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ORIGINAL RESEARCH

# Risk of Global Developmental Delay in Infants Born from Mothers with COVID-19: A Cross-Sectional Study

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**Purpose:** To investigate the risk of global developmental delay in infants born from mothers with COVID-19.

**Patients and Methods:** A cross-sectional study was conducted between March and November 2021, with 54 infants of both sexes aged between 1 and 12 months. Twenty-seven infants born from mothers diagnosed with COVID-19 during pregnancy composed the COVID-19 group, whereas infants born from mothers not exposed to COVID-19 composed the control group. Medical records and child health booklets provided neonatal and prenatal data. The Survey of Wellbeing of Young Children screened the risk of global developmental delay during a phone interview or home visit. Chi-squared, Mann–Whitney test, and binary logistic regression were applied.

**Results:** The risk of motor developmental delay was identified in 15 infants (12 in the COVID-19 group), while 36 were at risk of behavioral alteration (22 in the COVID-19 group). The COVID-19 group presented a 6.3-fold risk of motor developmental delay. Motor developmental delay was also significantly associated with socioemotional alterations (odds ratio = 6.4, p = 0.01). Regarding families of infants in the COVID-19 group, 63% of the mothers presented risk of depression, 51.9% risk of substance abuse, 40.7% risk of food insecurity, and 7.4% risk of domestic violence. The inflexibility subscale of the survey was a statistically relevant variable for the socioemotional domain.

**Conclusion:** Infants born from mothers with COVID-19 were at high risk of motor developmental delay and socioemotional alterations. Although, this study fills an important gap in the literature regarding the influence of maternal exposure to COVID-19 on infant development, new studies screening families with infants at risk of developmental delay may significantly impact maternal and child health-related indicators, such as physical health, emotional development and social behavior.

**Keywords:** infant development, COVID-19, infant well-being

## Introduction

Maternal and perinatal experiences may impact health in early childhood and affect motor, cognitive, and neurological development.[1] Also, lifestyle, medications, nutrition, and environmental factors during pregnancy can affect fetal development,[2–4] expose the infant to long-term illnesses, and increase the risk of altered development.[5–7]

Maternal exposure to environmental factors affects the chemical and structural maturation of the fetus, causing epigenomic changes and genotoxic responses that may alter intrauterine or postnatal development.[1,2] Although literature showed that the diagnosis of COVID-19 during pregnancy was associated with maternal death, prematurity, spontaneous miscarriage, and intrauterine growth restriction,[8] knowledge on the relationship between maternal exposure to COVID-19 and infant global development is still scarce.[9]

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In this sense, screening families with infants at risk of developmental delay may significantly impact maternal and child health-related indicators, such as physical health, emotional development and social behavior. Therefore, this study aimed to investigate the risk of global development delay in infants exposed to maternal COVID-19 infection. We hypothesized that exposure to COVID-19 during pregnancy might increase the risk of developmental delay.

# Methods

## Study Design

This cross-sectional study was conducted between March and November 2021. The study was approved by the research ethic committee of the Federal University of Rio Grande do Norte (4.566.209) and followed the Declaration of Helsinki and resolution 466/12 of the National Committee of Ethics in Research. The legal guardians of the research participants were previously informed about all phases of the study and signed the Free and Informed Consent Term.

## Sample

The COVID-19 group comprised infants of both sexes, aged between 1 and 12 months and born to mothers diagnosed with COVID-19 during pregnancy. This group was identified by searching the management system of a school maternity hospital and via disclosure on social networks. The control group comprised infants not exposed to maternal illness, evaluated before the COVID-19 pandemic. They were paired by sex, gestational age at birth, and chronological age. Both groups were assessed in the same conditions, and the assessments were conducted by phone or home visits. Those infants who died during the study or whose families could not be contacted in person or by phone were excluded. Mothers could be diagnosed using the reverse transcription-polymerase chain reaction or rapid tests, and sex and gestational age of infants were extracted from medical records and child health booklets.

