FACULTAD DE MEDICINA
UNIVERSIDAD DE CANTABRIA

GRADO EN MEDICINA

TRABAJO FIN DE GRADO

CHARACTERISTICS OF THE NEWBORNS DURING THE FIRST MONTHS OF THE COVID-19 PANDEMIC

Características de los recién nacidos durante los primeros meses de la pandemia de COVID-19

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Santander, Junio 2021

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1. ABSTRACT/RESUMEN

Objectives: The aim of this study is to report the impact of SARS-CoV-2 on neonatal outcomes. **Methods**: We conducted a cohort study including 654 newborns of 650 pregnant women in Cantabria, Spain, during the first months of the COVID-19 pandemic.Two sub-cohorts are identified in the recruitment. Sub-cohort 1 included female recruited retrospectively who gave birth between 23 March and 25 May 2020.Sub-cohort 2 included women recruited prospectively giving birth on or after 26 May 2020.All women were tested for SARS-CoV-2 infection using both RT-PCR for RNA detection and ELISA for SARS-CoV-2 antibodies.All newborns were tested for antibodies by immunochemiluminescence testing.**Results**:The neonates of COVID-19 mothers did not show adverse birth outcomes compared to the non-COVID-19.In just 44 cases (6.8%) the admission in neonatology ICU was needed, three of them were newborns of COVID-19 positive mothers.Upon delivery, 12 out of the 654 newborns studied were positive to SARS-CoV-2 (1.83% 95% CI (0.81-2.86)).The cesarean section rate was not higher in COVID-19 positive mothers.There was a trend to feed with mixed maternal and infant formula the newborns of positive mothers (p=0.063). **Conclusion**:neonates do not appear to have an increased risk to develop severe COVID-19 disease.It is suggested that COVID-19 should not be an indication for caesarean delivery, infant formula feeding or isolation from the mother.

***KEY WORDS*:** SARS-CoV-2; neonates; vertical transmission; cesarean section; breasfeeding.

RESUMEN

Objetivos: El objetivo de este estudio es informar del impacto del el SARS-CoV-2 en los resultados neonatales. **Métodos**: Hemos llevado a cabo un estudio de cohortes que incluyó a 654 recién nacidos de 650 mujeres embarazadas en Cantabria, Spain, durante los primeros meses de la pandemia de COVID-19. Se pueden identificar 2 sub-cohortes en el reclutamiento. La subcohorte 1 incluyó a las mujeres reclutadas retrospectivamente que dieron a luz entre el 23 de marzo y el 25 de mayo de 2020. La subcohorte 2 incluyó a las mujeres reclutadas prospectivamente que dieron a luz el 26 de mayo de 2020 o después. Todas las mujeres fueron sometidas a determinación de la infección por SARS-CoV-2 utilizando tanto la RT-PCR para la detección del ARN como el ELISA para los anticuerpos contra el SARS-CoV-2. A todos los recién nacidos se les hizo detección de anticuerpos mediante pruebas de inmunoquimioluminiscencia. **Resultados**: Los neonatos de madres con COVID-19 no mostraron resultados adversos al nacimiento en comparación con las que no tenían COVID-19. Sólo en 44 casos (6,8%) fue necesario el ingreso en la UCI de neonatología. En el momento del parto, 12 de los 654 recién nacidos estudiados fueron positivos al SARS-CoV-2 (1,83% IC 95% (0,81-2,86)). La tasa de cesáreas no fue mayor en las madres positivas con COVID-19. Hubo una tendencia a alimentar con leche de fórmula al recién nacido de madre positiva (p=0,063). **Conclusión**: Los recién nacidos no tienen un mayor riesgo de desarrollar enfermedad grave por COVID-19. Se sugiere que la enfermedad COVID-19 no debería ser una indicación para el parto por cesárea, la alimentación con leche de fórmula infantil o el aislamiento de la madre.

PALABRAS CLAVE: SARS-CoV-2; recién nacidos; transmisión vertical; césarea; lactancia materna.

2. INTRODUCTION

Since December 2019 the world has changed along with our lives. The human health is constantly threatened by a new coronavirus known as Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), causing an infectious disease named COVID-19. Globally, there have been 164.409.804 confirmed cases of COVID-19, including 3.409.220 deaths as of 19 May 2021, reported to WHO with an estimated case fatality rate of 3% [1][2].

SARS-CoV-19 is an enveloped virus with a positive-sense single-stranded RNA and a nucleocapsid of helical symmetry. Coronaviruses constitute the subfamily Orthocoronavirinae, in the family Coronaviridae. The protein which allows the SARS-CoV-2 to infect the host cell and start the fusion process is the glycoprotein E2 localised in the surface of the envelope, also known as Spike protein for its shape[3]. SARS-CoV-2 utilizes the receptor-binding domain (RBD) of the spike (S) glycoprotein to recognise angiotensin-converting enzyme 2 (ACE2) receptors on the human cells[4].

We shortly describe the timeline of the events that led the entire world into this shocking scenario:

On 17 November 2019 the first case of infection with SARS-CoV-2 was reported from the Chinese government sources and the World Health Organization (WHO)[5]. The outbreak was reported by China to the WHO on 31 December. As far as concern Spain, the first COVID-19 case was confirmed on 31 January 2020 on the Canary Islands; then, the first death related to the new virus was reported in Valencia on 13 February, a 69-year-old man, diagnosed post-mortem[6][7].

Following the statement made by WHO on 11 March, which declared global pandemic, the Spanish government declared the State of Emergency and announced the imposition of a national lockdown starting on 15 March as part of emergency measures to fight the coronavirus outbreak in the country. As 1 December 2020, there have been 1,628,208 confirmed cases of COVID.19 resulting in 44,668 deaths in Spain[8].

The vulnerable groups, which in case of disease are more likely to require hospitalisation, are particularly the elderly and individuals with underlying clinical conditions. So far research has not shed light on whether pregnant women and newborns should be considered as high-risk categories [9].

Muhidin et al, in a Systematic Review suggest that pregnant women are not at higher risk of developing COVID-19 infection, nor are they more susceptible to severe pneumonia than non-pregnant adults[10].

