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Neonatal Outcomes of SARS-CoV-2 Infection during Pregnancy: A Retrospective Case-control Study

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Neonatal outcomes of SARS-CoV-2 infection during pregnancy: a retrospective case-control study

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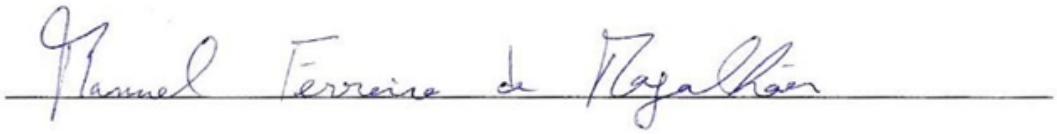

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RESUMO

Objetivo

Avaliar o impacto clínico da infeção por SARS-CoV-2 durante a gravidez nos resultados neonatais.

Metodologia

Estudo retrospetivo caso-controlo emparelhado de todos os recém nascidos de um hospital terciário entre março 2020 e dezembro 2021, cujas mães testaram positivo para SARS-CoV-2 durante a gravidez (casos), comparados com recém-nascidos emparelhados por data de nascimento e idade gestacional. Os resultados neonatais incluem idade gestacional ao nascimento, índice de Apgar, somatometria, complicações neonatais (admissão a UCI, sépsis, icterícia, alimentação e seguimento após a alta, morte neonatal). Os dados foram obtidos via registos clínicos eletrónicos.

Resultados

Foram incluídos 199 participantes, 100 no grupo dos casos e 99 no grupo de controlo (1 controlo para 1 par de gémeos). Os resultados maternos e neonatais foram semelhantes entre os dois grupos, exceto na alimentação e no período de seguimento. O grupo de casos era mais propenso a aleitamento misto, especificamente se a infeção por SARS-CoV-2 decorreu periparto; apenas significativo nos que nasceram em 2020. O grupo de casos teve maior número de consultas (caso vs controlo: 3 vs 1 consultas, $p<0.001$) e seguimento mais prolongado após alta (caso vs controlo: 46 vs 13 dias, $p<0.001$).

Conclusão

A infeção por SARS-CoV-2 durante a gravidez não foi associado a morbilidade clínica materna ou neonatal. No entanto, menor propensão para aleitamento materno exclusivo e período de seguimento mais prolongado foram observados no grupo de infeção por SARS-CoV-2 durante a gravidez. Estes resultados não suportam as diferenças alimentação e de seguimento, pela inexistência de morbilidade clínica.

Palavras-chave

SARS-CoV-2, Gravidez, Recém-nascidos, Transmissão vertical, Nascimento

ABSTRACT

Objectives

The main aim of this study is to assess the clinical impact of SARS-CoV-2 infection during pregnancy on neonatal outcomes.

Methods

Retrospective matched-pair case-control study of all newborns delivered at tertiary hospital between March 2020 and December 2021, whose mothers tested positive for SARS-CoV-2 during pregnancy (cases), compared with newborns matched for similar date of birth and gestational age. Primary neonatal outcomes include gestational age at birth, Apgar score, neonatal complications (NICU admission, sepsis, jaundice, feeding and post-discharge follow-up, death). Data were obtained from electronic clinical records.

Results

Were included 199 participants, 100 in the case group and 99 on the control group (1 control for a set of twin cases). Maternal and neonatal outcomes were similar between the two groups, except for the newborn feeding and post-discharge follow-up. The case group was more likely to be breast and formula fed, specifically if the SARS-CoV-2 infection occurred peripartum (OR 2,41, p=0,006); this was only significant in the ones born in 2020. The case group also had higher number of appointments (case vs control: 3 vs 1 appointments; p<0.001) and overall prolonged follow-up period after discharge (case vs control: 46 vs 13 days; p<0.001).

Conclusions

SARS-CoV-2 infection during pregnancy was not associated with any maternal or neonatal clinical morbidity. However, lower exclusively breastfeeding and prolonged follow-up period was seen in those with SARS-CoV-2 infection during pregnancy. Our date does not support the need for these differences in feeding and follow-up because clinical morbidity does not exist.

