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Risk of neurodevelopmental changes in 18-month-old children born to mothers infected with SARS-CoV-2

Risco de alterações no neurodesenvolvimento de crianças de 18 meses nascidas de mães infectadas pela SARS-CoV-2

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ABSTRACT

Purpose: To investigate the risk of child development in 18-month-old children born to mothers who were infected by the SARS-CoV-2 virus during pregnancy and identify possible delays in development indicators. **Methods:** Children who were born between January 2021 and August 2021, whose mothers tested positive for COVID-19 during pregnancy, participated in the research. To investigate linguistic, motor, cognitive and social development, the Ages & Stages Questionnaires (ASQ-3) was used in the five domains: Communication, Gross motor coordination, Fine motor coordination, Problem solving and Personal/social. Data were described using absolute and percentage frequencies and using mean, standard deviation, minimum, median and maximum. To analyze the association between the variables of interest, the Poisson regression model was used. Tukey's post-test was used for multiple comparisons. **Results:** The Personal-Social domains, followed by Fine motor coordination and Problem Solving were the best performing. The worst performance was observed in the Communication domain, followed by Gross motor coordination. Prematurity, birth weight, Apgar score and need for hospitalization of the child after birth were variables associated with low performance in the domains assessed. **Conclusion:** A risk of developmental delay was observed in 18-month-old children born to mothers who were infected with the SARS-CoV-2 virus during pregnancy. The domain with the greatest loss was Communication, followed by changes in Gross Motor Coordination.

Keywords: Triage; Early diagnosis; Post-acute Covid-19 syndrome; Language development; Speech, language and hearing sciences

RESUMO

Objetivo: Investigar risco de alterações no desenvolvimento infantil de crianças de 18 meses nascidas de mães que foram infectadas pelo vírus SARS-CoV-2 durante a gestação e identificar possíveis atrasos em indicadores de desenvolvimento. **Métodos:** Participaram da pesquisa 41 crianças que nasceram no período de janeiro de 2021 a agosto de 2021, cujas mães testaram positivo para a Covid-19 durante a gestação. Para a investigação do desenvolvimento linguístico, motor, cognitivo e social foi utilizado o *Ages & Stages Questionnaires* nos cinco domínios: Comunicação, Coordenação Motora Ampla, Coordenação Motora Fina, Resolução de Problemas e Pessoal/Social. Os dados foram descritos por meio de frequências absolutas e percentuais e por meio de média, desvio padrão, mínimo, mediana e máximo. Para analisar a associação entre as variáveis de interesse foi utilizado o modelo de regressão de Poisson. O pós-teste de Tukey foi utilizado para as comparações múltiplas. **Resultados:** Os domínios Pessoal/-Social, Coordenação Motora Fina e Resolução de Problemas, neste seguimento, foram os de melhor desempenho. O pior desempenho foi observado no domínio Comunicação, seguido da Coordenação Motora Ampla. A prematuridade, peso ao nascimento, índice de Apgar e necessidade de internação da criança pós-nascimento foram variáveis associadas ao baixo desempenho nos domínios avaliados. **Conclusão:** Foi observado risco de atraso no desenvolvimento de crianças de 18 meses nascidas de mães que foram contaminadas pelo vírus SARS-CoV-2 durante a gestação. O domínio com maior prejuízo foi o de Comunicação, seguido de alteração da Coordenação Motora Ampla.

Palavras-chave: Triagem; Diagnóstico precoce; Síndrome pós-Covid-19 aguda; Desenvolvimento da linguagem; Fonoaudiologia

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INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared the pandemic caused by the SARS-CoV-2 virus, known as COVID-19. By mid-December 2023, 38,210,864 million people had been infected in Brazil and more than 650 million worldwide[1]. SARS-CoV-2 infection is transmitted primarily by droplets. This virus is part of a family of RNA (ribonucleic acid) viruses that cause everything from the common cold to more serious and even fatal conditions, with significant lung involvement[2].

Although the first signs appear in the upper respiratory tract and lung tissue due to the portal of entry, other organs with this receptor can be likewise affected; thus, the individual may develop other clinical manifestations. Studies report that generalized inflammation and the lack of oxygen can also acutely damage the kidneys, liver, and gastrointestinal tract and cause changes in the coagulation cascade and hematopoietic system, heart and cardiovascular system, brain and central nervous system, and other organs[2,3].