In fact, risk factors for severe COVID-19 in pregnant women are the same as for the general population such as increasing maternal age, overweight and pre-existing medical conditions like hypertension and diabetes mellitus. Nevertheless, when COVID-19 pregnant women develop severe symptoms, they are more likely to need intensive care in relation to non-pregnant women of reproductive age, most probably due to the physiological compression of the uterus on the thorax reducing ventilation[11].

It is interesting to see how pregnant women with COVID-19 seem to experience more often preterm birth, preeclampsia and caesarean section [12]. In a research paper of BMC Medicine, Yang et al. found a higher rate (about three times more) of caesarean section among COVID-19 pregnant women than the rate of caesarean section in those negative.

Maternal breathlessness and related complications as well as foetal intrauterine distress, were the indications posed by SARS-CoV-2 to performed elective and early caesarean section, increasing both preterm birth and caesarean section rates [13].

Epidemic viral infections in past years have shown that pregnant women can suffer from more severe outcomes than non-pregnant ones. The risk of developing a viral infection like SARS- CoV, MERS-CoV, Ebola, H1N1, and influenza-A is higher in this group. These infections have been proven to be the direct cause of maternal mortality, intrauterine growth restriction, spontaneous abortion, stillbirth and preterm delivery. Pregnancy-related immunological and physiological changes that naturally occur during pregnancy can make pregnant women more susceptible to infectious disease. Increased heart rate, oxygen consumption, stroke volume, decreased pulmonary capacity and functional residual capacity are the main physiological changes in the cardiovascular and respiratory systems during pregnancy. This, along with an immunosuppression can increase the complications during infectious disease[10][14][15].

Regarding newborns, the first case of neonatal infection due to COVID-19 was reported in Spain in October 2020 [16]. SARS-CoV-2 infections are reported as rare in the current evidences. In a recent systematic review and meta-analysis conducted in China, which includes thirteen studies, the percentage of infected neonates was 6.0% [17]. On the other hand, about 90% of the infected infants younger than one year have either asymptomatic or mild disease, thus experiencing fever, cough, diarrhoea and other moderate symptoms. The other 10% develop severe illness which could require respiratory support and advanced care as well as mechanical ventilation when needed. Newborns with underlying medical conditions and preterm neonates may be at higher risk of severe illness from COVID-19 [18]. Term neonates born to COVID-19 mothers are usually asymptomatic [5].

Furthermore, in their review, Meng-Yao Zhou et al. found that gastrointestinal symptoms were the first signs to appear in infants, who would most likely develop a severe clinical condition[19].

Frequent abnormal findings in placental pathology have been reported among COVID-19-positive mothers. The most common finding is vascular malperfusion. Mulvey et al. investigated five placentas from COVID-19 patients who delivered at term. All five placentas showed foetal vascular malperfusion (FVM) with multiple thromboses[20][21].

Even though the efforts of the scientific community have been remarkable, during the past months, still not enough data have been collected referring to neonate infection. This lack of information causes concern about the infection's implications in newborns, both in terms of impact as well as appropriate care[22].

In this triangle made of mothers, their newborns and the virus, one of our main concerns was the possibility of vertical transmission.

There is a general scientific consensus about the horizontal transmission of the virus. It appears to occur mainly via direct contact with a patient whether symptomatic or asymptomatic and via droplet nuclei produced by her/his respiratory secretions. However, it is still debated whether or not there is the possibility of a vertical transmission due to still few researches in this regard [10][23][24].

Evaluating all the possible ways a mother can vertically infect her child means to analyse and eventually detect SARS-CoV-2 by RT-PCR in vaginal and rectal swab, milk sample, umbilical cord blood, neonatal blood collected within the first 12 hours of life or amniotic fluid collected prior to rupture of membrane. All of the above was carried out in order to study respectively intravaginal, breastfeeding and transplacental transmission [10]. Despite checking the literature thoroughly, it was extremely difficult to find studies describing every way of vertical transmission with a sufficient sample size or any systematic reviews [10][13][25]. Anyway, most of the studies did not show vertical transmission, as this type of transmission has never been demonstrated for SARS and MERS [22][24][26].

Preventive measures such as delivery by caesarean section, the avoidance of breastfeeding, the adoption of preventive practices by mothers concerning hygiene habits and child isolation upon birth have been taken. Still, some cases of infected newborns have been reported [27][28].

In October 2020 a study conducted on 31 women and their newborns was performed in Milan to find evidence of vertical transmission and 1 neonate turned out to have a possible congenital infection. The newborn could be classified as having a confirmed congenital infection because of the detection of viral genome by RT-PCR in a nasopharyngeal swab at birth. SARS- CoV-2 genome was detected also in maternal plasma samples, and in vaginal swabs, placental tissue and umbilical cord plasma[29].

Besides, in a French study published in July 2020 in Nature, Vivanti et al. demonstrated transplacental transmission of SARS-CoV-2 from a pregnant woman affected by COVID-19. Both the E and S genes of SARS-CoV-2 were detected in blood and in nasopharyngeal and vaginal swabs of the mother. Amniotic fluid sample was collected prior to rupture of membranes during caesarean section and tested positive for both the E and S genes of SARS-CoV-2. Nasopharyngeal and rectal swabs were first collected after having cleaned the baby at 1 h of life, and then repeated at 3 and 18 days of postnatal age; they were tested with RT-PCR and were all positive for the two SARS-CoV-2 genes. RT-PCR in the placenta was positive for both SARS-CoV-2 genes. The viral load was much higher in placental tissue than in amniotic fluid and maternal or neonatal blood[30].

In order to prevent congenital infections, the possibility of breastfeeding the child has been questioned. It is important to underline the role of breast milk for the baby. Breast milk is the best source of nutrition for infants, since it contains antibodies and other immune benefits which can help protect against respiratory and other diseases, environmental pathogens and internal inflammation. Moreover, it also provides remarkable benefits to both mothers and their newborns as the latter are more likely to develop better psychological and affective conditions in the future[31][32].

Nowadays, considering the fact that the virus was not detected in breast milk samples in most medical research, and that generally COVID-19 is not severe in infants, the WHO guidelines encourage also the mother who has COVID 19 to breastfeed the baby as long as appropriate precautions are taken. In fact, the main risk of transmission appears to come from the respiratory tract of an infected mother just like in general population; also between the mother and her child is still the horizontal transmission to prevail[31].

