



Cross-sectional Study

Observational study on necrotizing enterocolitis in neonates born to SARS-CoV-2-positive mothers

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ABSTRACT

Background: The impact of the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic on expectant mother and their babies extends to many aspects of life. Necrotizing enterocolitis (NEC) has been recognized as a life-threatening gastrointestinal inflammatory process in neonates that has high rates of morbidity and mortality.

Objective: To investigate factors associated with NEC in hospitalized neonates whose mothers were SARS-CoV-2-positive and their relationship to mortality.

Method: This observational study was conducted from May 2020 to March 2021. All neonates who were hospitalized, after confirming that the mother was SARS-CoV-2-positive, were included in this study. The confirmation of positive SARS-CoV-2 was determined according to the reverse transcription-polymerase chain reaction (PCR) assay. The neonatal SARS-CoV-2 test was performed on the first day of birth. NEC was established based on a suggestive clinical presentation and abnormal abdominal radiographs.

Results: Of the 125 neonates enrolled in this study, there were 5 neonates who developed NEC and only one survived. Significant associated factors with NEC included lower birth weight ($p < 0.001$), lower gestational age ($p < 0.001$), positive SARS-CoV-2 PCR results (OR = 15.333; 95% CI = 2.074–113.381, $p = 0.007$), asphyxia (OR = 13.143; 95% CI = 1.411–122.443, $p = 0.024$), and mortality (OR = 156.000; 95% CI = 13.157–1849.623; $p < 0.001$). Mortality was significantly associated with lower gestational age ($p = 0.025$), cesarean section delivery ($p = 0.025$), and asphyxia ($p = 0.025$).

Conclusion: Significant associated factors with NEC in neonates born to SARS-CoV-2-positive mothers included positive SARS-CoV-2 PCR results, asphyxia, lower gestational age, and lower birth weight. In addition to caesarean section delivery, these factors were related to mortality in neonates in such conditions.

1. Introduction

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) epidemic started in China and quickly disseminated to other countries and has become a major global health problem since then. As it has been labeled as a global pandemic in 2019, many expectant mothers and their babies have experienced serious health problems due to SARS-CoV-2, including expectant mothers and babies in Indonesia [1]. The government of Indonesia reported that the confirmed case in Indonesia has

reached 6 million positive cases with a total of more than 155,000 deaths [2]. When second-wave cases were identified, the prevalence of SARS-CoV-2 cases in Indonesia grew rapidly, with the average number of new confirmed around 4,000–5,000/day [3]. Based on the Indonesian Obstetrics Doctors Association (POGI) reports as of April 2021, there have been more than 500 cases of SARS-CoV-2 infected expectant mothers, 16 of whom died [4].

Although it is a newly recognized disease, many research centers have investigated this SARS-CoV-2 disease with many recent findings,

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furthermore it has led to the development of knowledge about SARS-CoV-2 infection, especially in pregnant women and newborns. Pregnant women belong to a population that is more susceptible to contracting coronavirus disease in comparison with other healthy adults. However, SARS-CoV-2 could increase the risk of pregnancy complications, such as the risk of preterm delivery, and affect newborn babies' organs system. One of the organs affected by SARS-CoV-2 infection is the gastrointestinal tract [5].

Necrotizing enterocolitis (NEC) has been recognized as a terrible inflammation of the gastrointestinal tract in neonates that often requires surgery. The contribution of NEC to neonatal morbidity and mortality is still high, particularly in developing countries. Surviving NEC infants may have poor growth and neurodevelopmental impairment [6]. Previous studies identified the incidence of NEC in preterm infants born to mothers with COVID-19 which correlated with the condition of the mother experiencing respiratory distress during delivery, asphyxia, and positive PCR results for infants [7]. However, the role of SARS-CoV-2 infections in expectant mothers on the incidence of NEC in their infants, regardless of gestational age or birth weight, has not been well established. Thus, this study aimed to find out the factors associated with NEC in hospitalized neonates whose mothers were SARS-CoV-2-positive and to investigate whether these factors were associated with mortality in such conditions.

