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Highlights

- A prospective cohort of infants exposed to maternal SARS-CoV-2 intra uterus.
- SARS-CoV-2 exposed infants had an increased risk of neurodevelopmental impairment.
- Fine motor and personal-social were the subdomains most at risk of delay.
- 10% of exposed infants had an abnormal result at cranial sonography.

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Developmental impairment in children exposed during pregnancy to maternal SARS-CoV-2: a Brazilian cohort study.

Abstract

Background

The effects of in-utero exposure to maternal SARS-CoV-2 infection on offspring's neurodevelopment are still unknown.

Methods

We performed a prospective cohort of babies exposed to SARS-CoV-2 during pregnancy, and a control group of unexposed babies in a low-income area in Brazil. Children's neurodevelopment was assessed using the guide for Monitoring Child Development in the IMCI context for both groups (at 1,2,3,4,5,6, 9 and 12 months), and the Ages & Stages Questionnaire (ASQ-3) for the exposed group (at 4, 6 and 12 months).

Results

We followed 127 children for one year, 69 in the COVID-19-exposed Group (EG), and 68 in the control group (CG). All mothers were unvaccinated at the time of cohort inclusion and maternal demographics were similar in the two groups. 20.3% of EG children and 5.9% of the CG received a diagnosis of neurodevelopmental delay within 12 months of life (p=0.013, RR= 3.44; 95% CI, 1.19- 9.95). For the exposed group, the prevalence of neurodevelopment impairment using ASQ-3 was 35.7% at 4 months, 7% at 6 months, and 32.1% at 12 months.

Conclusions

SARS-CoV-2 exposure was associated with neurodevelopmental impairment, and specific guidelines are needed for the follow-up of these high-risk children to mitigate the long-term effects on children's health.

Keywords: COVID-19; neurodevelopmental outcome**;** Maternal depression; Child Development; Social-emotional development.

Background

SARS-CoV-2 has infected over 620 million people and killed more than 6 million worldwide. [1] Since the beginning of the pandemic, Brazil has reported a disproportionately large number of infections and deaths of pregnant women attributed to COVID-19, [2] arguably caused by the disastrous response to the pandemic in its early months, with national policies contrary to scientific recommendations and against international infectious disease societies guidelines. [3]

Although several reports for SARS-CoV-2 indicated that the obstetric population is at an increased risk for severe illness, [4,5], the consequences of *in-utero* exposure to maternal SARS-CoV-2 infection are still limited. The negative influence of *in-utero* infections on fetal development and long-term outcomes was well documented for other pathogens, leading to placental function impairment or injury to the fetus, with long-term sequelae on the offspring, including neurodevelopmental disorders. [6,7] Multiple processes have been proposed to explain some of the likely factors contributing to fetal neurodevelopmental disorders from maternal infection, including genetic susceptibility, duration of infection and placental inflammation caused by a spike in pro-inflammatory markers in maternal circulation. [8, 9]

Despite the high prevalence of viral respiratory infections during pregnancy [10], little is known about the relationship between respiratory viruses and their impact on child development. In a systematic review addressing the link between maternal respiratory infections and childhood developmental outcomes, the authors found a possible association with early motor development alterations and attentional, behavioral/emotional minor problems. [11]

Recent evidence suggests that maternal SARS-CoV-2 infection during pregnancy may be associated with a greater rate of neurodevelopmental impairment during the first year of life, [12, 13,14], while other research was unsuccessful in demonstrating this association. [15]

The COVID-19 pandemic has also brought direct and indirect major impacts on maternal and perinatal health, especially in low and middle-income countries, such as a decrease in access to health and social services, including pre-natal visits; policies impacting pregnancy and parenting (limiting emotional support during labor and mandate early infant separation); spikes in domestic violence and childcare demands; loss of income and food insecurity and higher prevalence of depression and anxiety among the pregnant and postpartum population worldwide. [16, 17] Exposure *in utero* to high levels of maternal stress is well documented as cause of motor, cognitive and language development impairment in young children. [18,19]

Given the urgent need for new investigations addressing childhood development, especially among disadvantaged populations in low- and middle-income communities, we performed a prospective cohort study of babies exposed *in utero* to maternal SARS-CoV-2 infection, and a control group of unexposed babies to evaluate the association between viral infection during pregnancy and infant development during the first year of life in a low-income area in Northeastern Brazil.

