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Neuromotor repertoires in infants exposed to maternal COVID-19 during pregnancy: a cohort study

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ABSTRACT

Objective To evaluate neuromotor repertoires and developmental milestones in infants exposed to antenatal COVID-19.

Design Longitudinal cohort study.

Setting Hospital-based study in Los Angeles, USA and Rio de Janeiro, Brazil between March 2020 and December 2021.

Participants Infants born to mothers with COVID-19 during pregnancy and prepandemic control infants from the Graz University Database.

Interventions General movement assessment (GMA) videos between 3 and 5 months post-term age were collected and clinical assessments/developmental milestones evaluated at 6–8 months of age. Cases were matched by gestational age, gender and post-term age to prepandemic neurotypical unexposed controls from the database.

Main outcome measures Motor Optimality Scores Revised (MOS-R) at 3–5 months. Presence of developmental delay (DD) at 6–8 months.

Results 239 infants were enrolled; 124 cases (83 in the USA/41 in Brazil) and 115 controls. GMA was assessed in 115 cases and 115 controls; 25% were preterm. Median MOS-R in cases was 23 (IQR 21–24, range 9–28) vs 25 (IQR 24–26, range 20–28) in controls, p<0.001. Sixteen infants (14%) had MOS-R scores <20 vs zero controls, p<0.001. At 6–8 months, 13 of 109 case infants (12%) failed to attain developmental milestones; all 115 control infants had normal development. The timing of maternal infection in pregnancy (first, second or third trimester) or COVID-19 disease severity (NIH categories asymptomatic, mild/moderate or severe/critical) was not associated with suboptimal MOS-R or DD. Maternal fever in pregnancy was associated with DD (OR 3.7; 95% CI 1.12 to 12.60) but not suboptimal MOS-R (OR 0.25; 95% CI 0.04 to 0.96).

Conclusions Compared with prepandemic controls, infants exposed to antenatal COVID-19 more frequently had suboptimal neuromotor development.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Although early neurodevelopmental monitoring is challenging, the study implemented the use of the validated general movement assessment (GMA) tool predictive of future motor function in infants between 3 and 5 months of age.
⇒ An advantage of GMA is that it is not influenced by environment, socioeconomic status or other extrinsic conditions.
⇒ The study design included a comparator group of age-matched and gender-matched pre-COVID-19 pandemic control infants for GMA performance with cases consisting of infants exposed to maternal SARS-CoV-2 in utero.
⇒ Additional evaluations also included in person neurological evaluations at 6–8 months of age for monitoring of neurodevelopmental milestones.
⇒ A study limitation is the young age group with need for longer-term follow-up for monitoring of neurodevelopmental endpoints.

INTRODUCTION

Exposure to maternal infection during pregnancy can have devastating consequences for fetal brain development. Epidemiological studies have linked perinatal infections during pregnancy with risk of neurodevelopmental impairment such as cerebral palsy (CP) and neuropsychiatric disorders in the offspring, including autism spectrum disorder (ASD) in childhood and schizophrenia in adulthood.[1] Many perinatal infections can cause direct or indirect damage to the fetal brain, altering brain structure/function. Toxoplasmosis, other, rubella, cytomegalovirus, human herpesvirus (TORCH) infections are known to cause harm through teratogenicity by transplacental passage of the pathogen to fetal brain cells, inducing injury to the cortical white matter, eyes and ears.[2] Other infections, such as influenza, may potentially induce pathology to the fetal brain through inflammatory responses resulting in cytokine/chemokine dysregulation, cellular apoptosis and neuronal damage.[3] Maternal

immune activation (MIA), by creating a hostile in utero inflammatory environment during the course of SARS-CoV-2 infection in pregnancy, may adversely affect the fetus[4] but long-term neurodevelopmental impact is yet to be determined.