2. Materials and methods

2.1. Eligible participants

This study was conducted from May 2020 to March 2021. All neonates who were hospitalized, after confirming that his/her mother was SARS-CoV-2-positive, were included in this study. Neonates born outside the hospital were not included in this study. This hospital is a referral hospital for expectant mothers who are confirmed positive for SARS-CoV-2 in the eastern part of Indonesia.

2.2. Testing for SARS-CoV-2

In cases which the SARS-CoV-2 virus could be detected on a nose and throat swab through the reverse transcription-polymerase chain reaction (RT-PCR) assay, the case was then declared positive. The laboratory appointed to carry out the RT-PCR examination was an official laboratory established by the Government of Indonesia based on the Decree of the Minister of Health of the Republic of Indonesia (Reference Number: HK.01.07/Menkes/4642/2021), including the clinical pathology department at Soetomo Hospital. The RT-PCR examination (Abbot, Des Plaines, United States) was carried out by competent specialist doctors who had 24 h working hours with a certain schedule.

2.3. Necrotizing enterocolitis

NEC was diagnosed based on a suggestive clinical presentation and abnormal findings on abdominal X-rays. Clinical signs suggestive of NEC included an increase in the gastric residue of more than 20%, marked abdominal distension, emesis, abdominal tenderness, abdominal skin discoloration, bloody stools, and guaiac-positive stools. Meanwhile, abdominal X-ray findings that supported NEC included persistent bowel loops, bowel dilatation, portal venous gas, pneumatosis intestinalis, ileus, and pneumoperitoneum [8]. The diagnosis of spontaneous intestinal perforation was made if a focal gastrointestinal perforation was found during surgery, then the infant was excluded from this study [9].

2.4. Care for neonates born to SARS-CoV-2-positive mothers

An expectant mother who was confirmed positive for SARS-CoV-2 was cared for in a separate treatment room and monitored by a team of doctors dedicated to treating SARS-CoV-2 disease. The delivery was

deployed in a separate room specifically for SARS-CoV-2-positive patients, including the operating room which also used the SARS-CoV-2 operating room. At the time of delivery, the neonatal doctor team had been notified and had been present before delivery occurred. Neonates born either spontaneously or by cesarean section would be treated in the SARS-CoV-2 neonatal care room. Enteral nutrition was given using expressed breast milk or formula with the consent of the mother or the neonate's family. The RT-PCR examination of the neonate was performed within 24 h after birth. If the neonate's RT-PCR result was negative, the neonate could be transferred to a non-SARS-CoV-2-positive neonatal care room. The SARS-CoV-2-negative neonate could be cared for with the mother if the mother's RT-PCR result was negative. In this study, neonates were observed until the neonate was discharged from the hospital or until he/she died.

2.5. Data collection

Only mothers with positive SARS-CoV-2 were analyzed in this study. Variables were collected including neonatal factors (gestational age, birth weight, sex, mode of delivery, SARS-CoV-2 PCR swab result, asphyxia, multiple births, NEC, mortality) and maternal comorbidities (obesity, pre-eclampsia, hypertension, premature rupture of membranes, hepatitis B, placenta accrete) were selected as the variables analyzed in this study. Asphyxia is failure to establish adequate breathing at birth defined as a fifth-minute Apgar score of less than 7 [10]. Multiple births were confirmed when the mother gave birth to more than one baby in one delivery [11]. Data on neonates and maternal comorbidities were obtained from medical records. We also interviewed the mother to obtain information related to the mother's medical record, including the provision of feeding. The study report is based on Strengthening of Reporting of Cohort Studies in Surgery (STROCSS) guidelines 2021 [12].

2.6. Statistical analysis

Qualitative data were presented using numbers and percentages. Quantitative data were performed in terms of mean, minimum, maximum, and standard deviation. In this study, statistical analysis of the chi-squared and logistic regression tests was used. To predict the independent variable (sex, mode of delivery, SARS-CoV-2 RT-PCR result, asphyxia, mortality) to the dependent variable (necrotizing enterocolitis), this study used a logistic regression test. The chi-squared test was used to analyze selected variables (sex, birth weight, gestational age, mode of delivery, SARS-CoV-2 RT-PCR result, and asphyxia) with mortality in NEC neonates. Statistical analyses were interpreted using IBM SPSS Statistics 21 (IBM Corp., Armonk, NY, USA); this included descriptive and inferential analyses. A p -value <0.05 was considered significant.