Keywords

SARS-CoV-2, Pregnancy, Newborns, Vertical Infection Transmission, Birth

ABREVIATIONS AND ACRONYMS

SARS-COV-2: Severe Acute Respiratory Syndrome Coronavirus 2

COVID-19: Coronavirus Disease 2019

ARDS: Acute Respiratory Distress Syndrome

RT-PCR: Real Time - Polymerase Chain Reaction

WHO: World Health Organization

DGS: Direção Geral da Saúde

CMIN: Centro Materno Infantil do Norte

CHUP: Centro Hospitalar Universitário do Porto

NICU: Neonatal Intensive Care Unit

SCBU: Special Care Unit

HELLP: Syndrome characterized by Hemolysis, Elevated Liver enzymes, and Low Platelet count

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INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spread throughout the world and led to a pandemic, declared by World Health Organization (WHO) in March 2020. (1) Transmission occurs from person to person via respiratory dropplets via inhalation or (less frequently) contact with contaminated objects and the eyes, mouth, or nose. (2)

Multiple studies suggest that SARS-CoV-2 infection during pregnancy is associated with pregnancy-induced-hypertension disorders (preeclampsia, eclampsia, HELLP syndrome), infections and antibiotics use, increased risk of admission to ICU, prolonged hospitalization time, lower rates of spontaneous delivery, higher rates of cesarean delivery, preterm birth, lower birthweight, and lower rate of breastfeeding. Vertical transmission can occur, although horizontal transmission seems more plausible. (3) The presence of IgM antibodies in neonatal blood suggests intrauterine infection. (4) However, the presence of the virus on the placenta does not necessarily imply placental infection or transmission to the fetus nor does the placental infection always indicate fetal damage. (3, 5, 6)

Neonatal disease is rare and usually has favorable outcomes. (1, 7) The majority of neonates infected with SARS-COV-2 showed mild symptoms and required only supportive care. Cesarean delivery has been associated with higher risk of neonatal infection and males seem to be more affected than females. (8, 9) The use of corticosteroids in SARS-CoV-2 infected women at risk for preterm delivery seems to be beneficial for neonates. (3)

Having this into account, the scientific knowledge about the virus, the disease, and its short and long-term consequences, continues to evolve. There are several studies targeting maternal outcomes and neonatal outcomes directly associated with the infection, however the effects of maternal infection during pregnancy on neonates are still controversial. This understanding is paramount to provide the best of care to pregnant women and their newborns, avoiding unnecessary procedures and health costs.

The main aim of this study is to assess the clinical impact of SARS-CoV-2 infection during pregnancy on neonatal outcomes. Specific aims were: i) to evaluate differences on those whose mothers had gestational SARS-CoV-2 infection and those whose mothers had not SARS-CoV-2; ii) to understand the impact of prenatal conditions and mother's diseases; iii) do study differences in clinical follow-up.

METHODS

Study Design and Setting

This was a retrospective matched pair case-control diagnostic study of the perinatal outcomes associated with maternal infection with SARS-COV-2 during pregnancy. This study was performed at Centro Materno Infantil do Norte (CMIN) from Centro Hospitalar Universitário do Porto (CHUPorto) between March 2020 to December 2021.

The study was approved by local Ethics Committee. Informed consent was not obtained since the study did not interfere with clinical management and no contact with patients was needed.

We followed the STROBE statement for reporting case-control studies. (10)

Participants, Data collection and Variables

Inclusion criteria for the case group were all the newborns delivered at CMIN, whose mothers tested positive for SARS-CoV-2 during pregnancy. Exclusion criteria for the case group were follow-up (pregnancy and newborn periods) occurred in other hospital than CMIN, and absence of electronic clinical records that could hamper diagnosis classification. In the control group were included newborns matched for the same date of birth and similar gestational age (less than five days of difference) of the newborn included in the case group, in a one-to-one proportion.

A list of all the newborns from SARS-CoV-2 infected mothers was prospectively made since the beginning of the pandemic in March 2020. So, having this list, retrospective data collection was made by a clinical researcher via electronic records.

Collected data was the same for both case and control groups, except for clinical presentation variables or findings associated with maternal SARS-COV-2 infection, in the case group.

Included variables were those related with i) mother and pregnancy (age, tobacco use, body mass index [BMI], gestational ultrasounds, maternal serologies, stage of pregnancy and gestational age at diagnosis of SARS-CoV-2 infection, clinical presentation, hypertensive disorders, gestational diabetes, thyroid dysfunction and hospitalization time); ii) perinatal data (gestational age at birth, spontaneous or induced labor, delivery mode); iii) newborn (gender, Apgar score, birthweight, length and cephalic perimeter, physical examination at birth, neonatal complications, site of admission, hospitalization period, COVID-19 test result at 24h and at 48h, nutrition, follow-up in neonatology, outpatient clinic after discharge.

Outcomes definition

The considered main neonatal outcomes were gestational age at birth, Apgar score (1^{st}, 5^{th} and 10^{th} minute), birthweight, length, and cephalic circumference (absolute value, Z-score and Percentil), neonatal complications (death before hospital discharge, pulmonary, cardiovascular, gastrointestinal, nephrologic diseases, jaundice and need of phototherapy, sepsis and antibiotics use), nutrition (breastfeeding, formula milk) and follow up in Neonatology outpatient clinics.