General movement assessment (GMA) is a gestalt observational method to classify early neuromotor functions in the first months of life (0–5 months): it is non-invasive, cost-effective and highly reliable.[5–10] GMA can predict CP with a sensitivity and specificity of 97% and 89%, respectively.[11] General movements (GMs) are endogeneously generated, not influenced by culture, race/ethnicity or socioeconomic status.[12] This tool was particularly useful during the Zika epidemic in Brazil to evaluate risk of CP in exposed infants.[12] In recent years, a semiquantitative extension to the categorical GMA, the Motor Optimality Score-Revised (MOS-R),[13] was developed and proven to be a good predictor for motor, cognitive and neurodevelopmental outcomes.[14]

The COVID-19 Outcomes in Mother-Infant Pairs (COMP) study follows a longitudinal cohort of infants prenatally exposed to SARS-CoV-2 in Los Angeles, USA and Rio de Janeiro, Brazil.[4] In this study, we evaluated the integrity of the developing nervous system in infants exposed to maternal COVID-19 in pregnancy by analysing neuromotor development between 3 and 5 months post-term age and attainment of neurodevelopmental milestones between 6 and 8 months.

METHODS

This was an observational cohort study which followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline. Infants exposed to maternal COVID-19 during pregnancy were compared with control infants born before the onset of the COVID-19 pandemic from the Systemic Ethology and Developmental Science research database (GUARDIAN),[15] with over 2000 standardised GMA data sets collected worldwide.[12] The study was conducted at the University of California (Los Angeles, USA) and Hospital Universitario Gaffree-Guinle, Universidade do Rio de Janeiro, Brazil. The analysis encompasses infants enrolled between March 2020 and December 2021. Control infants were born prior to 2020.

Women with confirmed COVID-19 were recruited in the outpatient obstetric clinic and labour and delivery unit at UCLA and from a maternity hospital in Caxias, Rio de Janeiro, Brazil. All mothers were identified with SARS-CoV-2 infection via reverse transcriptase PCR of nasopharyngeal specimens. Infants were similarly screened for SARS-CoV-2 within 48 hours of life if mother was positive at delivery. Infants were videotaped for 2–3 min of active wakefulness lying in supine position without manipulation between 3 and 5 months for GMA evaluation and evaluated at 6–8 months in clinic (figure 1). All children selected from the Guardian database for this study were followed longitudinally in prior studies and identified as having normal development over time with normal motor, cognitive and language functions in the first 3 years of life. They were a reference for normal GMA results. Controls were matched to cases based on sex, gestational age at birth and post-term age at the time of the performance of the GMA. All children from the database had normal neurodevelopment, which is what defined them as neurotypical controls. They were prepandemic controls, which means they were unexposed to SARS-CoV-2. Cases were recruited prospectively during the COVID-19 pandemic and then based on the parameters described above matched 1:1 to prepandemic controls abstracted from the database. We did not have access to any maternal/neonatal comorbidity data regarding infants from the database, except for the information listed above. All GMA videotapes were analayzed by at least two certified GMA experts with interscorer agreements of Cohen or Fleiss κ statistics ranging from 0.88 to 0.96 and intraclass correlation coefficients exceeding 0.90.

Data on maternal SARS-CoV-2 disease severity were collected at enrolment, following the U.S. National Institutes of Health (NIH) COVID-19 guidelines.[16] Categories were collapsed into: asymptomatic, mild/moderate and severe/critical for analyses. COVID-19 exposed infants were matched 1:1 for gestational age at birth, age at GMA and gender to control infants.[12] An average MOS-R[13] greater than 20 was considered non-pathological.[17]

All infants exposed to SARS-CoV-2 in pregnancy were followed between 6 and 8 months of age with a complete history, physical examination and detailed neurological examination. Infants who failed to attain age-appropriate developmental milestones were considered to have developmental delay (DD).

Patient and public involvement

Patients or the public were involved in the design, conduct, reporting and dissemination plans of our research. The study was discussed with the parent community and prospective parents of study participants during the planning stages and thereafter to better understand parental concerns and priorities. Parents provided input into the study design and assisted with recruitment of potential participants by referring friends or relatives. Overall study findings were discussed with parents during study visits. Participants were offered access to study summaries, press releases and publications resulting from the study.