3. Result

3.1. Characteristics of all neonates

126 neonates fulfilled the inclusion requirements of this study, otherwise there was one parent who did not provide consent, then there were 125 neonates who were included in the final analysis. The minimum birth weight was 1000 g and the maximum birth weight was 4300 g (2867.60 ± 698.75), meanwhile the minimum gestational age was 28 weeks and the maximum gestational age was 41 weeks (37.05 ± 2.81). In this study, the majority of neonates (62.4%) were delivered by cesarean section. The majority of the neonate's gestational age (70.4%) was term and the majority of the neonate's birth weight (75.2%) was above 2500 g. Although as many as 25.6% of neonates born were asphyxiated, most of these neonates (94.4%) could survive. About 5.6% of neonates born had positive SARS-CoV-2 PCR results. The highest number of maternal comorbidities was pre-eclampsia. The detailed data

was exhibited in Table 1.

3.2. Characteristic differences between infants with NEC and without NEC

In this study, 5 neonates experienced NEC and only 1 survived. Most neonates with NEC were female (60%). All cases of NEC occurred at a lower gestational age (<37 weeks) and lower birth weight (<2500 g). Based on the distribution of birth weight and gestational age groups, in the group of neonates with NEC, as many as 3 (60%) neonates had a birth weight of 1500–2499 g and as many as 4 (80%) had a gestational age of <34 weeks. Most of the neonates (60%) had negative RT-PCR results and as many as 4 (80%) infants had a history of asphyxia at birth.

There were significant differences in gestational age ($p < 0.001$), birth weight ($p < 0.001$), positive RT-PCR results ($p = 0.007$), history of asphyxia ($p = 0.024$), and mortality ($p < 0.001$) between neonates with NEC and neonates without NEC. Meanwhile, there were no significant differences in sex ($p = 0.469$) and mode of delivery ($p = 0.422$) between neonates with NEC and neonates without NEC (Table 2).

3.3. Associated factors with NEC

Significant associated factors with NEC in this study included lower birth weight ($p < 0.001$), lower gestational age ($p < 0.001$), positive SARS-CoV-2 RT-PCR results (OR = 15.333; 95% CI = 2.074–113.381; $p = 0.007$) and asphyxia (OR = 13.143; 95% CI = 1.411–122.443; $p = 0.024$). This study found that the incidence of NEC had significant correlation with mortality (OR = 156.000; 95% CI = 13.157–1849.623; $p < 0.001$). The detail data was described in Table 2.

3.4. Associated factors with mortality in NEC infants

This study also analyzed the associated factors with mortality in neonates who experienced NEC related to SARS-CoV-2-positive mothers. From the statistical results, it was found that sex, birth weight, and positive SARS-CoV-2 RT-PCR results were not significantly associated

Table 2

Characteristic of comparison between infant with NEC and non-NEC.

Variable	NEC	non-NEC	OR	95% CI	p
Sex			0.510	0.082–3.163	
Male	2 (40)	68 (56.7)			0.469
Female	3 (60)	52 (43.4)			
Birth weight (gr)			N/A	N/A	
1000-1499	2 (40)	3 (2.5)			<0.001**
1500-2499	3 (60)	23 (19.1)			
>2500	0 (0)	94 (78.5)			
Gestational age (weeks)			N/A	N/A	
<34	4 (80)	13 (10.8)			<0.001**
34-36	1 (20)	19 (15.8)			
≥37	0 (0)	88 (73.4)			
Mode of delivery			2.486	0.270–22.940	0.422
Spontaneous	1 (20)	74 (61.7)			
Caesarean section	4 (80)	46 (38.3)			
COVID-19			15.333	2.074–113.381	0.007*
Positive	2 (40)	5 (4.2)			
Negative	3 (60)	115 (95.8)			
Asphyxia			13.143	1.411–122.443	0.024*
Yes	4 (80)	28 (23.3)			
No	1 (20)	92 (76.7)			
Mortality			156.000	13.157–1,849.623	<0.001**
Death	4 (80)	3 (2.5)			
Survive	1 (20)	117 (97.5)			

Note: NEC = Necrotizing enterocolitis; N/A = not applicable; OR = odd ratio; 95% CI = 95% confidence interval; *significant <0.05; **significant <0.001.

with mortality. Significant associated factors with mortality in this study included lower gestational age ($p = 0.025$), caesarean section delivery ($p = 0.025$), and asphyxia ($p = 0.025$). The detailed data was demonstrated in Table 3.