Data Management and Statistical Analysis

Statistical analyses were performed using SPSS® version 28 (SPSS IBM, New York, NY, USA).

Continuous variables were described using mean and standard deviation (SD) whenever the variable had a symmetric distribution, and using mean, 25th centile (P25) and 75th centile (P75) whenever the variable didn't have a symmetric distribution; for comparison analysis student t-test and Mann-Whitney U-test were used, respectively. Categorical variables were described using absolute and relative frequencies and compared with Pearson's chi-squared test. To further study the association of breast/formula fed newborns and the time of SARS-CoV-2 infection, a logic regression was

performed for calculation of odds ratio (OR). For interferential analysis, p-value <0.05 was considered statistically significant for all the inferential analysis.

RESULTS

The initial database included 113 newborns of SARS-CoV-2 infected mother during pregnancy. Of these 13 were excluded: 10 were repeated, 1 was not followed at CMIN (no clinical records from the pregnancy or newborn follow up), 1 woman had no record of SARS-CoV-2 infection, and 1 woman did not delivery at the institution. The case group included 100 participants. The control group includes 99 participants, since it was not possible to find a matched control that fulfilled the pair-matching criteria for one case.

The participant characteristics, and differences between case and control groups, are presented in Table I. There were 17 preterm newborns, 9 in the case group (9.0%) and 8 in the control group (8.0%, 1 control was used for a preterm set of twins). There were no significant differences between case and control groups, and the maternal or pregnancy studied factors. Also, mode of delivery, Apgar, birth measures and hospitalization characteristics did not differ between groups.

However, newborns from case group were less likely to had been exclusively breastfed and more likely to had mixed feeding (p=0.021). Odds ratio of having breast and formula fed was 2.41 (95%CI 1.28-4.53) if the mother was positive for SARS-CoV-2 during the hospitalization in the postpartum ward (p=0.006). Importantly, when we excluded the newborns of mothers infected at delivery or during the postpartum hospitalization, there were no differences between the proportion of exclusive breastfeed newborns between the case and control groups. Also, when we only analyzed the newborn delivered in 2021 (n=139), there were no differences between type of newborn feeding and peripartum SARS-CoV-2 infection (p=0,958).

Newborns from case group had significantly more scheduled medical appointments than those from control group (case vs control: 3 vs 1 appointments; p<0.001; Table II). Also, the median number of follow-up days after discharge was significantly higher in the case group (case vs control: 46 vs 13 days; p<0.001).

Regarding data on SARS-CoV-2 infection (Table II), the majority occurred at delivery or post-partum period (n=57, 57%). More than one third had no symptoms upon infection (n=35, 36%). The most common symptoms were anosmia (36%) and ageusia (34%), and cough (24%).

The protocol for the newborn included in this case group required a SARS-CoV-2 screening RT-PCR test, of which only one was positive (the same at 24 and 48 hours).

Physical examination at birth was abnormal in 33 newborns (33%) of case group and 25 newborns (25%) of control group (p 0,274). There were no significant differences in neonatal complications.

In this study, there was only one admission to Intensive care unit (severe hypoxic ischemic encephalopathy), with subsequent death in the case group. Also, there were only two hospitalizations within the first month, both in the case group motivated by jaundice in need of phototherapy.

DISCUSSION

To our knowledge, this was the first matched pair case-control study aiming to assess the effects of maternal SARS-CoV-2 infection during pregnancy on neonatal outcomes. In this case-control study, the case group (SARS-CoV-2 infection during pregnancy) and the control group (no SARS-CoV-2 infection during pregnancy) were similar, not only regarding matching variables, but also regarding the overall maternal characteristics, pregnancy factors and neonatal outcomes. In turn, there were significant differences between the groups on the duration of medical follow-up period after discharge of the newborns, and the type of newborn feeding.

According to previous studies, pregnancy was not associated with more COVID-19 respiratory morbidity, when compared to the general population. (4, 11-14) However, the first observational studies suggested that there were significant differences in adverse fetal and neonatal outcomes associated with maternal infection during pregnancy, such as miscarriages, increase in the proportion of cesarean sections, fetal growth restriction, pre-term delivery, low birthweight, neonatal disease/distress (lower APGAR score, respiratory distress, fever, feeding intolerance, neurological manifestations, laboratorial and radiological findings) and prolonged hospitalization period. (14, 15) In the other way, a recent meta-analysis showed that there were no significant effects on maternal diabetes, hypertensive disorders (hypertension, eclampsia, HELLP syndrome), preterm, labor induction, mode of delivery, neonatal death, low birthweight, intensive care admission or Apgar score below 7 at 5^{th} minute. (16) Our results were in line with this meta-analysis, since we found no differences on these outcomes between our matched pair groups, specifically in those outcomes related with hypertensive disorder, gestational diabetes, or newborn measurements.

