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Neonatal outcomes during SARS-CoV-2 pandemic

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O dia mais belo: hoje
A coisa mais fácil: errar
O maior obstáculo: o medo
O maior erro: o abandono
A raiz de todos os males: o egoísmo
A distração mais bela: o trabalho
A pior derrota: o desânimo
Os melhores professores: as crianças
A primeira necessidade: comunicar-se
O que traz felicidade: ser útil aos demais
O pior defeito: o mau humor
A pessoa mais perigosa: a mentirosa
O pior sentimento: o rancor
O presente mais belo: o perdão
O mais imprescindível: o lar
A rota mais rápida: o caminho certo
A sensação mais agradável: a paz interior
A maior proteção efetiva: o sorriso
O maior remédio: o otimismo
A maior satisfação: o dever cumprido
A força mais potente do mundo: a fé
As pessoas mais necessárias: os pais
A mais bela de todas as coisas: O AMOR!

Madre Teresa de Calcutá

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Neonatal outcomes during SARS-CoV-2 pandemic

Short running title: Neonatal impact of COVID-19

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Scientific divulgation

Ana Burgeiro, Marta Carvalho, Bárbara Oliveiros, Ana Rodrigues Silva, Ana Teresa Almeida Santos. *Neonatal outcomes during SARS-CoV-2 pandemic* (submitted)

Ana Burgeiro, Ana Rodrigues Silva, Ana Teresa Almeida Santos. *Case report: Neonatal Impact of SARS-CoV-2 infection during the first trimester of pregnancy* (submitted)

Abstract

Background. The impact of SARS-CoV-2 infection in the neonatal period remains a scientific and medical challenge with scarce published data. Since SARS-CoV-2 infection might occur during pregnancy, it is crucial to identify the effects of this infectious intercurrence in the neonatal period and in the medium-term paediatric follow-up.

Objectives/Study Design. A case-control study was conducted in a tertiary Portuguese neonatal centre. A population of neonates/children under 6 months-old, in which SARS-CoV-2 infection occurred during pregnancy, was analysed (COVID-19 group). COVID-19 group and a control group, including children from gestations without SARS-CoV-2, were studied. Growth pattern, respiratory complications and neurodevelopmental outcomes were compared between the two groups. In parallel, the relation between the trimester of gestation in which the infection occurred and the neonatal outcomes was analysed.

Results. n=42 neonates/children in each group. Pregnant women infected with SARS-CoV-2 during pregnancy were younger and with fewer comorbidities, when comparing with control group. Most of pregnant women in COVID-19 group were infected during the third trimester of pregnancy, presenting mild symptoms. Regarding obstetric complications, COVID-19 group had higher frequency of prolonged rupture of membranes and preeclampsia. COVID-19 mothers had a lower rate of breast milk abandonment. Regarding neonatal data and their follow-up up to 6 months-old, neonates/children from COVID-19 group tolerated well the birth process, had good adaptation to the extrauterine environment, did not have warning signs in psychomotor development and had fewer respiratory infections, when comparing with control group. Additionally, COVID-19 group showed a tendency (weight–p=0.219; length–p=0.010; head circumference–p=0.071) to have a stable growth during the follow-up.

Conclusions. This is the first case-control study that followed children, whose mothers were infected with SARS-CoV-2 during pregnancy. It seems like SARS-CoV-2 during pregnancy does not cause respiratory or neurologic complications until 6 months-old. Moreover, none of the mother had severe clinical presentations. Other larger multicentric studies could help to clarify these conclusions. Until then, all possible clinical reports will be useful in the clinical management of this paediatric population.

Keywords: Neonatal, SARS-CoV-2, Neurodevelopment, Respiratory complications

Resumo

Referencial teórico. O impacto da infeção por SARS-CoV-2 no período neonatal permanece um desafio científico e médico com escassos dados publicados. Podendo a infeção por SARS-CoV-2 ocorrer durante a gravidez, é fundamental identificar os efeitos dessa intercorrência infeciosa no período neonatal e no seguimento pediátrico a médio prazo.

Objetivos/Desenho do Estudo. Foi realizado um estudo caso-controlo num centro neonatal terciário português. Foi analisada uma população de neonatos/crianças com menos de 6 meses de idade em que a infeção por SARS-CoV-2 ocorreu durante a gravidez (grupo COVID-19). O grupo COVID-19 e o grupo controlo, incluindo crianças de gestações sem SARS-CoV-2, foram estudados. O padrão de crescimento, as complicações respiratórias e os resultados de neurodesenvolvimento foram comparados entre os dois grupos. Paralelamente, foi analisada a relação entre o trimestre da gestação em que ocorreu a infeção e os desfechos neonatais.

Resultados. n=42 neonatos/crianças em cada grupo. Mulheres grávidas do grupo COVID-19 eram mais jovens e com menos comorbilidades, quando comparadas ao grupo controlo. A maioria das gestantes do grupo COVID-19 foi infetada durante o terceiro trimestre da gravidez, apresentando sintomas leves. Relativamente às complicações obstétricas, o grupo COVID-19 apresentou maior frequência de rutura prolongada de membranas e pré-eclâmpsia. As mães do grupo COVID-19 tiveram menor taxa de abandono do leite materno. Relativamente aos dados neonatais e seguimento até aos 6 meses de idade, os neonatos/crianças do grupo COVID-19 toleraram bem o processo do parto, tiveram boa adaptação ao ambiente extrauterino, não apresentaram sinais de alerta no desenvolvimento psicomotor e tiveram menos infeções respiratórias, quando comparados com o grupo controlo. Além disso, o grupo COVID-19 apresentou uma tendência (peso–p=0,219; comprimento–p=0,010; perímetro cefálico–p=0,071) de crescimento estável durante o seguimento.

Conclusões. Este é o primeiro estudo caso-controlo que acompanhou crianças cujas mães foram infetadas com SARS-CoV-2 durante a gravidez. Parece que o SARS-CoV-2 durante a gravidez não causa complicações respiratórias ou neurológicas até aos 6 meses de idade. Ainda, nenhuma das mães apresentou quadros clínicos graves. Outros estudos multicêntricos maiores poderão ajudar a esclarecer essas conclusões. Até então, todos os relatórios clínicos possíveis serão úteis na gestão clínica desta população pediátrica.