Methods

From April 2020 to July 2021, 88 pregnant women with laboratory-confirmed COVID-19 and 88 controls were enrolled in a prospective follow-up at a maternal-child referral center for high-risk pregnancy in Northeast Brazil. Study procedures were approved by a local ethics committee and informed consent was obtained. The inclusion criteria for the exposed and nonexposed groups were singleton pregnancies followed at the center, no confirmed or suspected fetal congenital infection or chromosomal anomalies, no serious illness or complications during the pregnancy or delivery, and no substance use disorder. The exclusion criteria were failure to complete the follow-up until 1 year after birth, maternal or neonatal death and extremely preterm (< 28 weeks) or very preterm (< 32 weeks) babies. After informed consent, the mothers-to-be answered a questionnaire about sociodemographic data and medical history, and for the exposed group, information about COVID-19 was also collected (presence and duration of clinical symptoms, type of treatment received, need for hospitalization, oxygen support, and intensive care). All women were unvaccinated on enrollment due to the lack of a national vaccination policy at the time. The women in the COVID-19 group had at least one symptom when the RT-PCR was performed. The clinical spectrum of SARS-CoV-2 Infection was classified based on the NIH classification [20]. All controls had no history of suspected or confirmed COVID-19 and were paired by age on the same day of enrollment of a participant in the EG. During the follow up, if participants in the control group had any symptoms or close contact with a COVID-19 confirmed case, they were tested and subsequently excluded from the research if confirmed to have COVID-19. All mothers and infants participating in the study received prenatal care and pediatric follow-up at the same clinic by a multidisciplinary team (infectious disease specialist,

obstetrician, psychologist, pediatrician, and nurse), with the frequency recommended by the national guidelines for antenatal and child well care visits. At the first consultation postpartum (on average 30 to 45 days after birth), maternal depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS), [21] with the cutoff point for depression ≥ 11. Women diagnosed with depression were referred to psychotherapy and prescribed pharmacologic treatment as needed.

The following variables were prospectively recorded for both groups: maternal age; parity; maternal comorbidities; fetal death or neonatal death; preterm birth (<37 weeks); mode of delivery; gender; Apgar at 1 and 5 minutes; weight, length, and head circumference at birth; maternal separation at birth; duration of exclusive breastfeeding; and neurodevelopment screening. All newborns had hearing screened using the evoked otoacoustic emission (OAE) test at the clinic. The evaluation of neurodevelopment was based on the guide for monitoring child development in the Integrated Management of Childhood Illness (IMCI) context, [22] adapted for the Brazilian national child health handbook. The guide includes an assessment tool for motor and cognitive development in children. It is a sensitive, easy-to-apply checklist designed to standardize care and to be used by primary health care professionals. It utilizes developmental milestones expected for age and classifies as “normal development”, “developmental alert” and “probable developmental delay.” [22] The assessments were conducted by pediatricians and pediatric nurse practitioners during the well child visitis at 1 month, 2 months, 4 months, 6 months, and 12 months.

Additionally, during clinical follow-up, children *in utero* exposed to SARS-CoV-2 underwent a cranial ultrasound and neurodevelopment evaluations assessment using the Ages & Stages Questionnaire, 3rd Edition (ASQ-3), at ages 4, 6, and 12 months (Brazilian version), [23]

with age-adjusted for preterm infants. The ASQ-3 includes 30 items divided into 5 development domains, with six questions per domain (communication, gross motor skills, fine motor skills, problem-solving and personal-social skills), with scores ranging from 0 to 60 points in each domain, whether the skill or ability is achieved or not. ASQ scores were used as a means of the subscale scores and percentages of children below the expected cutoff. The evaluations were completed by two health professionals (physiotherapist and neuropsychologist) trained on the instrument, accompanied by the families, with the aim of extracting answers by observing the caregiver's interaction with the child. During the assessments, the children were in good clinical condition, fed, and rested. After the evaluations, if the professionals observed areas that the infant may need more stimulation or support, families were guided on how to play with their child at home to achieve those skills. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. [24]