## The Survey of Well-Being of Young Children (SWYC)

The SWYC validated for the Brazilian population was used to assess the risk of developmental delay. Five age-specific SWYC forms (from 1 to 12 months) were applied by phone or during a home visit with parents or primary caregivers. Each SWYC form has three main sections: developmental milestones (SWYC milestones), baby pediatric symptom checklist (BPSC), and family questions. This survey monitors the risk of developmental-behavioral disorders by assessing multiple domains of infant well-being.[10]

Cognitive, language, and motor development were assessed using the SWYC milestones,[11] while the BPSC assessed behavioral and emotional symptoms. The section regarding family questions assessed parental depression, violence, substance abuse, and food insecurity. Questions related to parental concerns about infant behavior, learning, or development were also asked.[12]

The SWYC milestones and BPSC were classified according to total scores.[12] Development was classified as "needs review" (scores lower than the minimum for the age of infants) or "appears to meet age expectations" (higher than the minimum for the age of infants). Regarding the socioemotional domain, infants were considered at risk of developmental-behavioral disorders if the score in any of the three subscales (irritability, inflexibility, and difficulty with routines) was equal to or higher than three.

A "yes" answer in the family questions component indicated risk of substance abuse and food insecurity. Parental depression was considered when scores related to this topic were equal or higher than three, whereas family violence was considered when caregivers answered "yes" to at least one of two questions. Parental concerns about infant behavior, learning, or development were classified as "a little" or "very" concerned.[12]

## Data Analysis

Data normality was assessed using Kolmogorov–Smirnov test. Pearson's Chi-square test verified the associations between groups and variables (developmental milestones, family violence, parental depression, substance abuse, behavioral and emotional symptoms, food insecurity, and parental concerns about infant behavior, learning, or development).

The Mann–Whitney test compared groups and continuous variables (developmental milestones and gestational age), and median and interquartile range were presented according to groups. Multivariate binary logistic regression models assessed variables associated with the COVID-19 group. All variables with $p < 0.20$ in the bivariate analysis were included in the regression model. The final model included only variables with $p < 0.05$, and all statistical analyses were conducted using the Statistical Package for Social Science software (SPSS, IBM Corp., USA).

Regarding the developmental milestones, a post hoc analysis considering a Cohen's d effect size of 0.95 between the COVID-19 group and the control group showed a statistical power of 79.8% for this study.[13,14]

## Results

Thirty-seven pregnant women diagnosed with COVID-19 were identified between March and November 2021; 27 were included in the COVID-19 group. Fourteen assessments were conducted by phone and 13 by home visits (Figure 1). One mother died due to COVID-19 complications; thus, the assessment was conducted with the father (primary caregiver). Eleven out of 27 infants were preterm. The control group comprised 27 infants assessed by home visits. Table 1 shows descriptive data.

The risk of motor developmental delay was identified in 12 infants of the COVID-19 group (4 preterms), and 81.5% were at risk of socioemotional alterations. Twenty-one families were concerned about the behavior and development of infants; 17 were from the COVID-19 group ($p = 0.01$). Regarding family context, 63% of the families in the COVID-19 group presented risk of parental depression, 7.4% risk of family violence, 51.9% risk of substance abuse, and 40.7% risk of food insecurity.

The COVID-19 group was also associated with irritability ($p = 0.01$), inflexibility ($p = 0.02$), and difficulty with routines subscales ($p = 0.03$), separately or grouped in the category "risk of socioemotional developmental delay" ($p = 0.02$). No risk of food insecurity or family violence was identified in the control group. Nevertheless, 22.2% of the families included in this group were at risk of substance abuse and 3.7% at risk of parental depression (Table 2).