One concern during the pandemic isolation period was that of pregnant women infected by the virus. The coronavirus is known to infect human cells by binding to receptors for angiotensin-converting enzyme 2 (ACE2) molecules, expressed in various human tissues and organs, including the uterus and placenta[3]. However, little is known about the form of transplacental transmission; therefore, the possibility of maternal-fetal transmission of SARS-CoV-2 remains under discussion[4,5].

Unlike the Zika virus, which has a rather high rate of vertical maternal-fetal transmission and is associated with a well-described spectrum of congenital manifestations (including microcephaly, cerebral palsy and developmental delays)[4], some studies have shown that vertical transmission of SARS-CoV-2 is possible, although rare, and can occur through the passage of microorganisms during pregnancy, contact with blood and vaginal secretions at the time of delivery and through breast milk[6]. The placental membrane separates maternal and fetal blood, acting as a protective barrier, but some viruses and bacteria can permeate it through unknown mechanisms. Factors such as premature birth, low birth weight, and fetal malformations are directly related to the increased risk of vertical transmission[5].

Some studies have also demonstrated the potential risk of neurodevelopmental changes in children exposed to SARS-CoV-2 during the prenatal period[7-9]. According to a study[10], babies born to mothers infected with COVID-19 during pregnancy had a higher risk of developmental delay, with greater impairment in motor coordination domains. A systematic review and meta-analysis study suggested that general neurodevelopment in the first year of life was not altered by gestational exposure to SARS-CoV-2. However, it found that the children were at risk of communication delay[11].

Therefore, we must understand how gestational SARS-CoV-2 exposure impacts child neurodevelopment and monitor in the long run children of mothers with confirmed COVID-19, regardless of the gestational period and the intensity of clinical manifestations. They may present an unknown set of future impairments, secondary to the infection itself, or due to maternal inflammatory reactions observed during SARS-CoV-2 infection[12].

Therefore, this study aimed to investigate the development of 18-month-old children born to mothers infected with SARS-CoV-2 during pregnancy and identify possible delays in developmental indicators.

METHODS

This study was conducted after approval by the Research Ethics Committee of the University of Sorocaba – CEP/UNISO, under opinion number 5.440.030 (CAAE 57255822.9.0000.5500). All guardians signed an electronic informed consent form sent after being invited and agreeing to participate and before data were collected by telephone.

The study included 41 children born between January and August 2021, whose mothers tested positive for SARS-CoV-2 during pregnancy and were monitored by a municipal polyclinic's Newborn at Risk Program (NB at Risk Program). This program aims to monitor children born at neurodevelopmental risk, according to criteria preestablished by the program, and longitudinally monitor all 92 mothers who were hospitalized in maternity hospitals affiliated with the Brazilian Unified Health System (SUS) during this period and who tested positive for COVID-19. The convenience sample selected 41 mothers who accepted the invitation to participate in the study and had tested positive for SARS-CoV-2 during the period in question, regardless of the gestational period when they contracted the virus and the severity of the manifestations throughout the disease course. The mothers or primary caregivers – even those who were minors – responded to the questionnaires. The sample loss was due to a lack of response to the invitation and difficulties contacting mothers during the collection.

The study obtained data regarding maternal age, gestational age, type of delivery, child's sex, Apgar score, birth weight, the child's need for prolonged hospitalization after birth, and gestational trimester when the mother was exposed to the virus directly from the NB at risk Program database, collected by the nursing team that accompanied the mothers during childbirth hospitalization. Other information, such as the presence and/or absence of breastfeeding and the application of the investigative questionnaire, were collected by telephone. The mothers and children were not contacted in person during data collection.