The precaution to manage the risk of infection are listed in the WHO as follow:

1. *Practicing respiratory hygiene during feeding, including wearing a mask covering mouth and nose.*

2. *Washing hands with soap and water for 20 seconds before and after touching the baby.*

3. *Routinely cleaning and disinfecting surfaces they have touched* [31].

The WHO guidelines strongly promote close and early contact between the mother and her child. Holding the baby skin-to-skin and sharing the room with him also if SARS-CoV-2 positive and always with the preventive measure. It is known how essential is early skin-to-skin contact to stimulate milk production from the mother and newborns who have prolonged skin-to-skin contact are more likely to breastfeed successfully. Beyond all the breast milk property, Campione et al. believed that lactoferrin could be a protective natural barrier of both respiratory and intestinal mucosa against SARS-CoV-2. It also has important anti-inflammatory effects and could revert the iron dysregulation induced by SARS-CoV-2 infection. Lactoferrin is not the only item which could help us explain why in babies the SARS-CoV-2 infection is usually mild or even asymptomatic. Recent studies have reported a robust and specific secretory IgA against SARS-CoV-2 in human milk which could protect infants and young children from COVID-19. [31][33][34][35][36].

In this paper we are reporting the first results of the outcomes in newborns from a cohort of pregnant women and their neonates during the first months of COVID-19 pandemic in Spain, one of Europe's most affected countries by COVID-19. Our main aims describe:

1. The rate of vertical transmission among newborns born to mothers with SARS-CoV-2 infection.

2. The general outcomes of these neonates at birth reporting the clinical characteristics and the neonate development.

3. The clinical courses, with the specific management performed by our physician regarding the complications when these occurred (health care during pregnancy and at delivery).

3. MATERIAL AND METHODS

3.1 DESING AND STUDY POPULATION

The Mother And Child Covid-19 cohort (MOACC-19) is a cohort study that includes children born during the COVID-19 pandemic in the University Hospital Marqués de Valdecilla (HUMV) and their mothers[37]. The HUMV, Cantabria (Spain), is a third level hospital with 900 beds. About 2500 deliveries are attended in HUMV in a year (about 90% of all deliveries in the region), but during the COVID-19 pandemic, all pregnant women had been referred to the HUMV at time of delivery. In the light of the current situation, the expectant mothers admitted for delivery were tested to SARS-CoV-2 active infection using RT-PCR from 23 March 2020.

In our hospital HUMV on 17 March 2020 an algorithm for the management of the newborns to a confirmed or suspected COVID-19 infected mother was created (figure 1).

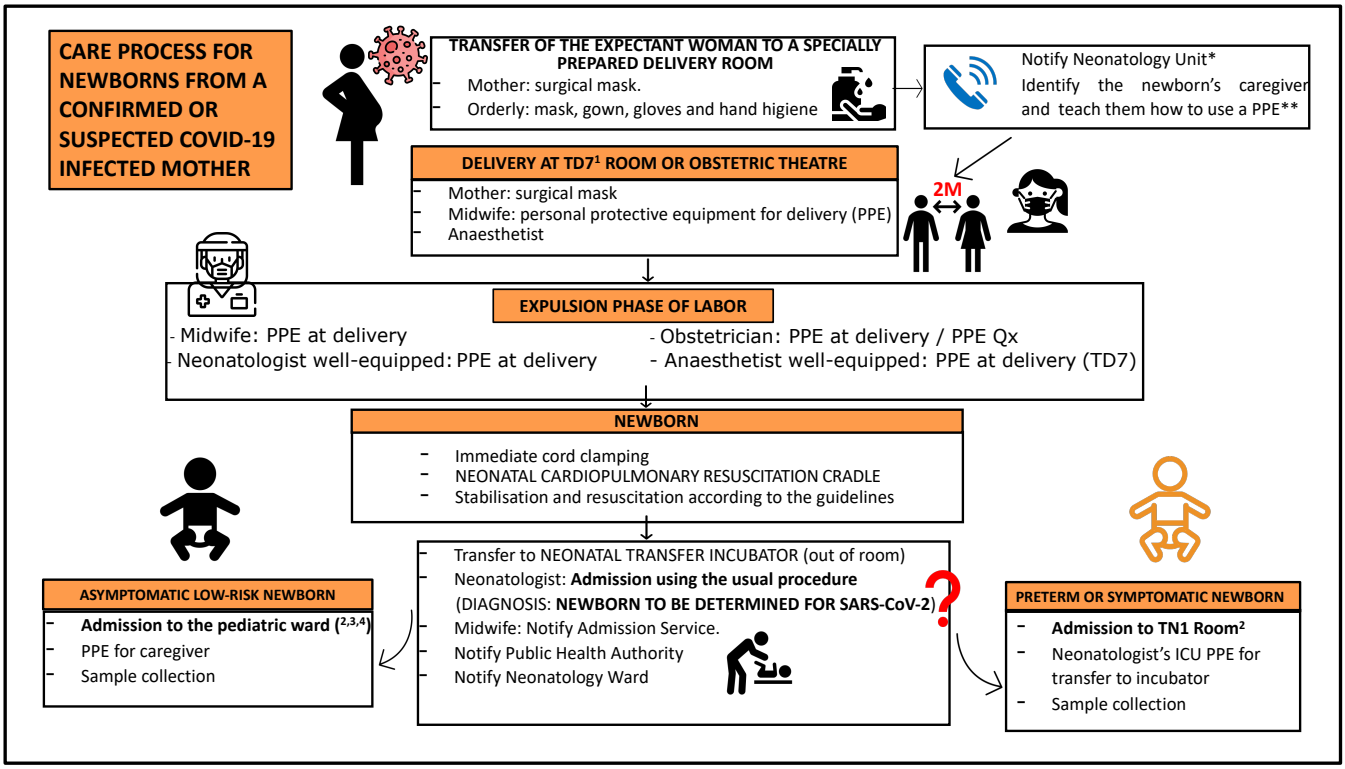

Figure 1 Infographic showing neonatal management from a confirmed or suspected COVID-19 infected mother

*In each case of a pregnant woman who is a confirmed case or to be determined, you should contact neonatology and collect the information available at that time on weeks of gestation, obstetric situation and probable date of delivery. The information will be updated on successive visits.