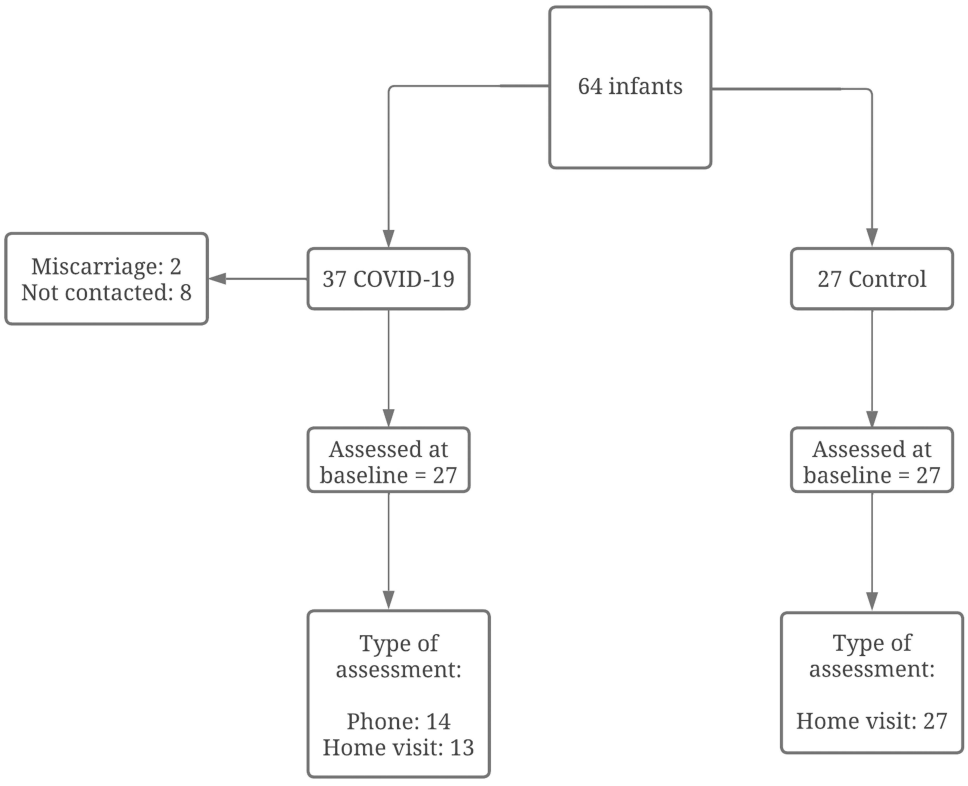


**Figure 1** Flowchart of study design and participants.

**Table 1** Descriptive Data of the Sample

| | COVID-19 Group | Control Group | p-value |
|---|---|---|---|
| **Sex** | | | |
| Female* | 13 (48.1) | 13 (48.1) | 1.00[a] |
| Male* | 14 (51.9) | 14 (51.9) | |
| **Gestational age classification** | | | |
| Preterm* | 11 (40.7) | 07 (25.9) | 0.250[a] |
| Full-term* | 16 (59.3) | 20 (74.1) | |
| **Gestational age at birth**[†] | 38 (36–39) | 38 (36–39) | 0.701[b] |
| **SWYC milestones**[†] | 13 (11–16) | 16 (14–18) | 0.020[b] |
| **Baby Pediatric Symptom Checklist**[†] | 09 (6–14) | 04 (3–6) | <0.001[b] |

**Notes**: Categorical data presented as n (%); *Expressed variable with n and percentage; [†]Expressed as median (interquartile range, 25th–75th); [a]p-value for comparison test; [b]p-value for Mann–Whitney test.
**Abbreviation**: SWYC, Survey of Well-being of Young Children.

The logistic regression demonstrated that behavioral alterations (ie, motor developmental delay; socioemotional developmental delay; inflexibility; and parental concerns about behavior, learning, or development of the infant) were significantly associated with the COVID-19 group ($\chi^2[4] = 14.872$; $p = 0.005$, $R^2$ Nagelkerke = 0.334). The regression model also indicated that belonging to the COVID-19 group predicted motor developmental (95% CI: 1.51–26.2; $p = 0.01$) and socioemotional delay (95% CI: 1.194–13.978; $p = 0.02$) (Table 3).

## Discussion

Infants born from mothers diagnosed with COVID-19 during pregnancy presented a greater risk of developmental delay and socioemotional alterations and lived in a familiar context of risk for substance abuse and food insecurity.

