliance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[17].

The SPIDER strategy[18] was adopted for research design, in which Sample consisted of: infants up to one year of age exposed to intrauterine SARS-CoV-2 infection; Phenomenon of Interest: neurodevelopment throughout the first postnatal year; Design: prospective and/or retrospective cohort studies; Evaluation: neurodevelopment measurement scales; Research Type: quantitative epidemiological research. The guiding question was: "What are the neurodevelopmental changes identified during the first postnatal year in the motor, personal-social, socio-emotional, and communication and language domains in children exposed to SARS-CoV-2 during the gestational period?"

To identify eligible articles, searches were conducted in the U.S. National Library of Medicine National Institutes of Health (PubMed), Latin American and Caribbean Literature in Health Sciences (LILACS/BIREME), and EMBASE (Elsevier) databases, from April to July 2023. A specific search strategy was used for each database, due to the particularities of each one. The descriptors in the English language were identified in the Health Sciences Descriptors (DeCS) of the Latin American and Caribbean Center on Health Sciences Information (BIREME) or in the terms from the Medical Subject Headings (MeSH) of PubMed, as well as their synonyms. The Boolean operator

OR was used within categories and between term variations, and the operator AND was adopted between categories to combine them, as follows: (SARS-CoV-2) OR (coronavirus) OR (COVID-19) OR (Severe Acute Respiratory Syndrome) AND (embryogenesis) OR (fetal medicine) OR (maternal infection) OR (intrauterine) AND (Infant) OR (newborn) OR (toddler) OR (neonate) AND (follow-up) OR (neurodevelopmental disorders) OR (neurodevelopmental outcomes) OR (motor outcome) OR (motor development) OR (motor function assessment) OR (neural impairment).

The inclusion criteria were: studies with children up to one year old born to mothers exposed to SARS-CoV-2, at any gestational period, with positive PCR testing; studies that assessed aspects of motor, personal-social, socio-emotional, and communication and language neurodevelopment, using instruments clearly identified in the study methodology; prospective or retrospective cohort studies published from January 2020 to June 2023. The exclusion criteria were: review studies, protocols, letters, and editorials; ongoing research; studies that did not use standardized neurodevelopment assessment instruments; studies that assessed the consequences of maternal exposure to other viral pathogens; studies that assessed congenital or genetic childhood conditions that could affect neurodevelopment; studies that did not address neurodevelopmental conditions; studies that assessed children over one year old; and studies that presented low methodological quality.

Five stages of analysis were established[18]: 1) Selection by title and abstract; 2) Application of inclusion and exclusion criteria; 3) Selection of article by full-text reading; 4) Data extraction and 5) Qualitative synthesis.

Two independent researchers performed the initial selection by reading the title and abstract and applying the inclusion and exclusion criteria. Duplicate titles were eliminated using the Rayyan application[19], ensuring reliability in information selection, and methodological accuracy and precision. Once the potentially eligible articles were identified, full-text reading was conducted to finalize the sample. In cases of disagreement, a third reviewer was consulted regarding article inclusion.

Data from the selected studies were extracted independently and entered into a Microsoft Excel spreadsheet. The following data were extracted: authors, year and country; study objective; methodology - including design, sample characteristics (age in months) and neurodevelopment assessment instrument - and outcomes.

The outcomes were categorized as: gross and/or fine motor development, personal-social interaction, socio-emotional aspects, and communication and language, in accordance with the domains used in the diagnostic concept of neurodevelopmental disorders[3] and which are also presented according to the neurodevelopment assessment tools present in the included studies. The age of the children in months was considered, since the studies periodized reassessments in the third, sixth, and twelfth postnatal month.

The assessment of the methodological quality of the articles was performed using the Newcastle-Ottawa Scale[20,21], which has specific questions for cohort studies divided into three sections: selection of study groups; comparability of groups; and exposure or outcome of interest. The questions are answered with a number of stars, with a maximum possible score of 9. The more stars, the better the study. Good quality is defined by 3 or 4 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain. Reasonable/intermediate quality is indicated by 2 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain. Poor quality is identified by 0 or 1 star in the selection domain, 0 stars in the comparability domain, or 0 or 1 star in the outcome/exposure domain[20].

RESULTS

A total of 746 articles were found, 23 of which were selected after reading the title and abstract, and 17 articles were included after applying the inclusion and exclusion criteria and assessing methodological quality. Figure 1 represents the flowchart of the article selection process from the chosen database.