4. Discussion

Since SARS-CoV-2 infection was first recognized in 2019, the SARS-CoV-2 disease has become more widespread and its impact has permeated the entire world, including Indonesia. The impact is not only on the burden of disease but also on all aspects of human life. Previous prospective cohort reported that there was a link between SARS-CoV-2 infection and pregnant women, even maternal death. The main causes of mortality for pregnant women with positive COVID-19 were a respiratory failure, severe preeclampsia, and hemorrhage [13]. A study by Villar et al. showed that pregnant women infected with SARS-CoV-2 with co-morbidities such as pre-existing overweight, diabetes, hypertension, or chronic respiratory disease, were at higher risk of developing preeclampsia or eclampsia [14]. A systematic review conducted by Ciapponi et al. demonstrated that the most frequent maternal outcomes due to SARS-CoV-2 infection were C-sections (23%–96%) and preterm deliveries (14%–64%) [15]. These maternal antenatal factors could increase the risk of necrotizing enterocolitis in neonates [16,17].

Table 1

Characteristics of all infants.

Variable	n (%)
Sex	
Male	70 (56)
Female	55 (44)
Birth weight (gr)	
1000-1499	5 (4)
1500-2499	26 (20.8)
>2500	94 (75.2)
Gestational age (weeks)88 (70.4)	
<34	17 (13.6)
34-36	20 (16)
≥37	88 (70.4)
Mode of delivery	
Spontaneous	47 (37.6)
Caesarean section	78 (62.4)
Multiple birth	1 (0.8)
SARS-CoV-2 RT-PCR result	7 (5.6)
Positive	118 (94.4)
Negative	
Asphyxia	32 (25.6)
Necrotizing enterocolitis	5 (4)
Mortality	
Death	7 (5.6)
Survive	118 (94.4)
Mother's comorbid	
Obesity	3 (2.4)
Pre-eclampsia	20 (16)
Hypertension	5 (4.0)
Premature rupture of membrane	3 (2.4)
Hepatitis B	2 (1.6)
Placenta accrete	2 (1.6)

Table 3
Associated factor with mortality in NEC infant.

Variable	Death	Survive	OR	95% CI	p
Sex			0.500	0.188–1.332	0.361
Male	2	0			
Female	2	1			
Birth weight (gr)			0.667	0.300–1.484	0.361
1000-1499	2	0			
1500-2499	2	1			
>2500	0	0			
Gestational age (weeks)			N/A	N/A	0.025*
<34	4	0			
34-36	0	1			
≥37	0	0			
Mode of delivery			N/A	N/A	0.025*
Spontaneous	0	1			
Caesarean section	4	0			
COVID-19			0.250	0.046–1.365	0.171
Positive	1	1			
Negative	3	0			
Asphyxia			N/A	N/A	0.025*
Yes	4	0			
No	0	1			

Note: NEC = Necrotizing enterocolitis; N/A = not applicable; OR = odd ratio; 95% CI = 95% confidence interval; *significant <0.05; **significant <0.001.

This study indicated that the majority of SARS-CoV-2-positive mothers gave birth to term infants, although they were also likely to give birth prematurely, which was also shown in other studies [18,19]. A previous study showed that most infants of SARS-CoV-2-positive mothers (73.3%) were born at term and weighed more than 2500 g at birth [18]. In contrast, another study reported that infants born to coronavirus-positive mothers are liable to be born premature (51%) rather than at term (49%) [19]. This study showed that, apart from the majority of neonates born at term, neonates delivered from SARS-CoV-2-positive mothers had birth weights >2500 g. On the other hand, neonates with NEC, all of them had a gestational age of <37 weeks and a birth weight of <2500 g.