Statistical analysis

All statistical analyses were performed using IBM's SPSS Statistics v26 software. Categorical variable values were reported as numbers with the relative percentage (%), and continuous variables were expressed using mean/standard deviations (SD) or median/ interquartile ranges (IQRs) whether the data were normally distributed or not. Chi-Square or Fisher's exact test was used to estimate the association between categorical variables, and Student's t-test for independent samples or Mann-Whitney U test was used for continuous variables as appropriate. A paired t-test or Wilcoxon test was used for the analysis of repeated measures observations**.** In order to control for potential confounding variables, we balanced the groups using propensity score weighting for the exposed and unexposed groups. Weights were calculated for each individual as a 1/propensity score for the exposed group and 1/(1−propensity

score) for the unexposed group. This score consisted of a weighted composite considering maternal age, parity, race, and comorbidities. To ensure balance between the two groups, we accessed the standardized differences of baseline characteristics included in the propensity score model before and after weighting, and all standardized differences were <0.10. Next, we incorporated the weights in a weighted logistic regression analysis with neurodevelopment delay as the dependent variable adjusted to prematurity, gender of the offspring and maternal depression scores. Statistical significance was considered with a $p < 0.05$ for all analyses.

Results

We followed 127 children, 69 infants in the SARS-CoV-2 exposed group (EG) and 68 in the control group (CG). Mothers of the exposed group were from 8 to 39 weeks pregnant when infected, and the majority (94.2%) experienced mild disease, while 5.8% (4/69) had severe disease; 15 women (21.7%) had the infection in the first trimester, 36 (52.1%) in the second and 18 (26.1%) in the third. There were no significant differences between EG and CG in maternal age, comorbidities, race, and in the number of pregnancies. No fetal or neonatal deaths occurred in either group. Premature birth occurred in 21.7% (15/69) of the EG, compared to 8.8% (6/68) of the CG, (p=.036 relative risk [RR], 2.46; 95% CI, 1.01-5.97). There was no difference in rates of cesarean delivery, small for gestational age, Apgar scores at 1 and 5 minutes, average birth weight, length at birth, head circumference, admission to neonatal intensive care unit, or mother-infant neonatal separation at birth among groups. Maternal characteristics and infant outcomes between groups are reported in Table 1.

Table 1. Maternal profile and children outcomes comparing babies with and without SARS-CoV-2 intra-uterine exposure.

During follow-ups in the first year of life, all infants in both groups had a normal hearing assessment (evoked otoacoustic emissions). According to the IMCI tool, 14 (20.3%) of the EG children were categorized as "probable neurodevelopment delay" in their first year, compared to 4 (5.9%) of the CG (p=.013 relative risk [RR], 3.44; 95% CI, 1.19- 9.95). A weighted logistic regression analysis with neurodevelopment delay as the dependent variable adjusted to prematurity, gender of the offspring, and maternal depression scores confirmed that Covid-19 exposure was associated to neurodevelopmental delay in the first year of life [OR 3.64 (95% CI, 1.37-9.67, p=.01).

Sixty neonates of the EG underwent cranial sonography in the first 12 weeks of life, and 6/60 (10%) had an abnormal result. The findings at cranial sonography included 4 (6.6%) infants with mild ventricular dilatation, 1 (1.7%) with moderate ventricular dilatation, and 1 (1.7%) with periventricular cysts. For the neonates with sonography abnormal results, we excluded TORCH (Toxoplasma gondii, Treponema pallidum, Rubella virus, Cytomegalovirus, Herpes simplex virus 1/2, Parvovirus B19) and Zika infections using multiple serological tests. Also, the infant with moderate ventricular dilatation had a normal karyotype analysis. There was no association between cranial sonography results and prematurity, time of maternal infection, mode of delivery, or disease severity. Infants with abnormal results had a higher risk of being categorized with developmental delay using IMCI tool (*p=.011*).