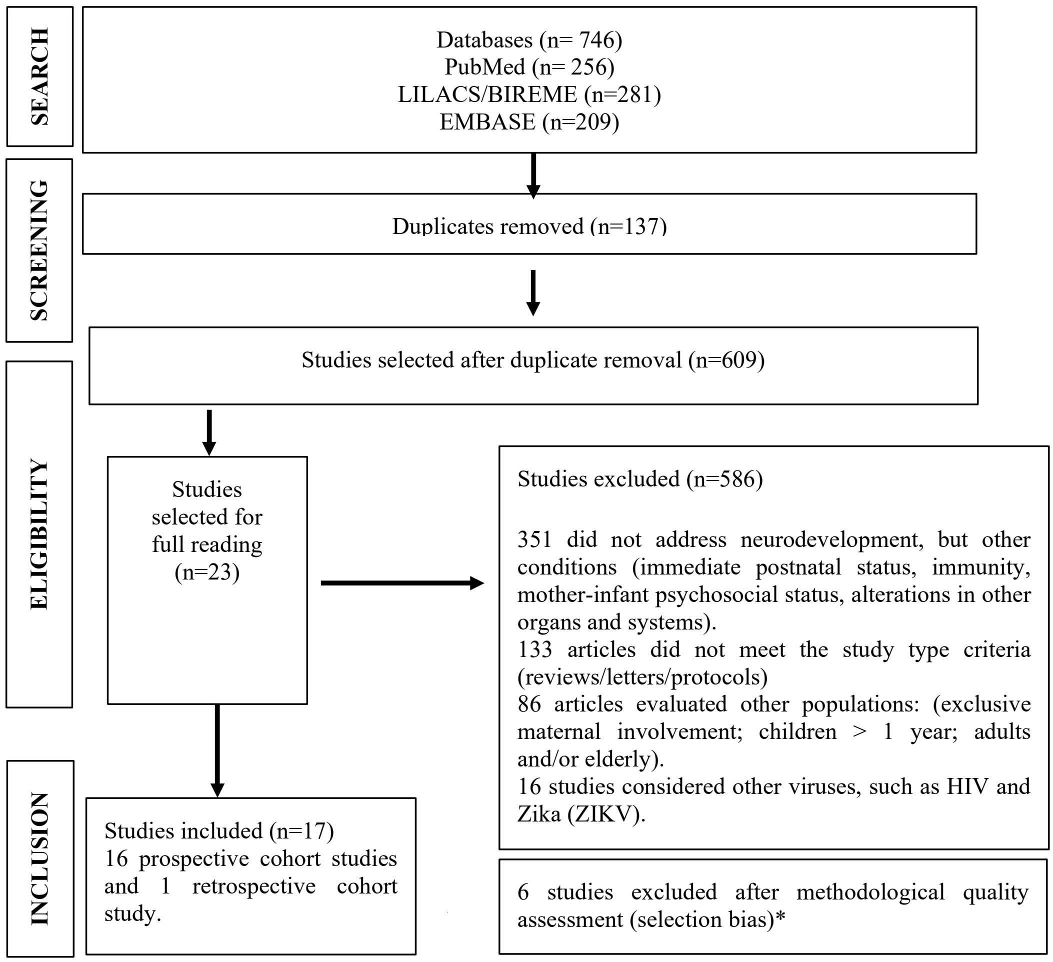
Sixteen prospective cohort studies and 1 retrospective cohort study were included, 1 published in 2020, 4 in 2021, 7 in 2022 and 5 in 2023, all in English.

The results were organized according to neurodevelopmental aspects: motor, personal-social, socio-emotional and communication and language. To facilitate the understanding of these aspects, this review describes the instruments used to characterize the outcomes.

All included studies considered, in the initial assessment of the newborn: gestational age; type of delivery; immediate health condition; diagnosis or non-diagnosis of COVID-19; immunization factor or immune sensitization; Apgar score at the first, fifth and tenth minutes; the need for ventilatory support and the major symptoms and complications during birth.

Regarding birth characteristics, although 11 articles identified the presence of preterm birth[22–32], most infants presented weight, Apgar scores at the first and fifth minutes, and gestational age within normal parameters. Among preterm infants who presented alterations in neurodevelopment, these were associated with longer hospital stays and respiratory complications, which were related to severe forms of maternal COVID-19.

