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Characteristics and Outcome of Neonates Born from Mother with Confirmed SARS-Cov-2 Infection at Prof. Dr I.G.N.G Ngoerah Hospital and Udayana University Hospital Bali

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19), firstly emerge in Wuhan-China in early December 2019. The virus has rapidly spread causing global pandemic. Infection of SARS-CoV-2 in pregnancy tend to be severe and associated with adverse neonatal outcomes. Investigation the number and evaluate clinical feature also outcome of neonates that born from positive COVID-19 mother especially in Prof. DR I.G.N.G Ngoerah Hospital and Udayana University Hospital is required as baseline data.
Methods: This is descriptive observational study. Data on neonates age 0 days - 28 days old born from mother with confirmed COVID-19 were collected from medical record at Prof. DR I.G.N.G Ngoerah Hospital and Udayana University Hospital, during period of March 2019 until December 2020 registry taken from patients from October 2017 to August 2020. We exclude subject with incomplete data.
Results: Total of 90 infants were included in this study, positive swab results were 6 (6%) and negatives were 84 (93.3%). Of 90 infants as many as 50 (55.5%) were males, and 40 (44.4%) were females. Most babies were born by Cesarean delivery 81 (90%). Of 76 (84.4%) samples had full term gestational age and 75 (83.3%) samples born with birth weight more than 2500 grams. Total 80 (88.8%) born with APGAR score 7-10. Most comorbidities we found were respiratory distress and use of antibiotic each 10 (11.1%). Most of the samples that 64 (71.1%) had length of stay less than eight days. One patient died in the group of infants with positive swabs, while none in the group with negative swab results.
Conclusion: Six of the total 90 samples of babies were confirmed to have COVID-19 infection through the RT PCR swab examination. One patient died in this study. Currently the risk of vertical transmission of COVID-19 infection cannot be excluded, it is important to carry out prevention strategies, to make babies are not exposed by viral exposure (prevent maternal infection and reduce the possibility of neonatal exposure to the virus). We suggest multicenter research to provide a more specific description of the outcomes of babies born from mothers with confirmed COVID-19.

Keywords: COVID-19, SARS-CoV-2, neonatal outcomes.

INTRODUCTION

Novel severe acute respiratory syndrome coronavirus 2 or mostly known as SARS-CoV-2 causes disease termed as coronavirus disease 2019 (COVID-19), firstly emerge in Wuhan-China in early December 2019. Firstly report as cluster of pneumonia patient with unknown cause that epidemiologically linked to a seafood and wet animal wholesale market in Wuhan-China. Coronaviruses belonging to the

Nidovirales which include Coronaviridae, Arteriviridae, Mesoniviridae, and Roniviridae families. Coronaviruses is a virus that enveloped with positive-sense RNA and characterized by club-like spikes that project from their surface, an unusually large RNA genome, and a unique replication strategy [1].

The virus has rapidly spread causing global pandemic. Transmission mainly occurs via droplets, but there is some other way like skin to skin contact, faecal-oral transmission, and ocular surface contact. The virus could be detected by real time polymerase chain reaction (RT-PCR) examination that use sample from bronchoalveolar lavage, sputum, saliva, and nasopharyngeal swab which are gold standard for the diagnosis. All age groups are susceptible, but people with comorbidities are more vulnerable to have severe symptom. Although children seem have less severe symptom when infected, but the potential harm in neonates population remains unknown [2].

Data from one study indicates that infection of SARS-CoV-2 in pregnancy tend to be severe and associated with adverse neonatal outcomes, including increased risk of miscarriage, fetal growth restriction, and preterm birth [3]. Perinatal transmission of SARS-CoV-2 infection from mother to their babies are thought to be occurs via transplacental or through environment exposure to aerosol droplets of viral particle after birth. Some report of potential transplacental transmission have shown reactive IgG and IgM antibody of SARS-CoV-2 in neonates that born from positive COVID-19 mother, but all of these babies were negative from PCR result [4]. Because of high pathogenicity of the virus, not much study shows how the influence of COVID-19 pregnant women on their babies.