For the SARS-CoV-2 exposed infants the ASQ-3 was assessed at three times. The infant's mean age at 4-month evaluation was 4 months 3 days (SD= 2.09 weeks), at 6 months was 6 months 21 days (SD=2.44 weeks), and at 12 months was 12 months 16 days (SD= 1.77

weeks). For the 4-and 6-month questionnaires, 42 and 43 infants completed the evaluation respectively, while 28 completed it at 12 months. The prevalence for atypical development (<-2SD) was 35.7% (15/42) at 4 months, 7% (3/43) at 6 months, and 32.1% (9/28) at 12 months (FIGURES 1, 2, and 3). There was no significant difference in ASQ-3 scores when comparing male and female babies, except for the personal-social domain at 12 months, where females had higher scores than male babies ($U = 41.5$, $p = .049$).

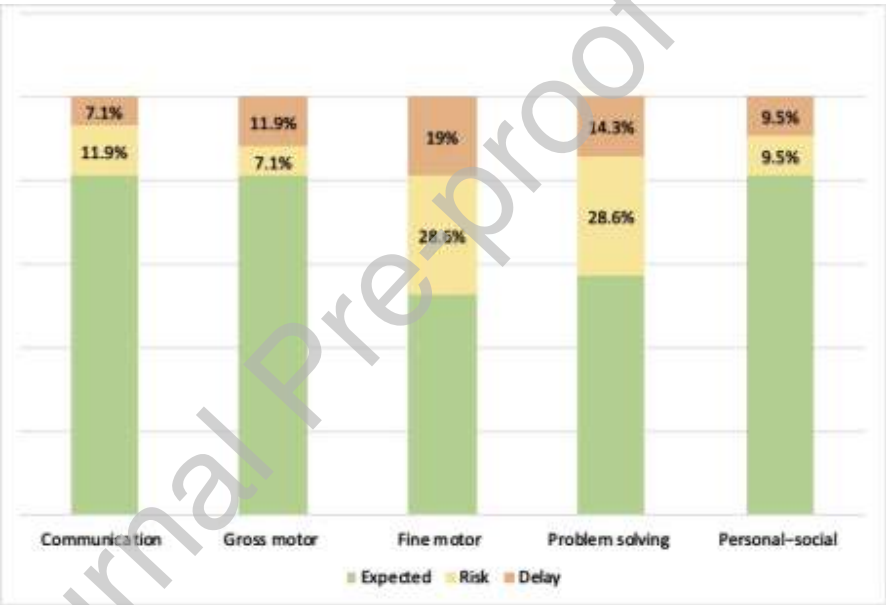

Figure 1. ASQ-3 at 4 months among Brazilian infants exposed to maternal SARS-CoV-2 *in utero* showing domain percentages of children below the expected cutoff for neurodevelopment risk and delay.