**Identify the caregiver for the newborn and instruct him to use the PPE. The caregiver should be an asymptomatic adult, defined by the mother, who meets the guidelines of Public Health criteria for caregivers.

[1] **TD7:** place of birth for newborns from a confirmed or suspected COVID-19 infected mother.

[2] In case to not to have a caregiver who can care for the newborn in the room until discharge home, admission will be in **TN1-Room2**. Room2 of TD1 is a separate circuit from the rest of the Neonatology Unit where preterm or symptomatic newborns from a confirmed or suspected COVID19+ mother can go.

[3] In cases of **mothers to be determined for SARS-CoV-2** and asymptomatic neonate, if mother's PCR for SARS-CoV-2 is negative, the neonate can stay with her and breastfed.

[4] In case of an asymptomatic newborn with negative test for SARS-CoV-2 in which infection is ruled out, the newborn will be transferred to TN1 - Room 3 in the absence of a healthy support person who can care for the newborn in the room until discharge home.

Recruitment began on 26 May 2020. The study population was divided into two sub-cohorts according to the date of the delivery. Sub-cohort 1, which included children born from 23 March to 25 May 2020, was recruited from 26 May by telephone call. Sub-cohort 2, including those born from 26 May to 14 October 2020, was recruited at the time of admission to delivery.

In the first sub-cohort, the information (pregnancy, delivery, and early months of life) was collected retrospectively, while in the second sub-cohort the information was prospectively gathered. The mothers of the newborns belonging to the sub-cohort 1 have been exposed to SARS-CoV2 in the third trimester of their pregnancy, whereas the pregnant women admitted to delivery as of 26 May 2020 have been exposed to SARS-CoV-2 during the second and third trimesters of their pregnancy. All the mothers involved in this study gave express consent on their behalf which, in turn, included that of their newborns to participate in the research. Further information can be found elsewhere[37]. Figure 2 summarises the process of recruitment.

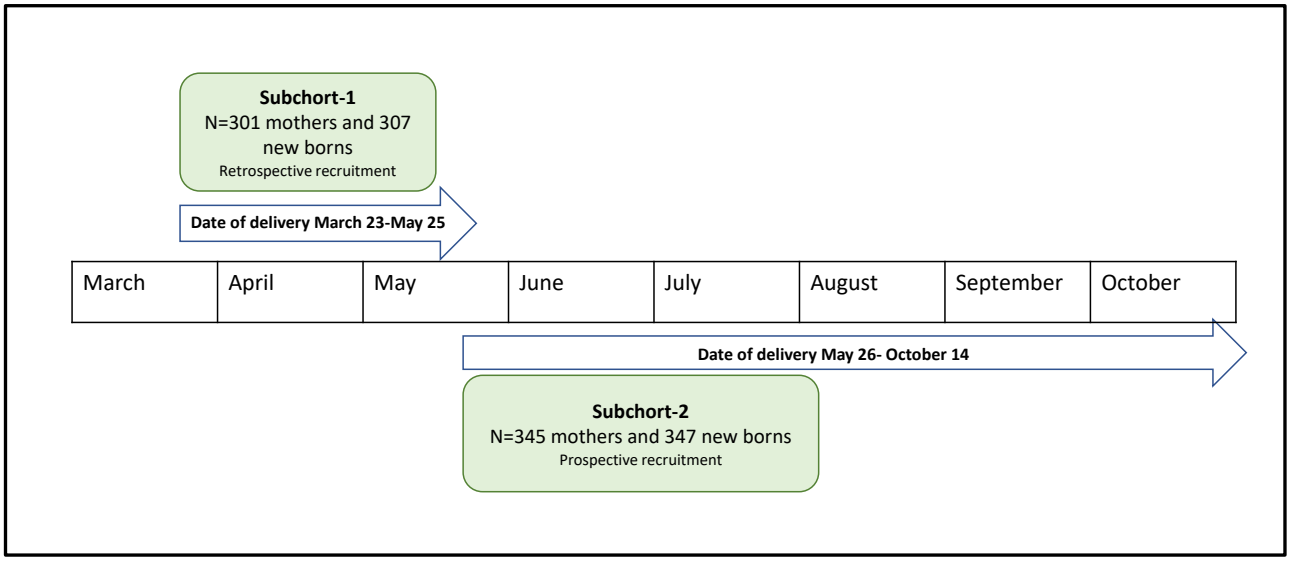

Figure 2 Recruitment flowchart

3.2 DATA COLLECTION

Maternal and Newborn Testing for SARS-CoV-2

In order to detect possible SARS-CoV-2 infections and the presence of SARS-CoV-2 antibodies, several tests have been performed in the mothers as well as in the newborns. Concerning the mothers, a blood sample by venepuncture was being obtained to analyse the presence for anti-SARS-CoV-2 spike protein IgG and IgM using ELISA at the recruitment. Furthermore, all of them underwent a nasopharyngeal swab. The samples were being tested for SARS-CoV-2 infection via RT-PCR.

When one of the tests above was positive, viral RNA in placenta and breast milk via RT-PCR was searched. Likewise, both RT-PCR and antibody determinations via ELISA for the neonates and the mother's partner were performed. Regardless of the mothers' outcome, from each neonate we took a blood sample from the heel to study IgG and IgM antibodies via immunochemoluminiscency. This prick has been taken in the same procedure which in Spain is used to screen congenital metabolopathies in each neonate in the first few days of life. Further information can be found elsewhere[37].

Maternal and newborn variables

Socio-demographic data, obstetrics history, medical history, exposure to COVID-19 and symptoms compatible with COVID-19 of all the mothers were obtained in a face-to-face interview by healthcare professionals, while going through their medical records both obstetrics and medical history were completed.

For the newborns, medical records were reviewed in order to obtain information **of** characteristics at birth (birth weight, birth size, birth cephalic perimeter, Apgar, gestational age…), perinatal pathology (including respiratory distress among others), causes of admission in neonatal ICU, congenital malformations and type of feeding at hospital discharge.

