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COVID-19 during the Third Semester of Pregnancy: Maternal Characteristic, Possibility of Intrauterine Transmission and Neonatal Outcome in Aceh, Indonesia

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Abstract

BACKGROUND: Pregnant women are vulnerable against COVID-19 infection due to physiological and immunological changes. COVID-19 in pregnancy affects fetal well-being with a potential for vertical infection.

AIM: This study aims to determine the incidence of vertical infection and anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies in infants born to mothers with positive COVID-19 infection.

MATERIALS AND METHODS: Amniotic fluid, swabs of the newborn's nasopharynx and oropharynx, and swabs of the placenta were examined using reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2. Serological examination was performed by Electro-Chemiluminescence Immunoassay on infant's blood.

RESULTS: Four of 33 pregnant women gave birth to infants positive SARS-CoV-2 infection. RT-PCR examination of all amniotic fluid and placental swabs was negative for SARS-CoV-2. Four of 33 infants (12.1%) showed negative polymerase chain reaction (PCR) results but positive SARS-CoV-2 antibodies, another 4 newborns (12.1%) showed positive PCR results, but no SARS-CoV-2 antibodies detected. The remaining 25 babies (75.8%) showed both negative PCR and serologic results.

CONCLUSION: No evidence of vertical transmission found in this study.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has become a rapidly growing global pandemic worldwide. Although COVID-19 can affect anyone, pregnant women may be more susceptible to this viral infection because of the physiological and immunological changes during pregnancy, and one of the main consequences of viral pneumonia is death during pregnancy that occurs worldwide [1]. COVID-19 in both mother and fetus also required placental tropism of the virus, so that the virus will infect placental cells and thereby be transmitted to the fetal side [2].

To date, there are limited cases of placental infection caused by SARS-CoV-2 have been reported from the previous studies [3], [4], [5], [6], [7]. In five previous publications, there were seven placentas from 19 patients examined using reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2; however, no SARS-CoV-2 infection was found in each of these placentas. Furthermore, histopathological analysis of the three placentas did not reveal any significant lesions [8], [9], [10], [11], [12]. Congenital infection in intrauterine fetal death or stillbirth is confirmed if virus is detected by polymerase chain reaction (PCR) examination of fetal tissue and placenta or from microscopy electrolysis by detecting the presence of viral particles in tissue or on viral growth in fetal tissue/placental tissue [13].

Zeng *et al*. found that infants from COVID-19-infected mother had IgG and IgM concentrations higher than the normal level (<10 AU/mL), although the throat swabs and blood samples all had negative RT-PCR test results, and none of them showed signs of infection. Zeng *et al*. emphasized that the newborn may develop

IgM antibodies during the gestational period if the virus has crossed the placental barrier [14]. In the study about SARS-CoV, Wong *et al*. found that the placenta from a woman with SARS-CoV infection during the first trimester was normal. However, placentas from women with confirmed SARS-CoV during the third trimester show increased intervillous or subchorionic fibrin, which is associated with impaired placental blood flow due to respiratory disease associated with hypoxia [15]. Infant outcomes of convalescent women infected with SARS-CoV during the third trimester include fetal growth restriction and small gestational age [16]. Therefore, there is concern regarding adverse pregnancy and infant outcomes due to intrauterine transmission of infection to the fetus from mothers with confirmed COVID-19. This study was conducted to investigate the incidence of vertical transmission in infants born to pregnant women with confirmed COVID-19.

Materials and Methods

Ethical approval

This study has ethical clearance from the Health Research Ethics Commission (KEPK) Faculty of Medicine, Syiah Kuala University, and Dr. Zainoel Abidin General Hospital Banda Aceh with no. 126/EA/FK-RSUDZA/2021. Written informed consents were also collected from all participants.