Shalish et al shows data that indicate low rates of perinatal acquisition among neonates that born from positive COVID-19 mother. Review from 27 studies including data from United States, China, Italy, Sweden, South Korea, and Honduras shows 4 from 137 neonates born from positive COVID-19 mother had positive viral PCR testing, the other 3 had equivocal testing [5]. A cohort study from Spanish shows 5 baby got positive COVID-19 from 72 subject that born from positive COVID-19 mother, this report also shows no difference was found from vaginal or cesarean birth [6]. Report from United Kingdom with a population based cohort studies shows only 12 neonates positive COVID-19 infection from 265 subject that born from positive COVID-19 mother [7]. Data from National Registry for Surveillance and Epidemiology of Perinatal COVID-19 Infection (NPC-19) found 44 babies from 2287 subject got positive COVID-19 test, all subject was born from positive mother from COVID-19 [8]. Yang et al on a study to know the characteristic of newborns born to mothers with COVID-19 shows 4 from 7 newborns were late preterm with gestational age between 36 weeks and 37 weeks, and the other were full-term infants. The average birth weight was 2096 + 660 grams. All were born without asphyxia. Two premature infants show mild grunting after birth, but heal by non-invasive continuous positive airway pressure (nCPAP) ventilation. Three cases had chest X-ray, 1 was normal and 2 showed neonatal respiratory distress syndrome (NRDS). There was no positive result of SARS-CoV-2 nucleic acid in all cases [9].

The effects of COVID-19 on mother to the physiological state of their babies are still unclear. Data and evidence collected especially from Prof. DR I.G.N.G Ngoerah Hospital have not been published yet. Based on these descriptions, we aim to investigate the number and evaluate clinical feature and outcome of neonates that born from positive COVID-19 mother in Prof. DR I.G.N.G Ngoerah Hospital and Udayana University Hospital.

MATERIALS & METHODS

This descriptive observational study was conducted at Prof. DR I.G.N.G Ngoerah Hospital and Udayana University Hospital,

during period of March 2020 until December 2020. This study involved neonates age 0 days - 28 days old that born from mother with confirmed COVID-19 infection. The inclusion criteria of this study are neonates age 0 days - 28 days old born from mother with confirmed COVID-19. We exclude subject that have incomplete data. Sample size was calculated by formula for descriptive category study. With the assumption of error alpha is 5%, Proportion from category that be the point of interest about 9% [10], and research precision 7,5% The total sample required is 56 patients. In our center, pregnant mother screened for COVID-19, if the result positive then health workers must carried out treatment with level 3 personal protective equipment. All the procedure must be done at negative pressure isolation room. Cesarean delivery performed by indication. Newborn neonate should be separated with the mother for treatment in the isolation room and swab done for the neonate. If the neonate got positive result they concluded as confirmed case. Swab evaluated done at 7th day of treatment, if still got positive result, swab should evaluate on next 7 days. If the neonate got negative result for two times with interval 24 hour, they should be taken out from isolation room.

COVID-19 infection was defined by the positive result from RT-PCR from nasopharyngeal swab sample. Birth weight was defined by weight of the neonate that weighed within the first hour of birth. Data are grouped into (1) normal birth weight, any neonates weighing >2500 grams; (2) low birth weight (LBW) is any neonate weighing >1500 grams- <2500 grams; (3) very low birth weight (VLBW), any neonate weighing >1000 gram -<1500 grams; (4) extremely low birth weight (ELBW); any neonate weighing less than 1000 grams. Gestational age was defined as period from conception to birth, calculated using the New Ballard Score for infants aged < 4 days old and, grouped into (1) <28 weeks; (2) 28-32 weeks; (3) >32-36 weeks; and (4) > 37 weeks. Comorbidities were defined the condition that happen to the newborn after delivery, condition includes respiratory distress syndrome, sepsis, pneumonia, hypoglycemia, necrotizing enterocolitis, icterus neonatorum. Outcome was defined of final condition of the subject until discharged from the hospital that divide into two categories with deceased or live. Delivery mode was defined of way babies born from mother we divide into vaginal and cesarean delivery. Laboratory test that conducted from the baby that extracted from the medical record, included leukocyte, neutrophil, lymphocyte, hemoglobin, platelet and neutrophil lymphocyte ratio. Gender was determined from physical examination divide into male and female. APGAR was defined by examination that use APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score right after baby born as a rapid method for evaluating neonates in response to resuscitation. We categorize it into vigorous (score 7-10), moderate asphyxia (score 4-6), and severe asphyxia (score 0-3). We also counted the total amount of time spent by the patient using mechanical ventilation or CPAP.