Palavras-chave: Neonatais, SARS-CoV-2, Neurodesenvolvimento, Complicações respiratórias

Abbreviations

ACE2: Angiotensin-converting enzyme 2

COVID-19: Coronavirus disease 2019

HELLP: Haemolysis, elevated liver enzymes, and low platelet count.

NICU: Neonatal intensive care unit

p/P: percentile

p: *p* value

PROUDEST: Pregnancy outcomes and child development effects of SARS-CoV-2 infection study

RT-PCR: Real time-polymerase chain reaction

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

WHO: World Health Organization

Introduction

Since the first report of the novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1), more than 200,000 deaths worldwide were observed (2). The well-known relative immunosuppressed state, as well as the restricted respiratory capacity of pregnancy, account for a reserved maternal-fetal prognosis when pregnant women are faced with respiratory infections (2). So, pregnant women infected with SARS-CoV-2 are a high-risk group for complications, such as fetal growth restriction and preterm birth, conditions that cause comorbidities in neonate too (1-3).

Maternal severity of SARS-CoV-2 infection ranges from asymptomatic to critical illness (4). Some authors suggest pregnant women as a more-likely group to be asymptomatic when compared to reproductive age non-pregnant women (2, 3, 5). Also, COVID-19 related symptoms, like fever, dyspnoea, and myalgia are less observed when compared to non-pregnant women with COVID-19 (1). However, severity of SARS-CoV-2 disease, measured by myocardial infarction, venous thromboembolic and other thrombotic events, preeclampsia and HELLP, seems to be higher in SARS-CoV-2 positive pregnant women, as well as prematurity (6). This group is also more likely to be admitted to the intensive care unit, needing invasive ventilation and extracorporeal membrane oxygenation than non-pregnant women of reproductive age (1, 4).

Regarding neonatal outcomes, current knowledge suggests that the clinical presentation of COVID-19 in neonates may range from asymptomatic to severe respiratory distress (5). Several studies also reported fetal growth restriction and low birth weight (7-10), fetal distress (7, 8, 11), and complications at birth, such as respiratory distress syndrome, pneumonia, fever (4), tachycardia, vomiting, pneumothorax (1, 2, 4), thrombocytopenia (4), abnormal liver function (4), lymphocytopenia (4), elevated creatine kinase and disseminated intravascular coagulation (1, 2, 4). Nevertheless, infants who test positive in the hospital have none or mild signs of disease, most of which could also be attributable to prematurity (6). Fortunately, the overall rates of stillbirth and neonatal death are low in women with confirmed COVID-19 (1); however, none of stillbirths and neonatal deaths had a clear correlation with the infection reported (8, 12), suggesting that fetal and neonatal mortality risk is extremely low (13). Regarding vertical transmission of the infection, studies carried out seem to disagree (3, 14-16). So, until now, what is known is that congenital and intrapartum SARS-CoV-2 infection in the fetus/newborn is possible, but rarely reported (17). Although SARS-CoV-2 virus primarily targets the respiratory and enteric systems, this virus has been associated with severe neurological complications in children (18, 19), being this group of patients uniquely vulnerable to long-term cognitive or behavioural sequelae because of injury during critical stages of neurodevelopment (20, 21).

More than a year and a half after the start of this SARS-CoV-2 pandemic, many questions still remain without answer. This work attempts to clarify the impact of SARS-CoV-2 during pregnancy in the clinical outcomes after birth. As far as we know, this is the first medium-term follow-up of this group of children. Moreover, we evaluated whether maternal risk factors and comorbidities were linked to severe maternal

and perinatal outcomes and associated the gestational age at which the infection occurred with the perinatal outcomes.

Materials and methods

A case-control study was conducted in Neonatologia A Service - Coimbra's Hospital and University Center, Portugal. Neonates born between April 1st, 2020, and July 31st, 2021, whose mothers had SARS-CoV-2 nucleic acid positive tested by RT-PCR during pregnancy, were selected to data collection. Mother's clinical variables were also analysed. Regarding the control group, it was randomly selected and consisted of newborns born in the same service, with birth dates and sex on par with the newborns from COVID-19 group, whose mothers had not COVID-19 during pregnancy; their mothers were also included. As exclusion criteria, disabled adult pregnant women or minors were not included.

Regarding mothers, demographic data were collected, presence of comorbidities, gestational age at which SARS-CoV-2 infection was identified, clinical presentation, laboratory evaluation, imaging findings, need for intensive care and/or mechanical ventilation (invasive or non-invasive). Regarding the newborn, birth data were collected, including type of delivery, gestational age, weight, length, and head circumference at birth, as well as the existence of fetal growth restriction, Apgar score at the 1st, 5th and 10th minutes, neonatal asphyxia, neonatal admission to the NICU and neonatal mortality. Subsequently, these newborns were followed up in a General Pathology consultation at the Neonatology Service, and, through consultation of the clinical file allowed to mother's information, the neurodevelopment, growth, and occurrence of respiratory events were evaluated up to a maximum follow-up of 6 months (until August 2021). Neurodevelopment was assessed through the Modified Mary-Sheridan Developmental Rating Scale, growth through the Fenton preterm growth charts and the growth curves included in the Child and Youth Health Bulletin (WHO), and the occurrence of respiratory events through consultation of the clinical file and maternal information.

This study was subjected to the standards of good clinical practice and protected the privacy of included patients, respecting the Helsinki Declaration. Data confidentiality was always respected, through the anonymity of data in a database, in accordance with the Data Protection Regulation (European Union) 2016/679.

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS), version 27.0 (SPSS, Inc., Chicago, IL). The normality of continuous variables was tested with the Kolmogorov-Smirnov test and the following analyses were performed according to these results. Statistical analysis was indicated in each section of the results. All tests were two-tailed and statistical significance was accepted at the $p<0.05$ level.

Results

A) Pregnant women

1. Demographic characteristics and clinical comorbidities

In this study population, we found that mothers infected with SARS-CoV-2 during pregnancy were younger (COVID-19 group: 31.12 ± 5.12 vs. control group: 33.57 ± 5.00; *p*=0.029) and presented fewer comorbidities (COVID-19 group: 30 vs. control group: 38; *p*=0.011) when compared to mothers not infected with SARS-CoV-2 (Table 1). It should be noted that the most frequent comorbidities in COVID-19 group were metabolic (16.6%), orthopaedic and/or rheumatologic (16.6%), endocrine (13.3%) and psychiatric (13.3%). On the other hand, in control group, the most frequent comorbidities were endocrine (21.0%), orthopaedic/rheumatological (15.8%), haematological (13.2%) and metabolic (9.5%).