**Table 2** Comparison of the Survey of Well-Being of Young Children Components Between the Groups

| | COVID-19 Group n (%) | Control Group n (%) | p-value |
|---|---|---|---|
| **Risk of motor developmental delay** | | | |
| Yes | 12 (44.4) | 03 (11.1) | 0.007 |
| No | 15 (55.6) | 24 (88.9) | |
| **Risk of socioemotional developmental delay** | | | |
| Yes | 22 (81.5) | 14 (51.9) | 0.021 |
| No | 05 (18.5) | 13 (48.1) | |
| **Parental depression** | | | |
| Yes | 17 (63.0) | 01 (3.7) | <0.001 |
| No | 10 (37.0) | 26 (96.3) | |
| **Violence** | | | |
| Yes | 02 (7.4) | 00 (0) | 0.245 |
| No | 25 (92.6) | 27 (100) | |
| **Substance abuse** | | | |
| Yes | 14 (51.9) | 06 (22.2) | 0.024 |
| No | 13 (48.1) | 21 (77.8) | |

(*Continued*)

**Table 2** (Continued).

| | COVID-19 Group n (%) | Control Group n (%) | p-value |
|---|---|---|---|
| **Food insecurity** | | | |
| Yes | 11 (40.7) | 00 (0) | <0.001 |
| No | 16 (59.3) | 27 (100) | |
| **Irritability** | | | |
| Yes | 23 (85.2) | 15 (55.6) | 0.018 |
| No | 04 (14.8) | 12 (44.4) | |
| **Inflexibility** | | | |
| Yes | 13 (48.1) | 05 (18.5) | 0.021 |
| No | 14 (51.9) | 22 (81.5) | |
| **Difficulty with routines** | | | |
| Yes | 23 (85.2) | 16 (59.3) | 0.033 |
| No | 04 (14.8) | 11 (40.7) | |

**Table 3** Variables of the Final Multivariate Binary Logistic Regression Model for the Survey of Well-Being of Young Children Components

| | Odds Ratio (95% CI) | p-value |
|---|---|---|
| **Risk of motor developmental delay** | 6.3 (1.5–26.2) | 0.01 |
| **Risk of socioemotional developmental delay** | 4.0 (1.1–13.9) | 0.02 |
| **Inflexibility** | 14.0 (1.3–140.7) | 0.02 |
| **Irritability** | 1.79 (0.4–7.5) | 0.42 |
| **Difficulty with routines** | 1.70 (0.3–7.4) | 0.48 |
| **Parental concerns about behavior, learning, or development of the infant** | 9.7 (2.6–36.5) | 0.01 |

**Abbreviation**: CI, confidence interval.

It is known that several viral infections during pregnancy increase the risk of altered child development,[5,15] since they can produce an intense immune response with massive activation of inflammatory cytokines. The interleukin-6, the main mediator involved in the inflammatory response, in high concentrations generates fetal neuroinflammation and microglial activation with long-term effects on neurodevelopment.[16,17] This biological response to stress conditions at a cellular level may increase DNA damage,[2,16] causing alterations associated with a major risk of chronic diseases or motor,[6] cognitive,[7] and neurological development.[18]

Although studies investigating the transmission of SARS-CoV-2 have not reported evidence of vertical contamination from mothers to infants,[19,20] the infection caused by SARS-CoV-2 during pregnancy may cause the same immune activation with long-term effects, since brain development is a dynamic process that extends into adolescence.[16] In addition, factors such as maternal and perinatal experiences, social isolation, exposure to viral infections, and maternal depression and illness may also contribute to altered growth and child development.[3,21,22]

Most families in the COVID-19 group were at risk of food insecurity. Shonkoff et al[23] suggested that poverty and food insecurity were risk factors for adverse outcomes in childhood (eg, impaired motor and cognitive performance in the early childhood).[23] Food insecurity might influence the fetal and brain development, via indirect effects through the mother, since the calories and nutrients required for fetal growth are transferred from the mother, dependent on maternal food intake and influenced by maternal microbiota.[24] Microbes play an essential role in fetal development, because the maternal microbiota colonizes the newborn's body during a time when the brain is being shaped by key developmental processes.[24]