STATISTICAL ANALYSIS

Collected data were analyzed using the SPSS program for Mac OS, version 25.0. Univariate analysis was conducted and data with a categorical scale were reported in frequency distribution and percentage, then displayed in table. This study was approved by the Research Ethics Committee of the Faculty of Medicine University of Udayana and Prof. DR I.G.N.G Ngoerah General Hospital Denpasar.

RESULT

All infants aged 0-28 days born from mothers with positive SARSCOV-2 from the PCR swab results were included in the study consecutively. During the study period, a total of 90 infants were included in the study, divided into two groups, that positive swab results (6 infants) and negative (84 infants). Most babies were

born by Cesarean delivery (90%). All patients with positive swabs were born by caesarean delivery method. Both groups were dominated by male sex. Most cases have length of stay less than eight days. In babies with positive swab results, all babies born at term and birth weight more than 2500 grams, as well as in the negative swab group, dominated by full-term gestational age and birth weight more than 2500 grams. A total of 80 babies were born vigorously, but there were also babies with moderate and severe asphyxia with five babies each. (Table.1).

We found in the one sample in group with positive swab results, with two major sepsis risk factor such as fetal distress and mother with fever more than 38oC. In the group with negative swab results, there were seven samples with sepsis.

From swab positive group, we found eight samples with hyperbilirubinemia, two samples with meningitis, nine samples each with respiratory distress and use of antibiotics. A total of five samples with negative swab results used CPAP and two samples used mechanical ventilator. From both group, total of 64 babies were treated for less than eight days, 17 babies were treated for 8-14 days, and nine babies were treated for 15 days or more. Outcomes in this study showed that one patient died in the group of infants with positive swabs, while none in the group with negative swab results.

Table 1. Characteristic of neonates

Variable	Positive swab (n=6)	Negative swab (n=84)	Total (n=90)
Delivery mode			
Vaginal delivery (%)	0 (0)	9 (10.7)	9 (10)
Cesarean delivery (%)	6 (100)	75 (89.2)	81 (90)
Gestational age			
<28 week (%)	0 (0)	1 (1.1)	1 (1.1)
28-32 week (%)	0 (0)	1 (1.1)	1 (1.1)
33-36 week (%)	0 (0)	12 (14.2)	12 (13.3)
≥37 week (%)	6 (100)	70 (83.3)	76 (84.4)
Gender			
Male (%)	4 (66.6)	46 (54.7)	50 (55.5)
Female (%)	2 (33.3)	38 (45.2)	40 (44.4)
Birth weight			
<1000 grams (%)	0 (0)	1 (1.1)	1 (1.1)
≥ 1000-<1500 grams (%)	0 (0)	1 (1.1)	1 (1.1)
≥ 1500-<2500 grams (%)	0 (0)	13 (15.4)	13 (14.4)
≥ 2500 grams (%)	6 (100)	69 (82.1)	75 (83.3)
APGAR score			
Vigorous (%)	5 (83.3)	75 (89.2)	80 (88.8)
Moderate asphyxia (%)	1 (16.6)	4 (4.7)	5 (5.5)
Severe asphyxia (%)	0 (0)	5 (5.9)	5 (5.5)
Comorbidities			
Sepsis (%)	1 (16)	7 (8.3)	8 (8.8)
Hyperbilirubinemia (%)	0 (0)	8 (9.5)	8 (8.8)
Meningitis (%)	1 (16)	2 (2.3)	3 (3.3)
Respiratory distress (%)	1 (16)	9 (14)	10 (11.1)
Use of antibiotic (%)	1 (16)	9 (14)	10 (11.1)
Mechanical ventilation (%)	1 (16)	2 (2.3)	3 (3.3)
CPAP (%)	0 (0)	5 (5.9)	5 (5.5)
Length of stay			
<8 days (%)	2 (33.3)	62 (73.8)	64 (71.1)
8-14 days (%)	4 (66.6)	13 (15.4)	17 (18.8)
15-21 days (%)	0 (0)	3 (3.5)	3 (3.3)
>21 days (%)	0 (0)	6 (7.1)	6 (6.6)
Outcome			
Live (%)	5 (83.4)	84 (100)	89 (98.8)
Deceased (%)	1 (16.6)	0 (0)	1 (1.2)

CPAP (continuous positive airway pressure)

Table 2. Characteristics of laboratory test

Variable	Positive swab	Negative swab
	Mean/Median	Mean/Median
Leukocyte *	16.35 (11.5)	16.74 (5.85)
Neutrophil #	10.2 (Min 4.75-max 15.7)	9.27 (Min 3.95-max 66.9)
Lymphocyte #	12.9 (Min 3.98-max 21.95)	4.25 (Min 2.4-max 21.9)
Hemoglobin *	13.65 (0.34)	17.84 (3.06))
Platelet*	193.0 (61.8)	212.91 (87.7)
NLR*	2.08 (2.63)	2.47 (1.42)

NLR (Neutrophil lymphocyte ratio)
Absolute count
* Normal data distribution

The laboratory description, there were 22 babies who had complete blood count tests in this study. We divide it based on the PCR swab result. The result for mean leukocyte value in positive and negative swab result was 16.35 (SD 11.5) and 16.74 (SD 5.85). While the NLR result from positive and negative PCR swab result were 2.08 (SD 2.63) and 2.47 (SD 1.42).

DISCUSSION

Pregnant women are at high risk of SARS-COV-2 infection, and are prone to have serious complications after SARS-COV-2 infection [10]. This presents a challenge for medical institutions to evaluate the risk of infection in neonates. Newborns are affected by SARS-COV-2 infection in several ways, such as vertical or horizontal transmission, and indirectly as a result of maternal SARS-COV-2 infection (e.g. babies born prematurely due to maternal medical conditions) [12]. Several studies have reported that children tend to have milder symptoms of SARS-COV-2 infection than adults. And it has been hypothesized that children are more likely to have milder symptoms because they do not evoke a strong inflammatory reaction and thus show a partial response to lung damage [13, 14].

In this study, we evaluated the demographic characteristics, laboratory results, and outcomes of infants born from mothers with confirmed COVID-19. Total of six (6%) infants had positive NP/OP swab results for SARS-COV-2 infection. We did not evaluate pathology of the placenta. Sheth et al. (2020) reviewed 39 published studies and reported 326 pregnant women with confirmed COVID-19, 23 newborns (7.05%) were confirmed positive [15]. Gale et al. (2020) stated that in a study conducted in the UK, as many as 300 pregnant women with confirmed COVID-19, it was also found that the incidence of Covid infection in babies born was low, and the onset of symptoms was mild. Furthermore, seven babies with positive SARS-COV-2 results although the babies been separated immediately after the baby was born [12]. Another study conducted by Knight et al. (2020) found that there were 12 (5%) of 256 infants who had positive SARS-COV-2 results after caesarean section delivery, but there was not enough evidence about how infection transmission occurs [8]. Research conducted by Wei Liu et al. (2020) confirmed there was no strong evidence of vertical transmission of SARS-COV-2 infection in neonates where SARS-COV-2 RNA was not found in samples of breast milk, umbilical blood, amniotic fluid, feces and urine from infants. It was reported that there was little expression of angiotensin converting enzyme in the placenta, making it difficult for vertical transmission occur [13]. Report from Dong et al, showed a neonate delivered by cesarean section from an infected mother, there were elevated IgM antibody levels and abnormal test results for IL-6 and IL-10 cytokines 2 hours after birth. The elevated IgM antibody level suggests that the neonate was infected in utero. Although infection at delivery cannot be ruled out, IgM antibodies usually do not appear until 3 to 7 days after infection [16]. Case report from Parsa et al, one newborn from positive COVID-19 PCR swab on the first 24 hours after cesarean delivery. They also reported positive COVID 19 for

amniotic fluid, but did not done PCR for placenta. But, they concluded not enough data to proofed vertical transmission of COVID-19 through placenta [17].

Most babies were born by cesarean delivery (90%), this is in accordance with a study conducted by Zaigham et al. (2020) obtained from all samples of mothers with positive SARS-COV-2 infection, as many as 92% underwent cesarean delivery [18]. Cesarean delivery is intended to prevent intrauterine, perinatal and postnatal transmission of COVID-19 [19]. Mostly, in this study babies born with gestational age more than 37 weeks (84%) and body weight more than 2500 grams, this is in accordance with a study conducted in India by Tadas et al. (2021) which compared neonatal outcomes in mothers confirmed COVID-19 and negative, the mean gestational age was 37.5 weeks. They also found that the neonates had a birth weight with mean of 2.7 (SD 0.59) kg in the positive mother group and 2.5 (SD 0.56) kg in the negative mother group, this difference may be influenced by the residence area of the mother, most of the mothers with positive COVID-19 results came from urban areas with good nutrition, while most of the mothers with negative results came from rural areas with poor nutrition due to economic problems during the lockdown pandemic [20].

Neonate with a positive result of SARS-COV-2, there were more males than females in the demographic characteristics. In a study conducted by Shet et al. (2020) it was also found that more male babies were infected with COVID-19 than female [15]. As many as 15.5% of infants were born prematurely in this study. Theories suggest that COVID-19 infection in pregnant women can trigger hypoxemia and increase the risk of fetal distress, birth asphyxia, or the presence of meconium in the amniotic fluid. This increased need for oxygen causes fetal hypoxemia which indicates an early delivery [21]. However, it is said that the premature birth rate does not differ during the pandemic and pre-pandemic [22].

More patients were born with APGAR score 7-10, and only five patient was born with moderate asphyxia (5.5%), this is in accordance with a study conducted by Khong et al. (2020) most of the neonates born from COVID-19 positive mothers have a good APGAR score of more than 7 at 1-minute and 5-minute and APGAR scores were similar between asymptomatic and symptomatic COVID-19 positive pregnant women. It is suspected that in some cases babies born from COVID-19 mothers who have low Apgar scores may be was likely to be secondary to pulmonary immaturity if the neonates were born preterm [22].

In this study, we found some comorbidities, it's included in both group 10 (11%) infants had respiratory distress with five patients receiving CPAP and three patients with mechanical ventilation. According to a study conducted by Gale et al. (2020) of 66 infants with positive SARS-COV-2 results, 5% of infants were using mechanical ventilation and 33% of infants required other oxygen supplementation (non-intubation) and 64% of infants did not require oxygen therapy. This study also found 46 (70%) infants with SARS-COV-2 infection received antibiotic treatment, in our study only one patient in infants with SARS-COV-2 infection received antibiotic therapy [12].

In this study, 22 infants underwent complete blood counts examination. We divide it based on the PCR swab result. It was obtained from positive swab, the result that the mean value of leukocytes was 16.35 (SD 11.5). The median values for neutrophils and lymphocytes were 10.2 and 12.9, respectively. The mean levels of hemoglobin, platelets, and NLR respectively were 13.65 (SD 0.34), 193.0 (SD 61.8), and 2.08 (SD 2.63). In a study conducted by Wei Liu et al with the results of the value of leukocytes 16.19, lymphocytes 3.8, neutrophils 10.84, platelets 295 [13]. Other study provide data from positive swab neonates they found leukocyte around 19.2, lymphocytes was 2.6, and platelets was 245.

Outcome in this study was carried out by evaluating the length of stay and morbidity. The length of stay in this study was found to be dominantly less than eight days (71%), in a study conducted by Trevisanuto et al. (2020) which obtained outcomes in infants with SARS-COV-2 infection based on length of stay, the median was ten days [23]. In our study, one case of infant died in positive SARS-COV-2 swab results groups with cause of death was sepsis shock. Patient had severe respiratory distress symptom with pneumonia and late onset neonatal sepsis, high level of procalcitonin and positive bacterial culture. In the study conducted by Tadas et al. (2021) it was also found that one patient died from the mother with a positive SARS-COV-2 result, but it was due to severe birth asphyxia and concluded that in general there was no increase in adverse outcomes caused by maternal COVID-19 infection [20]. Another study conducted by Gale et al. (2020) of 66 infants with positive SARS-COV-2 results, one patient died but it was concluded that the cause of death was not related to SARS-COV-2 infection [12].

CONCLUSION

This study describes characteristics and outcomes of babies born from COVID-19 positive mothers. Six of the total 90 samples of babies were confirmed to have COVID-19 infection through the RT PCR swab examination. One patient died in this study. Currently the risk of vertical transmission of COVID-19 infection cannot be excluded, it is important to carry out prevention strategies, to make babies are not exposed by viral exposure (prevent maternal infection and reduce the possibility of neonatal exposure to the virus). The results of this study can be used as a reference for further research or for medical practices purposes. As covid still need to study more, there will be more data available that could lead to significant changes in the current associations and recommendations

Declaration by Authors

Ethical Approval: This study was already approved by ethic committee at Faculty of Medicine Udayana University/Prof. Dr. I.G.N.G Ngoerah General Hospital

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