3.3 FOLLOW-UP

The data of all the neonates were collected at birth and the follow-up was performed for all the hospitalisation time (perinatal follow-up). General development and psychomotor development were examined by a paediatrician. The follow-up will be updated at 6 and 12 months. In this paper the first results are shown.

3.4 STATISTICAL ANALYSIS

Descriptive statistics are reported as frequency and percentage for categorical variables and mean and SD for continuous variables. Statistical comparisons are performed via $\chi 2$ test or independent samples Student's t-test. Prevalence of anti-SARS- CoV- 2 antibodies and its 95% confidence intervals (CI) in pregnant women and their newborns was estimated assuming a binomial distribution (or a Poisson distribution in case of a small number of positives).

Unconditional logistic regression was used to assess the relationship between mother positive to SARS-CoV-2 and 1) newborn morbidity risk, 2) type of feeding or 3) anti-SARS-Cov-2 antibodies in neonates. To estimate the magnitude of the associations, multivariate-adjusted odds ratios (OR) and their corresponding 95% CI were calculated. All models were adjusted for pregnancy control (yes, non), mother age at delivery, gestational pathology (yes, non) and education level of the mother (Primary school, Secondary school, Advanced vocational education, University).

All statistical analyses were performed using the package Stata 16/SE (StataCorp, College Station, Tx, US).

3.5 ETHICAL APPROVAL

The study was approved by the Clinical Research Ethics Committee of Cantabria (reference:2020.174). Two different written informed consents -one for the mother and one for the child have to be signed by the mother before being admitted in the study.

4. RESULTS

The present study includes six hundred and fifty-four newborns born from six hundred and fifty mothers; of which 338 were male (51.7%) and 8 twins (1.2%). Regarding the anthropometric parameters, 94.7% of the newborn weighed more than 2500g and the length at birth was in the normal range in most cases. The length of pregnancy in 621 (95.8%) was more than 37 weeks.

In just 44 cases (6.8%) the admission in neonatology ICU was needed. Calculating the Apgar score at 1´and 5´was more than 8 in 589 (93.2%) and 630 cases (99.7%). Maternal exclusive breastfeeding at hospital discharge was granted to 393 neonates (60.3%). The distribution of all the newborn characteristics is shown in Table 1.

Table 1.- Newborn and delivery characteristic

Variable	Category	N(%)
Gender	Female	316(48.32)
	Male	338(51.68)
Twin pregnancy	Singelton	646(98.78)
	Twin	8(1.22)
Breastfeeding at hospital	Maternal exclusive	393(60.28)
	Mixed maternal and formula	142(21.78)
	Formula	117(17.94)
Weight at birth	≥2500 g	619(94.65)
	<2500 g	35(5.35)
Length of pregnancy	≥37 weeks	621(95.83)
	<37 weeks	27(4.17)
Length at birth	Percentile 10 or higher	607(92.81)
	Lower than percentile 10	47(7.19)
Cephalic perimeter at birth	Percentile 10 or higher	595(90.98)
	Lower than percentile 10	59(9.02)
Apgar 1'	8 or higher	589(93.20)
	Lower than 8	43(6.80)
Apgar 5'	8 or higher	630(99.68)
	Lower than 8	2(0.32)
Hypoglycemia	No	634(96.94)
	Yes	20(3.06)
Congenital malformations	No	645(98.62)
	Yes	9(1.38)
Neonatology admission ICU	No	599(93.16)
	Yes	44(6.84)
pH at birth		7.27 (0.06)
Transcutaneous bilirubin (mean±sd)		8.05 (0.16)
Percentile loss of weight at 2nd day of life(mean±sd)		-5.45 (0.12)
Cephalic perimeter at birth(mean±sd)		34.42 (.05)
Size at birth(mean±sd)		50.38 (.66)
Weight at birth(mean±sd)		3271.86 (17.81)

At the time of delivery 31 out of 650 mothers tested positive for SARS-CoV-2 (4.74% 95%CI (3.11-6.36)). Table 2 shows the main characteristics of delivery and the risk factors of the mother according to SARS-CoV-2 serological status of the aforementioned. The two groups of positive and negative mothers were homogeneous by age. The length of pregnancy was less than 37 weeks just in 29 cases and all of them occurring in negative mothers. In COVID-19 positive female, a higher proportion of instrumental assisted delivery (12.9% vs 6.4%) and caesarean section (25.8% vs 17.6%) were observed without reaching the statistical significance. There were no differences between gestational week at delivery or mother´s age.

Table 2.- Delivery and mother characteristics by SARS-CoV-2 serological status of the mother

Variable	**Category**	**Mother serology**		**p-value**
		Negative N (%)	**Positive N (%)**	
Birth type	Eutocic	463(76.03)	19(61.29)	0.148
	Instrumentally assisted	39(6.40)	4(12.90)	
	Caesarean section	107(17.57)	8(25.81)	
Length of	≥37 weeks	590(95.32)	31(100.00)	0.218
	<37 weeks	29(4.68)	0(0.00)	
Prenatal	No	405(65.64)	20(64.52)	0.898
	Yes	212(34.36)	11(35.48)	
Mother´s age	<25 years	33(5.31)	1(3.23)	0.792
	25-34 years	305(49.04)	14(45.16)	
	35-39 years	210(33.76)	13(41.94)	
	40 years or more	74(11.90)	3(9.68)	
Mother´s	Primary school	83(13.54)	4(12.90)	0.973
	Secondary school	53(8.65)	3(9.68)	
	Advanced vocational	200(32.63)	9(29.03)	
	University	277(45.19)	15(48.39)	
Mother´s	No	549(90.44)	29(93.55)	0.564
	Si	58(9.56)	2(6.45)	
Face-to-face work	No	336(96.83)	13(100.00)	0.514
	Si	11(3.17)	0(0.00)	
Sick leave	18th week or before	111(25.52)	5(22.73)	0.964
	19th - 25th week	111(25.52)	5(22.73)	
	26th - 32nd week	120(27.59)	7(31.82)	
	33rd week or later	93(21.38)	5(22.73)	
People living in	2	71(11.87)	5(16.67)	0.585
	3	248(41.47)	10(33.33)	
	4 or more	279(46.66)	15(50.00)	
Gestational_week		39.29(0.06)	39.29(0.26)	0.990
Mother age		33.54(0.20)	33.03(0.91)	0.583
Number of people		3.55(0.04)	3.77(0.19)	0.266

Regarding the influence of maternal serological status on the characteristics of the newborn, more than two thirds of the positive mothers gave birth to a male child (p = 0.067) and there no twins were reported in this group (Table 3). No differences were found in anthropometric parameters of the newborns according to the serological status of the mother.