Figure 1 – Flowchart of the process of identification, selection and eligibility of articles. Goiânia, Goiás, Brazil, 2023.



Source: Prepared by the authors, 2023.
Legend: *Studies also included infants over 12 months of age.

To minimize biases in the effect of prematurity and infection on development, four studies used multiple linear regression modeling, adjusting for preterm birth (yes or no), sex, neonatal intensive care unit admission, maternal SARS-CoV-2 infection status, maternal age (years), and ethnicity[24,25,28,31]. Another study mentioned linear mixed-effect models to determine whether age, sex, and SARS-CoV-2 infection status were able to predict infant development, but there was no statistical significance for the prematurity factor[26].

For the other studies, there was also no statistical significance for the prematurity factor among the groups, and the analysis of covariance with maternal age, gestational age, and infant sex was adopted to compare the groups (exposed and unexposed to the virus),[22] or the Student's t-test and Mann-Whitney test[23,29].

Regarding maternal characteristics, most mothers were diagnosed with SARS-CoV-2 in the third trimester of pregnancy[22–24,29,31,33], with the majority being asymptomatic and fever being the main symptom, when present[30,33]. The disease was confirmed by laboratory testing.

Immune testing of babies was identified in 13 articles. The Polymerase Chain Reaction (RT-PCR) technique was used for both mothers and infants. Most of the babies tested were significantly negative for SARS-CoV-2 at birth[23,26–28,30–37]. In addition to the PCR evaluation, some studies also analyzed umbilical cord blood, amniotic fluid, breast milk, meconium and placenta, which identified the presence or absence of the virus[31,32].

The instruments used to assess child development were: Ages & Stages Questionnaires Third Edition (ASQ-3)[23,27,29–33,36,38], Age and Stage Questionnaire Social–Emotional (ASQ:SE- 2)[31,32], Developmental Profile (DP-3)[34], Amiel-Tison Method[34], Denver Developmental Screening Test II (Denver II)[26], General Movements Assessment (GMA) e Motor Optimality Score (MOS)[28,35], Neonatal Behavioral Assessment Scale (NBAS)[22], Baby Pediatric Symptom Checklist (BPSC)[38], Van

Wiechen Schem[37] and Developmental Assessment of Young Children, 2nd edition (DAYC-2)[25].

The ASQ-3, the main instrument used, is an easy-to-apply, low-cost and a sensitive tool for different cultural contexts, which makes it widely used[39]. The domains assessed are: communication, gross motor coordination, fine motor coordination, problem-solving, and personal-social skills. Although children exposed to SARS-CoV-2 are more likely to score below the normative averages[38], most studies using the ASQ-3 reported that the neurodevelopment of infants born to mothers with SARS-CoV-2 infections was within the expected range[27,30,32,33] or found no significant difference between those exposed and non-exposed to the virus[23,36]. In one study, developmental delays occurred significantly more frequently based on the trimester of SARS-CoV-2 infection: they were more common in infants born to mothers infected during the first and second trimesters ($p<0.001$)[33].

Chart 1 presents a description of the articles included regarding the outcome for the motor domain. When assessed between eight and twelve months, newborns of mothers infected with SARS-CoV-2 during the gestational period had significantly lower scores in the fine motor domain ($P = 0.03$)[23].

Infants of symptomatic mothers more frequently (compared to those of asymptomatic mothers) presented abnormal neurological examinations for age and ASQ-3 scores close to or below cutoff points for all domains. The differences were significant for fine motor ($p = 0.01$) and personal-social ($p = 0.02$) domains[29].

The Amiel-Tison method detects warning signs of psychomotor development abnormalities, such as persistent primitive reflexes, changes in tone (decreased or increased) and posture, asymmetry, and cervical and axial hypotonia. Using this method, it was identified that 42.1% of the children in the cohort of mothers who tested positive for SARS-CoV-2 had below-average development, while the percentage was 25.9% among the negative cohort. However, there was no significant difference in growth, neurodevelopment, or hospital readmission rate among newborns[34].

For the GMA and MOS instruments (from 3 to 6 months), the exposed group had a significantly reduced total motor optimization score compared to the unexposed group. Only atypical body symmetry was significantly different[35]. Another study using these instruments revealed that, compared to pre-pandemic control groups, infants exposed to SARS-CoV-2 in the prenatal phase had more frequent suboptimal neuromotor development[28]. These instruments are reliable and used for quantifying the quality of fidgety movements.