Clinical, obstetrical and laboratory results were abstracted from medical records. Data included: country of enrolment, assigned sex, mode of delivery, preterm delivery (<37+0 weeks and <34+0 weeks), birth weight, APGAR scores (1 and 5 min) and neonatal comorbidities. Maternal characteristics included: COVID-19 disease severity, presence of fever during COVID-19, trimester at diagnosis, multiple versus singleton gestation and maternal comorbidities. MOS-R, scores, subscales and results from clinical assessments were included. Maternal comorbidities were classified as hypertensive disorders of pregnancy, diabetes mellitus (including gestational

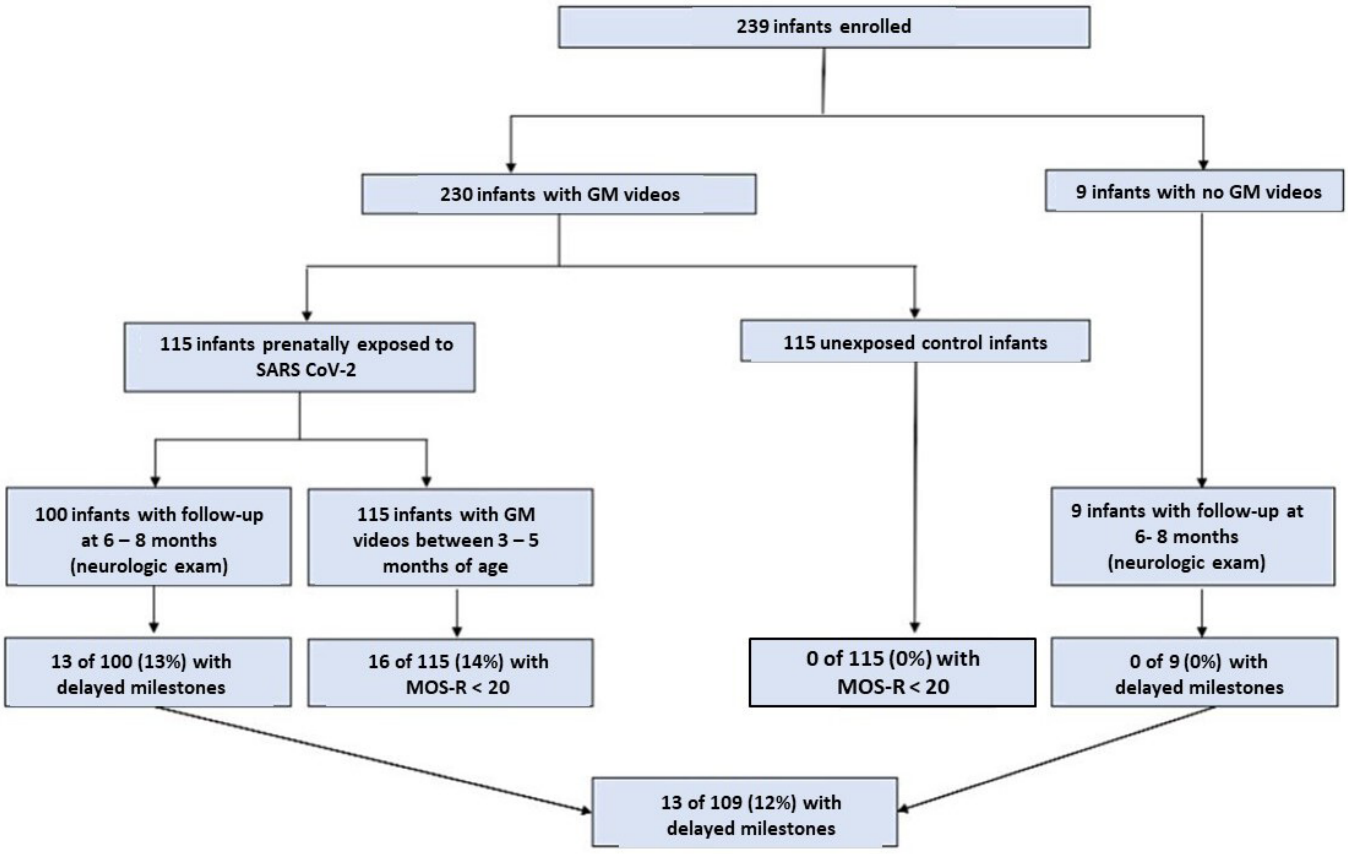

Figure 1 Prospective cohort of infants prenatally exposed to SARS-CoV-2 (n=124) and prepandemic controls (n=115). Eighty-three case infants were recruited in the USA and 41 were recruited in Brazil. All 115 prepandemic controls were recruited from the University of Graz database. A total of 109 case infants had in person follow-up with neurological assessments. All control infants had been followed over time and had normal neurodevelopment. GM, general movement; MOS-R, Motor Optimality Scores Revised.