The Ages & Stages Questionnaires third edition (ASQ-3) [13] translated into Portuguese was applied to 18-month-old children to investigate their development. This instrument identifies risk in children aged 1 to 66 months. Parents/primary caregivers answered questions read by the researcher about the child's skills. The questionnaires have five blocks, one for each developmental domain – Communication, Gross Motor Coordination, Fine Motor Coordination, Problem-Solving, and Personal/Social. Each block has six questions, totaling 30 questions. A score is assigned according to the answers: "yes" (10 points), "sometimes" (5 points), and "not yet" (0 points). Each block can have a maximum score of 60 points. The total ASQ-3 score is the sum of the points of the caregivers' responses in relation to a cutoff predefined by the test. Thus, the assessment result is classified as "above the cutoff", when development is within expectations, "close to the cutoff", indicating the need for monitoring, and "below the cutoff", already evidencing developmental impairment and the need for specialized assessment. This study's analysis considered children with a score "close to the cutoff" as "below the cutoff" since both cases perform below the expected for their age.

The data were described using absolute and percentage frequencies and measures such as mean, standard deviation, minimum, median, and maximum values. The Poisson regression model with robust variance and logarithmic link function

analyzed the association between the variables of interest and outcomes, estimating the corresponding relative risks[14]. The Tukey post-test was used for multiple comparisons of variables with more than two response levels. The significance level was set at 5%.

RESULTS

The maternal age range, type of delivery, and gestational trimester when the mother was infected with COVID-19 are described in Table 1. Most mothers were under 30 years old (mean of 28 years and 2 months), with a mean gestational age of 37.85 weeks (ranging from 30 to 41 weeks), and were infected with COVID-19 in the third trimester of pregnancy. The most prevalent type of delivery was vaginal. Regarding children, the percentage data on sex, prematurity, 1-minute Apgar score, birth weight, post-birth hospitalization, COVID-19 test result, comorbidities, and breastfeeding are also described in Table 1. Most were females, with a mean age of 17 months and 9 weeks, born at term, with a 1-minute Apgar score equal to or greater than 7, weighing over 2,500 g, with a mean of 3,079 g (±559.10). Most children were not tested for COVID-19. There was a higher percentage of pulmonary changes (19.51%) than other comorbidities. Only five children were not breastfed, and 37.5% maintained breastfeeding for over 12 months.

Table 1. General characteristics of the mothers and children

Variable	Total number of cases	Percentage (%)
MOTHER'S AGE		
< 30 years	24	58.54
>= 30 years	17	41.46
TYPE OF DELIVERY		
Cesarean	18	43.9
Vaginal	23	56.1
MOTHER'S COVID – PREGNANCY		
1st trimester (0-12 weeks)	5	12.2
2nd trimester (12-26 weeks)	9	21.95
3rd trimester (26 weeks-birth)	27	65.85
CHILD'S SEX		
Females	21	51.22
Males	20	48.78
PREMATURITY		
No	34	82.93
Yes	7	17.07
1-MINUTE APGAR		
< 7	4	9.76
>= 7	37	90.24
BIRTH WEIGHT		
< 2500 grams	5	12.2
>= 2500 grams	36	87.8
CHILD'S HOSPITALIZATION		
No	33	80.49
Yes	8	19.51
COVID-19 SEROLOGY		
Negative	9	21.95
Not tested	32	78.05
COMORBIDITIES		
Cardiological	3	7.32
Cardiological and pulmonary	2	4.88
Neurological	1	2.44
Pulmonary	8	19.51
Absent	27	65.85
BREASTFEEDING DURATION		
No breastfeeding	5	12.5
< 6 months	5	12.5
6 months to 1 year	15	37.5
Over 1 year	15	37.5
Frequency Missing = 1		

Subtitle: < less than; > greater than; >= equal to or greater than
Source: Developed by the authors, 2023

ASQ-3 (for 18-month-old children)

The ASQ-3 domains had the following mean scores: Communication (33.41±12.57), Gross Motor Coordination (47.44±12.8), Fine Motor Coordination (52.93±13.6), Problem-Solving (41.22±14.04), and Personal/Social (50.37±8.83).

Figure 1 shows the percentage of children whose responses were below the cutoff established by the test. The worst percentage of responses below the cutoff was found in Communication (53.66%), followed by Gross Motor Coordination (46.34%).

Regarding Communication, Table 2 shows that the average risk of being below expected was 82% higher in premature children than those born at term. Children who remained hospitalized after birth were at a 92% risk of being below expected in this domain than children who did not need hospitalization. Also, babies born weighing less than 2,500 g were at an average 2.12 times greater risk of low performance in this domain. The other variables analyzed (child's sex, trimester of pregnancy, maternal age range, Apgar score, and breastfeeding duration) were not associated with low performance in Communication.