In our cohort all the underweight neonates came from negative mothers. The length at birth and the cephalic perimeter at birth less than 10th percentile were more represented in the group of the newborns from negative mothers than in the group of positives.

Table 3.- Newborn characteristics by SARS-CoV-2 serological status of the mother

Variable	**Category**	**Mother serology**		**p-value**
		Negative	Positive	
Newborn gender	Female	306(49.12)	10(32.26)	0.067
	Male	317(50.88)	21(67.74)	
Weight at birth	≥2500 g	588(94.38)	31(100.00)	0.175
	<2500 g	35(5.62)	0(0.00)	
Length at birth	Percentile 10 or higher	577(92.62)	30(96.77)	0.382
	Lower than percentile 10	46(7.38)	1(3.23)	
Cephalic perimeter at birth	Percentile 10 or higher	564(90.53)	31(100.00)	0.072
	Lower than percentile 10	59(9.47)	0(0.00)	
Percentile weight loss in the 2nd day of life (mean±sd)		-5.45(0.12)	-5.25(0.56)	0.717
Transcutaneous bilirubin (mean±sd)		8.02(0.17)	8.53(0.94)	0.599

Maternal SARS-CoV infection -2 and newborn morbidity

Table 4 shows newborn morbidity and its relation to maternal infection by SARS-CoV-2.

Although no statistically significant differences were observed, a higher proportion of base excess was detected in newborns of positive mothers (6.5% vs. 0.5%), while in those of negative mothers there was a higher proportion of low pH (19.5% vs. 6.5%).

Newborns of SARS-CoV-2 positive mothers had a higher admission rate to the Neonatology ICU than those of mothers with negative results (9.6% vs 6.6%) without reaching statistical significance. No other relevant differences were observed between newborns according to maternal serological status (Table 4).

Table 4.- Relationship between mother positive to SARS-CoV-2 and newborn morbidity

Mother serology	**Type of morbidity (Cases/Total)**	**ORadj (95% CI)**	**p**
	Apgar 1'<8		
Negative	41/623	1(ref.)	.
Positive	2/31	0.90 (0.20-4.067)	0.893
	pH at birth<7.2		
Negative	123/623	1(ref.)	.
Positive	3/31	0.57 (0.16-1.95)	0.366
	Excess bases Higher than +2.5		
Negative	3/6123	1(ref.)	.
Positive	1/31	7.63 (0.53-110.18)	0.136
	Congenital malformations		
Negative	9/623	1(ref.)	.
Positive	0/31	1.00 (1.00-1.00)	.
	Hypoglycaemia		
Negative	19/623	1(ref.)	.
Positive	1/31	0.95 (0.12-7.51)	0.963
	Neonatology ICU admission		
Negative	41/623	1(ref.)	.
Positive	3/31	1.42 (0.41-4.91)	0.584

Adjusted for pregnancy control, mother age at delivery, gestational pathology (yes, non) and education level of the mother (Primary school, Secondary school, Advanced vocational education, University).

In our study, forty-two children were admitted to the neonatology ICU. Supplementary Table 1 describes the different reasons for admission to intensive care for newborns in the two groups.

Maternal infection to SARS-CoV-2 and type of newborn feeding

Regarding the relationship between maternal serological status and type of newborn feed (table 5), we observed a significant trend towards feeding with mixed (maternal and infant formula) or infant formula at the time of hospital discharge, in the newborns of positive mothers.

About 13 newborns from mothers who had tested positive (41.9%) were exclusively breastfed at hospital discharge. 10 neonates (32.3%) from positive mothers received mixed feeding (p = 0.063) and 8 (25.8%) neonates from mother who had tested positive were fed with an infant formula (p = 0.086).

The rate of mixed feeding for neonates born from women who had tested positive was similar to the rate of infant formula (Table 5).

Table 5.- Relationship between mother positive to SARS-CoV-2 and type of feeding at hospital discharge

Type of feeding at hospital discharge	Mother positive/Total	OR (95% CI)	p *
Maternal exclusive	13/393	1(ref.)	
Mixed maternal and infant formula	10/142	2.25 (0.96-5.34)	0.063
Infant formula	8/117	2.27 (0.89-5.78)	0.086

**p for trend 0.053*

Adjusted for pregnancy control, mother age at delivery, gestational pathology (yes, non) and education level of the mother (Primary school, Secondary school, Advanced vocational education, University).

Maternal infection to SARS-CoV-2 and newborn infection

At time of delivery, 14 mothers had active infection (PCR-positive); resulting in one neonate testing IgG positive (IgM and PCR negative). The transmission rate in positive mothers upon delivery was 7.1% CI95% (0-19).

At time of delivery, 12 out of the 654 newborns studied were positive to SARS-CoV-2 (1.83% 95% CI (0.81-2.86)). Eleven of them had antibodies detected in their serum (1.68% 95% CI (0.70-2.67)), nine were IgG positive and IgM negative (1.38% 95% CI (0.48-2.28)) and 2 were IgG and IgM positive (0.30 95%CI (0-0.07)). Only one of the 654 newborns evaluated was PCR-positive (0.15% 95% CI (0-0.46)). In this case, mother PCR and antibodies were negative.

Table 6 shows the distribution of antibodies against SARS-CoV-2 (IgG and IgM) in the newborns of mothers testing positive and negative for the same virus.

Consequently, it turned out that the newborns were 19.78% more likely to have IgG antibodies and 16.92% more likely to have both IgG or IgM if the mother was positive to SARS-CoV-2 RNA (p<0.001).