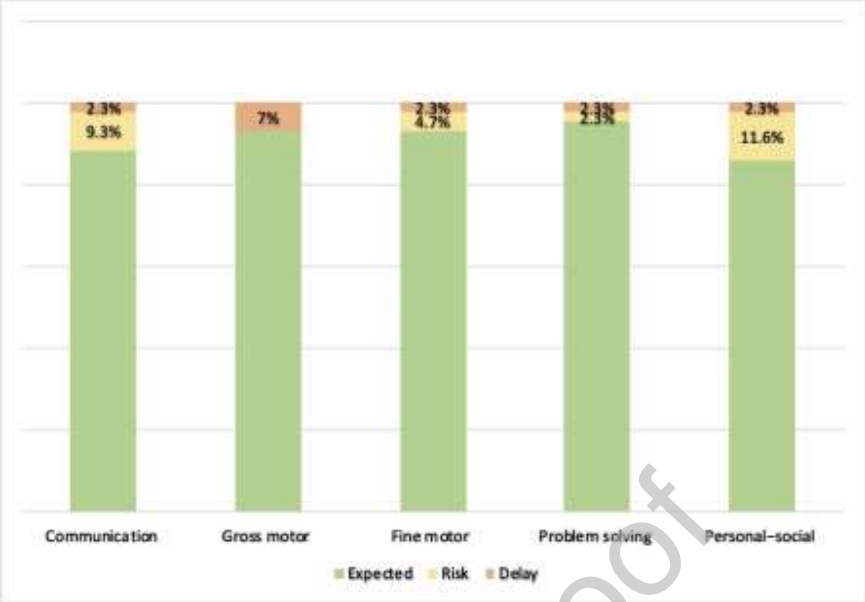

Figure 2. ASQ-3 at 6 months among Brazilian infants exposed to maternal SARS-CoV-2 *in utero* showing domain percentages of children below the expected cutoff for neurodevelopment risk and delay.

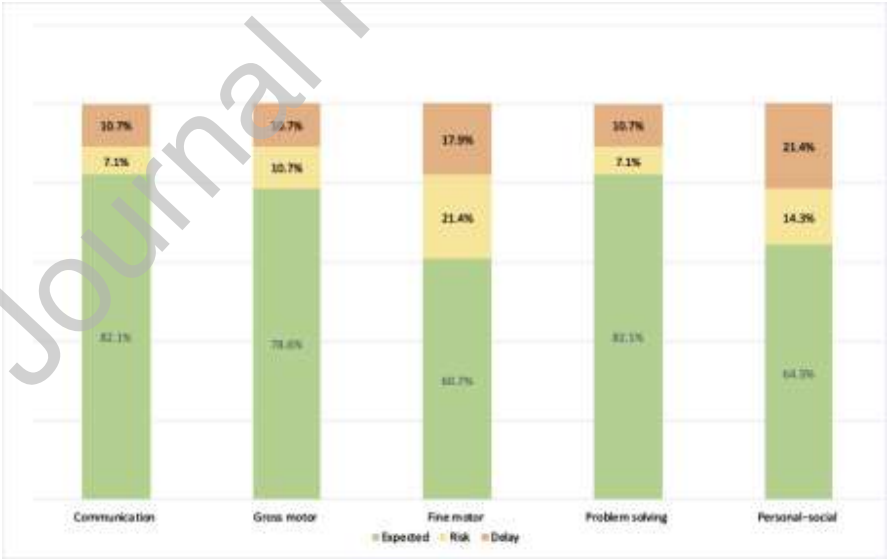

Figure 3. ASQ-3 at 12 months among Brazilian infants exposed to maternal SARS-CoV-2 *in utero* showing domain percentages of children below the expected cutoff for neurodevelopment risk and delay.

At the ASQ-3 4-month evaluation there was a significant impairment in fine motor and problem-solving (FIGURE 1, TABLE 2). These impairments were improved at the 6-month follow-up. Analyzing ASQ-3 subdomain scores between the infants evaluated at 4 and 6 months (31 infants performed the two evaluations), the results showed improvement in fine motor (Wilcoxon signed-rank test, Z= -3.43, p= <.001) and problem-solving (Wilcoxon signed-rank test, Z=-2.40, p=.016), in 64.5% (20/31) and 51.6% (16/31) of the children, respectively, at 6 months. Compared with the 4-month evaluation, the gross motor subdomain scores decreased at the 6-month in 74.1% (23/31) of the children (Wilcoxon signed-rank test, Z = -3.49, p = <.001). At the 12-month evaluation, 21.4 % of the infants presented personal-social subdomain impairment and a worsening of the fine motor scores (FIGURE 3, TABLE 2). Comparing the infants assessed at 6 and 12 months (19 infants performed both evaluations), the personal-social scores decreased at the 12-month evaluation in 73.7% (14/19) of infants (Wilcoxon signed-rank test, Z=-2.86, p=.004). No association was found between ASQ-3 scores when comparing the clinical severity of maternal infection, nor with the trimester of the infection.

Table 2. ASQ-3 mean/SD domains scores and overall neurodevelopment delay and risk of delay prevalence at 4, 6 and 12 months in infants with SARS-CoV-2 intra-uterine exposure.