DM) or prepregnancy obesity body mass index >30 kg/m^2. Maternal mental comorbidities included depression, anxiety or substance use disorder.

A Pearson χ^2 test or Fisher's exact test was used to compare categorical data of infants prenatally exposed to SARS-CoV-2 versus age-matched controls. Comparisons of medians were analysed by the Mann-Whitney U test for comparing two groups and Kruskal-Wallis for comparing multiple groups. Unadjusted and adjusted multivariable logistic regression analyses were performed to evaluate potential associations between MOS-R and maternal/infant clinical parameters, DD and maternal/infant clinical parameters. Predictor variables included COVID-19 severity, trimester of infection, neonatal and maternal comorbidities, fetal sex, maternal age, maternal fever during COVID-19 and preterm birth (the latter for DD only since GMA corrects for post-term age). COVID-19 disease severity (asymptomatic=0, mild/moderate=1 and severe=2), trimester of infection (first, second and third) and maternal age were analysed as continuous variables, with ORs predicting risk with each increasing unit. Other variables (fetal sex—reference is female, neonatal and maternal comorbidities—reference is none, maternal fever during COVID-19—reference is none and preterm birth—reference is none) were classified as dichotomous. Analysis was done with simple logistic regression for each predictor variable, and then all variables were included in a full model for potential confounding effects. Two-sided p<0.05 was considered statistically significant. The sample size of 115 cases and 115 controls demonstrated a post hoc achieved power of 72% when comparing age-appropriate repertoires using PROC Power in SAS V.9.4.

RESULTS

From March 2020 to December 2021, 239 infants were enrolled, including 124 exposed to prenatal SARS-CoV-2 (83 from the USA and 41 from Brazil) and 115 prepandemic unexposed neurotypical controls. Figure 1 details enrolment of cases and matched unexposed controls. Between 10 and 20 weeks of post-term age, 115 of 124 case infants (92.7%) had GMA videos recorded. One hundred and nine of 124 prenatally exposed infants (87.9%) were clinically evaluated between 6 and 8 months of age. None of the exposed infants were positive for SARS-CoV-2 infection at delivery. Distribution by SARS-CoV-2 variants included: 22.6% infants born in 2020 (n=28) when Zeta and Epsilon strains circulated, 47.6% infants exposed

Table 1 Demographics and clinical characteristics of all infants exposed to in utero SARS-CoV-2 Infection during any trimester in pregnancy (n=124)

N	124
Country of enrolment	n (%)
USA	83 (66.9)
Brazil	41 (33.0)
Median maternal age (IQR)	32 (27–35)
Maternal conditions	n (%)
Comorbidities*	60 (48.4)
Mental health disorders†	13 (10.5)
SARS-CoV-2-associated fever during pregnancy	38 (30.6)
COVID-19 severity	n (%)
Asymptomatic	18 (14.5)
Mild/moderate	84 (67.7)
Severe/critical	22 (17.7)
Trimester at diagnosis	n (%)
1st	17 (13.7)
2nd	37 (29.8)
3rd	70 (56.5)
Mode of delivery	n=123
Vaginal delivery	63 (51.2)
C-section	60 (48.8)
No of pregnancies	n=117
No of multiple gestations‡	7 (6.0)
Fetal sex	n (%)
Male	64 (51.6)
Female	60 (48.4)
Preterm delivery	n (%)
<37w0d	31 (25)
Neonatal comorbidities	n (%)
Respiratory distress	22 (17.7)
Congenital cardiac/pulmonary abnormalities—Congenital Heart Disease (CHD)/Congenital Diaphragmatic Hernia (CDH)	4 (3.2)
Sepsis	4 (3.2)
Small for gestational age	11 (8.9)
Low birth weight (<2500 g)	29 (23.4)
APGARS	
Median APGAR Score at 1 min of life (IQR)	8 (7–9)
Median APGAR Score at 5 min of life (IQR)	9 (9–9)