Table 6.- Relationship between anti-SARS-CoV-2 antibodies in neonates and mother tested positive to SARS-CoV-2

Mother serology	Neonate antibodies positives/Total	OR (95% CI)	p
	IgG		
Negative	6/623	1(ref.)	.
Positive	5/31	19.78 (5.67-69.02)	<0.001
	IgM		
Negative	2/623	1(ref.)	.
Positive	0/31	1.00 (1.00-1.00)	.
	Either IgG or IgM		
Negative	7/623	1(ref.)	.
Positive	5/31	16.92 (5.03-56.91)	<0.001

5. DISCUSSION

Despite the efforts of the scientific community in order to collect as many data as possible to identify the groups most vulnerable to SARS-CoV-2 infection, newborns have not been studied properly yet in relation to this infection.

In our study, SARS-CoV-2 infection in newborns was an uncommon finding. There was no difference between newborns from mothers COVID-19 positive and negative, in all the variables and the parameters studied (prematurity, underweights, born vaginally, maternal exclusive feeding etc.) There was not enough evidence of vertical transmission, which support the idea of continuation breastfeeding, early skin-to-skin contact and not preventive cesarean section.

Newborns had not an increased risk of infection and disease. Therefore, by applying a standardised preventive protocol, the delivery and perinatal management should not make a difference from those performed before the COVID-10 pandemic.

5.1 COMORBIDITIES

The neonates of COVID-19 mothers did not show adverse birth outcomes compared to the non-COVID-19 like low weight at birth, prematurity, cephalic perimeter at birth lower than percentile 10 or Apgar Score 1' less than 8.

However, different studies found that SARS-CoV-2 infection can cause complications for both the mother and the newborns. Preterm birth rates appear to be higher in pregnant women COVID-19 positive than in non-COVID-19 [11][13]. Muhidin S et al. in a Systematic Review and Meta-analysis described data of 89 neonates, seven of whom were low birth weight [10]. No secondary studies have established any correlation between COVID-19 and 1-min Apgar Score less than 8 until now [38].

Even though the admission rate to Neonatology ICU was higher in the group of newborns born to mothers with COVID-19 than in negative mothers, this difference was not statistically significant. A total of three newborns of COVID-19 mothers were admitted to Neonatology ICU for the following different causes: hypoglycaemia, respiratory distress or social cause.

The literature fairly agrees with our results. Many groups of studies analysed the admission to neonatal UCI of newborns from SARS-CoV-2 positive mothers in terms of risk and causes. Allotey J et al. in a Systematic Review and Meta-analysis showed that neonates of COVID-19 mothers were more frequently admitted to Neonatology ICU than those born to negative mothers [11]. Nonetheless, the different causes were markedly heterogeneous in all the studies we took into consideration (prematurity, congenital malformations, hypoalbuminemia, haemolytic anaemia, respiratory distress syndrome or sepsis) [22][23][28][39][40][41][17].

5.2 SEROLOGY OF THE NEWBORNS

Our study has also shown that, at time of delivery, fourteen mothers out of six hundred and fifty had active infection (PCR-positive); resulting in one neonate testing IgG positive (IgM and PCR negative).

Only one neonate out of six hundred and fifty-four tested PCR positive whilst the mother had negative PCR and antibodies, which is interpreted as horizontal transmission or a probable false positive.

Eleven of the newborns had positive antibodies to SARS-CoV-2 detected in their serum, nine were IgG positive and IgM negative and 2 were IgG and IgM positive. Four IgG positive neonates were born to mothers with IgG positive, which could prove a mother-to-infant antibody transmission. Positive IgM was not found in any neonates born from mothers with serology or PCR positive. Those findings sustain the idea of no vertical transmission in SARS-CoV-2 infection [10] [13][22][23][24][38][40].

Zeng and colleagues reported a study on six mothers COVID-19 positive and SARS-CoV-2 was not found by RT-PCR in any of their newborns. Virus-specific antibodies were detected in neonatal blood samples. Five infants had high value of serum IgG, which suggests that IgG is passively transmitted across the placenta. The IgG transmission is transferred at the end of second trimester, when the placenta is mature, and reaches high level at time of delivery [42].

Just case reports and case series revealed newborns who have tested positive for SARS-CoV-2 by RT-PCR. Zeng et al. reported on 3 positive neonates out of 33, born to COVID-19 positive mothers, with persisting positive viral detection by RT-PCR within a few days of the first positive RT-PCR [43]. In a case report, Alzamora et al. described a severe clinical presentation of SARS-CoV-2 infection during pregnancy. The neonate was positive for COVID-19 by RT-PCR in first day of life. A new RT-PCR 48 hours later was also positive. The neonate required invasive ventilation for 12 hours. Later the neonate was extubated with a favourable outcome[27].

5.3 CESAREAN SECTION RATE

Worldwide cesarean section has been used from the onset of COVID-19 as a way to prevent COVID-19 intrauterine, perinatal and postnatal transmission. However, vertical transmission has not been surely demonstrated.

In our study, positive mothers did not have a significantly higher rate of cesarean section or instrumental delivery than negative mothers. In March 2020, a team of obstetricians and neonatologist from HUMV developed a protocol to control the horizontal transmission of SARS-CoV-2 infection. The protocol allowed the physician to choose cesarean section or vaginal birth following clinical criteria and obstetric judgement based on maternal and foetal health indicators.

In China, Wuhan, studies performed on pregnancy outcomes at the beginning of the COVID-19 pandemic, described an increased rate of cesarean section among pregnant women who were positive for SARS-CoV-2 [13][23][38].

A systematic review and meta-analysis including 39 studies, showed a prevalence of cesarean delivery in mothers COVID-19 positive of 57% [24].

The cesarean section was chosen not only for the concerns about the risk of intrapartum mother-to-child transmission, but also for severe pre-eclampsia, symptomatic maternal infection and foetal intrauterine distress [13][23][38].

In the US, New York City, various experiences found that there were no differences in the cesarean section rate during the COVID-19 pandemic between positive mothers for SARS-CoV-2 and negative mothers. Yogangi Malhotra et al. had a total of 1952 pregnant women who delivered in their hospitals. Of these, 131 (6.7%) were confirmed positive for COVID-19. Only around one third of positive mothers underwent cesarean section, nearly the same percentage from past years (31%). Those findings suggest that there was a steady adherence to better practices for the care of their pregnant patients and, therefore, cesarean section rates did not increase. They concluded that infection of SARS-CoV-2 does not affect the route of delivery [44]. Patil et al. showed, in a retrospective cross-sectional study, that the majority of their neonates were born via vaginal delivery as well [39].