***Table* 1**. Demographic characteristics and comorbidities of mothers infected with COVID-19 during pregnancy (COVID-19 group) and mothers not infected with COVID-19 during pregnancy (control group). The number of mothers in each group is indicated between parentheses. The frequency of each maternal comorbidity is indicated for each group. Statistical analysis: age is displayed as mean ± standard deviation, being t-student performed. Maternal comorbidities were analysed using Fisher's exact test.

	Control (n=42)	**COVID** (n=42)	***P* value**
Age (years)	33,57 ± 5,00	31,12 ± 5,12	0,029
Maternal comorbidities			
Total	38	30	0.011
Endocrine	8	4	
Orthopaedic and/or rheumatologic	6	5	
Haematological	5	0	
Metabolic	4	5	
Gynaecological	3	1	
Cardiovascular	2	3	
Neurological	2	1	
Psychiatric	2	4	
Infectious	1	1	
Respiratory	1	2	
Cardiac	1	1	
Renal	1	2	
Vascular	1	0	
Ophthalmic	1	0	
Gastrointestinal	0	1	

2. Characterization of SARS-CoV-2 infection in pregnancy

In this study population, the pregnancy trimester with the highest infection rate was the 3rd (52.4%), followed by the 2nd trimester of pregnancy (35.7%) (Table 2). More infections were observed in the 3rd trimester and less in the 1st trimester; however, in the 2nd trimester, the number of infections was slightly higher (goodness of fit chi-square test chi-square test: p=0.005).

Most pregnant women were symptomatic (84.6%). From the symptomatic group, the most frequent symptoms were anosmia (51.3%), ageusia (48.7%), tiredness/weakness/asthenia (35.9%), nasal congestion (25.6%), myalgias (25.6%), cough (25.6%) and headache (12.8%) (Table 2). None of the pregnant women underwent laboratory evaluation and/or imaging, admission to intensive care and/or mechanical ventilation (invasive or non-invasive) (Table 2).

***Table* 2**. Characterization of SARS-CoV-2 infection in pregnancy. The number of infected pregnant women per trimester is indicated, as well as the corresponding percentage of the SARS-CoV-2 infection per trimester. 84.6% of pregnant women infected were symptomatic, with the percentage of incidence of symptoms reported by them being detailed below.

Pregnancy trimester in which the infection occurred (n=42)		
	Infected pregnant women per trimester	Percentage of infection per trimester
1º trimester	5	11.9%
2º trimester	15	35.7%
3º trimester	22	52.4%
Symptomatology (n=39)		
	Affected pregnant women	Incidence of symptoms (%)
Symptomatic	33	84.6%
Anosmia	20	51.3%
Ageusia	19	48.7%
Tiredness/weakness/asthenia	14	35.9%
Nasal congestion	10	25.6%
Myalgias	10	25.6%
Cough	10	25.6%
Headache	5	12.8%
Diarrhoea	3	7.7%
Fever (≤ 38º C)	3	7.7%
Tachycardia	2	5.1%
Odynophagia	2	5.1%
Anorexia	2	5.1%
Other symptoms (sneezing, nausea, eye itching, vomiting,	8	20.5%

back pain, chest pain, dyspnea)		
Asymptomatic	6	15.4%
Clinical Evaluation (n=39)		
Laboratory evaluation, imaging evaluation, admission to intensive care and/or mechanical ventilation (invasive or non-invasive)	0	0%

3. Characterization of obstetric outcomes

Regarding obstetric complications, and although the reduced number of observed cases did not allow a test to be performed with sufficient robustness, we found that these complications occurred more frequently in COVID-19 group, specifically, prolonged rupture of the membranes (> 18 hours; COVID-19 group: 7 vs. control group: 4), preeclampsia (COVID-19: 3 vs. control group: 0), fetal growth restriction (COVID-19 group: 1 vs. control group: 0) (Table I).

Despite the higher incidence of obstetric complications, we did not find statistically significant differences regarding the type of delivery performed (Table I).

4. Breastfeeding: time perspective

Upon hospital discharge, we found statistically significant differences in the type of breastfeeding (p=0.004). The majority of newborns in our study population was breastfed: 26 in the COVID-19 group (61.9%) and 29 in the control group (69.0%), with only 2 newborns in the COVID-19 group (4.8%) and 3 newborns in the control group (7.1%), being artificially breastfed (Table 3). In August 2021, only 70 children in our study population had completed 4 months of chronological age. In these children, the feeding type performed was evaluated, with no statistically significant differences in milk type that both groups had (p=0.178) (Table 3). However, it should be noted that of those children who had completed 4 months of chronological age, in COVID-19 group, 18 children were still breastfed, comparing to only 14 were breastfed in control group (Table 3).

***Table* 3**. Temporal evolution of the type of breastfeeding (at the date of hospital discharge and at 4 months of chronological age) in control group and in COVID-19 group. The number of children in each group and in each type of breastfeeding is indicated. Statistical analysis: Breastfeeding at hospital discharge and at 4 months of chronological age was analysed using Fisher's exact test.

	Breastfeeding at hospital discharge (n=84)			**Breastfeeding at 4 months of chronological age** (n=70)			**Breastfeeding abandonment rate** (Birth to 4 months)	
Type of breastfeeding	**Control** (n=42)	**COVID-19** (n=42)	***p* value**	**Control** (n=35)	**COVID-19** (n=35)	***p* value**	**Control**	**COVID-19**
Breastfeeding (exclusive)	29	26	0.004	14	18	0.178	57.7%	30.8%
Artificial breastfeeding (exclusive)	3	2		12	10			
Mixed breastfeeding	9	10		9	3			
No information	1	4		0	4			

B) Newborns and follow-up in the first 6 months of life

1. Prematurity

In this study population, we did not find statistically significant differences regarding gestational age at which delivery took place (gestational age as median [Q1; Q3]: COVID-19 group: 39 [38,0; 40,0] vs. control group: 39 [38,0; 40,0]; *p*=0.286) (Table II). Likewise, there were no statistically significant differences between the number of term and preterm newborns (preterm newborns – COVID-19 group: 3 vs. control group: 2; *p*=0.645; Table 4).