In this study, most of the methods of delivery were by cesarean section. Previous studies reported that cesarean section was the majority mode of delivery for SARS-CoV-2-positive pregnant women [15,20]. The preferred mode of delivery by cesarean section primarily aimed to prevent the transmission of coronavirus infection in the environment [21]. The possible cause of the high rate of cesarean delivery could be due to the constraints of appropriate recommendations during the pandemic considering that this coronavirus disease is newly recognized [13,22]. Nevertheless, based on recommendations from The American College of Obstetricians and Gynecologists, indications for delivery are not only from SARS-CoV-2 infection but also obstetric indications from comorbidities that burden the expectant mother [23]. Other studies have reported that expectant mothers who are infected with SARS-CoV-2 often come with breathing difficulties that can endanger the lives of the mother and baby, so quick decisions are needed to deal with these difficult situations [15]. The condition of pregnant women with severe respiratory failure is influenced by the absence of adequate antenatal care. During the pandemic, apart from the lockdown policy, pregnant women in our country have a high fear of coming to health facilities so that their health conditions and pregnancy are not properly monitored [4]. In this study, of the 5 neonates who experienced NEC in this study, 4 neonates underwent cesarean section and all four had a gestational age of <34 weeks and a birth weight of <2500 g. However, preterm delivery increases the consequent immaturity of organs and immunity in the newborn which makes the neonate susceptible to any infection.

This study exhibited that about 5% of all neonates born to SARS-CoV-2-positive mothers had positive PCR results for SARS-CoV-2 and 40% of them experienced NEC. Similar results were reported by other studies [19,24]. Based on a study conducted by Yuan et al., currently there is not

sufficient evidence that there is vertical transmission of SARS-CoV-2. However, it was also reported that neonates born to mothers infected with SARS-CoV-2 had elevated blood levels of IgM antibodies against SARS-CoV-2 within 2 h of birth, which suggests that SARS-CoV-2 could potentially transmit vertically, despite the risks that could be small [25]. A cohort study reported that pregnant women infected with coronavirus increased the risk of developing a neonatal early-onset infection. Therefore, protocols for screening for SARS-CoV-2 in all pregnant women, strict infection control, and monitoring of newborns at risk of SARS-CoV-2 are crucial [26,27].

In this study, there were 5 neonates diagnosed with NEC. Variables found to be associated with the occurrence of NEC included lower gestational age, lower birth weight, positive RT-PCR results for SARS-CoV-2, and asphyxia. Expectant mothers suffering from SARS-CoV-2 infection often experience severe and life-threatening respiratory problems, so pregnancy termination must be carried out. The condition of severe respiratory distress in an expectant mother will have a detrimental impact on the baby so that it contributes to the baby being born with asphyxia [1]. Other than those maternal antenatal factors, there was also the nutritional factor that should be taken into consideration regarding the incidence of NEC in neonates of SARS-CoV-2-positive mothers. As it has been known, breastmilk is one of the most effective ways to prevent NEC. Though coronavirus hasn't been detected in breast milk, the time provided for mothers with coronavirus infection to breastfeed their child has been limited and this could lead to lower defensive mechanism of infants' gastrointestinal system [28]. This study also demonstrated that the occurrence of NEC was strongly related to mortality. The presence of lower birth weight and gestational age may be aggravating factors of death in NEC cases in this study considering that all NEC patients in this study had lower birth weight and gestational age [7,29].

The diagnosis of NEC is challenging because the symptoms may go unnoticed by the clinician even though it is progressive and causes high mortality. Intestinal fatty acid-binding protein (I-FABP) has good accuracy in early detection and predicting the severity of NEC with a sensitivity of 90% and a specificity of 100% [30]. In this study, the diagnosis of NEC was based on clinical symptoms that support NEC and abnormal abdominal radiographs. In our country, the I-FABP examination is not always available and is not easy to obtain. Abdominal ultrasonography (USG) has recently been used as a diagnostic imaging option in NEC because abdominal USG has a good ability to detect intestinal peristalsis, bowel wall thickening, and free air in the abdominal cavity. The combination of abdominal ultrasound with abdominal X-ray is a powerful imaging tool to detect the presence of NEC [31]. Unfortunately, abdominal USG has not become a routine examination to detect NEC in our hospital.