*Includes hypertensive disorders of pregnancy, DM (including gestational DM) or prepregnancy obesity BMI >30 kg/m^2.
†Depression, anxiety or substance use disorder.
‡Five viable twin deliveries, two triplet deliveries.
BMI, body mass index; DM, diabetes mellitus.

to maternal infection during the Alpha variant surge (n=59) and 29.8% exposed to maternal infection during the Delta surge (n=37). We did not observe clustering of reduced MOS-R or DD by circulating variants, p=0.39 and 0.53, respectively (online supplemental figure S1).

Table 1 describes cohort demographics and clinical characteristics. The median maternal age was 32 years; 2/3 of the cohort was from the US. Most women had mild/moderate SARS-CoV-2 (68%), with infection occurring in the 3rd (56%) and 2nd trimesters (30%) of pregnancy. Fever during COVID-19 occurred in 31% of women. A small proportion of mothers (10%) had history of mental health disorders (depression, anxiety or substance abuse). One-quarter of infants were preterm. The most common neonatal comorbidities were low birth weight (<2500 g, 23.4%) and respiratory distress (17.7%). Median APGAR scores were high: 8 at 1 min and 9 by 5 min.

Antenatally SARS-CoV-2 exposed infants had significantly lower median MOS-R than controls (23 vs 25, p<0.001; table 2, online supplemental figure S2) and higher frequency of abnormal movement patterns, postural patterns and movement character as compared with neurotypical unexposed controls (table 2). Eight infants (7.0%) had abnormal fidgety movents (FMs) (table 2). Overall, only 20 infants (17%) scored within the optimal range (25–28). Sixteen infants (14%) scored below 20 (reduced MOS-R), which reportedly is associated with higher risk of adverse neurodevelopmental outcomes.[13 17] Eight infants (7%) scored between 17 and 19, and another 8, all with abnormal FMs, scored between 9 and 16. Only 3 of 29 preterm infants (10.3%) had reduced MOS-R, which makes it unlikely that this finding was driven by preterm birth.

Logistic regression analysis failed to identify parameters associated with MOS-R (table 3). Neither maternal disease severity (p=0.96, online supplemental figure S3) nor trimester of infection (p=0.88, online supplemental figure S4) predicted reduced MOS-R. COVID-19 in pregnancy was the only parameter associated with poor MOS-R in the cohort (table 2, online supplemental figure S2).

One hundred and nine infants exposed to maternal COVID-19 were evaluated between 6 and 8 months of age. Of these, 9 did not have GMAs, and had normal development and growth on examination; 100 of 109 exposed infants (92%) had both GMAs and neurological assessments. Of these 109 infants, 13 presented with DD (failure to attain age-appropriate milestones between 6 and 8 months, online supplemental table S1). Five of 109 exposed infants had poor growth (weight, length and/or head circumference <10th percentile); 2 of 13 infants with DD (15%) had poor growth. Among infants with DD, 2 had abnormal FMs and severely reduced MOS-R of 9 and 10 (online supplemental table S1). Logistic regression demonstrated that maternal fever during pregnancy was associated with DD (tables 3 and 4).

Unadjusted logistic regression analysis demonstrated an association between maternal fever and DD (OR 3.7, 95% CI 1.12 to 12.60, p=0.03), but this was not seen in the adjusted analysis, (OR 4.11, 95% CI 0.98 to 18.77, p=0.06). Prevalence of DD was higher yet non-significant (p=0.40) in infants born to mothers infected in the first trimester (23.1%, online supplemental figure S5).