For the Denver II instrument, at 12 months, early fine motor alterations were identified with a higher incidence in the group exposed to SARS-CoV-2, compared to the unexposed group, and with a short-term neurological effect. The growth curve was similar between the two cohorts[26].

In utero exposure was not associated with significant differences in any subdomain of the ASQ-3 instrument, although infants born during the pandemic had lower scores in the gross and fine motor and personal-social domains[31].

For the ASQ:SE-2, which tracks social and emotional behaviors such as self-regulation, adaptive functioning, autonomy, affection, and interaction, the proportion of risk classification for infants exposed to SARS-CoV-2 reached 63.6%[31].

Chart 2 presents the description of the included articles regarding outcomes for the personal-social and socio-emotional domains.

Legend: ASQ-3: Ages & Stages Questionnaires Third Edition. NBAS: Neonatal Behavioral Assessment Scale. ASQ:SE-2: Age and Stage Questionnaire Social–Emotional. BPSC: Baby Pediatric Symptom Checklist.

SARS-CoV-2 infection during pregnancy did not significantly increase the risk of socio-emotional delay, according to the ASQ-3 and ASQ:SE-2[32]. When the BPSC instrument was used, 53% of the children in the cohort exposed to SARS-CoV-2 exceeded the threshold of clinical concern, with irritability being the most widespread behavior[38].

Regarding the results for the NBAS instrument, the infants' skills and performances were similar in the exposed and non-exposed groups to SARS-CoV-2. A significant difference was found in the less optimized response to affection, particularly in infants born to mothers exposed in the third trimester of pregnancy[22].

Chart 3 presents the description of the included articles regarding the outcome for the communication and language domain. Diagnoses, based on the ICD-10, for neurodevelopmental disorders were significantly more common among children exposed to SARS-CoV-2 during the gestational period, particularly in the third trimester. Most diagnoses reflected motor function or speech and language developmental disorders[24].

Regarding environmental aspects, there was a negative association between the days of mother-infant separation and the scores in the gross motor, communication, and personal-social domains of the ASQ-3, regardless of intrauterine exposure to the virus[31,32].

The methodological quality scores of the articles, according to the Newcastle-Ottawa Quality Assessment Scale, ranged from 4 to 8, with a mean of 6, representing an overall quality considered from intermediate to good[20], as expressed in Chart 4.

The most frequent methodological deficits were the lack of description or lack of clarity in the statistical presentation of sample representativeness and the inadequate description of participants lost throughout the research.

Chart 1 – Overview of studies retrieved and included in the final sample, considering motor outcome. Goiânia, Goiás, Brazil, 2023.

Age (months)	Authors/ Country/Year	Objective	Design/ Sample/ Instrument	Motor outcome
0 to 3	Wang et al.[31] China, 2020.	Assess the impact of SARS-CoV-2 infection during pregnancy on baby development.	Prospective cohort. Sample: 57 babies born to mothers infected with SARS-CoV-2 during pregnancy. Instrument: ASQ-3.	**Gross and fine motor skills:** low proportion of babies classified as at risk (23.1%). Negative association between mother-baby separation days and gross motor skills.
3 to 6	Munian et al.[34] India, 2021.	Compare the development of SARS-CoV-2 positive newborns versus negative ones, all born to SARS-CoV-2 positive mothers.	Prospective cohort. Sample: 133 babies born to SARS-CoV-2 positive mothers. Instrument: Amiel-Tison Method and DP3.	**Persistence of primitive reflexes, tone and posture abnormalities, cervical and axial hypotonia, asymmetry**: 42.1% of SARS-CoV-2 positive cohort children had below-average development.
	Wu et al.[32] China, 2021.	Compare the development of two cohorts (exposed and unexposed to SARS-CoV-2) and explore secondary effects of the pandemic on development.	Prospective cohort. Sample: 57 mother-baby dyads in the infection cohort and 78 dyads without infection. Instrument: ASQ-3.	**Gross and fine motor skills**: linear regression models showed that mother-baby separation was negatively correlated with gross motor scores, with statistical significance.
	Aldrete-Cortez et al. [35] Mexico, 2022.	Assess if babies prenatally exposed to SARS-CoV-2 are at risk of developing developmental disorders.	Prospective cohort. Sample: 28 exposed babies and 28 unexposed babies. Instrument: GMA.	**Quantity and quality of spontaneous movement in supine position:** in the exposed group, 11% of infants had a significantly reduced total motor optimization score, compared to the unexposed group.
	Schuh et al.[30] USA, 2022.	Assess hospital management, transition to home, breastfeeding, growth, and clinical outcomes of babies born to mothers diagnosed with SARS-CoV-2 during pregnancy.	Prospective cohort. Sample: 33 babies born to mothers with SARS-CoV-2 infection. Instrument: ASQ-3.	**Gross and fine motor skills:** ASQ-3 results were available for 15 infants and in all cases the child's development was within the expected range, both motor and in the other domains.