Study design and population

This study was a prospective and cross-sectional study based on patient data from the Department of Obstetrics and Gynaecology, Dr. Zainoel Abidin General Hospital in Aceh Province, Indonesia, from March 2021 to August 2021. This study included 33 pregnant women in the third trimester (gestational age >30 weeks) who were admitted for delivery, positive for COVID-19 based on RT-PCR, had not received any therapy for COVID-19, and had not undergone self-isolation. The newborns of these pregnant women were separated from their mothers immediately after delivery and received no therapy from the perinatology department until RT-PCR examination of nasopharyngeal and oropharynx swabs were taken within 1 × 24 h. All the patients delivered infants by caesarean section, and then the neonates were transferred to the neonatology department.

Specimen collection and diagnostic test

Nasopharyngeal swabs were obtained during pregnant women admission to test positivity for SARS-CoV-2. Nasopharyngeal and oropharyngeal swab of the newborns was also taken within 1 × 24 h after delivery. The placental swab and 3 cc of amniotic fluid was collected during caesarean section. The integrity of the lower uterine segment-preserving membranes was cut, and then the amniotic fluid was withdrawn using a 10-mL sterile syringe; no contamination with blood or meconium was observed. Maternal bloods were collected for routine and D-dimer examination. All COVID-19 and routine blood examination were performed in the clinical microbiology laboratory of dr. Zainoel Abidin General Hospital. Sample collection, processing, and laboratory testing followed the World Health Organization guidance [17]. Neonatal blood was also collected at birth for serological test using the Electro-Chemiluminescence Immunoassay (ECLIA) method (Elecsys SARS CoV 2 Antigen assay, Roche) according to the manufacturer's instruction.

Statistical analysis

Data were presented as medians and ranges were reported for quantitative variables. All ranges are indicated as minimum–maximum values. Fisher's exact test was used with $p < 0.05$ considered significant. The analyses were performed using SPSS Statistics, Version 24.0 (IBM Corp., NY), together with GraphPad Prism 8 (GraphPad Software, Inc, CA, USA).

Results

Of all 33 infants born to COVID-19 positive mothers, 29 infants (29/33, 87.88%) showed negative PCR results for COVID-19. Only 4 infants (4/33, 12.12%) showed positive COVID-19. The mothers who gave birth to COVID-19 (+) infants were older than the mothers with COVID-19 (−) infants with an average of 35.75 ± 5.73 years. The average obstetric status of mothers with COVID-19 (+) infants is G3P2A0. Routine evaluation of maternal blood, kidney, and liver function in this study were within normal limits and did not show any difference between the two groups. The D-dimer level of mothers who gave birth to COVID-19 (+) infants was higher than the group of mothers with COVID-19 infants (−) with an average of 2.525 (1.310–3.780) ng FEU/mL (Table 1). All amniotic fluid and placenta were negative for COVID-19.

The characteristics of infants with confirmed COVID-19 showed an equal percentage of males and females (50%). Routine blood examination of infants in this study showed normal values. One of 4 (25%) infants with confirmed COVID-19 were asphyxiated at birth (Table 2). The weight of infants with confirmed COVID-19 was lower than infants without COVID-19 (2.792.5 ± 660.97 g).

Based on serological examination, infants with positive COVID-19 did not show any antibody formation

(Table 3). However, four of 29 infants with negative COVID-19 showed positive antibody results (Figure 1). Statistically using the Fisher's exact test, although not significant, there is no difference in the formation of SARS-CoV-2 antibodies in infants with and without COVID-19.