Table 2 Clinical characteristics and motor behaviour at 3–5 months post-term age by GMA

	Covid-19 exposed (n=115)	Neurotypical unexposed controls (n=115)	P value
Male, no (%)	59 (51.7)	63 (54.8)	0.69
Preterm birth, no (%)			
<34w0d gestation	12 (10.5)	12 (10.4)	0.999
34w0d–36w6d gestation	17 (14.9)	16 (13.9)	0.999
Weeks of gestation at the time of infection, wk, no (%)			
≤13w6d	17 (14.9)	NA	NA
14w0d–28w6d	36 (31.6)	NA	
≥29w0d	62 (53.9)	NA	
Age at GMA, wk, no (%)			
9–12	39 (33.9)	39 (33.9)	NA
13–16	46 (40.0)	46 (40.0)	
17–20	30 (26.1)	30 (26.1)	
Fidgety movements, no (%)			
Normal	107 (93.0)	115 (100)	0.007
Abnormal exaggerated	8 (7.0)	0	
Absent	0	0	
MOS-R			
Median (IQR) (range)	23 (21–24) (9–28)	25 (24–26) (20–28)	<0.001
Optimal range of 25–28, no (%)	20 (17.4)	63 (54.8)	<0.001
MOS-R≤24, no (%)	95 (82.6)	52 (45.2)	
MOS-R<20, no (%)	16 (14.0)	0	<0.001
Repertoire, no (%)			
Age adequate	32 (27.8)	48 (41.7)	0.038
Not age adequate	83 (72.2)	67 (58.3)	
Movement patterns, apart from fidgety movements, no (%)			
More normal than abnormal	102 (88.7)	115 (100)	<0.001
Normal equals to or less than abnormal	13 (11.3)	0	
Postural patterns, no (%)			
More normal than abnormal	33 (28.7)	86 (74.8)	<0.001
Normal equals to or less than abnormal	82 (71.3)	29 (25.2)	
Movement character, no (%)			
Smooth and fluent	25 (21.7)	55 (47.8)	<0.001
Abnormal but not cramped-synchronised	90 (78.3)	60 (52.2)	
Cramped synchronised	0	0	NA

GMA, general movement assessment; MOS-R, Motor Optimality Scores Revised; NA, not available.

DISCUSSION

Endogeneously generated movements start around 8 weeks of gestation and continue until about 20 weeks post-term age being an excellent readout of developing brain integrity.[18] These movements can be impacted by pregnancy-related factors including hypertensive disorders, diabetes, maternal stress, substance abuse, medications, infections, fetal growth restriction and oligohydramnios.[19] We did not uncover associations between MOS-R and specific maternal or obstetrical parameters, except for SARS-CoV-2 infection itself. It is likely that elevated stress triggered by maternal infection and pandemic circumstances contributed to suboptimal development reflected by a reduced MOS-R in cases as compared with controls. While suboptimal, the overall performance of the current cohort was substantially superior to that of children with CP,[13] which was reassuring. Specific associations between reduced MOS-R

Table 3 Logistic regression analyses

Predictor variables for Motor Optimality Scores Revised (MOS-R) n= 115	N	OR	95% CI	P value	Adjusted OR	Adjusted 95% CI	Adjusted p value
Maternal disease severity	115	0.34	0.26 to 1.68	0.34	0.97	0.30 to 3.24	0.96
Trimester of maternal SARS-CoV-2 infection	115	0.643	0.42 to 1.77	0.643	0.84	0.37 to 1.99	0.69
Maternal age	113	0.97	0.89 to 1.06	0.49	0.95	0.86 to 1.05	0.34
Maternal comorbidities	115	0.59	0.19 to 1.71	0.34	0.59	0.17 to 1.90	0.38
Maternal history of mental health disorders	115	1.14	0.17 to 4.87	0.87	1.4	0.18 to 7.28	0.71
Maternal fever during pregnancy	115	0.25	0.04 to 0.96	0.08	0.26	0.035 to 1.22	0.12
Neonatal comorbidities	115	0.95	0.28 to 2.86	0.93	1	0.24 to 3.59	0.99
Fetal gender	115	0.94	0.32 to 2.75	0.91	0.88	0.28 to 2.73	0.82
Predictor variables for Developmental Deviation (DD) n = 109	**N**	**OR**	**95% CI**	**P value**	**Adjusted OR**	**Adjusted 95% CI**	**Adjusted p value**
Maternal disease severity	109	1.8	0.64 to 5.53	0.26	0.96	0.26 to 3.52	0.95
Trimester of maternal SARS-CoV-2 infection	109	0.72	0.33 to 1.64	0.41	0.65	0.26 to 1.60	0.36
Maternal age	108	0.97	0.89 to 1.06	0.51	0.96	0.86 to 1.07	0.47
Maternal comorbidities	109	0.89	0.27 to 2.88	0.85	0.67	0.17 to 2.49	0.55
Maternal history of mental health disorders	109	2.9	0.58 to 11.73	0.15	3.01	0.53 to 14.59	0.82
Maternal fever during pregnancy	109	3.7	1.12 to 12.60	0.03	4.11	0.98 to 18.77	0.06
Neonatal comorbidities	109	1.25	0.35 to 4.06	0.71	1.36	0.31 to 5.63	0.67
Fetal gender	109	1.22	0.38 to 4.03	0.74	1.15	0.33 to 4.16	0.18
Preterm birth	109	2.1	0.58 to 6.98	0.23	2.38	0.55 to 10.05	0.23