Regarding prematurity, in COVID-19 group, two premature neonates were born at 32 weeks and at 33 weeks and one extreme premature newborn at 27 weeks, all by maternal causes: 27 weeks – haemorrhagic placenta previa; 32 weeks – preterm premature rupture of membranes and fetal growth restriction; 33 weeks – preeclampsia; regarding control group, two late premature newborns (both at 36 weeks' gestation) were born. In these cases, maternal causes for prematurity were preterm premature rupture of membranes and twin pregnancy. Although the number of premature newborns did not allow for a test to be carried out with sufficient robustness, it is noteworthy that the prematurity rate in the COVID-19 group was 60%, compared to 40% in control group (Table 4).

***Table* 4**. Prematurity in the study population and its classification. Newborns were classified according to their prematurity considering late preterm newborns born between 34 weeks and 36 weeks and 6 days of gestation, premature newborns born between 28 weeks and 33 weeks and 6 days of gestation, extremely premature newborns born before 28 weeks of gestation. The number of newborns in each group and in each prematurity class is indicated. Statistical analysis: prematurity analysis was analysed using Fisher's exact test.

	Control (n=42)	**COVID-19** (n=42)	***p* value**
Term newborn	40	39	0.645
Premature newborn	2	3	
Late preterm newborn	2	0	
Premature newborn	0	2	
Extreme premature newborn	0	1	
Prematurity Rate	40% (2/5)	60% (3/5)	

2. Apgar score and neonatal complications

In our study population, we did not observe statistically significant differences regarding Apgar score at 1st, 5th, and 10th minutes after birth (Table III). Regarding neonatal complications, and despite the number of complications not allowing a test to be performed with sufficient robustness, in COVID-19 group we observed a higher number of neonatal admissions to the intensive care unit (COVID-19 group: 3 vs. control group: 1), with increased need for mechanical ventilation due to peripartum respiratory symptoms (COVID-19 group: 5 vs. control group: 3) (Table 5). It should be noted that mothers who had COVID-19 during pregnancy and whose children had neonatal respiratory complications were infected during the 2nd (3 children, one being extremely premature, one premature and the other was term newborn) and the 3rd trimesters (2 children, both term newborn).

***Table* 5**. Neonatal complications in our study population. The number of newborn in each group and in each neonatal complication is indicated.

Neonatal complications	**Control** (n=42)	**COVID-19** (n=42)
Neonatal asphyxia	0	0
Neonatal admission to the intensive care unit	1	3
Mechanical ventilation (invasive or non-invasive)	3	5
Peripartum respiratory symptoms	3	5
Neonatal mortality	0	0

3. Length of stay in the maternity

Although there were no statistically significant differences in our study population (Table IV), three situations of increased stay in the maternity hospital should be mentioned: the 1st case was that of a premature newborn of 33 weeks of gestation, son of a mother who was diagnosed with COVID-19 in the 1st trimester of pregnancy. The neonate was hospitalized for 12 days due to his low birth weight (1995g) and neonatal jaundice. A 2nd case was also a premature newborn of 32 weeks of gestation, son of a mother who had COVID-19 during the 2nd trimester of pregnancy, who was hospitalized for 25 days due to his very low birth weight (1495g), premature rupture of membranes (> 18 hours) and fetal growth restriction. A 3rd case was an extreme premature of 27 weeks of gestation, daughter of a mother who contracted COVID-19 during the 2nd trimester of pregnancy who was hospitalized for 34 days due to her very low birth weight (1030g) and several respiratory complications.

4. Anthropometric data at birth and follow-up in the first 6 months of life - term newborns

Comparing the three anthropometric variables, at the various observation times, between the two observational groups, we found no statistically significant differences (Fig. 1).

In our study population, in COVID-19 group, there were no statistically significant differences in the percentiles referring to weight gain over the 6-month follow-up (p=0.219). Moreover, it should be noted that there was a trend towards a deceleration in weight gain in the assessment of the 4 months of age in this group (Fig.1, panel A). However, children in control group had a regular weight gain, with the difference between the percentiles (p) at birth and at 4 months of age being statistically significant (p=0.024). In addition, it should be noted that birth weight in COVID-19 group was in p50, while in control group was in p25-p50. Nevertheless, control group reached p75 at 6 months of age, without deceleration or lower percentile crossings (Fig.1, panel A).

Regarding length evolution, concerning COVID-19 group, a statistically significant difference in percentiles was observed between birth length and length at 6 months of age (p=0.010) (Fig.1, panel B). In control group, children had a regular length evolution, with the differences between the percentiles at birth and at 4 months (p=0.021), at 1 month and at 4 months (p=0.006) and at 1 month and at 6 months (p=0.044) being statistically significant (Fig.1, panel B). In addition, it should be noted that birth length in COVID-19 group was p50, while in control group was in p25-p50 (Fig.1, panel B). Nevertheless, in COVID-19 group there was a trend towards a deceleration in length gain in the assessment of the 6 months of age, with this group having a length percentile at 6 months of age of p50-p75; on the other hand, control group reached the p75 at 6 months of age, without deceleration or lower percentile crossings (Fig.1, panel B).

Concerning head circumference evolution, in COVID-19 group, there were no statistically significant differences in the percentiles referring to head circumference gain over the 6-month follow-up (p=0.071) (Fig.1, panel C). Unlike COVID-19 group, children in control group had a regular head circumference evolution, with the differences between the percentiles at birth and at 6 months (p=0.001) and at 1 month

and at 6 months (*p*=0.037) being statistically significant (Fig.1, panel C). At birth, both groups of newborns were in p50 in the head circumference, and at 6 months, COVID-19 stayed at p50-p75, while control group reached p75, without deceleration or lower percentile crossings (Fig.1, panel C); furthermore, it should be noted that there was a trend towards deceleration in head circumference gain in the assessment of the 2 months of age in COVID-19 group (Fig.1, panel C).

Furthermore, we evaluated whether there could be an association between the trimester in which SARS-CoV-2 infection occurred and anthropometric variables, and, for that, two timepoints were selected: at birth and at 6 months. In fact, we found that there was no association, and the closest association to having an impact could be weight and head circumference at 6 months, which correspond to higher percentiles when the infection was contracted earlier in pregnancy, despite strength of the association was weak and not statistically significant (respectively r = -0.365 and r = -0.326; statistical analysis: Spearman's correlation coefficient).