Chart 1 – Cont.

Age (months)	Authors/ Country/Year	Objective	Design/ Sample/ Instrument	Motor outcome
6 to12	Shuffrey et al. [36] USA, 2022.	Analyze the association between maternal SARS-CoV-2 infection during the COVID-19 pandemic and baby neurodevelopment in the first 6 months of age.	Prospective cohort. Sample:141 SARS-CoV-2 exposed babies and 114 unexposed babies. Instrument: ASQ-3.	**Gross and fine motor skills:** *in utero* exposure was not associated with significant differences in any ASQ-3 subdomain. Babies born during the pandemic had significantly lower scores in gross motor, fine motor, and personal-social domains.
	Cheng et al.[23] China, 2021.	Assess the potential influence of SARS-CoV-2 on infant neurobehavioral development.	Prospective cohort. Sample: Nine pregnant women with SARS-CoV-2 infection and nine matched controls. Instrument: ASQ-3.	**Gross and fine motor skills:** newborns of women infected with SARS-CoV-2 during pregnancy had lower scores in all domains; however, only fine motor skills reached statistical significance ($p = 0.03$).
	Roffman et al.[38] USA, 2021.	Report early outcomes of prenatal exposure to SARS-CoV-2 and broader pandemic-related stressors on child development.	Prospective cohort. Sample: 19 babies born to mothers diagnosed with SARS-CoV-2 during pregnancy and 15 matched babies from uninfected mothers. Instrument: ASQ-3.	**Gross and fine motor skills:** more generalized deficits in gross motor skills. Children exposed to SARS-CoV-2 were more likely to have lower scores across all domains.
	Ayed et al.[33] Kuwait, 2022.	Assess neurodevelopment in newborns of mothers infected with SARS-CoV-2 during pregnancy.	Prospective cohort. Sample: 298 babies exposed to SARS-CoV-2. Instrument: ASQ-3.	**Gross and fine motor skills:** most exposed babies had favorable outcomes. Only 10% showed developmental delays. Delays were more common in babies of mothers with infection in the first and second trimesters ($p<0.001$).
	Liu et al.[26] China, 2022.	Examine developmental outcomes of babies prenatally affected by SARS-CoV-2	Prospective cohort. Sample: 100 babies born to 98 mothers exposed to SARS-CoV-2 during pregnancy. Instrument: Denver II.	**Fine motor skills**: early fine motor changes were higher in the exposed group (15.2%).

Chart 1 – Cont.

Age (months)	Authors/ Country/Year	Objective	Design/ Sample/ Instrument	Motor outcome
6 to12	Mulkey et al.[29] USA, 2022.	Determine the impact of early exposure to SARS-CoV-2 on development.	Prospective cohort. Sample: 34 babies assessed in the SARS-CoV-2 impact follow-up program. Instrument: ASQ-3.	**Fine motor skills:** 69% of babies with symptomatic mothers had abnormal neurological exams for their age and ASQ-3 scores near or below cutoff points for all domains. Differences were significant for fine motor skills ($p = 0.01$)).
	Martinez al.[28] USA, 2023.	Assess the integrity of the developing nervous system in babies exposed to maternal SARS-CoV-2 infection during pregnancy.	Prospective cohort. Sample:124 SARS-CoV-2 exposed babies and 115 pre-pandemic controls. Instruments: GMA and MOS-R.	**Quantity and quality of spontaneous movement in supine position:** compared with the pre-pandemic control group, infants exposed to SARS-CoV-2 prenatally had more frequent suboptimal neuromotor development.
	Martenot et al.[27] France, 2023.	Monitor neurodevelopment outcomes of babies born to mothers diagnosed with SARS-CoV-2 infection.	Prospective cohort. Sample: 24 mother-baby dyads. Instrument: ASQ-3.	No adverse neurological or medical outcomes were detected at 10 months of age.