Adjusted for SARS-CoV-2 maternal disease severity, trimester of infection, neonatal comorbidities at birth, maternal comorbidities (mental and physical), gender, maternal age, maternal fever during pregnancy and prematurity (the latter for DD only since GMA corrects for post-term age).
DD, developmental delay; GMA, general movement assessment; MOS-R, Motor Optimality Scores Revised.

Table 4 Association between maternal fever and developmental deviation (DD) in 109 infants exposed to in utero SARS-CoV-2 infection during any trimester in pregnancy

	Maternal fever (n=30)	No maternal fever (n=79)	P value
DD (n=13)	(7) 23.3%	(6) 7.6%	0.02
No DD (n=96)	(23) 76.6%	(73) 92.4%	

and neonatal morbidities such as low birth weight, respiratory distress and small for gestational age were not identified, however, this could be a function of sample size. Neonatal complications following maternal SARS-CoV-2 infection in pregnancy have been reported,[20] especially preterm birth. Despite the fact that 25% of our cohort was preterm, prematurity did not explain reduced MOS-R, as GMA corrects for preterm age, that is, infants only reach the threshold for GMA evaluation of fidgety movements with a corrected post-term age of 12 weeks. In this situation, for an infant born at 35 weeks, the minimum age for performance of GMA would be 17 weeks, once corrections for prematurity are made. In a small sample evaluating GMA in 28 infants prenatally exposed to SARS-CoV-2, 6 exposed infants had poor performance (3 absent FMs and 3 abnormal exaggerated FMs).[21] This aligns with our findings showing an overall reduced MOS-R (including 7% abnormal FMs) in exposed infants compared with prepandemic controls. Although our proteomic analysis found an association between abnormal immune signatures in newborn infants and maternal disease severity,[4] we did not observe associations between MOS-R or DD and maternal disease severity in this study. It is recognised that maternal infection can induce inflammatory responses in both mother and fetus, leading to immune rewiring.[4] Proteomics of mother–infant pairs from the present cohort demonstrated altered Wnt signalling in newborns exposed to severe/critical maternal COVID-19, a finding potentially associated with poor long-term neurodevelopment.[4] Prior epidemiological data and animal model studies demonstrate MIA can have detrimental effects on infant brain development.[22 23]

We did not see a correlation between moderately reduced MOS-R and DD at 6–8 months; poor performance in both assessments was noted in only 2 of 13 children (15%). The predictive value of GMA in assessing developmental outcomes at 12 months of age and beyond is well documented, however, associations with earlier neurodevelopment are not as well established. It is important to distinguish the two measures, while GMA is a screening tool, DD reflects a clinical finding. This discrepancy between the two assessments could be further explained by preterm birth, which is corrected during GMA but not for neurodevelopmental milestones; 5 of 13 children (38%) with DD were preterm. Nevertheless, statistical analyses did not show associations between preterm birth and DD. Preterm birth of less than 31 weeks of gestation following maternal SARS-CoV-2 study was shown to be associated with DD.[24] However, a gestational birth age of 32 weeks or less is a known risk factor for poor neurodevelopmental outcomes regardless of COVID-19. Therefore, data should be interpreted with caution when evaluating SARS-CoV-2 infant cohorts, as preterm infants are at higher risk of adverse neurodevelopmental outcomes.