In Portugal, SARS-CoV-2 infected women during pregnancy are advised to be evaluated by a multidisciplinary team. (5) Current guidelines recommend thromboprophylaxis until 10 days after labor. (3) The SARS-CoV-2 infection implicates

hospital ambulatory follow-up, 3-4 weeks after the isolation period, and it should include: fetal growth, anatomic evaluation and flowmetry. When maternal hypoxemia occurs, neurosonography should be performed until 32 weeks. Any pregnant admitted for birth must have a COVID-19 test (PCR or antigen-test). (6) If positive at admission, the delivery should occur in a room with negative pressure. Placental tissue can be collected in order to assess the presence of SARS-CoV-2. (5) Updated Portuguese clinical guidelines also recommend that after birth care of newborns of SARS-CoV-2 infected mothers should be as usual. The neonate can be placed at least 2 meters away from the mother, who should wear a mask and sanitize her hands every time. Breastfeeding is recommended, as the virus genetic material was rarely found in breastmilk. (4, 7). The neonates whose mother is infected at birth should be tested at 24h and at 48h of life. (7) In spite of all these recommendations, there are lacking well-designed studies to assess to effectivity of these interventions. This is major point, since these non-pharmacological measures can impact the perinatal experience and mother-to-child bound. Also, in our study, there wasn't any difference in adverse clinical outcomes in newborns of infected mother (before or at the time of deliver), reinforcing that those measures should be studied and applied only if necessary for achieving better clinical outcomes.

A case-control study conducted in France (17) showed that there were no differences regarding maternal, fetal, or neonatal adverse outcomes, spontaneous delivery, mode of delivery, neonatal respiratory distress, neonatal infection, malformation or ICU transfer, prevalence of stillbirth, placental abruption and preeclampsia. It also showed a decrease in preterm labor. However, it is important to notice that, though it was a case-control study, the design was different from our study: the control group was obtained from women who delivered before the pandemic. Thus, the decrease in preterm birth could correspond to the effect of the pandemic itself and the lockdown measures, and not to the maternal infection during pregnancy. In our study, with a matched-pair sample for date of

birth and gestational age, we have not found an association of SARS-CoV-2 infection during pregnancy and prematurity rate.

A national cohort study conducted in England (14), comparing pregnant women with reported SARS-CoV-2 infection at time of birth and those without, stated that there were significant higher rates of fetal death, preterm birth, preeclampsia and emergency cesarean delivery, and lower rates of vaginal delivery. The hospitalization time was prolonged (>3 days) in women with SARS-CoV-2 infection. There were no additional differences in adverse neonatal outcomes when comparing only term delivered newborns. Also, a national cohort study conducted in Sweden (15) found that maternal infection was associated with preterm birth, higher mortality rate (although not linked to neonatal infection) and increased admission rates for neonatal care (in near-term or term infants). These findings might indicate that the adverse neonatal outcomes resulted directly from the prematurity. In our study, the direct effect of prematurity was surpassed, as the match-pairing of groups included similar gestational age. Indeed, we have not found significant differences in preterm delivery rate or in the mode of delivery.

In the present study, there was only one case of neonatal death. It occurred in the case group, after being in the NICU for five days, with perinatal asphyxia, seizures and the diagnosis of hypoxic-ischemic-encephalopathy. Post-mortem autopsy report confirmed severe hypoxic-ischemic-encephalopathy, bilateral multifocal pneumonia, pulmonary alveolar hemorrhage, signs of acute anoxia and no malformations. Genetic results showed mutations in FLAD1 gene. Although he belonged to the case group, we cannot conclude whether the cause of death was related to the maternal SARS-CoV-2 infection, even though the newborn pre- and post-mortem PCR analysis for SARS-CoV-2 were negative.

Our data also revealed that the post-discharge follow-up period of neonates in the case group was significantly longer, when compared to the control group, despite the non-existence of more health morbidity in this group. Knowing the results of our study, one can hypothesize that the prolonged follow-up time might be associated with higher burden,

specifically, higher health costs and unnecessary appointments for these infants, with no clinical additional benefit.