A single medical centre cohort study, in Israel and a Systematic review in the UK including 49 studies support the view not to take COVID-19 infection during delivery as an indication for cesarean section[45][46].

A retrospective multicentre analysis carried out in Northern Italy by the University of Milan, in April 2020, suggested that vaginal delivery may be associated with a low risk of intrapartum SARS-CoV-2 transmission to the newborn. Vaginal delivery was performed in about 60% of the women in this study[26].

Lately, the WHO published a recommendation in reference to the delivery route. Cesarean section should be chosen just based on obstetric indications like gestational age, severity of maternal condition and foetal viability[47].

5.4 BREASTFEEDING:

In accordance with previous studies performed during the first months of the COVID-19 pandemic, our study found a significant trend towards feeding with mixed maternal and infant formula or solely infant formula among the newborns of COVID-19 positive mothers.

Two main reasons led to the increase in the use of mixed maternal and infant formula or exclusively infant formula. In a context of lack of data, the infant formula was used as a conservative guidance to avoid the possibility of vertical transmission since there were not enough information of the presence of the virus in breast milk. Moreover, in some cases the postpartum clinical condition of the mother did not allow her to feed the newborn (mothers could be clinically unstable or on admission to the respiratory ward) with breast milk forcing the physicians to turn to infant formula [10][23].

As the pandemic progressed and new studies were published, direct breastfeeding continued to be recommended because the virus had not been found in breast milk. A retrospective cohort analysis of 101 neonates born to 100 mothers positive for SARS-CoV-2 infection from 13 March to 24 April 2020, revealed the benefits of not separating mothers positive for SARS-CoV-2 from their infants, by encouraging breastfeeding and suggesting that avoiding direct breastfeeding may not be a guarantee to prevent SARS-CoV-2 transmission [22].

No short-term adverse neonatal outcomes after skin-to-skin care or breastfeeding in neonates of SARS-CoV-2 positive mothers was recorded in two different studies in NYC; one counting 45 neonates from 45 positive mothers and the second 120 neonates from 116 positive mothers. Both papers concluded that mothers could practice skin-to-skin care and breastfeed in the delivery room. Nevertheless, these practices need to be paired with specific preventive measures, such as the use of a surgical mask when close to a neonate as well as the practice of proper hand hygiene before skin-to-skin contact, breastfeeding and routine care [39][40].

Breastmilk could play a significant role also in the presence of lactoferrin. This protein could be a protective factor against COVID-19 and other viral infections as described in some studies. It was found that lactoferrin interfered on cell receptors preventing viral anchoring, surface accumulation and cell entry. Lactoferrin could counteract the SARS-CoV-2 infection and inflammation. Early breastfeeding provides vital prevention during viral epidemics due to the specific role of lactoferrin [34][35].

It is well-known that breast milk is one the first immunoglobulin source for the babies. Immunoprotection from breast milk immunoglobulin for SARS-CoV-2 has been and is still questioned. A case report of a COVID-19 positive mother, reported how specific antibodies against SARS-CoV-2 had been detected in breast milk. The neonate was negative at RT-PCR for SARS-CoV-2 at birth, but the neonate had elevated IgG in serum. Breastfeeding also protects against the horizontal transmission of SARS-CoV-2[48].

Mother-infant contact and breastfeeding are essential to infant healthy development. The risk of COVID-19 disease should be balanced together with the risk of morbidity and mortality related to not breastfeeding and the benefits associated with skin-to-skin contact. Based on available evidence, the WHO encourages the mothers with suspected or confirmed COVID-19 to hold their newborns in the first moments of life and to initiate or continue to breastfeed. Nowadays, it is established that the advantages of breastfeeding largely outweigh the potential risks for transmission. The mothers should be properly informed to feel comfortable when breastfeeding even once at home [49].

6. CONCLUSIONS

Newborns do not appear to constitute a risk group to develop severe COVID-19 disease. According to our study, SARS-CoV-2 infection in newborns was an infrequent and especially asymptomatic finding. Because of the lack of studies, it is not currently possible to confirm or rule out vertical transmission. In our study, the caesarean section rate was not higher in COVID-19 positive women, comparing with other studies which performed more cesarean sections, but we observed a significant trend towards feeding with mixed (maternal and infant formula) or infant formula at the time of hospital discharge in the newborns of positive mothers.

The current literature does not support the abstention from breastfeeding or the separation of newborns from their mothers. Therefore, it is suggested that COVID-19 disease should not be an indication for caesarean delivery, infant formula feeding or isolation of the baby from the mother. However, more scientific evidence is needed to establish definitive guidelines and recommendations.

FUNDING

This work has been funded by a grant from the Ministerio de Educación (Beca de colaboración).

7. ACKNOWLEDGMENTS

First of all, I would like to mention Ms. Trinidad Dierssen Sotos and Ms. María Jesús Cabero Pérez, codirectors of this project, for their patience, enthusiasm, insightful comments and practical advice that has guided me in this process. Although being my first time performing a study of these characteristics, I always found support in them.

In second place, I would like to acknowledge the University of Cantabria for gave me the opportunity to carry out this project.

Likewise, I would like to express my sincere thanks to my parents and my grandma for their huge support though this long period from the moment I've decided to study this Degree, even in complicate moments.

I would like to mention my dearest friends with who I shared this experience Claudia, Cristina and Pablo.

Last, but by no means least; also, thanks to you, Giampaolo, for helping and supporting me every day and for being my life partner.

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9. SUPPLEMENTARY MATERIAL

Supplementary table 1.- Description of causes of admission in neonatology ICU

Cause of admission	Mother positive to SARS-CoV-2	Mother negative to SARS-CoV-2	Total
Jaundice	0	10	10
Hypoglycaemia	1	4	5
Respiratory distress	1	8	9
Sepsis	0	2	2
Seizures	0	1	1
Choking	0	4	4
Social	1	0	1
Prematurity	0	4	4
Thyroid hormones altered	0	1	1
Anaemia	0	1	1
Low birth weight	0	1	1
COVID-19 +	0	1	1
Mother admitted at ICU	0	1	1
Cystic adenomatoid malformation	0	1	1
Vomiting	0	1	1
Others	0	3	3