A few limitations need to be considered in this study. First, the sample size in this study was relatively small. However, SARS-CoV-2 infection is a newly recognized disease, while the impact is variable and can be very severe for some populations. In addition, there are not many similar studies, so this research can be taken into consideration, particularly in countries that have the same characteristics as ours. Second, this research was conducted in the course of the first wave and the beginning of the second wave of the SARS-CoV-2 outbreak in Indonesia. Results may differ in subsequent wave periods and this requires further multicenter research.

5. Conclusion

This study demonstrated that the existence of coronavirus infection in expectant mothers could be a significant factor in the incidence of NEC in their babies. Significant associated factors with NEC in neonates born to SARS-CoV-2-positive mothers included positive SARS-CoV-2 RT-PCR results, asphyxia, lower gestational age, and lower birth weight. In addition to cesarean section delivery, these factors are related to mortality in neonates in such conditions. Therefore, long-term researches is

required to evaluate the further development of neonates whose mothers were SARS-CoV-2-positive.

Ethical approval

We have conducted an ethical approval based on the Declaration of Helsinki with registration research at the Health Research Ethics Committee in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

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Author contribution

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Registration of research studies

Name of the registry: Health Research Ethics Committee in the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

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Guarantor

Risa Etika is the person in charge of the publication of our manuscript.

Consent

Written informed consent was obtained from the patient.

Provenance and peer review

Not commissioned, externally peer reviewed.

Declaration of competing interest

Dina Angelika, Risa Etika, Naomi Nathania Kusumawardani, Setya Mithra, and I Dewa Gede Ugrasena declare that they have no conflict of interest.