Mothers who had COVID-19 presented scores on the Edinburgh scale for postpartum depression significantly higher (M=11.0, SD= 6.0) than the control group (M=8.68, SD=4.72); t (77) = 2.0, p=.040. Infants of mothers classified as depressed were breastfed as often as those classified as non-depressed. There was no relationship between post-partum depression scores and neurodevelopment delay diagnosis with the IMCI tool, and with most of the ASQ-3 scores,

with the exception of lower scores in children of depressed mothers for the problem-solving domain at 4 months (U=58.00, p = .047) and communication at 6 months (U = 59.00, p = .043).

Discussion

In this prospective cohort of infants born from mothers with COVID-19 during pregnancy, we identified a higher risk of neurodevelopmental delay in the first year of life using the IMCI tool when compared with a not exposed group, even after adjusting for other confounding variables. Over 50% of the SARS-CoV-2 exposed infants presented ASQ-3 scores below the expected cutoff, with about half classified with neurodevelopmental delay, mainly at 4 and 12 months. To date, many studies [12-15, 25] have been published evaluating outcomes of exposed SARS-CoV-2 offspring, with none yet in the northeastern Brazilian population.

Our findings suggest that SARS-CoV-2 infection has a negative impact on the neurodevelopment status of children exposed during the intrauterine period. A retrospective cohort among American infants, comparing mother-offspring pairs exposed to SARS-CoV-2 with unexposed pairs, found that neurodevelopment delay diagnosis at 12 months was more common in the exposed group, [17] corroborating with our results. A study comparing neonates of SARS-CoV-2 exposed mothers with a non-exposed group, found an association between prenatal SARS-CoV-2 exposure and poorer development in motor skills and infant interactive behavior. [14] Another study analyzed the early motor repertoire by general movement assessment (MOS) comparing babies who were prenatally exposed to SARS-CoV-2 with a control group not exposed, between three to five months of age, found lower total MOS scores in the exposed group, including abnormal or absence of fidgety movements [13] In contrast, in

another cohort study of 255 infants born in 2020, exposure to maternal SARS-CoV-2 infection was not associated with differences in neurodevelopment at 6 months, but the authors found that infants born during the pandemic period had significantly lower neurodevelopment scores compared with a historical cohort of infants born before the COVID-19 pandemic. [25] Likewise, Firestein et al, [15] using telehealth assessment, compared infant neurodevelopment at ages 5 to 11 months from exposed to asymptomatic maternal SARS-CoV-2 infection vs not exposed, finding no differences in cognitive, gross motor, fine motor, expressive language, or receptive language between groups. In a multicenter cohort study (including 41 infants from Brazil), the authors demonstrated an association of SARS-Cov-2 uterine exposure with suboptimal neuromotor development when measured by General Movement Assessment with delayed milestones. [26] In none of these articles was maternal mental health assessed, despite being a major factor related to child development.

The mechanisms underlying the potential impact of maternal COVID-19 infection on fetal brain development encompass both direct pathways, such as vertical transmission, and indirect routes, as a result of either uteroplacental insufficiency or as a consequence of the maternal immune and inflammatory responses during the prenatal period. [27] Prenatal infections have been associated with the appearance of unspecific early risk markers implicated in cognitive, emotional and behavioral deviations in the development in early childhood [28, 29], which could explain our cohort's higher prevalence of neurodevelopmental impairment among infants with in-utero exposure to maternal SARS-CoV-2.

In our cohort only the exposed group underwent the ASQ-3 evaluations, as in our center only babies at higher risk undergo such evaluations, being impossible to compare with the control group. But comparing with the scores in our study at 4 and 12-month evaluations, a

previous pre-pandemic population-based study using the same standardized tests in the Northeast of Brazil, found an overall prevalence of developmental delay in at least one domain much lower (9.2%). [30] In a systematic review evaluating the association of being born and raised during the COVID-19 pandemic using the ASQ-3 tool, the authors found that the pandemic cohort had a significantly higher chance of presenting communication impairment than the pre-pandemic cohort. [31] Also, in accordance with our findings, when comparing 77 infants with maternal exposure to SARS-CoV-2 with 691 non-exposed, the exposed babies had a higher prevalence of fine motor impairment during the first year of life. [31]