Source: Prepared by the authors, 2023.
Legend: ASQ-3: Ages & Stages Questionnaires Third Edition. DP-3: Developmental Profile. GMA: General Movements Assessment. MOS-R: Motor Optimality Score. Denver II: Denver Developmental Screening Test II.

Chart 2 – Overview of studies retrieved and included in the final sample, considering the personal-social and socio-emotional outcomes. Goiânia, Goiás, Brazil, 2023.

Age (months)	Authors/ Country/Year	Objective	Design/ Sample/ Instrument	Personal-social and socio-emotional outcomes
0 to 3	Ayesa-Arriola et al.[22] Spain, 2023.	Explore the consequences of prenatal exposure to SARS-CoV-2 on neurodevelopment.	Prospective cohort. Sample: 21 babies exposed and 21 babies not exposed prenatally to SARS-CoV-2. Instrument: NBAS.	**Interaction and responsiveness to the environment. Habituation, orientation, motor system, organization, and state regulation**: performances of babies were similar in both SARS-CoV-2 exposed and non-exposed groups. There was a significant difference in less optimized response to affection.
	Wang et al.[31] China, 2020.	Assess the impact of SARS-CoV-2 during pregnancy on the baby's behavioral development.	Prospective cohort. Sample: 57 babies born to mothers with SARS-CoV-2 infection during pregnancy. Instrument: ASQ-3.	**Social and emotional behaviors in domains such as self-regulation, compliance, social communication, adaptive functioning, autonomy, affection, and interaction with people:** low proportion of babies were classified as at risk (23.1%). A negative association was found between days of mother-baby separation and scores in the personal-social domain.
3 to 6	Wu et al.[32] China, 2021.	Compare the development of babies exposed and not exposed to SARS-CoV-2 during pregnancy.	Prospective cohort. Sample: 57 mother-baby dyads in the infection cohort and 78 mother-baby dyads in the non-infection cohort. Instrument: ASQ:SE-2	**Social and emotional behaviors including self-regulation, adaptive functioning, autonomy, affection, and interaction with people:** SARS-CoV-2 infection during pregnancy did not increase the risks of socio-emotional and general developmental delays. In the infection group, 13.6% of children showed socio-emotional developmental delays and 13.5% showed general developmental delays.
	Shuffrey et al.[36] USA, 2022.	Analyze the association between maternal SARS-CoV-2 infection during the pandemic and its impact on development.	Prospective cohort. Sample: 141 babies exposed to SARS-CoV-2 and 114 non-exposed babies. Instrument: ASQ-3.	**Personal-social:** *In utero* exposure was not associated with significant differences in any subdomain of the ASQ-3. However, babies born during the pandemic had significantly lower scores in the gross motor, fine motor, and personal-social domains.

Chart 2 – Cont.

Age (months)	Authors/ Country/Year	Objective	Design/ Sample/ Instrument	Personal-social and socio-emotional outcomes
6 to 12	Roffman et al.[38] USA, 2021.	Report how prenatal exposure to SARS-CoV-2 and pandemic-related stressors affected developmental milestones.	Prospective cohort. Sample: 19 babies born to mothers diagnosed with SARS-CoV-2 and 15 matched babies whose mothers were not known to be positive for the virus. Instrument: BPSC	**Child well-being and aspects of behavior and self-regulation:** 53% of children in the SARS-CoV-2 exposed cohort surpassed the clinical concern threshold, with irritability being the most widespread behavior in each group.
	Mulkey et al.[29] USA, 2022.	Determine the impact of early exposure to SARS-CoV-2 on neurodevelopment.	Prospective cohort. Sample: 34 babies assessed in the SARS-CoV-2 impact follow-up program. Instrument: ASQ-3.	**Personal-Social:** 69% of babies with symptomatic mothers had abnormal neurological exams for their age and ASQ scores near or below cutoff points across all domains. Differences were significant in the personal-social domain ($p = 0.02$).

Source: Prepared by the authors, 2023.
Legend: ASQ-3: Ages & Stages Questionnaires Third Edition. NBAS: Neonatal Behavioral Assessment Scale. ASQ:SE- 2: Age and Stage Questionnaire Social–Emotional. BPSC: Baby Pediatric Symptom Checklist.