According to Glazer et al (18), there was an increase in overall exclusive breastfeeding rates during the COVID-19 pandemic, but only in white and Asian women and in those SARS-CoV-2 negative women. In the other way, there was a decrease in breastfeeding in SARS-CoV-2 positive women that could be associated with the lack of scientific evidence, especially during the first months of the pandemic, regarding the safety of breastfeeding and the risk of vertical transmission. Initially it was recommended that infected mothers were isolated from their newborns, however, since May 2020 breastfeeding and skin-to-skin contact within the 1 hour was recommended. Neonatology Department followed these recommendations and updated their procedures accordingly, as new evidence and national or international guidelines were being published. According to Pace et al (19) and Laura Garcia et al (20), though RNA has been found in breastmilk, there were no viable viral particles. Furthermore, breastmilk from infected mothers contained SARS-CoV-2 specific IgA and IgG antibodies and a distinct immunological profile, which were able to neutralize the virus in vitro. The immunological effect of these specific antibodies in the newborn has not been assessed. We did observe less exclusive breastfeeding in the case group babies born in 2020, but not afterwards. As stated before, this seems to be indicative of an early more conservative intervention in the participants of case group, because of the unknown clinical consequences of the antepartum maternal infection on neonates.

Guidelines were being published regarding the level of care of the pregnancy, for low-risk women and for women with reported SARS-CoV-2 infection, and for the approach of newborns born during the pandemic period, especially the ones whose mother was infected at the time of delivery. According to these (5-7), the SARS-CoV-2 infected pregnant women and respective newborn were assessed differently than the non-SARS-CoV-2 pregnant women and respective neonates where infection was not present. This was

probably due to the fear of adverse outcomes, when there was not enough knowledge or scientific and clinical evidence to support the measures applied. According to the results of our analysis, the approach, and the follow-up of neonates after pregnancy infection does not need to differ from what is offered to neonates whose mother has no reported infection during pregnancy.

Strengths and limitations

This study had the strength of include all the neonates born at CMIN, whose mothers had COVID-19 during pregnancy, between March 2020 and December 2021. Also, cases and controls were matched according to date of birth and approximate gestational age. This matching method allowed us to reduce the bias associated to potential confounding factors, such as the pandemic epidemiological context, direct effect of prematurity, health professionals at delivery date and clinical records registries.

This study had also expected limitations.

Firstly, it only included data from one hospital, specifically a tertiary referral hospital with potential more complex clinical cases. Even though all pregnant women with SARS-CoV-2 reported infection were included, there were only 100 participants in the case group. Furthermore, 35% of the pregnant with reported infection were asymptomatic and the positive result was obtained from the obligatory screening at admission to delivery or after direct contact with an infected person. This might imply that there were more cases of infection during the pregnancy that were not tested and thus, creating a classification bias of the groups. Additionally, the data were collected from the clinical records, that differ in detail depending on the doctor in charge for admission and release. Moreover, there was a theoretical risk of bias of maternal and neonatal outcomes reporting, since pregnant with COVID-19 diagnosis and their newborns may have been more carefully evaluated; however, the comprehensive clinical assessment protocols of evaluation of every newborn at CMIN (at birth, during hospitalization and discharge) should have eliminated this kind of bias. Also, the hospital protocols were updated accordingly to scientific evidence, which is

beneficial in terms of clinical outcomes, but may input a potential risk of bias in the approach to these newborns throughout time.

Future directions

The follow-up period of these infants and their age so far does not allow to evaluate long-term complications of maternal infection during pregnancy. Therefore, new studies should be designed to better understand the long-term effects of pregnancy infection or even neonatal infection (although it is rare and usually benign). It is also relevant to assess, and support, the motivations for nutrition differences in SARS-CoV-2 infected mothers, considering that breastfeeding is recommended and considered beneficial even in COVID-19 positive mothers.

CONCLUSIONS

This retrospective matched pair case-control study showed that there were no significant differences in neonatal outcomes between the case group (neonates whose mothers were infected with SARS-COV-2 during pregnancy) and the control group (neonates whose mothers were not infected), except for the extent of the follow-up period and nutrition type (breast/formula feeding). Newborns in the case group had prolonged follow-up period and more neonatology appointments, despite the non-existence of diseases or complication related to the SARS-CoV-2 infection. These findings were reassuring and may support a similar clinical management of newborns from SARS-CoV-2 infected and non-infected mother. Newborns in the case group were also more likely to have breastmilk and formula milk, in contrast to exclusive breastfeeding, but only in the first year of pandemic (2020). This finding was specifically relevant in women with peripartum SARS-CoV-2 infection.

TABLES

Table I: Mother, pregnancy and newborn characteristics of the total sample, and comparison between groups.