Moreover, poor performance in Fine Motor Coordination (Table 3) was associated with prematurity and birth weight. Premature children were at an average 7.28 times greater risk of responses below the cutoff than full-term children. Children born with low weight (less than 2,500 g) were at 4.8 times greater risk of responses below the cutoff than children weighing more than 2,500 g. The other variables analyzed were not associated with this domain, whereas none of the variables analyzed was significantly associated with Gross Motor Coordination (Table 4).

Poor performance in Problem-Solving was associated with prematurity, 1-minute Apgar score, and breastfeeding duration. Premature children were at an average 2.91 times greater risk of underperformance than children born at term, as did children with Apgar scores lower than 7, who were at a 2.13 times greater risk than children with Apgar scores equal to or greater than 7 at birth. Children who were not breastfed also were at greater risk of poor performance in this domain than children who were breastfed. The other variables analyzed were not significantly associated with this domain (Table 5).

Lastly, poor performance in the Personal/Social domain was associated only with the 1-minute Apgar score. Children with a score lower than 7 were at an average estimated 9.25 times greater risk of a low score than children with an Apgar score equal to or greater than 7 (Table 6).

Table 2. Association of the variables of interest with the performance in the COMMUNICATION domain (Ages & Stages Questionnaires-3)

Variable	ASQ-3 Communication		Relative risk (95% CI)	p-value*
	Below	Above	Communication "below"	
SEX				
Females	10 (47.62%)	11 (52.38%)	0.79 (0.45; 1.41)	0.43
Males	12 (60%)	8 (40%)	ref.	
MOTHER'S COVID – PREGNANCY				
1st trimester	2 (40%)	3 (60%)	0.72 (0.19; 2.77)	0.84
2nd trimester	5 (55.56%)	4 (44.44%)	1 (0.45; 2.24)	0.99
3rd trimester	15 (55.56%)	12 (44.44%)	ref.	
MOTHER'S AGE				
< 30 years	16 (66.67%)	8 (33.33%)	1.89 (0.94; 3.82)	0.08
>= 30 years	6 (35.29%)	11 (64.71%)	ref.	
PREMATURITY				
No	16 (47.06%)	18 (52.94%)	ref.	
Yes	6 (85.71%)	1 (14.29%)	1.82 (1.14; 2.91)	0.01
CHILD'S HOSPITALIZATION				
No	15 (45.45%)	18 (54.55%)	ref.	
Yes	7 (87.5%)	1 (12.5%)	1.92 (1.22; 3.04)	<0.01
1-MINUTE APGAR				
< 7	3 (75%)	1 (25%)	1.46 (0.76; 2.79)	0.25
>= 7	19 (51.35%)	18 (48.65%)	ref.	
BIRTH WEIGHT				
< 2500 grams	5 (100%)	0 (0%)	2.12 (1.5; 2.99)	<0.01
>= 2500 grams	17 (47.22%)	19 (52.78%)	ref.	
BREASTFEEDING DURATION				
No breastfeeding	4 (80%)	1 (20%)	2 (0.74; 5.41)	0.28
< 6 months	2 (40%)	3 (60%)	1 (0.2; 5.08)	0.99
6 months to 1 year	9 (60%)	6 (40%)	1.5 (0.57; 3.98)	0.71
Over 1 year	6 (40%)	9 (60%)	ref.	

*Poisson regression model with robust variance

Subtitle: ASQ-3 = Ages & Stages Questionnaires-3; < less than; > greater than; >= equal to or greater than; % = percentage; CI = confidence interval

Table 3. Association of the variables of interest with the performance in the FINE MOTOR COORDINATION domain (Ages & Stages Questionnaires-3)