The pregnant population has been immensely affected by the SARS-CoV-2 pandemic worldwide. [32] Several reports evaluating mental health in pregnant and postpartum women have identified elevated rates of depressive and anxious symptoms among this population since the beginning of the COVID-19 Pandemic. [17] In accordance with the scenario, our cohort had a greater prevalence of postpartum depression than in pre-pandemic studies for a similar population in Brazil, [33] but mothers infected during the pregnancy presented significantly higher depression scores, likely related to COVID-19 infection. Previous studies have shown an association between COVID-19 infection and an increased risk of mood and anxiety disorders after a few months. [34] Maternal depression is known to negatively impact mother-infant bonding and is linked to adverse child outcomes, such as health problems, developmental delays, and behavioral problems. [35] Using the more general developmental score (IMCI tool), there was no association between maternal depression and diagnosis of developmental delay in the offspring during the first year in any of the groups. But using ASQ-3, we identified significantly higher development impairment in infants of depressed mothers in the problem-solving domain at 4 months and in the communication domain at 6 months. Despite the lack of studies

comparing the two development tools, the ASQ-3 has been associated with high sensitivity and specificity for screening neurodevelopmental delay, [36] which can explain the association with maternal mental health found with ASQ-3 evaluation only. Although the early diagnosis and treatment may have mitigated the impact on the mother-infant relationship, we cannot rule out the possibility of long-term effects in the offspring.

In our cohort, the ASQ-3 scores at 6 months were remarkably better than the scores at 4 and 12 months. We hypothesized that the improvement in the fine motor and problem-solving subdomains at 6 months was most likely due to the individual interventions that the mothers of infants below the appropriate score received after the 4-month evaluation. Despite scarce data available on interventions to improve child development in early years, some studies have shown that interventions with parents may have a short-term effect of improving ASQ scores. [37] The improvement identified at the 6 months visit in the ASQ-3 evaluation scores had possibly led to a relatively lesser concern with the babies and thus less intervention which may explain the impairment identified at 12 months.

During the follow-up of the exposed babies, 10% had an abnormal result on cranial ultrasonography, mainly mild ventriculomegaly, that has been described with other congenital infections, like cytomegalovirus and Zika virus. [38,39] Although the findings were mostly mild, there was an association between the diagnosis of abnormalities and the risk of developmental delay. Previous observational studies with premature babies or low birth weight have demonstrated that ventricular dilatation is predictive of cognitive impairment, especially related to moderate to severe ventriculomegaly. [40,41] In a study reporting outcome of horizontal and possible vertical transmission among 66 neonates who received inpatient hospital care in the UK,

no abnormalities were detected at the cranial ultrasound, but only eight babies underwent the exam. [42]

The loss of follow-up in our cohort during the first year (around 20% of the mothers recruited during the pregnancy), was acceptable especially given the high impact of the pandemic on low-income populations or vulnerable groups in Brazil, with food insecurity, unemployment, fear of infection, mental health issues and lack of money for transportation and lockdowns. For the ASQ-3 evaluation, patients often needed to make extra visits to the health center, which resulted in fewer infants undergoing the assessments due to difficulties in paying for transportation, even with a great effort by the researchers to make contact and reschedule the evaluations.

This study has some limitations: it was conducted in a single healthcare center; the ASQ-3 evaluations were not available for the control group; and we couldn't make a definitive diagnosis of congenital infection with the available criteria, as none of the infants performed SARS-CoV-2 RT-PCR tests after birth. Also, the number of participants in both groups was small, limiting the ability to identify differences between subgroups. Participants in our study were a convenience sample of pregnant women with COVID-19, which could leave more vulnerable groups underrepresented. Plus, as the participants were recruited from 2020 to 2021, the majority were unvaccinated, so the outcomes may vary depending on vaccination status or COVID-19 variant types.