	Total sample (n=199)	Case (n=100)	Control (n=99)	p
MOTHER				
Age, mean (SD)	31.3 (5.7)	31.3 (6,0)	31.2 (5.3)	0.916
BMI, mean (SD)	30.4 (4.5)	30.8 (4,6)	29.5 (4.3)	0.131
1st pregnancy	85 (42.7)	41 (41.0)	44 (44.4)	0.623
Primiparous	105 (52.8)	51 (51.0)	54 (54.5)	0.616
PREGNANCY				
Gestational disorder, n (%)				
Hypertension	10 (5.0)	7 (7.0)	3 (3.0)	0.343
Diabetes	38 (19.1)	22 (22.0)	16 (16.2)	0.490
Pre-eclampsia, n (%)	6 (3.0)	3 (3.0)	3 (3.0)	1.000
Antenatal US changes, n (%)				
1st trimester	4 (2.1)	0 (0.0)	4 (4.0)	0.121
2nd trimester	9 (4.6)	4 (4.1)	5 (5.1)	1.000
3rd trimester	12 (6.1)	5 (5.1)	7 (7.1)	0.449
Gestational age, mean (SD)	38.9 (1.5)	39.0 (1.5)	38.9 (1.5)	0.849
Hours of membranes rupture, median (P25-75)	4.0 (0.7-9.0)	4.0 (0.7-10.5)	4.0 (0.5-8.0)	0.408
Delivery mode, n (%)				
Eutocic	98 (49.2)	46 (46.0)	52 (52.5)	
Instrumental	39 (19.6)	24 (24.0)	15 (15.2)	0.482
Scheduled cesarean	35 (17.6)	17 (17.0)	18 (18.2)	
Unplanned cesarean	27 (13.6)	13 (13.0)	14 (14.1)	
NEWBORN				
Male, n (%)	101 (50.8)	54 (54,0)	47 (47.5)	0.396
Apgar index, mean (SD)				
1st minute	9 (1)	9 (1)	9 (1)	0.142
5th minute	10 (1)	10 (1)	10 (1)	0.067
Birth measures, means (SD)				
Weight, in gr	3,141 (460)	3,142 (460)	3,140 (475)	0.979
Length, in cm	48.5 (2.5)	48.5 (2.0)	48.5 (2.5)	0.598
Head circumference, in cm	34.0 (1.5)	34.0 (1.5)	34.0 (1.5)	0.520
Site of hospitalization, n (%)				
Transitional care	193 (97.0)	97 (97.0)	96 (97.0)	1.000
SCBU	7 (3.5)	4 (4.0)	3 (3.0)	1.000
NICU	1 (0.5)	1 (1.0)	0 (0.0)	1.000
Length-of-stay days, median (P25-75)	3 (3-4)	3 (3-4)	3 (3-4)	1.000
Jaundice, n (%)	79 (39.7)	39 (39.0)	30 (40.4)	0.885
Neonatal sepsis, n (%)				
Early	3 (1.5)	1 (1.0)	2 (2.0)	0.619
Late	1 (0.5)	0 (0.0)	1 (1.0)	0.495
Feeding, n (%)				
Breast	112 (57.4)	48 (49.0)	64 (66.0)	
Breast and formula	60 (30.8)	39 (39.8)	21 (21.6)	0.021*
Formula	23 (11.8)	11 (11.2)	12 (12.4)	
Neonatal death, n (%)	1 (0.5)	1 (1.0)	0 (0.0)	1.000
Outpatient follow-up, median (P25-75)				
Number of appointments	2 (1-3)	3 (2-4)	1 (1-2)	<0.001*
Days of follow-up after discharge	25 (11-73)	46 (21-128)	13 (8-30)	<0.001*

BMI: body mass index; SD: standard deviation; P25-75: 25thcentile – 75thcentile; *Statistically significant.

Table II: Data on SARS-CoV-2 infection.

	Case group (n=100)
Time of infection, n (%)	
1st trimester	12 (12.0)
2nd trimester	19 (19.0)
3rd trimester	12 (12.0)
At delivery	56 (56.0)
Postpartum	1 (1.0)
Weeks until deliver after infection, median (P25-75)	1.8 (0-13.1)
Clinical presentation at infection, n (%)	
No symptoms	35 (36.1)
Anosmia	35 (36.1)
Ageusia	33 (34.0)
Cough	23 (23.7)
Fever	20 (20.6)
Myalgias	18 (18.6)
Headache	14 (14.4)
Rhinorrhea	14 (14.4)
Shortness of breath	6 (6.2)
Sore throat	5 (5.2)
Newborn SARS-CoV-2 positive test, n (%)	
24h of life	1 (1.0)
48h of life	1 (1.0)

P25-75: 25th centile – 75th centile

APPENDIX

I: Parecer do Conselho de Administração do CHUPorto

[REF2021.293 (239-DEFI/247-CE)]

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

centro hospitalar do Porto

Exma. Sra. Ana Teixeira

Estudante do ICBAS

ASSUNTO: Trabalho Académico - MIM - **"Burden of COVID-19 pandemic on neonatal outcomes"** – N/ REF.ª 2021.293(239-DEFI/247-CE)

O Conselho de Administração do CHUPorto autoriza a realização do estudo acima mencionado, a realizar no Serviço de Pediatria desta Instituição e tendo como Investigador Principal Ana Teixeira, estudante do ICBAS.