Variable	ASQ-3 Fine Motor Coordination		Relative risk (95% CI)	p-value*
	Below	Above	Fine Motor Coordination "below"	
SEX				
Females	4 (19.05%)	17 (80.95%)	3.81 (0.46; 31.23)	0.21
Males	1 (5%)	19 (95%)	ref.	
MOTHER'S COVID – PREGNANCY				
1st trimester	1 (20%)	4 (80%)		0.47**
2nd trimester	0 (0%)	9 (100%)		
3rd trimester	4 (14.81%)	23 (85.19%)		
MOTHER'S AGE				
< 30 years	3 (12.5%)	21 (87.5%)	1.06 (0.2; 5.69)	0.94
>= 30 years	2 (11.76%)	15 (88.24%)	ref.	
PREMATURITY				
No	2 (5.88%)	32 (94.12%)	ref.	
Yes	3 (42.86%)	4 (57.14%)	7.28 (1.48; 35.86)	0.01
CHILD'S HOSPITALIZATION				
No	3 (9.09%)	30 (90.91%)	ref.	
Yes	2 (25%)	6 (75%)	2.75 (0.55; 13.81)	0.22
1-MINUTE APGAR				
< 7	1 (25%)	3 (75%)	2.31 (0.33; 15.98)	0.40
>= 7	4 (10.81%)	33 (89.19%)	ref.	
BIRTH WEIGHT				
< 2500 grams	2 (40%)	3 (60%)	4.8 (1.04; 22.06)	0.04
>= 2500 grams	3 (8.33%)	33 (91.67%)	ref.	
BREASTFEEDING DURATION				
No breastfeeding	2 (40%)	3 (60%)		0.09**
< 6 months	0 (0%)	5 (100%)		
6 months to 1 year	2 (13.33%)	13 (86.67%)		
Over 1 year	0 (0%)	15 (100%)		

*Poisson regression model with robust variance. **Fisher's exact test

Subtitle: ASQ-3 = Ages & Stages Questionnaires-3; < less than; > greater than; >= equal to or greater than; % = percentage; CI = confidence interval

Table 4. Association of the variables of interest with the performance in the GROSS MOTOR COORDINATION domain (Ages & Stages Questionnaires-3)

Variable	ASQ-3 Gross Motor Coordination		Relative risk (95% CI)	p-value*
	Below	Above	Gross Motor Coordination "Below"	
SEX				
Females	11 (52.38%)	10 (47.62%)	1.31 (0.67; 2.57)	0.43
Males	8 (40%)	12 (60%)	ref.	
MOTHER'S COVID – PREGNANCY				
1st trimester	2 (40%)	3 (60%)	0.83 (0.21; 3.26)	0.95
2nd trimester	4 (44.44%)	5 (55.56%)	0.92 (0.34; 2.49)	0.98
3rd trimester	13 (48.15%)	14 (51.85%)	ref.	
MOTHER'S AGE				
< 30 years	8 (33.33%)	16 (66.67%)	0.52 (0.26; 1)	0.06
>= 30 years	11 (64.71%)	6 (35.29%)	ref.	
PREMATURITY				
No	15 (44.12%)	19 (55.88%)	ref.	
Yes	4 (57.14%)	3 (42.86%)	1.3 (0.62; 2.73)	0.50
CHILD'S HOSPITALIZATION				
No	14 (42.42%)	19 (57.58%)	ref.	
Yes	5 (62.5%)	3 (37.5%)	1.47 (0.76; 2.87)	0.26
1-MINUTE APGAR				
< 7	3 (75%)	1 (25%)	1.73 (0.88; 3.41)	0.11
>= 7	16 (43.24%)	21 (56.76%)	ref.	
BIRTH WEIGHT				
< 2500 grams	3 (60%)	2 (40%)	1.35 (0.6; 3.02)	0.46
>= 2500 grams	16 (44.44%)	20 (55.56%)	ref.	
BREASTFEEDING DURATION				
No breastfeeding	4 (80%)	1 (20%)	2 (0.74; 5.41)	0.28
< 6 months	4 (80%)	1 (20%)	2 (0.74; 5.41)	0.28
6 months to 1 year	4 (26.67%)	11 (73.33%)	0.67 (0.17; 2.62)	0.87
Over 1 year	6 (40%)	9 (60%)	ref.	