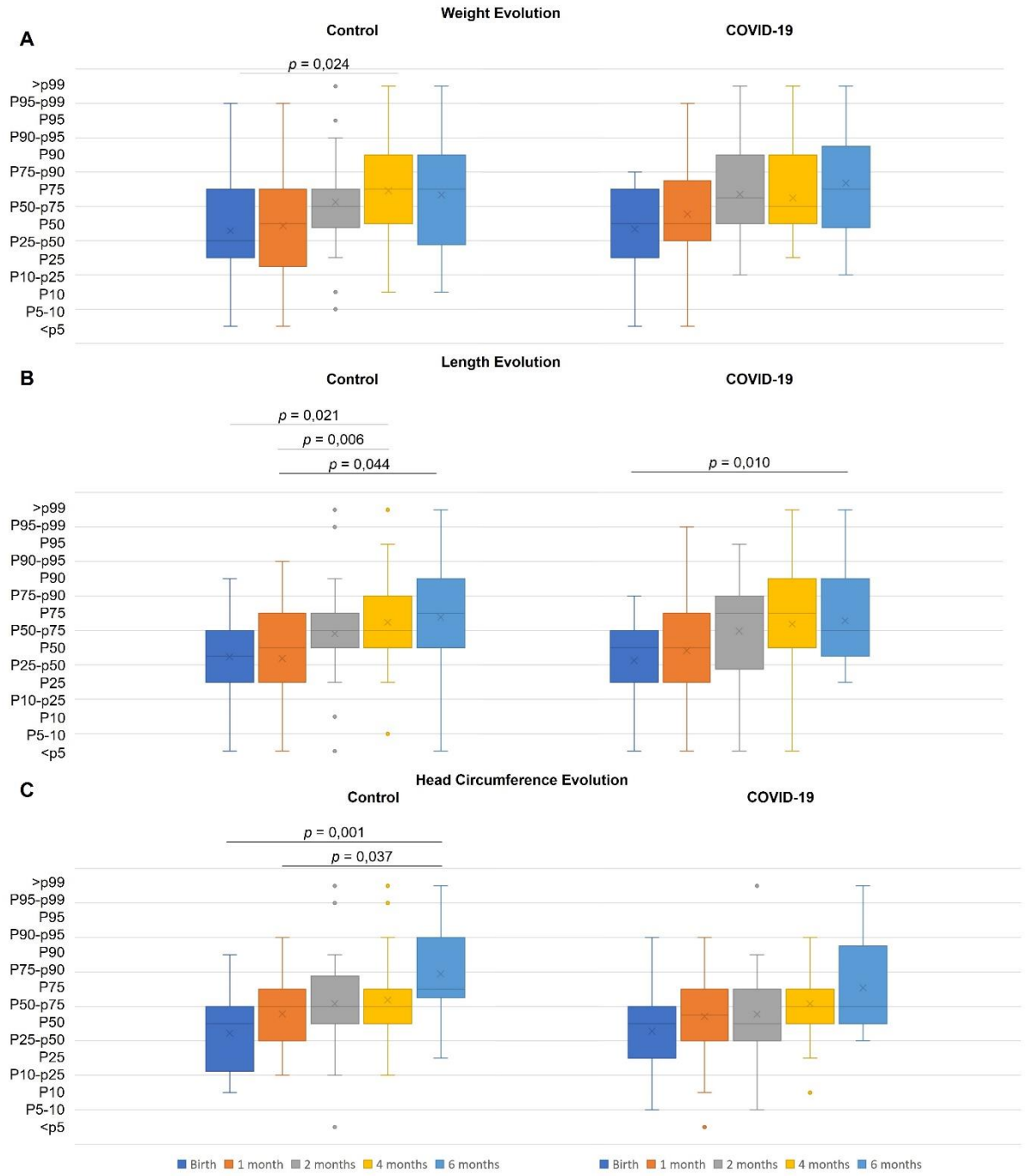

***Figure* 1**. Anthropometric data at birth and follow-up in the first 6 months of life in term newborns. Panel **A**: Weight evolution of our study population of term newborns from birth to 6 months of age. Number of children in each timepoint in control group: birth – *n*=40; 1 month – *n*=38; 2 months – *n*=38; 4 months – *n*=33; 6 months – *n*=18. Number of children in each timepoint in COVID-19 group: birth – *n*=39; 1 month – *n*=37; 2 months – *n*=34; 4 months – *n*=27; 6 months – *n*=14. Panel **B**: Lenght evolution of our study population of term newborns from birth to 6 months of age. Number of children in each timepoint in control group: birth – *n*=40; 1 month – *n*=37; 2 months – *n*=37; 4 months – *n*=32; 6 months – *n*=17. Number of children in each timepoint in COVID-19 group: birth – *n*=39; 1 month – *n*=36; 2 months – *n*=34; 4 months – *n*=27; 6 months – *n*=14. Panel **C**: Head circumference evolution of our study population of term newborns from birth to 6 months of age. Number of children in each timepoint in control group: birth – *n*=40; 1 month – *n*=35; 2 months – *n*=36; 4 months – *n*=32; 6 months – *n*=17. Number of children in each timepoint in COVID-19 group: birth – *n*=39; 1 month – *n*=34; 2 months – *n*=33; 4 months – *n*=25; 6 months – *n*=13.

Statistical analysis: Weight, lenght and head circumference evolution were evaluated using Friedman test, being significance values adjusted by the Bonferroni correction for multiple tests. p/P – percentile.

5. Anthropometric data at birth and follow-up in the first 6 months of life – preterm newborns

Regarding COVID-19 group, 2 premature newborns were born at 32 weeks (case 1) and at 33 weeks (case 2), respectively (Table V) and one extreme premature newborn at 27 weeks (case 3) (Table VI). Specifically, for cases 1 and 2 (Table V), we observed a deceleration in head circumference growth. Regarding case 3 (Table VI), both weight and head circumference evolution were, most of the times, parallel, reaching p50-p75 in both anthropometric variables at 3 months (corrected age); regarding length, at this age, she reached p25. For detailed description, see Tables V and VI.