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References

- V. Vardhelli, A. Pandita, A. Pillai, S.K. Badatya, Perinatal COVID-19: review of current evidence and practical approach towards prevention and management, *Eur. J. Pediatr.* 180 (4) (2021) 1009–1031, <https://doi.org/10.1007/s00431-020-03866-3>.
- B. Nugraha, L.K. Wahyuni, H. Laswati, P. Kusumastuti, A.B. Tulaar, C. Gutenbrunner, COVID-19 pandemic in Indonesia: situation and challenges of rehabilitation medicine in Indonesia, *Acta. med. Indones.* 52 (3) (2020) 299–305.
- M.I.A. Akbar, K.E. Gumilar, R. Andriya, M.P. Wardhana, P. Mulawardhana, J. Y. Anas, et al., Clinical manifestations and pregnancy outcomes of COVID-19 in Indonesian referral hospital in central pandemic area, *Obst. Gynecol. Sci.* 65 (1) (2022) 29–36, <https://doi.org/10.5468/ogs.21135>.
- N. Ariani, Antenatal care services utilization during COVID-19 second wave attack in Pasuruan, Indonesia, *J. Med. life* 15 (1) (2022) 7–14, <https://doi.org/10.25122/jml-2021-0238>.
- R. Yang, H. Mei, T. Zheng, Q. Fu, Y. Zhang, S. Buka, et al., Pregnant women with COVID-19 and risk of adverse birth outcomes and maternal-fetal vertical transmission: a population-based cohort study in Wuhan, China, *BMC Med.* 18 (1) (2020) 330, <https://doi.org/10.1186/s12916-020-01798-1>.
- A. Allendorf, R. Dewitz, J. Weber, S. Bakthiar, R. Schloesser, U. Rolle, Necrotizing enterocolitis as a prognostic factor for the neurodevelopmental outcome of preterm infants - match control study after 2years, *J. Pediatr. Surg.* 53 (8) (2018) 1573–1577, <https://doi.org/10.1016/j.jpedsurg.2018.01.006>.
- D. Angelika, R. Etika, A.D. Vita, S. Mithra, I.D.G. Ugrasena, Necrotizing enterocolitis in preterm infants born to mother with COVID-19, *Open Access Macedonian J. Med. Sci.* 9 (B) (2021) 1499–1504, <https://doi.org/10.3889/oamjms.2021.7326>.
- B.S.R. Allin, A.M. Long, A. Gupta, K. Lakhoo, M. Knight, One-year outcomes following surgery for necrotising enterocolitis: a UK-wide cohort study, *Arch. Dis. Child. Fetal Neonatal Ed.* 103 (5) (2018), <https://doi.org/10.1136/archdischild-2017-313113>. F461-f6.
- C. Tiwari, G. Sandlas, S. Jayaswal, H. Shah, Spontaneous intestinal perforation in neonates, *J. Neonatal Surg.* 4 (2) (2015) 14.
- R.A. Abdo, H.M. Halil, B.A. Kebede, A.A. Anshebo, N.G. Gejo, Prevalence and contributing factors of birth asphyxia among the neonates delivered at Nigist Eleni Mohammed memorial teaching hospital, Southern Ethiopia: a cross-sectional study, *BMC Pregnancy Childbirth* 19 (1) (2019) 536, <https://doi.org/10.1186/s12884-019-2696-6>.
- O.A. Uthman, M.B. Uthman, I. Yahaya, A population-based study of effect of multiple birth on infant mortality in Nigeria, *BMC Pregnancy Childbirth* 8 (2008) 41, <https://doi.org/10.1186/1471-2393-8-41>.
- G. Mathew, R. Agha, Stross 2021: Strengthening the reporting of cohort, cross-sectional and case-control studies in surgery, *Int. J. Surg.* 96 (2021) 106165, <https://doi.org/10.1016/j.ijsu.2021.106165>.
- A.T. Papageorgiou, P. Deruelle, R.B. Gunier, S. Rauch, P.K. Garcia-May, M. Mhatre, et al., Preeclampsia and COVID-19: results from the INTERCOVID prospective longitudinal study, *Am. J. Obstet. Gynecol.* 225 (3) (2021) 289, <https://doi.org/10.1016/j.ajog.2021.05.014>, e1.-e17.
- J. Villar, S. Ariff, R.B. Gunier, R. Thiruvengadam, S. Rauch, A. Kholin, et al., Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the INTERCOVID multinational cohort study, *JAMA Pediatr.* 175 (8) (2021) 817–826, <https://doi.org/10.1001/jamapediatrics.2021.1050>.
- A. Ciapponi, A. Bardach, D. Comandé, M. Berrueta, F.J. Argento, F. Rodriguez Cairoli, et al., COVID-19 and pregnancy: an umbrella review of clinical presentation, vertical transmission, and maternal and perinatal outcomes, *PLoS One* 16 (6) (2021), e0253974, <https://doi.org/10.1371/journal.pone.0253974>.
- H. Zhu, L. Wang, C. Fang, S. Peng, L. Zhang, G. Chang, et al., Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia, *Transl. Pediatr.* 9 (1) (2020) 51–60, <https://doi.org/10.21037/tp.2020.02.06>.
- N. Samuels, R.A. van de Graaf, R.C.J. de Jonge, I.K.M. Reiss, M.J. Vermeulen, Risk factors for necrotizing enterocolitis in neonates: a systematic review of prognostic studies, *BMC Pediatr.* 17 (1) (2017) 105, <https://doi.org/10.1186/s12887-017-0847-3>.
- A. Ayed, A. Embaireeg, A. Benawadh, W. Al-Fouzan, M. Hammoud, M. Al-Hathal, et al., Maternal and perinatal characteristics and outcomes of pregnancies complicated with COVID-19 in Kuwait, *BMC Pregnancy Childbirth* 20 (1) (2020) 754, <https://doi.org/10.1186/s12884-020-03461-2>.
- P. Anand, A. Yadav, P. Debata, S. Bachani, N. Gupta, R. Gera, Clinical profile, viral load, management and outcome of neonates born to COVID 19 positive mothers: a tertiary care centre experience from India, *Eur. J. Pediatr.* 180 (2) (2021) 547–559, <https://doi.org/10.1007/s00431-020-03800-7>.
- J.S. Brandt, J. Hill, A. Reddy, M. Schuster, H.S. Patrick, T. Rosen, et al., Epidemiology of coronavirus disease 2019 in pregnancy: risk factors and associations with adverse maternal and neonatal outcomes, *Am. J. Obstet. Gynecol.* 224 (4) (2021) 389, <https://doi.org/10.1016/j.ajog.2020.09.043>, e1.-e9.
- L.M. Savitsky, C.M. Albright, Preventing COVID-19 transmission on labor and delivery: a decision analysis, *Am. J. Perinatol.* 37 (10) (2020) 1031–1037, <https://doi.org/10.1055/s-0040-1713647>.
- M. Papanou, M. Papaioannou, A. Petta, E. Routsis, M. Farmaki, N. Vlahos, et al., Maternal and neonatal characteristics and outcomes of COVID-19 in pregnancy: an overview of systematic reviews, *Int. J. Environ. Res. Publ. Health* 18 (2) (2021), <https://doi.org/10.3390/ijerph18020596>.
- A. Barrero-Castillero, K.S. Beam, L.B. Bernardini, E.G.C. Ramos, P.E. Davenport, A. R. Duncan, et al., COVID-19: neonatal-perinatal perspectives, *J. Perinatol. : off. j. Calif. Perinat. Assoc.* 41 (5) (2021) 940–951, <https://doi.org/10.1038/s41372-020-00874-x>.
- M.L.B. Teixeira, O.D. Costa Ferreira Júnior, E. João, T. Fuller, J. Silva Esteves, W. Mendes-Silva, et al., Maternal and neonatal outcomes of SARS-CoV-2 infection in a cohort of pregnant women with comorbid disorders, *Viruses* 13 (7) (2021), <https://doi.org/10.3390/v13071277>.
- J. Yuan, H. Qian, S. Cao, B. Dong, X. Yan, S. Luo, et al., Is there possibility of vertical transmission of COVID-19: a systematic review, *Transl. Pediatr.* 10 (2) (2021) 423–434, <https://doi.org/10.21037/tp-20-144>.
- L. Zeng, S. Xia, W. Yuan, K. Yan, F. Xiao, J. Shao, et al., Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in wuhan, China, *JAMA Pediatr.* 174 (7) (2020) 722–725, <https://doi.org/10.1001/jamapediatrics.2020.0878>.
- A.A. Rabaan, S.H. Al-Ahmed, A. Al-Mutair, S. Alhumaid, A.A. Sule, R. Tirupathi, et al., Immunopathogenesis and immunobiology of SARS-CoV-2, *Infezioni Med. Le* 29 (2) (2021) 167–180.