*Poisson regression model with robust variance

Subtitle: ASQ-3 = Ages & Stages Questionnaires-3; < less than; > greater than; >= equal to or greater than; % = percentage; CI = confidence interval

Table 5. Association of the variables of interest with the performance in the PROBLEM-SOLVING domain (Ages & Stages Questionnaires-3)

Variable	ASQ-3 Problem-Solving		Relative risk (95% CI)	p-value*
	Below	Above	Problem-Solving "below"	
SEX				
Females	8 (38.1%)	13 (61.9%)	0.95 (0.44; 2.05)	0.90
Males	8 (40%)	12 (60%)	ref.	
MOTHER'S COVID – PREGNANCY				
1st trimester	1 (20%)	4 (80%)	0.39 (0.05; 3.28)	0.55
2nd trimester	1 (11.11%)	8 (88.89%)	0.21 (0.02; 2.04)	0.24
3rd trimester	14 (51.85%)	13 (48.15%)	ref.	
MOTHER'S AGE				
< 30 years	10 (41.67%)	14 (58.33%)	1.18 (0.53; 2.62)	0.68
>= 30 years	6 (35.29%)	11 (64.71%)	ref.	
PREMATURITY				
No	10 (29.41%)	24 (70.59%)	ref.	
Yes	6 (85.71%)	1 (14.29%)	2.91 (1.6; 5.32)	<0.01
CHILD'S HOSPITALIZATION				
No	11 (33.33%)	22 (66.67%)	ref.	
Yes	5 (62.5%)	3 (37.5%)	1.88 (0.91; 3.86)	0.09
1-MINUTE APGAR				
< 7	3 (75%)	1 (25%)	2.13 (1.04; 4.37)	0.04
>= 7	13 (35.14%)	24 (64.86%)	ref.	
BIRTH WEIGHT				
< 2500 grams	3 (60%)	2 (40%)	1.66 (0.72; 3.84)	0.23
>= 2500 grams	13 (36.11%)	23 (63.89%)	ref.	
BREASTFEEDING DURATION				
No breastfeeding	5 (100%)	0 (0%)	3.75 (1.25; 11.27)	0.01
< 6 months	3 (60%)	2 (40%)	2.25 (0.53; 9.55)	0.47
6 months to 1 year	3 (20%)	12 (80%)	0.75 (0.13; 4.2)	0.97
Over 1 year	4 (26.67%)	11 (73.33%)	ref.	

*Poisson regression model with robust variance

Subtitle: ASQ-3 = Ages & Stages Questionnaires-3; < less than; > greater than; >= equal to or greater than; % = percentage; CI = confidence interval.

Table 6. Association of the variables of interest with the performance in the Personal/Social domain (Ages & Stages Questionnaires-3)

Variable	ASQ-3 Personal/Social		Relative risk (95% CI)	p-value*
	Below	Above	Personal/Social "below"	
SEX				
Females	3 (14.29%)	18 (85.71%)	2.86 (0.32; 25.24)	0.35
Males	1 (5%)	19 (95%)	ref.	
MOTHER'S COVID – PREGNANCY				
1st trimester	1 (20%)	4 (80%)		0.41**
2nd trimester	0 (0%)	9 (100%)		
3rd trimester	3 (11.11%)	24 (88.89%)		
MOTHER'S AGE				
< 30 years	3 (12.5%)	21 (87.5%)	2.13 (0.24; 18.73)	0.50
>= 30 years	1 (5.88%)	16 (94.12%)	ref.	
PREMATURITY				
No	2 (5.88%)	32 (94.12%)	ref.	
Yes	2 (28.57%)	5 (71.43%)	4.86 (0.82; 28.89)	0.08
CHILD'S HOSPITALIZATION				
No	3 (9.09%)	30 (90.91%)	ref.	
Yes	1 (12.5%)	7 (87.5%)	1.37 (0.16; 11.54)	0.77
1-MINUTE APGAR				
< 7	2 (50%)	2 (50%)	9.25 (1.75; 48.97)	<0.01
>= 7	2 (5.41%)	35 (94.59%)	ref.	
BIRTH WEIGHT				
< 2500 grams	1 (20%)	4 (80%)	2.4 (0.31; 18.85)	0.41
>= 2500 grams	3 (8.33%)	33 (91.67%)	ref.	
BREASTFEEDING DURATION				
No breastfeeding	2 (40%)	3 (60%)		0.17**
< 6 months	0 (0%)	5 (100%)		
6 months to 1 year	1 (6.67%)	14 (93.33%)		
Over 1 year	1 (6.67%)	14 (93.33%)		