In analysing DD by timing of maternal infection, although statistical significance was not reached, DD was present in over twice the number of infants exposed to COVID-19 in the first trimester. This was independent of maternal disease severity or preterm birth. There is biological plausibility in that viral infections during pregnancy more commonly affect the fetal central nervous system (CNS) early in gestation.[2 25] A higher prevalence of DD was seen in one study where SARS-CoV-2 infection occurred in the first and second trimesters of pregnancy.[24] It is important to highlight that SARS-CoV-2 is not a teratogenic virus. Thus, repercussions to the fetal brain would derive from a potential deleterious effect of MIA, carrying higher risk during early CNS development. Therefore, it is important to further evaluate potential correlations between first trimester SARS-CoV-2 infection and paediatric neurological outcomes.

Studies have investigated potential associations between maternal fever and infant neurodevelopmental disorders.[23 26] Maternal fever during pregnancy has been associated with DD, attention deficit hyperactivity disorder and ASD. This is thought to occur due to MIA during a vulnerable period in fetal brain development. An association between maternal fever in pregnancy and DD was noted, but not between fever and reduced MOS-R. The association between DD and maternal fever requires further investigation in larger cohorts and also further follow-up beyond 6–8 months of infant age.

Selected studies investigated neurodevelopment in infants exposed to SARS-CoV-2 in utero, with different methodologies applied.[27 28] Ages and Stages Questionnaires, Third Edition was employed in one study between 10 and 12 months of age, finding DD in 10% of children.[27] It is unclear how much the pandemic itself may contribute to DD in young children, due to reduced physical stimuli and social interactions. Some studies have suggested this may be the case.[29] We acknowledge DD at such a young age can be preliminary and may subsequently resolve in some children, while in others neurodevelopmental abnormalities may continue to appear over time. It is necessary to continue long-term follow-up to further evaluate correlations between MOS-R and neurodevelopmental outcomes.

A strength of this study is that it is the largest, longitudinal cohort to date to monitor neuromotor function using GMA in infants prenatally exposed to SARS-CoV-2 matched to prepandemic controls. The study was done at two locations, Los Angeles and Rio de Janeiro, countries

with high COVID-19 caseloads. Infants were also evaluated clinically at 6–8 months of age, with detailed in person assessment of neurodevelopmental milestones.[30] Study procedures were performed consistently by study personnel with rigorous protocols followed for assessments, interpretation of GMA findings and neurological evaluations.[31] Although GMA acessors were not blinded to SARS-CoV-2 infant exposure, it is important to highlight that novel artificial intelligence (AI) techniques are available for interpreting GMA results and evaluation by AI methodology does not change GMA results when there is high interscorer agreement.[32] Study limitations include the lack of non-exposed control infants for assessment of DD, difficult to attain during the pandemic when most adults have contracted COVID-19 and over 90% of the population is seropositive. We would be unable to exclude gestational exposure to SARS-CoV-2 in mothers of control infants. We could not perform comparisons regarding attainment of developmental milestones between cases and control children from the GMA prepandemic database because controls were selected based on a normal neurodevelopmental profile, which was part of the inclusion criteria. We had a small number of infants born to mothers infected in the first trimester of pregnancy, which potentially limited the ability to evaluate the role of timing of infection. Another limitation is that Bayley-III assessments were not performed, although this was still an early age where Bayley-3 assessments can be less informative. We are following the cohort prospectively and performing Bayley-III assessments in the second year of life.

In summary, most antenatally COVID-19 exposed infants (83%) presented with reduced MOS-R, suggesting potential risk for neurodevelopmental deficits. Twelve per cent of the cohort exhibited DD at 6–8 months of age, a finding potentially associated with maternal fever during COVID-19. Studies using other approaches highlight similar findings. Emerging data underscores the need for ongoing neurodevelopmental follow-up of children born during the pandemic, with social and environmental variables also taken into consideration.

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