In the control group, two late preterm newborns were born, both with 36 weeks of gestation – case 1 and case 2, who had, overall, a favourable and positive extrauterine development and up to 5 months (corrected age). For detailed description, see Table VII.

6. Psychomotor development in the first 6 months of life

The assessment of psychomotor development in our study population over the 6-month follow-up was based on the Modified Mary-Sheridan Developmental Rating Scale. Having as data source, either through the application of a questionnaire to the mother, or through clinical process assessment, we did not notice signs of alarm in any child in our study population. In the case of premature newborns, the psychomotor competences assessed were adjusted according to their corrected age.

7. Respiratory complications in the first 6 months of life

The assessment of respiratory complications of our study population over the 6-month follow-up has, as data source, either mother's information or through clinical process assessment (Table VIII). Regarding COVID-19 group, we found statistically significant differences when comparing the number of respiratory infections occurring in the 1st trimester with other trimesters (p<0.001), with more infections occurring in the 2nd and 3rd trimesters (1st vs. 2nd trimesters: p=0.001; 1st and 3rd trimesters: p=0.001; 2nd vs. 3rd trimesters: p=0.553) (statistical analysis performed: binomial test with adjusted multiple comparisons with Bonferroni correction).

Although the number of cases of respiratory complications in our study population did not allow us to perform a test with sufficient robustness, there are points that deserve our attention (Table VIII): in COVID-19 group, we found a lower incidence of respiratory complications during the 6-month follow-up; specifically, we observed 3 cases of nasopharyngitis (vs. 5 nasopharyngitis cases in the control group), one acute bronchiolitis (vs. two bronchiolitis case in the control group) and one postnatal SARS-CoV-2 infection in the control group, with no postnatal COVID-19 disease in COVID-19 group. It should also

be noted that in both groups of our study population, no respiratory infections were observed before 28 days of life.

When analysing the possible association between the rate of breast milk abandonment at 4 months and the occurrence of respiratory infections in the first 6 months of life, we found that this association did not exist in both groups (COVID-19 group: p=0.460; control group: p=0.095). However, it seemed to be a trend in control group for children who at 4 months of age were exclusively fed with artificial milk to have more respiratory infections, the opposite occurring when children had mixed breastfeeding, and no association with respiratory infections when children had exclusive breastfeeding.

Discussion

Whenever there is a pandemic, the main concern is to protect the most vulnerable, who are usually at the extremes of age, namely, elderly and children.

In this study maternal analysis', mothers included in the COVID-19 group were younger, with fewer comorbidities, with the most prevalent comorbidities in this group being metabolic, orthopaedic and/or rheumatologic, and endocrine. Furthermore, most of these pregnant women were infected during the 3rd trimester of pregnancy, presenting mild symptoms. Regarding obstetric complications, these pregnant women had also higher frequency of prolonged rupture of membranes and preeclampsia. No differences were observed regarding the type of delivery, with mothers in the COVID-19 group having a lower rate of breast milk abandonment.

Previous studies have reported the need to assess maternal comorbidities as possible predictors of the impact of COVID-19 on pregnancy (1). In fact, in pregnant women with COVID-19, increased maternal age, high body mass index, non-white ethnicity, any pre-existing maternal comorbidity, including chronic hypertension and diabetes, and preeclampsia were associated with serious complications (1). In this case-control study, metabolic comorbidities were present in pregnant women (5): gestational diabetes, type 1 diabetes, excess weight, obesity; however, neither these pregnant women nor their newborns had complications requiring admission to intensive care unit. Regarding preeclampsia and prolonged rupture of membranes cases found in this study, maternal-fetal prognosis was always favourable, without need for intensive care. Concerning the only newborn with fetal growth restriction, he had neonatal respiratory complications, requiring admission to intensive care unit. In this maternal population, we can infer that it was the mild infectious clinical condition of the mothers that allowed pregnancy to develop without serious complications requiring hospital care, in agreement with previous studies (2, 3, 5). Also, earlier reports showed that the most common clinical manifestations of COVID-19 in pregnancy were fever and cough (1). However, in this study population, the most prevalent symptoms were anosmia and ageusia, which is in line with a large cohort study of 147 pregnant women with COVID-19 which reported only 8% and 1% severely and critically ill, respectively, suggesting that most pregnant women with COVID-19 have milder symptoms compared with the general population (published by the WHO-China Joint Mission on Coronavirus Disease 2019).

Since SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) receptor to invade cells (22, 23) and it is highly expressed in placenta and fetus throughout gestation, placenta can be a target of infection by this virus (24-26), modifying placental vascularization and causing maternal blood pressure elevation and adverse pregnancy outcomes associated with placental dysfunction (27), such as extensive thrombotic vasculopathy on the fetal side (28, 29), chorangiosis, chorioamniotis, fetal vascular malperfusion or fetal vascular thrombosis (30, 31), villous edema and retroplacental hematoma (32), massive fibrin deposition along with chronic histiocytic intervillositis (33, 34), and more villous agglutination and subchorionic thrombi than placentas from SARS-CoV-2-negative women (35). Regardless of the placental injury, these injuries can lead to obstetric complications such as miscarriage, intrauterine growth restriction, small for gestational age/fetal growth restriction, stillbirth, preeclampsia, and premature births. In two of the preeclampsia cases observed, mothers were previously healthy, with SARS-CoV-2 diagnosed in the 1st and 3rd trimesters, respectively. Since no histopathological study of the placentas was performed, we cannot exclude that preeclampsia may be due to previous infection by SARS-CoV-2. In the 3rd case of preeclampsia, the woman had chronic hypertension, having been infected with SARS-CoV-2 in the 2nd trimester; so, in this case, COVID-19 disease may have decompensated her underlying disease (27), leading to preeclampsia. Regarding the case of fetal growth restriction, although we cannot exclude some contribution from SARS-CoV-2 infection during pregnancy, the existence of a bicornuary uterus and a benign ovarian tumour may explain the situation. Moreover, in our study, the high rate of prematurity observed in COVID-19 group always had a maternal cause, and it was not possible to establish that SARS-CoV-2 infection was the only factor.