Chart 3 – Overview of studies retrieved and included in the final sample, according to communication and language outcomes. Goiânia, Goiás, Brazil, 2023.

Age (months)	Authors/ Country/Year	Objective	Design/ Sample/ Instrument	Communication and language outcome
0 to 3	Rood et al.[37] Suriname 2023	Describe clinical characteristics of neonates born to mothers diagnosed with SARS-CoV-2 infection and report development at 3 months of age.	Prospective cohort. Sample: 18 babies born to mothers diagnosed positive for SARS-CoV-2. Instrument: Van Wiechen Scheme.	**Checklist with language milestones completed by the professional, based on observation or parents report**: neurodevelopmental delay was found in 14.3% of patients.
6 to 12	Edlow et al.[24] USA 2022	Assess if intrauterine exposure to SARS-CoV-2 is associated with the risk of developmental disorders.	Prospective cohort. Sample: 222 babies born to mothers positive for SARS-CoV-2. Instrument: ICD-10	Neurodevelopmental disorders are proportionally more common among those exposed (6.3%), particularly in the third trimester. Most diagnoses reflected motor development or speech and language disorders.
	Firestein et al.[25] USA 2023	Assess if mild or asymptomatic maternal SARS-CoV-2 infection is associated with differences in development.	Prospective cohort. Sample: 258 non-exposed babies and 112 exposed to SARS-CoV-2. Instrument: DAYC-2.	No association between prenatal exposure to maternal SARS-CoV-2 infection and child neurodevelopment.

Source: Prepared by the authors, 2023.
Legend: ICD-10: International Statistical Classification of Diseases and Related Health Problems. DAYC-2: Developmental Assessment of Young Children, 2nd edition.

Chart 4 – Characterization and scoring of articles, according to the Newcastle-Ottawa Quality Assessment Scale criteria. Goiânia, Goiás, Brazil, 2023.

Study	Selection	Comparability	Exposure Outcome	Total (max: 9)
Ayesa-Arriola et al. [22]	☆☆☆	☆	☆	5
Cheng et al.[23]	☆☆☆	☆	☆☆☆	7
Edlow et al.[24]	☆☆☆	☆	☆	5
Firestein et al.[25]	☆☆☆	☆	☆☆☆	7
Liu et al.[26]	☆☆☆	☆☆	☆☆☆	8
Martenot et al. [27]	☆☆	NA	☆☆☆	5
Martinez et al. [28]	☆☆☆	☆	☆	5
Mulkey et al. [29]	☆☆☆	NA	☆☆	5
Schuh et al. [30]	☆☆☆	NA	☆☆	5
Wang et al.[31]	☆☆☆	NA	☆	4
Wu et al. [32]	☆☆☆☆	☆☆	☆	7
Ayed et al.[33]	☆☆☆	☆☆	☆☆	7
Munian et al. [34]	☆☆☆	☆	☆☆☆	7
Aldrete-Cortez et al.[35]	☆☆☆	☆	☆☆☆	7
Shuffrey et al.[36]	☆☆☆☆	☆☆	☆☆	8
Rood et al.[37]	☆☆	NA	☆☆☆	5
Roffman et al.[38]	☆☆☆	☆	☆☆	6

Source: Prepared by the authors, 2023.

DISCUSSION

Most infants exposed to the SARS-CoV-2 virus during pregnancy presented development in line with what is expected for their age. However, studies have detected mild changes in the neurodevelopment of infants aged zero to one year born to mothers exposed to SARS-CoV-2 during pregnancy. Changes in the gross and fine motor skills domains were prominent up to six months, and in the social and language domains they emerged more frequently between six and twelve months.

Maternal immune activation is a signature of SARS-CoV-2 infection during pregnancy, regardless of the severity of the disease[40]. This activation causes placental changes, such as poor vascular perfusion, elevated cytokine production, increased abnormal mitochondria and high number of mitochondrial DNA copies, as well as decreased oxygen and nutrient transport capacity, contrasting with increased levels of IL-2, IL-6, TNF-α and IFN-γ in maternal blood trophoblastic cells[26,29].