*Poisson regression model with robust variance. **Fisher's exact test
Subtitle: ASQ-3 = Ages & Stages Questionnaires-3; < less than; > greater than; >= equal to or greater than; % = percentage; CI = confidence interval

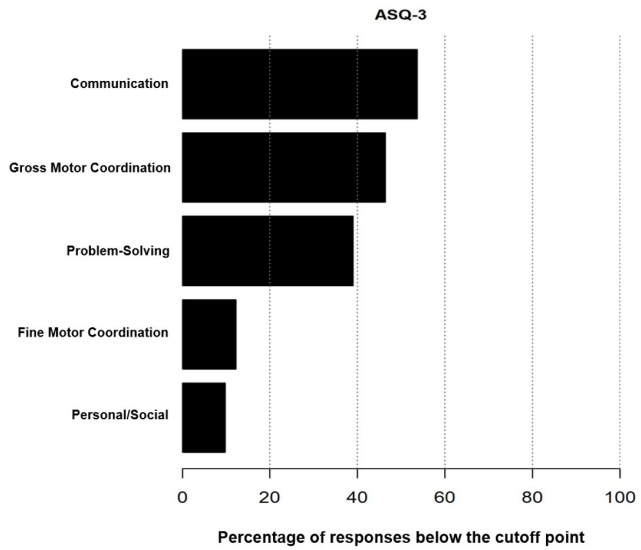

Figure 1. Performance below the cutoff point in the Ages & Stages Questionnaires-3 domains
Subtitle: ASQ-3 = Ages & Stages Questionnaires-3

DISCUSSION

Characteristics of the mothers and children

Scientific information on the impact of SARS-CoV-2 on the health of pregnant women, fetuses, and newborns is still being collected and is often considered biased and lacking in comprehensive understanding. The authors of an integrative review[15] reported that pregnant women who contracted the virus may experience spontaneous abortions, premature births, and fetal distress, including other systemic maternal factors triggered by the disease. The association between SARS-CoV-2 infection and premature birth has not yet been fully established, and some authors differ in their opinions and studies[15,16]

In a meta-analytic study[17], the authors found that the most frequent adverse obstetric outcome of COVID-19 was premature birth, occurring in 41.1% of cases. Cesarean delivery was also the most common. Another study selected 137 meta-analysis studies on risks during pregnancy and concluded that neonates born to women with SARS-CoV-2 infection were more likely to be admitted to a neonatal care unit after birth, be born prematurely or moderately prematurely, and have low birth weight[18].

Most children in the present study were born at term, with a low incidence of prematurity (17%) and low birth weight (12%). Vaginal delivery was the most prevalent (56%). Furthermore, only a few children had a 1-minute Apgar score lower than 7 (9.76%) and required hospitalization after birth (19.51%). These findings disagree with data from the literature researched, indicating most babies had a good general clinical condition at birth. This may be justified by the gestational trimester when the mothers contracted the virus since most mothers in this study were infected in the third trimester of pregnancy when fetal development is already advanced. Some authors describe the importance of monitoring infected mothers, especially in

the first and second gestational trimesters, due to the increased systemic risks caused by the disease[19].

Furthermore, only five children (12.5%) were not breastfed at some point in their lives, and most (73%) were breastfed up to 6 months or older. This result is inconsistent with findings from American infants who were followed from birth to 6 months old and were born to mothers with severe acute respiratory syndrome due to COVID-19 infection[20]. Breastfeeding rates in this group decreased compared to the historical pre-pandemic cohort (18% vs. 36%), although 97% of mothers intended to breastfeed.

It is important to emphasize that the mothers in this study were part of a municipal program that monitors high-risk pregnancies and encourages prenatal, perinatal, and postnatal care. Because the births occurred in a hospital managed by the Unified Health System (SUS), they were encouraged to have vaginal delivery and breastfeed, which may explain the results.

Furthermore, soon after birth, the baby establishes a direct relationship with their mother through breastfeeding, when several functions develop – e.g., oral feeding reflexes and the beginning of the linguistic cognitive process, which directly influence the child's overall development[21,22].