Conclusion

Our findings indicated that intrauterine exposure to SARS-CoV-2 infection can have consequences for offspring in the first year of life, including developmental delay. Given the importance of appropriate early child development for improved future health and educational

outcomes, it is extremely important to understand the maternal infection impact on infant exposed developmental trajectories to identify the need to recommend appropriate early interventions. Also, healthcare providers should be aware of the needs of pregnant and postpartum women, and public measures should guarantee the appropriate support for families with young children, in order to mitigate long-term effects on maternal and children's health.

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Ethical Approval statement

This study was approved by the Federal University of Rio Grande do Norte ethics committee (CAAE: 32451120.8.0000.5537) and has been processed in concordance with the General Data Protection Regulation (GDPR). Written consent was obtained from participants, and all methods were performed in accordance with the relevant guidelines and regulations by including a statement in the methods section.

Data availability Policy

The datasets generated during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Table 1. Maternal profile and children outcomes comparing babies with and without SARS-Cov-2 intra-uterine exposure.

		Exposed Group (N=69)	Control Group (N=68)	p[a]
Maternal Age, mean (SD), years		30.29 (6.58)	30.03 (7.08)	.824
Parity	Nulliparous, n/N(%)	22/69 (31.9%)	17/68 (25%)	.372
	Primiparous, n/N(%)	20/69 (29%)	27/68 (39.7%)	.409
	Multiparous, n/N(%)	27/69 (39,1%)	24 (35.3%)	.772
Comorbidities, n/N (%)		35/69 (50.7%)	27/68 (39.7%)	.195
Race	White	12/69 (17.3%)	10/68 (14.7%)	.678
	Black	7/69 (10.1%)	9/68 (13.23%)	.413
	Mixed race	47/69 (68.1%)	49/68 (72%)	.778
	Yellow	2/69 (2.8%)	0/68 (0%)	.943
Offspring's gender	Male	39/ 69 (56.5%)	32/68 (47.1%)	.268
	Female	30 /69 (43.5%)	36/68 (52.9%)	
Cesarean delivery, n/N (%)		45/69 (65.2%)	41/68 (60.3%)	.551
Postpartum depression score[b] mean (SD)		11.00 (6.00)	8.68 (8.68)	.040
Preterm birth (less than 37weeks), n(%)		15 (21.7%)	6 (8.8%)	.036
Birth weight, mean (SD), grams		3175.5 (523.98)	3207.03 (465.35)	.707
Apgar score 5° min < 7, n (%)		7 (10.1%)	1 (1.5%)	.063
Head circumference, mean (SD), cm		34.33 (1.75)	34.50 (1.72)	.567
Exclusive breastfeeding, n (%)		27 (39.1%)	27 (39.7%)	.945
Neurodevelopmental delay (IMCI[c] tool), n (%)		14 (20.3%)	4 (5.3%)	.013

SD, standard deviation; IQR, interquartile range.
[a] Chi-Square test or Fisher's exact test was used for categorical variables and Student's t-test or Mann Whitney U test was used for continuous variables;
[b] Edinburgh Postnatal Depression Scale (EPDS).

[c] Integrated Management of Childhood Illness

Table 2. ASQ-3 mean/SD domains scores and overall neurodevelopment delay and risk of delay prevalence at 4, 6 and 12 months in infants with SARS-Cov-2 intra-uterine exposure

	ASQ<threshold for delay n/N,(%)*	ASQ<threshold for risk of delay n/N,(%)**	Communication (Mean/SD)	Gross Motor (Mean/SD)	Fine Motor (Mean/SD)	Problem-solving (Mean/SD)	Personal-social (Mean/SD)
4 months	15 (35.7%)	13/42 (31%)	51.42 (9.8)	52.97(11.5)	41.2(14.3)	45.0 (14.3)	50.23(12.9)
6 months	3/43 (7%)	7/43 (16.3%)	48.54 (11.6)	46.54(12.8)	54.16(11.4)	52.61(11.5)	48.92(11.8)
12 months	9/28 (32.1%)	6/28 (21.4%)	46.78 (16.9)	46.25(17.4)	44.82(14.7)	47.14(15.5)	36.96(15.3)

*Number of infants with development delay (<-2 SD) in at least one subdomain
** Number of infants with risk of delay (<-1 SD) in at least one subdomain

Declaration of Interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: