Original Article

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Clinical Features and Outcome of Confirmed COVID-19 Neonates in North Sulawesi, Indonesia: Serial-Cases, Single-Centre

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Abstract

As the research of COVID-19 is still ongoing, especially in neonates, this case series aimed to establish new information regarding clinical manifestations that might be accompany neonates who were COVID-19 confirmed, regardless the route of transmission. We report five confirmed COVID-19 infants. Data were collected from the patients' medical records in COVID-19 Neonatal Isolation Ward, Prof. Dr. R. D. Kandou Hospital, Manado, North Sulawesi, Indonesia. The clinical findings among neonates with confirmed COVID-19 appeared to be varied. Some shows mild symptoms, while the others died from complication of sepsis. This studies also found congenital anomaly might be one of the manifestations of COVID-19 infection. Further researched is needed to established the route of COVID-19 transmission to the infants.

Keywords: COVID-19, Neonates, Case Series, Outcome.

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Introduction

Due to immaturity of immune system and the possibility of mother to fetal vertical and aerosol transmissions, neonates are particularly vulnerable to the coronavirus (SARS-CoV-2) infection.[1] Recent studies show immunoglobulin (Ig)-M antibodies have been detected in newly born infants, although viral RNA has not been isolated, suggesting a possibility of vertical transmission. Moreover, disturbance of the placental barrier in placental abruption or maternal-fetal haemorrhage may become the entrance for virus and/or IgM antibodies transmission to the fetal circulation.

Pregnant women seem to be more susceptible to viral infections due to partial immune suppression. During the last trimesters, it is reported that fever, dry cough, fatigue, myalgia, and sore throat are the main clinical findings of COVID-19 in pregnant women. From laboratory findings, peripheral white blood cell counts are either normal or decreased, it is often lymphopenia, mild thrombocytopenia, and elevated levels of liver enzymes, creatine phosphokinase, and C-reactive protein have been reported. Detection of viral nucleic acid from SARS-CoV-2 using RT PCR has been referenced as the standard diagnostic. Specimens from saliva, nasopharyngeal and oropharyngeal swabs, sputum, endotracheal aspirate, or bronchoalveolar lavage, urine, and stool should be evaluated using RT-PCR.[2]

Study has found neonates with COVID-19 do not have any specific clinical findings. The relationship between postnatal tachypnea, feeding intolerance, mechanical ventilation requirement and abnormal laboratory results and COVID infection is not fully established. Fever, respiratory distress, dyspnea, cyanosis, tachycardia, feeding intolerance, vomiting, and lethargy are reported to be common symptoms in neonates with COVID-19 infection.[3] Duran P et al conducted a systematic review of 222 newborns whose mothers were suspected or confirmed to be SARS-CoV-2 positive perinatally were evaluated, it was concluded that some of the most common clinical findings were increased preterm delivery rate, intrauterine fetal distress, respiratory failure findings (Respiratory Distress Syndrome and Transient Tachypnea of Newborn), pneumonia, low birth weight, chorioamnionitis, and meconium-stained amnion. Among them only 13 were reported as positive for SARS-CoV-2; while most were reported no or mild symptoms and no adverse perinatal outcomes. Two studies among those neonates who tested positive reported moderate or severe clinical findings.[4]

Kanburoglu MK et al,[5] performed a study on 37 babies whose mothers did not have COVID-19 infection during pregnancy

and had community-based COVID-19 infection after. From the calculation 49% experienced fever, 41% hypoxemia, 27% cough, and 24% experienced tachypnea. Other findings detected with less frequency are feeding difficulty, retraction, diarrhea, nasal congestion, runny nose, and exanthema. [5]

Our series of neonates' cases with confirmed COVID-19 were taken place during the first outbreak of SARS CoV-2 infection in North Sulawesi, Indonesia, occurring between March 2020 and June 2021. Among 564 neonates with suspected SARS CoV-2 infection who admitted to COVID-19 Neonatal Isolation Ward in Prof. Dr. R. D. Kandou Hospital, there were 5 of them, confirmed positive of COVID-19. The suspected COVID-19 neonates were either born from suspected or confirmed COVID-19 mother or having referred from peripheral health care facility with SARS CoV-2 infection suggestive symptoms. Prof. Dr. R. D. Kandou Hospital is the only referral hospital and treatment centre for SARS CoV-2 infection in North Sulawesi, Indonesia, which is facilitated with COVID-19 Neonatal Isolation Ward. All neonates with suspected or confirmed COVID-19 infections around the province will be referred to Prof. Dr. R. D. Kandou Hospital for further management.

Case Presentation 1

The mother of the newborn is 43 years old with G2P1A0, 38-39 weeks of gestation age who lives in Manado. On December 15th 2020, she had caesarean delivery due to uterine fibroid, high risk pregnancy, oligohydramnios, intrauterine growth retardation, and breech presentation. Her rapid SARS-CoV-2 test was reactive. She denied having contact with confirmed or suspected COVID-19 patient. She had no history of hypertension, diabetes, or heart disease. Fever, cough, swallowing pain, and shortness of breath before delivery were also denied. She delivered a baby boy weighing 1,500 gr, with body length of 39 cm. Apgar scores were 5 and 7, with muscle tone weak but crying was loud. During observation after delivery, the baby down score was 2 with respiratory rate 68 times per minute and minimal retraction. The mother had been wearing an N95 mask throughout the operation, and baby had no contact with mother after birth. The mother and her infant were both transferred to the COVID-19 room isolation, with the later was treated separately in incubator inside COVID-19 neonatal isolation ward.

His vital signs were stable with the blood oxygen saturation maintained above 95% with oxygen nasal cannula, the respiratory rate was 68 times per minute, his pulse was 130 beats per minute with strong and regular pulse and temperature of 36.6 degrees Celsius. Upon physical examination, the baby was found to have paraphimosis, his preputium was retracted beyond the corona of penis and unable to be pulled back. However, there were no swelling and redness observed around the area.

Blood tests of the newborn revealed within normal limit, with white blood cell 12,200 /mm^3, haemoglobin 19.5 g/dL, hematocrit 55.1 %, platelets 213,000/mm^3, eosinophil 1%, basophil 0 %, band neutrophil 0 %, segment neutrophil 66%, lymphocyte 25 %, monocyte 8 %, IT ratio 0, and CRP <6 mg/dL. Rapid test of SARS-CoV-2 was negative. The result of first pharyngeal swab obtained on December 17th, 2020 for SARS-CoV-2 was negative. However, the second SARS-CoV-2 pharyngeal swab performed on the very next day was revealed positive. The chest radiograph of the neonate taken on December 15th, 2020 showed no abnormalities in the lung and heart.

The newborn was treated with oxygen via nasal cannula, 10% dextrose for fluid maintenance on the first day, ampicillin antibiotic intravenous 100 mg/kgBW/day divided into two doses, and gentamycin intravenous 5 mg/kgBW/day. He was temporarily oral stop. On the fifth day of observation, his hemodynamic was unstable, he had bradycardia with heart rates was 84 beats per minute, respiratory rate was 72 times per minute, oxygen saturation was 88%. He looked icteric and his total bilirubin result showed 11.58 mg/dL, with direct bilirubin 0.34 mg/dL. He was then diagnosed with Septic Shock, Symmetrical IUGR, Hyperbilirubinemia, Paraphimosis, and Confirmed COVID-19. He was given oxygen via nasal cannula and titrated with dobutamine 5 mcg/kgBW/min. Second line antibiotics were administered; ceftazidime 50 mg/kgBW/12 hours and amikacin 7.5 mg/kgBW/12 hours to treat his worsening condition. Phototherapy was performed for his hyperbilirubinemia. He was immediately transferred to NICU for further care, after his SARS-CoV-2 pharyngeal swab revealed negative. During the care in NICU, his overall condition gradually improved.

Case Presentation 2

The neonate was being referred on December 17th, 2020 from peripheral hospital with diagnosis of term neonate appropriate of gestational age, moderate respiratory distress, and intraabdominal tumor. She was born on December 15th, 2020 through caesarean delivery due to breech presentation. Her birth weight was 2,900 gram and birth length 44 cm. She was born with Apgar score 5 and 7. Her mother was 36 years old woman with G4P3A0, 38-39 weeks of gestation age. During pregnancy, she has no complaints of hypertension, shortness of breath, fever, or cough. Her SARS CoV2 test was not performed. She routinely controlled her pregnancy to the nearest public health centre and no concern raised regarding to her fetus. Right after the baby was born, she had grunting and nasal flaring, her subcostal and intercostal retractions were deep, and her breathing was distressed. Down score was 6. On her physical examination, there was visible mass on the right

side of abdominal region. Inspection on the mass revealed no redness or discoloration. Upon palpation, the size of mass was around 5 cm, tender, immobile, and had smooth surface. There was no temperature difference around the mass.

On laboratory examination from December 17^{th}, 2020, white blood cell 17,100/mm^3, haemoglobin 15.9 g/dL, hematocrit 45%, platelets 236,000/mm^3, eosinophil 0%, basophil 0%, band neutrophil 3%, segment neutrophil 79%, lymphocyte 9%, monocyte 9%, IT ratio 0.03, CRP <6 mg/dL, ALT 3 U/L, AST 30 U/L. The baby was being screened for SARS-CoV-2 infection on December $18^{th,}$ 2020 and the nasopharyngeal swab revealed positive. The babygram obtained on December 17^{th}, 2020 showed no abnormalities in the lung and heart, but there was suspected hepatomegaly.

She was treated in neonatal isolation ward for COVID-19 with Continuous Positive Airway Pressure (CPAP) 40% PEEP 7 cmH_2O, ampicillin antibiotic intravenous 100 mg/kgBW/day divided into two doses and gentamycin intravenous 5 mg/kgBW/day. She was temporarily oral stop. After 4 days of first line antibiotics, the baby showed no improvement and started to develop gastrointestinal bleeding. The antibiotics were then changed to second line with ceftazidime 50 mg/kgBW/12 hours and amikacin 7.5 mg/kgBW/12 hours. On the eight days of treatment, her conditions declined and she was died because of multiple organ failure caused by sepsis.

Case Presentation 3

A baby girl was born at December 7^{th}, 2020 through caesarean delivery with indication of mother with severe preeclampsia and sustained fetal heart rate >160 beats per minute. The infant was born with birth weight 2,800 gram and birth length 48 cm. Her Apgar score were 1, 3, 5, and 6. The mother was only 17 years old with high-risk pregnancy (her weight was 100 kg), anemia, severe preeclampsia, and bilateral pneumonia. During the end of her third trimester, she experienced cough and shortness of breath. The mother's chest x ray showed ground glass opacity bilateral and she was later diagnosed with Confirmed COVID-19. The baby was having respiratory distress and grunting right after birth. Sepsis risk factor for this baby is low Apgar score and sustained fetal heart rate >160 beats per minute. Her down score was 2.

Upon physical examinations, her vital signs were normal. However, there were found some congenital anomalies, such as unilateral athelia, where the areola was missing on right side of chest and rachitic rosary was also prominent on that very side. Her laboratory examinations were all within normal limit. Her nasopharyngeal swab for COVID-19 on December 8^{th}, 2020, showed positive result.

The newborn was treated with oxygen via nasal cannula, ampicillin antibiotic intravenous 100 mg/kgBW/day divided into two doses and gentamycin intravenous 5 mg/kgBW/day. He was consulted to pediatric endocrinology division for further diagnostic evaluation of the anomalies.

Case Presentation 4

A 10 days old neonate was referred from peripheral area in North Sulawesi to our centre. The neonate was a girl, born on April 4^{th}, 2020 from spontaneous delivery. Her mother was G1P0A0, with full term gestational age. Mother had no clinical symptoms. There was no screening performed to the mother regarding SARS-CoV-2 infection prior to delivery. The newborn birth weight was 3,100 gram and birth length 48 cm. The Apgar score was unclear; however, it was said the baby cried right after she was born. There were no risk factors for sepsis. She was then discharged from primary health care facility with her mother.

When she was 9 days old, she suddenly developed fever complicated with seizure. Shortness of breath and cough were denied. There was no family member diagnosed with COVID-19. Contact with COVID-19's patient was also denied. Mother was tested negative for COVID-19 on June 13^{th}, 2020. The baby was diagnosed with term infant appropriate for gestational age, neonatal pneumonia, probable late onset of sepsis, seizure et causa Probable Sepsis, and Probable COVID-19.

On physical examination, her vital signs were within normal limit. From laboratory result upon admission; white blood cell 14,600 /mm^3, hemoglobin 14.3 g/dL, hematocrit 39.8 %, platelets 231,000/ mm^3, eosinophil 4 %, basophil 0 %, band neutrophil 0 %, segment neutrophil 25 %, lymphocyte 52 %, monocyte 19 %, IT ratio 0, and CRP <6 mg/dL. Babygram was performed and showed diffuse reticular nodular appearance on both lung fields suggesting bilateral pneumonia neonatal.

She was screened for SARS-CoV-2 infection, and her first nasopharyngeal swab on June 14^{th}, 2020 showed negative result. However, the result for the second swab done on the next day showed positive.

Patient was treated with oxygen via nasal cannula, maintenance intravenous fluid, ampicillin antibiotic intravenous 100 mg/kgBW/day divided into two doses and gentamycin intravenous 5 mg/kgBW/day, phenytoin injection with loading dose 20 mg/kgBW within 30 minutes and continued with maintenance dose 5 mg/kgBW/12 hours, given 12 hours later, and temporally oral stop.

Case Presentation 5

A baby boy was born on July 9^{th}, 2020 through caesarean delivery with indication of mother confirmed COVID-19 (her nasopharyngeal swab for COVID-19 was positive). Despite of

the positive swab, mother had no complaints. She was known to have arthritis rheumatoid since 9 years ago. She had no other comorbid, her blood pressure and blood glucose were normal. There was no known contact with other confirmed COVID-19 person. The baby's birth weight was 3,000 grams, birth length 42 cm, and Apgar score were 6 and 8 respectively. There was no risk factor for sepsis. The newborn developed shortness of breath 5 hours after he was born.

From physical examination, the baby looked less active. His heart rate was 150 beats per minute, respiratory rates 60 times per minute, body temperature was 36.7^{0}C, and oxygen saturation was 96%. Upon chest examination, there was found mild retraction at subcostal region, otherwise everything was within normal limits. His down score was 2. Laboratory results white blood cell 16,000 /mm^3, haemoglobin 15.2 g/dL, hematocrit 40.6 %, platelets 198,000/ mm^3, eosinophil 1 %, basophil 0 %, band neutrophil 1 %, segment neutrophil 67 %, lymphocyte 23 %, monocyte 8 %, IT ratio 0.01, and CRP <6 mg/dL. His first nasopharyngeal swab on July 10th, 2020 for COVID-19 appeared positive.

He was then diagnosed with term infant appropriate for gestational age, suspected with transient tachypnea of newborn with differential diagnosis of neonatal pneumonia, and Confirmed COVID-19. The baby was treated with oxygen via nasal cannula, intravenous fluid maintenance, ampicillin antibiotic intravenous 100 mg/kgBW/day divided into two doses and gentamycin intravenous 5 mg/kgBW/day.

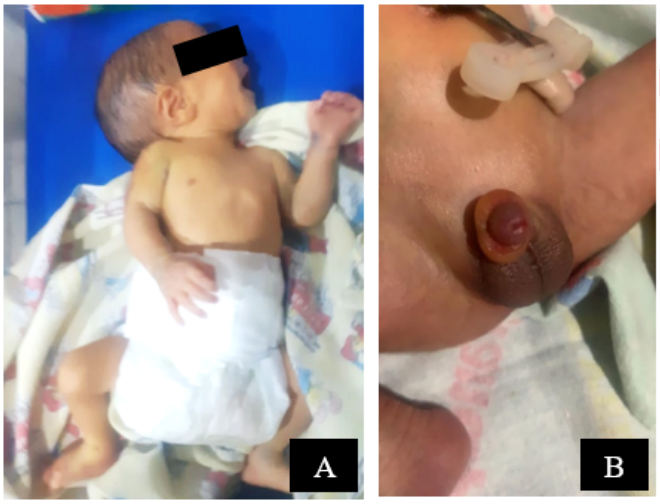

Figure 1: (A) Clinical picture of patient 1; (B) Paraphimosiswas observed on confirmed COVID-19 neonate. The inspection revealed no rednessand swelling on the foreskin and penile. Upon retraction, the foreskin wasfailed to be pulled back to cover the tip of penile.

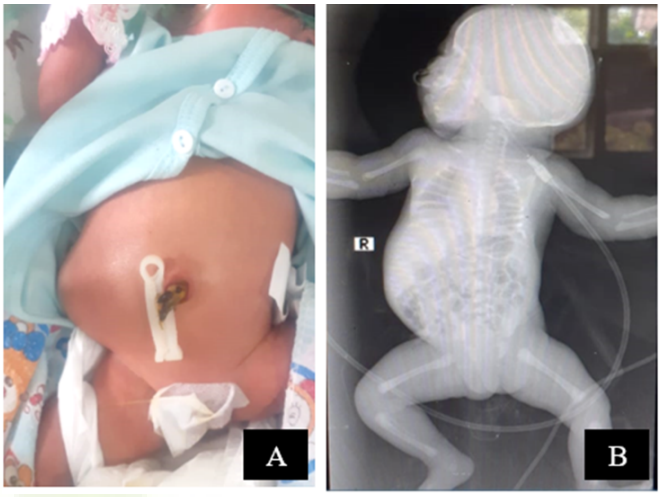

Figure 2: (A) Clinical picture of patient 2. Intraabdominal masswas visible and palpable on the right abdominal quadrant; (B) Babygram of theneonate showed normal appearance of heart and lung. There was mass on the rightupper quadrant of abdomen with suspected of hepatomegaly.

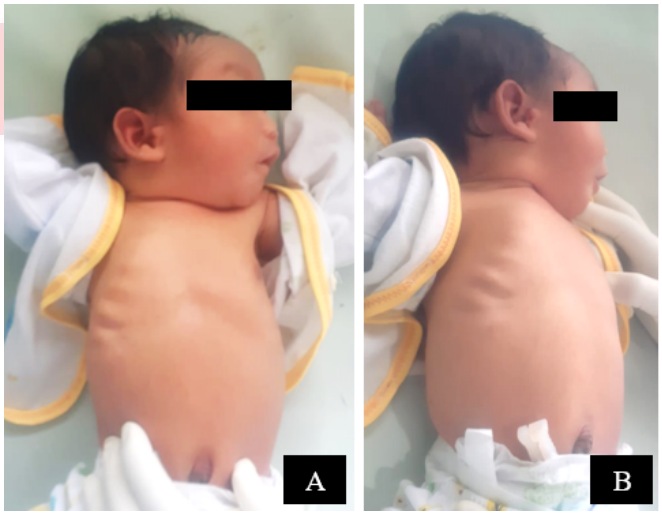

Figure 3: Unilateralathelia and rachitic rosary on the right side of chest were observed fromconfirmed COVID-19 neonate (A) front view, (B) side view.

Table 1: Characteristics,clinicalfindings,and neonataloutcomesfrom fiveconfirmedCOVID-19 neonates

	Patient I	Patient II	Patient III	Patient IV	Patient V
Neonatal Outcomes	Discharge	Died from multiple organ failure caused by sepsis	Discharge	Discharge	Discharge
Neonatal birthweight	1,500 grams	2,900 grams	2,800 grams	3,100 grams	3,000 grams
Apgar Score (1 minute)	5	5	1	unknown	6
Apgar Score (5 minute)	7	7	3	unknown	8
Neonate's status of COVID-19	Confirmed COVID-19	Confirmed COVID-19	Confirmed COVID-19	Confirmed COVID-19	Confirmed COVID-19
First RT PCR on nasopharyngeal swab for SARS-CoV-2	Negative (24 hours after birth)	Positive (24 hours after birth)	Positive (24 hours after birth)	Negative (10 days after birth)	Positive (24 hours after birth)
Second RT PCR on nasopharyngeal swab for SARS-CoV-2	Positive (48 hours after birth)	Positive (48 hours after birth)	Positive (48 hours after birth)	Positive (11 days after birth)	Positive (48 hours after birth)
Congenital Anomaly	Paraphimosis	Intraabdominal mass	Unilateral athelia and rachitic rosary	no	no
Neonatal Complications	Septic shock, symmetrical IUGR, hyperbilirubinemia, mild respiratory distress	Severe respiratory distress, late onset sepsis, GIT bleeding	Mild respiratory distress	Fever, seizure, no respiratory distress	Mild respiratory distress
Mother's Status of COVID-19					
First Trimester	SARS-CoV-2 test was not performed	SARS-CoV-2 test was not performed	SARS-CoV-2 test was not performed	SARS-CoV-2 test was not performed	SARS-CoV-2 test was not performed
Second Trimester	SARS-CoV-2 test was not performed	SARS-CoV-2 test was not performed	SARS-CoV-2 test was not performed	SARS-CoV-2 test was not performed	SARS-CoV-2 test was not performed

Discussion

Several previous studies concluded the most common clinical findings on neonates infected with SARS-CoV-2 are respiratory failure findings (RDS and TTN), pneumonia, low birth weight, chorioamnioitis, and meconium-stained amnion.[3,4] Similar with existing studies, neonates with confirmed COVID 19 in our center also shows respiratory manifestations, including fast breathing and chest retraction, which lead to pneumonia suggestive symptoms. Low birth weight newborn was also observed in one of our cases.[6–12]

A retrospective case-control study in China reported outcomes of neonates born to mothers with COVID-19.[13] In that study, from January 24^{th} to February 29^{th}, 2020, neonatal outcomes of 36 pregnant women with COVID-19 pneumonia were compared with those of 121 pregnant women without COVID-19 admitted during the same period (2020 control group) and 121 women admitted between January 24 and February 11, 2019 (2019 control group). The results showed that rates of low birth weight (13.9%) and premature birth (22.2%) among neonates born to mothers with COVID-19 were significantly higher than those in the 2 control groups (2.5% and 5.4%,

Third Trimester	SARS-CoV-2 test was not performed	SARS-CoV-2 test was not performed	SARS-CoV-2 test was not performed	SARS-CoV-2 test was not performed	SARS-CoV-2 test was not performed
Prior to Delivery	Rapid SARS-CoV-2 test was reactive	SARS-CoV-2 test was not performed	Confirmed COVID-19 (positive RT PCR on nasopharyngeal swab for SARS-CoV-2)	SARS-CoV-2 test was not performed	Confirmed COVID-19 (positive RT PCR on nasopharyngeal swab for SARS-CoV-2)
Postnatal	Confirmed COVID- 19 (positive RT PCR on nasopharyngeal swab for SARS-CoV-2)	SARS-CoV-2 test was not performed	Confirmed COVID-19 (positive RT PCR on nasopharyngeal swab for SARS-CoV-2)	Negative (negative RT PCR on nasopharyngeal swab for SARS-CoV-2)	Confirmed COVID-19 (positive RT PCR on nasopharyngeal swab for SARS-CoV-2)

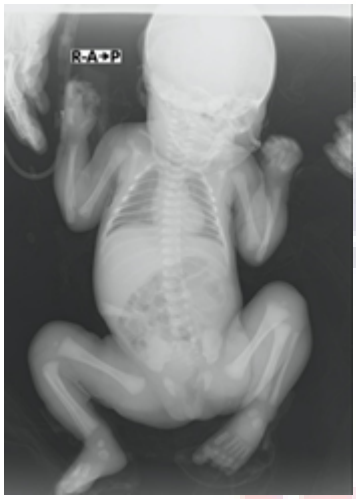

Figure 4: Babygram photo of case 4, obtained from 10 days oldneonate with confirmed COVID-19. It showed diffuse reticular nodular appearance on both lung fields suggestingbilateral pneumonia neonatal.

respectively).[7,13]

Although data on outcomes of patients with maternal and neonatal COVID-19 are still limited, pregnant women and their neonates might be at increased risk for developing severe COVID-19 and experiencing unfavourable birth outcomes. From our study, two of the cases in which the mother was confirmed COVID-19, the newborns developed shortness of breath not long after being born. Our finding also goes along with previous study from Zhu et al.[14] The study described six of the newborns from mother with COVID-19 developed shortness of breath. Similar with study of newborns with positive SARS-CoV-2 infection in Tongji Hospital in Wuhan conducted by Yu et al.[15] They found the clinical manifestations relatively modest, with only mild shortness of breath, and no fever or cough. Another case reports showed three patients developed disseminated intravascular coagulation (DIC), possibly because of immature immune function of the neonates and suspected sepsis.[16] One of them eventually died, one improved with antibiotic treatment, and the other also improved after receiving intravenous immunoglobulins (IVIG) transfusion.[16]From our study, most of newborns had only mild symptoms, mainly involving respiratory distress and improving after course of first line antibiotics, closely isolated monitoring, and other supportive therapies. Nevertheless, some neonates showed more complicated clinical findings, such as severe shortness of breath, fever, and seizure, which resulted in one of the neonates subsequently died from sepsis.[17–20]

Our findings also found two cases of confirmed COVID-19 neonates who were born from mother with unknown COVID-19 status. Both neonates were referral neonates from peripheral region. The neonates developed symptoms with unclear source of infection.[21,22] In one of the cases, the symptoms occurred after the neonates reached 9 days old, when he suddenly got fever and seizure. Upon investigation, mother was tested negative for SARS CoV-2 infection. However, it was not until infant's symptoms appeared, that mother and infant were both finally examined for SARS CoV-2 infection. This indicated that mother COVID-19 status was unknown while giving birth or during prenatal period.[23–25] The neonate's clinical symptoms were gradually improved after receiving adequate treatments. Another referral case of confirmed COVID-19 neonate was a neonates born with intraabdominal mass and having severe respiratory distress with down score of 6. Mother's examination for

SARS CoV-2 infection was not performed as there were no symptoms regarding the infection. However, as the newborn developed symptoms, she was immediately referred to our centre and complete examinations were conducted. Upon examination, she has severe respiratory distress, with nasal flaring, tachypnea, and deep retraction both on subcostal and intercostal.[26–29] From abdominal physical examination, we found the visible mass on the right upper quadrant with no redness or discoloration, palpation revealed the size of mass was around 5 cm, with tender consistency, smooth surface, immobile, and no heat from the area. From babygram's expertise, both heart and lung were within normal limit, however there was a mass at upper quadrant of abdominal cavity suggesting hepatomegaly. Result of nasopharyngeal swab for COVID-19 was positive. After 8 days of treatment, the baby's condition got worse, and subsequently died from complication of sepsis. Unfortunately, the route of SARS CoV-2 infection remained unknown, as both neonates were born at the peripheral health facility with limited examination regarding to SARS CoV-2 infection at that time.

The other case of confirmed COVID-19 neonate in our centre was a baby girl born from 17 years old mother with confirmed COVID-19 who showed severe SARS CoV-2 infection symptoms. Mother has complicated prenatal complications, including severe preeclampsia, anemia, high risk pregnancy, and pneumonia. The clinical findings from the mother were shortness of breath, cough, and fever. Her chest radiograph revealed ground glass appearance. The mother later died from respiratory failure. However, the neonate shows relatively mild respiratory symptoms, with down score of 2. She had fast breathing and mild subcostal retraction. Despite of modest clinical manifestations, we found some congenital anomalies, including unilateral athelia and rachitic rosary presented on this newborn. Following adequate therapies, the respiratory distress relieved and the neonate recovered well.

In term of Apgar score, from our findings, most newborns were reported to have Apgar score of 7-8 at five minutes. Although our case series don't have any comparisons to the non COVID-19 newborns, this result is in concordance with the study from Oncel et al,[7] in which the Apgar score at the 5^{th} minute was significantly lower in newborns with SARS-CoV-2 infection compared with neonates without SARS-CoV-2 (8 (7–9) vs. 9 (9–10), 95% CI 0.263– 0.998, p = 0.039). It was also established from their research, the need for mechanical ventilation or nasal CPAP was higher (75% vs. 19%, 95% CI 1.271–128.5, p = 0.028), and the duration of hospitalization was significantly longer in the newborns with SARS-CoV-2 infection (26 (15–48.5) vs. 7 (3–11) days, 95% CI 1.018–1.148, p = 0.033).[7] These findings were appropriate with several studies in which baby with confirmed COVID-19 showed respiratory distress manifestation. Our 5 neonates were also showed symptoms of shortness of breath, varied from mild to severe. However, as our centre lack of advanced oxygen supplementation machine, such as mechanical ventilation in neonate isolated ward for COVID-19, we could not establish the data regarding the matters.

The characteristics, clinical findings, and neonatal outcomes from five confirmed COVID-19 neonates are showed in [Table 1]. It is interesting to note that our case series show 2 neonates with negative result for first RT-PCR nasopharyngeal swab of SARS-CoV-2 infection, and turn out positive on the next swab. These findings are similar with case reported in Iran.[21] Recently, Zou et al in China reported the correlation between viral loads of SARS-COV-2 in RT-PCR test and the timing of swab sampling after symptoms occurred. They concluded the sensitivity of RT-PCR test depends on the source of sampling (e.g. throat, nose, etc.), time of sampling and the health care provider's skill in performing an accurate sampling.

Upon investigation of neonates with confirmed COVID-19 in our centre, we found three of the neonates were showing congenital anomalies, such as rachitic rosary, unilateral athelia, intraabdominal mass, and paraphimosis. While congenital anomaly in neonates with confirmed COVID-19 hadn't been reported yet, and not much study had mentioned it, we cannot rule out the possibility of SARS-CoV-2 in account for those congenital anomalies. Although, the studies and datas were still limited, the potential for vertical transmission cannot be excluded. The risks for birth defects in newborn from mother with SARS-CoV-2 infection need to be investigated, especially because there are several viral infections known that cause adverse outcomes in pregnancy, even when no vertical transmission is recognized.[24] Further researches were needed to establish the mechanism involving the matters.

Confirmation regarding SARS-CoV-2 infection transmission in neonates has not been established. There were several hypotheses being investigated. The infection of SARS-CoV-2 could be from mother to fetal (vertical transmission) or droplets. It is also proposed SARS-CoV-2 infection of pregnant mother led to the increasing of fetal immune response and affect its development. Vivanti et al,[8] demonstrated a neonatal case of SARS-CoV-2 through vertical or transplacental transmission. Such vertical transmission following maternal viremia, placental infection, and neonatal viremia was confirmed by comprehensive virological and pathological investigations. The viral load of SARS-CoV-2 in the placental tissue was much higher than that in any other specimen such as the maternal and neonatal blood. A placental histological examination also revealed placental inflammation.[9] Study from Kirtsman et al and Kulkarni et al also supported placental infection of SARS-CoV-2 in two neonates with COVID-19.[10,11]

From recent studies proposed, it is possible the SARS-CoV-2 infection to alter the development of fetus during pregnancy through several possible mechanisms. According to Shi L et al,[22] viral infection can affect the fetus through the

maternal inflammatory response. Inflammatory response can be manifested as histological chorioamnionitis or leukocyte infiltration into the chorion and amniotic membrane in uterus.[23]

During pregnancy, there were many changes in the body of woman to tolerate the development of fetus that presents non-self-antigen and prepare for the potential pathogen invasion. These require immune adaptations both systemically and locally.[25] Immune system shows a dynamic adaptation throughout the different stages of gestation. In the first trimester, it is important to have a pro-inflammatory environment in order to succeed embryo implantation and placentation. While during the second trimester, around the 13^{th} week of gestation, the immune system needs to create an anti-inflammatory state to help the growth and development of fetus. Finally, at the end of pregnancy, a pro-inflammatory state is developed to prepare the delivery.[26] These recent years, numerous studies have suggested the important role of placenta in immune system regulation of maternal-fetal. Placenta and fetal membranes are selective barriers that critical to nourish and protect the developing fetus. Besides, the placenta is well known as immunity-modulating organ which regulates the immune responses of cells present both at the implantation site and systemically. This immune mechanism was performed by trophoblast, especially if there is a serious infection at the maternal-fetal interface.[27–29]

In general, viral infections interfere gestation through some manners. The virus capable of crossing the placenta can reach the fetus and cause serious damages of its development. In addition, the viral infection of cells at the maternal-fetal interface can interrupt placental function, cause miscarriages, intrauterine growth restriction and preterm birth.[30] On the other hand, the soluble immune factors produced by viral infection of the decidua and placenta can pass through and reach the fetus causing disruption of its growth and development. This disruption subsequently leads to altered organogenesis. The last mechanism explains the virus itself doesn't need to be transmitted to the fetus in order to damage its development. The virus is capable of indirectly affect the fetus through immune response. A study was performed on animal model to assess the consequences of a viral infection characterized by absence of transmission to the fetus.[28] Viral infection of maternal can lead to productive replication in the placenta and cause increase of fetal inflammatory response, even when the virus is not detected in the fetus. They propose this inflammatory response may induce organ damage and developmental deficiencies. Moreover, the viral infection may sensitize the pregnant mother towards bacterial products and induce preterm labor.[28]

Another interesting finding related to placenta of mothers with COVID-19 from third trimester was found.[31] They have increased features of maternal vascular malperfusion (MVM) in comparison to control. These features include abnormal maternal vessels and intervillous thrombi, which influence physiology of placenta, causing a systemic inflammatory or hypercoagulable state.[31] A study described the pathology and clinical information on 20 placentas whose mother tested positive for the COVID-19; 10 from 20 cases showed evidence of fetal vascular thrombosis suggesting that maternal COVID-19 infection might be associated with propensity for thrombosis in the fetal circulation.[32]

Another supporting researches also indicate that SARS-CoV-2 is capable to cross both placental barrier and blood brain barrierbecause of the viral IgM detected in infants hours after birth and in cerebrospinal fluid.[33,34] Vertical transmission of SARS-CoV-2 from mother to fetus was mediated through entry receptor, namely angiotensin-converting enzyme 2 (ACE2) and S protein proteases, as both of them were expressed in developing human embryo. SARS-CoV-2 enters the cell through the binding of viral spike (S) protein to the cellular receptor Angiotensin-converting Enzyme 2 (ACE2) and protein priming mediated by serine protease Transmembrane Protease Serine 2 (TMPRSS2), which cleaves the S protein.[35] The ACE2 gene is expressed in endometrium and different cell types in early placenta, including stromal cells and syncytiotrophoblast.[20,36,37] In early pregnancy, a very low ACE2 level of expression was detected in trophoblast. Its expression gradually increases along with the trimester of pregnancy and being able to transfer the virus trans placentally to the fetus much more during the later stage of gestation. Animal data shows that ACE2 expression changes in fetal tissues over time and reaches a peak between the end of gestation and the first days of postnatal life,[20] which suggest that transplacental transmission is indeed possible in the last weeks of pregnancy. Meanwhile, in the developing fetus, ACE2 is widely expressed in many different organs including kidney, heart and liver.[37,38]

In addition, the TMPRSS2 gene was modestly expressed in early pregnancy and increases over time in endometrium and placenta, but with lower levels than ACE2.[20,36,37] TMPRSS2 is co-expressed with ACE2 in the embryonic heart and lungs, suggesting a possible fetal infection during pregnancy.[20,37,38]

Another interesting notes regarding these receptors, it is notably, ACE2 and S protein proteases are expressed in early gametes, zygotes, and 4-cell embryos.[39] Thus, direct transmission of infection of blast cells by SARS-CoV-2 may be possible, but remains to be confirmed. In developing embryos, the health of these cells of the epiblast is crucial as these cells undergo organogenesis. Any functionally alterations in early embryonic cells by the viral infection may lead to adverse birth defects. These findings raise our concern regarding screening and studies that widely performed mainly during the last trimester of pregnancy, while many researches have shown the SARS-CoV-2 infection was capable to causing

adverse outcome from the very beginning of gestation.[40]

Conclusion

In spite of the mild symptoms showed by most newborn with confirmed COVID-19, it was also noticed, some developed more severe clinical manifestations. Our findings found some confirmed COVID-19 neonates were born with congenital anomaly. Whether SARS-CoV-2 infection can contribute to these findings was remain to be investigated. Some existing researches had proposed the possible mechanisms, but they were needed further scrutinises for confirmation. The routes of SARS-CoV-2 infection in neonates were also still being examined. Direct invasion of the virus to the fetus by crossing the placenta cause disruption to fetus growth and development has been proposed. This possible mechanism was supported by the discovery that ACE2 and TMPRSS2 as two major host factors that contribute to the virulence of SARS-CoV-2 were widely expressed in human embryo. Immune system was also found to play important role in indirect infection of virus to the fetus which capable of causing similar adverse outcomes. These findings also raise our concern regarding earlier and routine antenatal screening for SARS-CoV-2 infection in pregnant woman to detect and prevent any unfavourable outcomes from the very beginning of gestation. On top of that, further researches are needed to support previously existed studies.

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