Previous studies failed to confirm SARS-CoV-2 presence in umbilical cord blood, placenta, and/or amniotic fluid (9), having no evidence of its vertical transmission (8, 9). At presence, elective caesarean section is not indicated (13) and experts suggest vaginal delivery whenever possible (36). In this study, there were no differences among type of delivery between the two groups, in agreement with previous studies (37). In COVID-19 group, caesarean sections were performed due to obstetric indications (preeclampsia, amniotic fluid abnormalities, fetal distress, failed eutocic birth induction, haemorrhagic placenta previa, prolonged rupture of membranes, pelvic presentation, previous rectovaginal fistula, foetopelvic incompatibility).

Regarding neonatal data and their 6 months follow-up, we concluded that newborns from COVID-19 tolerated well birthing process and had good adaptation to the extrauterine environment. Also, no warning signs in psychomotor development were seen in the COVID-19 group who had fewer respiratory infections in the first 6 months of life, when comparing with control group. Moreover, we observed in COVID-19 group a tendency to have a more constant development rhythm, with no ascending percentile crossings.

Mainly due to SARS-CoV-2 infection impact on the placenta, there is an increased risk of abnormalities in fetal oxygenation that could induce cardiac, neurological disorders (38) and respiratory complications, in foetuses and neonates. In accordance with previous studies (37, 39), neonates from COVID-19 tolerated well birth process, being asymptomatic, with the exception of five neonates (11.9%): two of

them (term newborns, whose SARS-CoV-2 infection occurred in the 2nd and 3rd trimesters of pregnancy) had to undergo a positive pressure ventilation cycle for respiratory distress syndrome. The other 3 neonates were admitted to the neonatal intensive care unit also due to respiratory distress syndrome and, in two cases, due to prematurity, with SARS-CoV-2 infection occurring during 2nd and 3rd trimesters. Thus, in our sample SARS-CoV-2 infections in the 2nd and 3rd trimester of pregnancy are more associated with worse neonatal outcomes than SARS-CoV-2 infections occurring in the 1st trimester. However, it should be noted that in this study group we had only 5 newborns whose mothers were infected during the 1st trimester, so it seems prudent to wait for further studies evaluating SARS-CoV-2 infections in the 1st trimester of pregnancy and their neonatal respiratory outcomes.

It is crucial to know if the stressful uterine environment at the time of the maternal infection had, somehow, impact on the fetus and how this will impact in the long term. In fact, there are few studies that have addressed this perspective of follow-up (40-42).

Thus, this is the first study, until now, following newborns and children from mothers with SARS-CoV-2 during pregnancy, until 6 months-old. In this study, no differences in growth between the two groups were found; however, children in COVID-19 group did not grow as regularly as children in control group, and there was, in some timepoints, a tendency for lower percentile crossings in this group. This data brings interest in the scientific and medical communities and alert to the urgent need for more studies of follow-up to clarify these conclusions. In fact, PROUDEST project is the first ongoing long-term follow-up study that will assess the effects of SARS-CoV-2 exposure during pregnancy on children's growth, neurodevelopment, and metabolism from birth up to 5 years of age (43).

Previous studies reported the occurrence of Kawasaki disease-like “multisystem inflammatory syndrome in children” (44), acute flaccid paralysis, acute disseminated encephalomyelitis, encephalitis, seizures, ischemic, haemorrhagic and microvascular strokes, pseudotumor cerebri syndrome, and cytotoxic lesions of deep brain structures (45) following SARS-CoV-2 infection in children. This might result in neurodevelopmental impairment, specially more subtle and may not be apparent in the first-time following infection, appearing later with increasing demands or when a child reaches an age where a particular skill is expected to develop (45). However, as far as we know, there are no studies that have evaluated the effect of COVID-19 on the neurodevelopment of infants, whose mothers were infected during pregnancy. In this study, we verified the absence of alarm signs in psychomotor development during the first 6 months of life, when the children's mothers were questioned. It should be noted that data regarding psychomotor development was based on the telephone application of a questionnaire to the mother of each child in which alarm signals were surveyed based on the Modified Mary-Sheridan Developmental Rating Scale. Also, whenever available, we used data present in the clinical process of these children regarding their psychomotor skills. So, as sometimes it was not possible to assess the psychomotor development by a health professional, caution is required in interpreting these results, requiring further studies that can assess these children in person and, when necessary, imaging studies.

Since RNA virus was rarely detected in maternal milk, breastfeeding during maternal COVID-19 should not be contraindicated, according to WHO guidelines (5, 13). In fact, at 4 months of life, around 70% of mothers who had COVID-19 during pregnancy continued to breastfeed their children. Moreover,

breastfeeding is included as one of the known protective factors for infectious diseases in children (46-53). Thus, the increased number of respiratory infections in the control group may be, at least in part, associated with a higher rate of breast milk abandonment. On the other hand, although there were fewer respiratory infections in the COVID-19 group over 6 months, we found that these occurred more when SARS-CoV-2 infection had occurred during the 2nd (3 cases) and 3rd (1 case) trimesters of pregnancy. Taking this into account, this could indicate that respiratory infections occurring during these gestational periods still have foetal pulmonary implications since it is during the 1st, but also, in the 2nd trimester of pregnancy that foetal respiratory system is in intense development and growth (54). The fact that we did not see more respiratory infections in COVID-19 group is possibly due to the number of pregnant women infected early in pregnancy (5 in 1st trimester and 15 in 2nd trimesters), which possibly did not allow us to have enough sampling to have a more notable effect of the repercussion of COVID-19 at the level of foetal lung development.

Study limitations

This study has a number of limitations, namely: 1) the placentas of the pregnant women were not evaluated histologically, and it was not possible for us to correlate the gestational infection by SARS-CoV-2 and the occurrence of obstetric complications; 2) neither the search for active infection by SARS-CoV-2, nor the presence of anti-SARS-CoV-2 antibodies was evaluated either in the mother or in the newborn, at birth; this information would allow us to know if there was a congenital infection or if, during childbirth, the pregnant woman could be infected, in an asymptomatic way; 3) due to the small sample size, there was few positive sampling in some data in children (namely, reduced number of obstetric complications, premature newborns, neonatal complications and respiratory infections over the 6 months of follow-up), not allowing us to have a real magnitude of the effect of COVID-19 in these children; 4) in a pandemic period, and as pregnant women are often asymptomatic, this risk group should have been regularly tested and, possibly, new cases of newborns, children of mothers with previous SARS-CoV-2 infection during pregnancy, would have been identified in our centre.