O estudo foi previamente analisado pela Comissão de Ética do CHUPorto|ICBAS, pelo Serviço de Investigação Clínica, pela Direção do Departamento de Ensino, Formação e Investigação do CHUPorto e pelo Presidente do Conselho de Administração, tendo obtido parecer favorável.

Cumprimentos,

CONSELHO DE ADMINISTRAÇÃO
09/03/2020
Dr. PAULO BARBOSA — Presidente
Dr.ª RITA [illegible]EIRA — Vogal Executiva
Prof. Doutor JOSÉ BARROS — Diretor Clínico
Dr.ª RITA VELOSO — Vogal Executiva
Enf.º EDUARDO ALVES — Enfermeiro Diretor

* Em todas as eventuais comunicações posteriores sobre este estudo é indispensável indicar a nossa ref.ª.

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

centro hospitalar do Porto

APRECIAÇÃO E PARECER PARA A REALIZAÇÃO DE **TRABALHO ACADÉMICO - MIM**

Título: **"Burden of COVID-19 pandemic on neonatal outcomes"**		Ref.ª: **2021.293(239-DEFI/247-CE)**
		Investigador: **Ana Teixeira** **Estudante do ICBAS**

DIREÇÃO DE ENFERMAGEM:	**PRESIDENTE DO CONSELHO DE ADMINISTRAÇÃO:**
☒ **NÃO SE APLICA**	☒ **PARECER FAVORÁVEL**
☐ **PARECER FAVORÁVEL**	☐ **PARECER NÃO FAVORÁVEL**
☐ **PARECER NÃO FAVORÁVEL**	
Data:	Data: 07 MAR. 2022
	Dr. PAULO BARBOSA Presidente do Conselho de Administração do CHUP

PARECER FAVORÁVEL

07 MAR. 2022

Dr. SEVERO TORRES
Assessor do Presidente do Conselho de Administração

Em conformidade. Pode ser autorizado.

Prof.ª Doutora Luísa Lobato
Diretora do DEFI

04/03/2022

Luísa Lobato
Diretora do DEFI

Resumo das avaliações dos Intervenientes no Circuito de Submissão dos Estudos de Investigação

	Parecer	Data
Serviço de Investigação Clínica	Favorável	06/12/2021
Comissão de Ética CHUP|ICBAS	Favorável	12/01/2022
Encarregada da Proteção de Dados (EPD)	NA	
Responsável pelo Acesso à Informação (RAI)	Deferido	26/02/2022
Direção do DEFI	Pode ser autorizado	02/03/2022

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COMISSÃO DE ÉTICA CHUPorto / ICBAS

APRECIAÇÃO E VOTAÇÃO DO PARECER

Deliberação	Data: 12/1/2022	Órgão: Reunião Plenária

Título: **"Burden of COVID-19 pandemic on neonatal outcomes"**		Ref.ª: **2021.293(239-DEFI/247-CE)**
Protocolo/Versão: **MIM**	Promotor: **o(a) próprio(a)**	Investigador / Local: **Ana Teixeira Serviço de Pediatria - CHUPorto**

A Comissão de Ética CHUPorto / ICBAS, ao abrigo do disposto no Decreto-Lei n.º 80/2018, de 15 de Outubro, em reunião realizada nesta data, apreciou a fundamentação do relator sobre o pedido de parecer para a realização do **MIM** acima referenciado:

Ouvido o Relator, o processo foi votado pelos Membros da Comissão de Ética CHUPorto / ICBAS presentes:

Presidente: Prof. Doutor João Nuno Melo Beirão
Vice-Presidente: Dr.ª Paulina Aguiar

Dr. Aníbal Albuquerque, Prof.ª Doutora Carla Teixeira, Dr.ª Cármen de Carvalho, Dr.ª Fernanda Manuela Costa, Dr. Gonçalo Senra, Prof. Doutor José António Pinho, Prof.ª Doutora Margarida Araújo, Prof.ª Doutora Maria Strecht, Prof.ª Doutora Susana Magalhães.

Resultado da votação:

PARECER FAVORÁVEL

Sem voto Dr. Carmen Carvalho

A deliberação foi aprovada por unanimidade.

Pelo que se submete à consideração superior.