ASQ-3 (18-month-old children)

Maternal and perinatal experiences influence children's health in their early years. Although viral infections during pregnancy can impair child development, little is known about the effects of maternal COVID-19 exposure during pregnancy on children's overall and socioemotional development[9].

This study found a risk of abnormal Communication in 22 children (53.66%), significantly associated with prematurity, history of hospitalization after birth, and low birth weight. Prematurity is an important risk factor for neuropsychomotor development. Numerous studies on child development investigate the association between preterm birth and developmental impairments, encompassing motor, cognitive, and linguistic delays. These domains are interdependent – i.e., each one influences and is influenced by the others[23].

Cognitive-linguistic development can be affected by several complications during the gestational, perinatal, and/or postnatal periods, among which prematurity is a risk factor for linguistic changes[24]. According to the literature, this delay is due to intrauterine growth restriction, increased risk of mortality, cognitive dysfunctions, and increased frequency of neurological morbidity, including subtle forms of developmental delay[25].

The present study found a risk of change in Gross Motor Coordination, as 19 children performed below expectations. Fine motor coordination, although below expected in only five children in the study, was influenced by prematurity and low birth weight. The fetal central nervous system undergoes a rapid maturation sequence in the third trimester of pregnancy, and interrupting this process due to preterm birth impairs the structures and functions underlying human behavior. This can generate deficits in sensorimotor processing and integration, inferior performance in fine and gross motor skill tasks, and delayed development of visual-motor integration, bimanual coordination, and laterality[25].

Some studies have investigated the neuropsychomotor development of children born to mothers infected with COVID-19 during pregnancy. Authors[10] analyzed 222 children at 12 months old, daughters of mothers infected with SARS-CoV-2 during pregnancy, and observed that motor or speech and language developmental disorders are more common in this population. Moreover, these changes were more frequent in mothers infected in the third trimester of pregnancy, as in the present study.

A longitudinal cohort study with 57 infants with prenatal SARS-CoV-2 exposure in China identified socioemotional deficits on neurodevelopmental tests at 3 months old[26]. Another study, in which 272 mothers of infants born during the pandemic (exposed and not exposed to SARS-CoV-2 during pregnancy) answered the ASQ-3 at 6 months old, found deficits in the Gross Motor Coordination, Fine Motor Coordination, and Personal/Social domains in both groups. The authors suggest that the deficits may be due to pregnancy during the pandemic, rather than SARS-CoV-2 exposure[8].

A Brazilian study[9] with 56 infants aged 1 to 12 months – 27 of whom were born to mothers with COVID-19 during pregnancy – found that 15 babies were at risk of delayed motor development (12 in the COVID-19 group) and 36 at risk of behavioral changes (22 in the COVID-19 group).

A meta-analysis synthesized 10 studies on the effect of intrauterine exposure to SARS-CoV-2 on child development and behavior, but found no evidence to confirm the association between gestational SARS-CoV-2 exposure and neurodevelopmental delays in children up to 12 months old[27]. However, the study indicated through the ASQ-3 that gestational exposure negatively affected fine motor and problem-solving skills. In the present study, these two domains were not the most affected, therefore not confirming the literature researched. The fact that this study's sample group was older than the children in the previously published studies may justify the greater impairment in Communication, since it is from 18 months onwards that language develops significantly with the appearance of speech to express one's needs[28] and the demands in this area begin to be more easily noticed. Furthermore, maternal stress associated with the pandemic, the children's restricted socialization, and prolonged confinement in the first year of life may also have led to poorer Communication and Gross Motor Coordination performance.

This study presented important preliminary data. However, it has some limitations, such as the small sample size, the absence of a control group of children not exposed to maternal COVID-19, and the lack of data on the family's socioeconomic status and on the severity of maternal infection during COVID-19 contamination (recently associated with the risk of premature birth)[29]. These require expanded, more robust studies with fewer confounding factors to truly understand the impact on the development of children born to mothers infected with COVID-19 during pregnancy.

CONCLUSION

This study found a risk of developmental delay in Communication and Gross Motor Coordination in 18-month-old children born to mothers infected with COVID-19 during pregnancy. These results suggest the importance of longitudinal monitoring of

children exposed to the virus during pregnancy and the need for further studies addressing this relationship.

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