Conclusions

This is the first study evaluating the follow-up of children born from mothers with SARS-CoV-2 in gestation. Until 6 months-old, no respiratory or neurological complications were found in this group. Obstetric complications, in line with previously reported, were causes of preterm birth and some neonatal complications. Growth pattern showed slightly differences in SARS-CoV-2 group. Other larger multicentre studies are crucial to clarify these conclusions

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Appendix

Supplementary Tables

***Table* I**. Characterization of obstetric outcomes in the study population. The number of mothers in each group is indicated between parentheses. For each obstetric complication, as well as for each type of delivery, the number of pregnant women is indicated. Statistical analysis: Delivery type was analysed using Fisher's exact test.

	Control (n=42)	**COVID-19** (n=42)	***p* value**
Obstetric Complications			
Prolonged rupture of membranes (> 18 hours)	4	7	
Preeclampsia	0	3	
Fetal growth restriction	0	1	
Delivery type			***p* value**
Eutocic	15	21	0.186
Dystocic	27	21	
Instrumented (Forceps and/or Suction Cup)	9	8	0.352
Caesarean	18	13	

***Table* II**. Fetal gestational age at delivery. Between parentheses is indicated the number of newborns included in each observational group. Statistical analysis: Gestational age is displayed as median [Q1; Q3], being Mann-Whitney U test performed.

	Control (n=42)	**COVID-19** (n=42)	***p* value**
Gestational age (weeks)	39 [38,0; 40,0]	39 [38,0; 40,0]	0.286

***Table* III**. Apgar score at 1st, 5th, and 10th minutes after birth in our study population. The number of children in each group and in each evaluation of the Apgar score is indicated. Statistical analysis: Apgar score was analysed using Fisher's exact test.

Apgar score	**Control** (n=42)	**COVID-19** (n=42)	***p* value**
1st minute			
≤ 7	3	4	0.693
> 7	39	38	
5th minute			
< 9	3	1	0.306
9-10	39	41	
10th minute			
< 10	2	1	0.584
10	42	41	

***Table* IV**. Length of stay in the maternity in our study population. Between parentheses is indicated the number of newborns included in each observational group. Statistical analysis: Length of stay in the maternity is displayed as median [Q1; Q3], being Mann-Whitney U test performed.

	Control (n=42)	**COVID-19** (n=42)	p value
Length of stay in the maternity	2.0 [2,0; 3,0]	3.0 [2,0; 3,0]	0,332

***Table* V**. Weight, length, and head circumference evolution of two preterm newborns in the COVID-19 group (case 1 - gestational age at birth: 32 weeks; case 2 – gestational age at birth: 33 weeks). The indicated age is the corrected age considering their prematurity. Data presented at birth, for 37 weeks and for 41 weeks (corrected age) were calculated using Fenton curves. Data presented for corrected ages of 2 and 4 months were calculated using WHO curves.

Preterm newborns in the COVID-19 group					
Weight evolution	**Birth (32 weeks; 33 weeks)**	**37 weeks**	**41 weeks**	**2 months**	**4 months**
Case 1	p50	p10-p50	p90-P97	p90	p75-p90
Case 2	p10	p3	<p3	p50-p75	p25-p50
Length evolution	**Birth (32 weeks; 33 weeks)**	**37 weeks**	**41 weeks**	**2 months**	**4 months**
Case 1	p10-p50	p10-p50	p90	p90	p75-p90
Case 2	p3-p10	<p3	<p3	p10	p3-p10
Head circumference	**Birth (32 weeks; 33 weeks)**	**37 weeks**	**41 weeks**	**2 months**	**4 months**
Case 1	p50-p90	p10-p50	p50-P90	p25-p50	p25-p50
Case 2	p3	<p3	<p3	p10-p25	p3-p10

***Table* VI.** Weight, length, and head circumference evolution of one extreme preterm newborn in the COVID-19 group (case 3 - gestational age at birth: 27 weeks). The indicated age is the corrected age considering their prematurity. Data presented at birth and for 35 weeks (corrected age) were calculated using Fenton curves. Data presented for corrected ages of 1 and 3 months were calculated using WHO curves.

Extreme preterm newborns in the COVID-19 group				
Weight evolution	**Birth (27 weeks)**	**35 weeks**	**1 month**	**3 months**
Case 3	p50-p90	p50-p90	p75-p90	p50-p75
Length evolution	**Birth (27 weeks)**	**35 weeks**	**1 month**	**3 months**
Case 3	p50-90	p10-p50	p5	p25
Head circumference	**Birth (27 weeks)**	**35 weeks**	**1 month**	**3 months**
Case 3	p50-90	>p97	p75	p50-p75

***Table* VII**. Weight, length, and head circumference evolution of two late preterm newborns in the control group (gestational age at birth in cases 1 and 2: 36 weeks). The indicated age is the corrected age considering their prematurity. Data presented at birth, for 40 weeks and for the 1st month of life (corrected age) were calculated using Fenton curves. Data presented for corrected ages of 3 and 5 months were calculated using WHO curves.

Late preterm newborns in the control group					
Weight evolution	**Birth (36 weeks)**	**40 weeks**	**1 month**	**3 months**	**5 months**
Case 1	> p97	p50-p90	>p95	>p95	p90-p95
Case 2	p10-p50	p10-p50	p50-p75	p75-p90	*No data*
Length evolution	**Birth (36 weeks)**	**40 weeks**	**1 month**	**3 months**	**5 months**
Case 1	p50-p90	p50-p90	p75-p90	p75-p90	p75-p90
Case 2	p10-p50	p10-p50	p75-p90	p50-p75	*No data*
Head circumference	**Birth (36 weeks)**	**40 weeks**	**1 month**	**3 months**	**5 months**
Case 1	p90-p97	*No data*	p97	>p95	>p95
Case 2	p50	p50-p90	p50	p50-p75	*No data*

***Table* VIII**. Respiratory pathology in the first 6 months of life. The number of children in each group and in type of respiratory complication is indicated.

Respiratory complications in the first 6 months of life		
	Control (n=41)	**COVID-19** (n=39)
Nasopharyngitis	5	3
Acute bronchiolitis	2	1
Postnatal SARS-CoV-2 infection	1	0
Respiratory infection before 28 days of life	0	0