Activation of the anti-inflammatory cholinergic pathway (both maternal and fetal) and placental interactions may modulate the neuroimmune mechanisms employed to mitigate cytokine storm syndrome. This reduce tissue and cell damage, and the effects of SARS-CoV-2 infection on the fetus are minimized, implying births of babies negative for the virus(41). Neonatal SARS-CoV-2 infection was found to be uncommon in the studies, and vertical transmission was considered unlikely, supporting international recommendations to avoid mother-infant separation(42).

SARS-CoV-2 replicates in cells expressing angiotensin-converting enzyme-2 in the lungs, nasopharynx, and small intestine and can persist in tissues for extended periods(43). Most infected newborns are asymptomatic at birth or present mild symptoms, such as rhinorrhea and fever. Adequate respiratory support, such as continuous positive airway pressure (CPAP), was necessary for newborns with anatomical and functional alterations of the respiratory system, regardless of the diagnosis of SARS-CoV-2 infection(44).

Trunk hypotonia and changes in head control were found in the neurological examination of infants exposed to SARS-CoV-2 and were associated to lower scores in the motor domain(29). Gross motor development is influenced by various factors, including muscle tone and the acquisition of stability to overcome the action of gravity and assume higher postures (sitting, standing, walking)(45). Proper posture allows for limb movements and maintaining it provides the necessary conditions for looking around, handling objects, sustaining conversations, or moving around. Thus, most developmental skills, including those not directly related to posture, depend to some degree on the development of sufficient postural control. Increasing mobility skills and the ability to manipulate and explore objects can boost the cascade of learning opportunities and impact the development of language and social interactions(15).

Increased prenatal maternal distress contributes to poorer socio-emotional development in children. Maternal pre and postnatal distress accounted for 13.7% of the variance in infants' socio-emotional development. Anxiety and depressive symptoms during pregnancy have been associated with premature birth, low birth weight, and developmental delays. Impaired placental function in pregnant women with high stress levels increases the risk that the fetus - and potentially the baby through breastfeeding - will be exposed to inflammatory markers that may have deleterious effects on brain and behavioral development(46).

Delays in communication and language are also correlated with maternal stress and decreased stimulation. There are a greater number of mothers with caregiving skills affected by psychological distress. Such distress, combined with measures to limit the spread of the SARS-CoV-2 virus, such as physical distancing and the use of masks, can deprive infants of interactions and their consequent opportunities to learn about communication and emotions(46).

As a maternal stressor, the SARS-CoV-2 infection may imply fetal endocrine and neuroimmune sensitization, given that traumatic events in early life and childhood alter the dynamic gene-environment interaction and the programming of the neurological, immune, and endocrine systems(47,48,41).

Although analyses of neurodevelopment are still inconclusive regarding the persistence of developmental delays after the first year of life, understanding early manifestations provides a parameter for designing long-term monitoring and early stimulation programs for children at risk. In this context, physicians, nurses, physical therapists, speech therapists and other healthcare professionals must be attentive to child development and maternal health conditions, monitoring them and intervening to prevent harm(49). This not only impacts the quality of life of infants and families but also involves adopting care strategies with rigorous assessment of exposure to environmental factors, contributing to health system management.

Although the results of this study indicated that infants exposed to the SARS-CoV-2 virus during pregnancy may present neurodevelopmental delays, it is worth considering that there was a limitation of the small number of databases consulted in this review. Additionally, the variety of development assessment instruments used by the researchers made it difficult to compare and describe the results. It is also worth considering that there was little or no information about the expertise of the evaluators in applying the instruments and about the standardization in the assessment and interpretation of findings.

Additional studies with long-term follow-up of babies exposed to SARS-CoV-2 during the prenatal period are suggested, as the impact on neurodevelopment may be delayed and more sensitive to detection in older children, especially concerning disorders related to social interactions, behavior, cognition, and language.

CONCLUSION

Most studies identified that infants exposed to the SARS-CoV-2 virus during pregnancy presented development according to what is expected for their age. However, when infants with neurodevelopmental delays were identified, the proportion varied from 6.3% to 69%, according to the domain analyzed and the instrument used. Delays were particularly evident in the gross and fine motor domains among children up to six months of age and in the communication and personal-social domains among children aged six to twelve months.

Future exposures to SARS-CoV-2 during gestational period should be monitored and receive attention by healthcare professionals regarding neurodevelopmental milestones in the first year of life, to prevent delays evidenced in this review. For infants identified with deficits, it is suggested that they be referred to early intervention programs to encourage the achievement of expected motor, communication, and interactive skills, in line with age milestones of child development.

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