Moreover, food insecurity may reflect low socioeconomic levels, which harms the well-being, socioemotional, cognitive, and language development of children and adolescents.[25] A low socioeconomic level also leads to

environmental restrictions and poor sensory and motor stimuli for infants.[26] In this context, an appropriate interaction between biological and environmental factors within a favorable family context improves infant development.[27]

According to our results, other environmental factors investigated through SWYC forms, such as substance abuse, family violence and parental depression, may have influenced the neurodevelopmental outcomes. Parental substance abuse contributes to impaired intrauterine and infant development (eg, poor motor and cognitive outcomes and socio-emotional and learning difficulties) and increases the chances of long-term intellectual disability[28] and adolescence and adulthood depression.[4] Nair et al[29] observed that cumulative environmental factors (eg, maternal depression, domestic and non-domestic violence, number of family members, lack of shelter, incarceration, partner absence, psychological status, and severity of dependence) in infants born from mothers with substance abuse issues led to cumulative negative effects on motor development and high risk of maternal negligence and childhood abuse.[29]

Our results also indicated that most infants lived with mothers at risk of depression. Recent studies indicated anxiety, depression, and maternal stress as regulatory factors influencing neurodevelopmental outcomes in the fetal programming process.[30,31] Infants born from mothers with depression also presented a high risk of cognitive and motor delay and negative behavior disorders in adulthood.[30,31] Studies using animal models showed a direct relationship between altered development and behavior and cortisol levels;[32,33] the latter can be intensified by lack of social support.[34]

Furthermore, stressful situations during the prenatal period, even when isolated (eg, snowstorms, hurricanes, and other natural disasters), might affect the cognitive and socioemotional development of infants in the long term.[35,36] Thus, the pandemic-related stress experienced by mothers during pregnancy can act as a risk factor for changes in child development, especially when associated with other negative variables, such as maternal illness, inadequate support network, food insecurity and domestic violence.[29,37] Therefore, birth during the COVID-19 pandemic, even without maternal infection, can be associated with regulatory problems related to sleep and child irritability.[38]

Based on this background, Gabbard[39] demonstrated that developmental disorders were associated with hormonal and biochemical alterations caused by environmental factors and gene expression. Jiang et al[40] also showed that inflammatory cascades due to psychosocial stress may affect the behavioral and neurological development of fetuses and infants exposed to adverse situations in childhood.

Although this study highlights the main factors related to the global development of children exposed to maternal illness, it is not free of limitations. The COVID-19 pandemic and social isolation hindered an outpatient assessment, so a screening questionnaire applied via phone was an alternative to monitor and carefully assess infants. Also, other conditions in conjunction with COVID-19 could not be paired between the samples and the inclusion criteria restricted our sample size. Additionally, the infants included in our sample were not tested for COVID-19, because in Brazil, during the time this study, only the symptomatic subjects were being tested.

Thus, we suggest that the future longitudinal studies monitoring the development of these infants be carried out with predictive developmental scales, as Bayley-III, as they can track not only the development of infants at risk but of all babies born in conditions as peculiar as the pandemic and social isolation. Further, longitudinal studies with larger samples should investigate neuromotor outcomes and consider the biopsychosocial model and biological aspects to interpret findings related to developmental delay.[41]

Nevertheless, in the Northeast of Brazil, this is the first study assessing the risk factors of socioemotional and motor delay in infants born from mothers diagnosed with COVID-19 during pregnancy. The Northeast Region has many social inequalities even between areas of the same city[42] and the development of a Brazilian infant can be impaired by environmental deprivation.

Considering the existence of a direct relationship between socioeconomic conditions, biological factors and neuro-developmental outcomes, it is clear that this study fills an important gap in the literature regarding the influence of maternal exposure to COVID-19 on infant development. Maternal illness may predispose alterations in child development, mainly if associated with risk factors, while the environmental context lived by the mother (eg, prolonged social isolation and psychosocial vulnerability) may negatively impact infant motor and socioemotional development.

## Ethics Approval and Informed Consent

This study was approved by the research ethics committee (n°4.566.209) of the Federal University of Rio Grande do Norte and followed the Declaration of Helsinki and resolution 466/12 of the National Committee of Ethics in Research.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no competing interests in this work.

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