Data 12/1/2022

O Presidente da Comissão de Ética CHUPorto / ICBAS

Prof. Doutor João Nuno Melo Beirão

Imp.10/2019

II: Explicação das variáveis envolvidas neste estudo.

Variáveis maternas / associadas à gravidez		
Idade	Numérica	anos
Tabagismo	Não fumadora	0
	Fumadora	1
	Ex-fumadora	2
IMC	Numérica	Kg/m2
Gesta/Para	Numérica	
Ecografias pré-natais	Normal	0
	Anormal	1
	Não realizada / sem registo	2
Rastreio bioquímico 1ºTrimestre	Baixo risco	0
	Risco alto/intermédio	1
	Não realizado	2
Serologias		
AgHBs	Negativo	0
	Positivo	1
	Desconhecido	2
VIH	Negativo	0
	Positivo	1
	Desconhecido	2
VDRL	Negativo	0
	Positivo	1
	Desconhecido	2
Toxoplasmose	Imune	0
	Não imune	1
	Desconhecido	2
Rubéola	Imune	0
	Não imune	1
	Desconhecido	2
CMV	"Imune"	0
	Não imune	1
	Desconhecido	2
Rastreio SGB	Negativo	0
	Positivo com profilaxia adequada	1
	Positivo sem profilaxia adequada	2
	Desconhecido	3
Patologia materna (hipertensão arterial, diabetes, disfunção tiroideia)	Não	0
	Sim	1
	Prévia à gravidez	2
TRABS	Negativos	0
	Positivos	1
Pré-eclâmpsia	Não	0
	Pré-eclâmpsia	1
	Eclâmpsia	2
	Síndrome de HELLP	3
Corticoterapia pré-parto	Não	0
	Sim	1

Variáveis associadas a infeção por SARS-CoV-2		
SARS-CoV-2	Controlo (sem infeção) Caso (com infeção)	0 1
COVID-19	Sem infeção Infeção no 1º trimestre Infeção no 2º trimestre Infeção no 3º trimestre Infeção periparto	0 1 2 3 4
IG COVID-19	Idade gestacional em que testou positivo	
TLP	Tempo de latência até ao parto (IG ao nascimento – IG COVID-19)	
Apresentação clínica (assintomática, febre, tosse, rinorreia / congestão nasal, odinofagia, dispneia, anosmia, ageusia, cefaleias, mialgias)	Sim Não	0 1
RN SARS-CoV-2 24h / 48h	Teste negativo Teste positivo	0 1

Variáveis associadas ao parto		
Parto	Espontâneo Induzido	0 1
Tipo de parto	Eutócico Distócico instrumentado Cesariana eletiva Cesariana não eletiva	0 1 2 3 4
Rotura de membranas	Numérica	Horas
Líquido amniótico	Normal Meconial Hemático	0 1 2

Variáveis neonatais		
IG	Idade gestacional Nº semanas + 0,14 por cada dia	
Sexo	Feminino Masculino	0 1
Apgar 1º/5º/10º minutos	Numérico	
Peso	Numérico, z-score, percentil	Gramas
Comprimento	Numérico, z-score, percentil	cm
Perímetro cefálico	Numérico, z-score, percentil	cm
Duração do internamento (aplicável para cada local de admissão: UCIN, UCEN, Cuidados Normais)	Numérico	Dias
Morte neonatal	Não Sim	0 1
Exame objetivo*	Normal Anormal	0 1

Patologia neonatal (respiratória, cardíaca, gastrointestinal, nefrológica, hematológica, icterícia e fototerapia, patologia do cordão umbilical)	Não Sim	0 1
Rastreio séptico	Não realizado Realizado	0 1
Sépsis **(Precoce e tardia)**	Não Sim	0 1
PCR máxima	Numérica	
Antibioterapia	Não Ampicilina + Gentamicina Trimetoprim	0 1 2
Nutrição	Aleitamento materno exclusivo Aleitamento misto Aleitamento de fórmula	0 1 2
Seguimento	Não Sim	0 1
Número de consultas **(apenas de neonatologia)**	Numérico	
Duração do seguimento	Numérica	Dias
Tipo de 1ª consulta	Presencial Teleconsulta	0 1
Destino	Alta Mantém consultas Internamento	0 1 2
Reinternamento no 1º mês	Não Sim	0 1

*Achados encontrados ao exame físico (anormal): apêndice cutâneo, máscara equimótica, petéquias, mancha hipo e/ou hiperpigmentada, apêndice auricular, auscultação pulmonar / cardíaca anormal, hidrocelo, hipospádias, fratura da clavícula, clicks da anca ou manobras de Ortalani/Barlow positivas, hipotonia, hipoglicemia, desidratação.

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