- [28] R. Davanzo, G. Moro, F. Sandri, M. Agosti, C. Moretti, F. Mosca, Breastfeeding and coronavirus disease-2019: ad interim indications of the Italian society of neonatology endorsed by the union of European neonatal & perinatal societies, *Matern. Child Nutr.* 16 (3) (2020), e13010, <https://doi.org/10.1111/mcn.13010>.
- [29] M.A.A. Farghaly, F. Kupferman, F. Castillo, R.M. Kim, Characteristics of newborns born to SARS-CoV-2-positive mothers: a retrospective cohort study, *Am. J. Perinatol.* 37 (13) (2020) 1310–1316, <https://doi.org/10.1055/s-0040-1715862>.
- [30] O.M. Abdel-Haie, E.G. Behiry, E.R. Abd Almonaem, E.S. Ahmad, E.H. Assar, Predictive and diagnostic value of serum intestinal fatty acid binding protein in neonatal necrotizing enterocolitis (case series), *Ann. med. surg.* 2017 (21) (2012) 9–13, <https://doi.org/10.1016/j.amsu.2017.05.010>.
- [31] G. D'Angelo, P. Impellizzeri, L. Marseglia, A.S. Montalto, T. Russo, I. Salamone, et al., Current status of laboratory and imaging diagnosis of neonatal necrotizing enterocolitis, *Ital. J. Pediatr.* 44 (1) (2018) 84, <https://doi.org/10.1186/s13052-018-0528-3>.