Table 1: Characteristics of the mother based on the results of the mother's PCR examination

Variable	Infants		p-value
	COVID-19 (−) (n = 29)	COVID-19 (+) (n = 4)	
Age (years), mean ± SD	28.07 ± 5.58	35.75 ± 5.73	0.019
Gravida, median (min–max)	2 (1–6)	3 (2–8)	0.105
Para, median (min–max)	1 (0–4)	2 (1–5)	0.055
Abortus, median (min–max)	0 (0–2)	0 (0–2)	0.811
Hemoglobin, median (min–max)	11.06 (9.04–14.01)	10.04 (9.3–12.05)	0.295
Leukocytes, median (min–max)	8.06 (3.07–22.04)	10.04 (7.01–12.05)	0.690
Trombocytes, mean ± SD	222 ± 74.66	315 ± 168.87	0.352
Ureum, mean ± SD	13.45 ± 4.24	16.25 ± 8.5	0.285
Creatinin, median (min–max)	0.6 (0.4–1.1)	0.6 (0.5–0.9)	0.576
SGOT, median (min–max)	27 (16–54)	29.5 (16–358)	0.894
SGPT, median (min–max)	15 (6–46)	12.5 (10–223)	0.852
PT, median (min–max)	12.05 (10.4–72)	13.5 (12.4–14.3)	0.149
APTT, median (min–max)	31.5 (11.5–56.2)	22.4 (27.1–34.1)	0.811
D-Dimer, median (min–max)	1450 (350–4000)	2525 (1310–3780)	0.149
Fibrinogen, median (min–max)	434 (147–667)	429 (343–525)	0.852
BMI, mean ± SD	30.03 ± 4.22	30.75 ± 1.86	0.744

BMI: Body mass index, SD: Standard deviation, PCR: Polymerase chain reaction.

Table 2: Characteristics of infants based on PCR examination results

Variable	Infants		p-value
	COVID-19 (−) (n = 29)	COVID-19 (+) (n = 4)	
Gender, n (%)			0.586
Boys	20 (69)	2 (50)	
Girls	9 (31)	2 (50)	
Hemoglobin, median (min–max)	15.07 (9.09–19.02)	12.53 (12–18.09)	0.439
Trombocytes, mean ± SD	247.52 ± 118.32	292.75 ± 23.12	0.457
Leukocytes, mean ± SD	17.28 ± 6.59	16.06 ± 1.4	0.394
Birth weight, mean ± SD	3.066.9 ± 493.59	2.792.5 ± 660.97	0.323
Apgar Score 1, median (min–max)	8 (5–9)	8 (7–9)	0.576
Apgar Score 5, median (min–max)	9 (6–10)	9 (9–10)	0.246
Balard Score, n (%)			
30–32	1 (3.4)	0	
30–40	1 (3.4)	0	
32–34	0	1 (25)	
34–36	1 (3.4)	0	
36–38	4 (13.8)	0	
38–40	20 (69)	3 (75)	
40–42	2 (6.9)	0	
Asphyxia, n (%)			1.000
Yes	6 (20.7)	1 (25)	
No	23 (79.3)	3 (75)	
ECLIA, n (%)			1.000
Reactive (+)	4 (13.8)	0	
Non-Reactive (−)	25 (86.2)	4 (100)	

ECLIA: Electro-Chemiluminescence immunoassay, PCR: Polymerase chain reaction, SD: Standard deviation.

Discussion

Many studies of SARS-CoV-2 infection showed evidence of transmission from an infected mother to the fetus [18], [19]; however, vertical transmission from an infected mother to an infant is still a point of debate [20], [21], [22], [23]. Our result showed no viral RNA found in amniotic fluid and placenta, which suggested that vertical transmission from mother to neonates intrauterine was unlikely. The absence of maternal viremia and decreased expression of placental angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) might be possible mechanisms [24]. The expression of ACE2 also changed significantly in the placenta during the different trimesters [25], [26]. This receptor is found in the syncytiotrophoblast, cytotrophoblast, and vascular smooth muscle of the primary and secondary villi [25]. Another study found that ACE2 is expressed in stromal and perivascular of decidual cells in placenta [26]. Several recent case reports provided evidence that COVID-19 can infect the placenta with confirmed presence of SARS CoV-2 viral RNA and protein in the placenta and evidence of virions in syncytiotrophoblasts [3], [4], [6], [7]. Fenizia *et al*. also reported two cases of vertical transmission in which viral RNA was detected in placental tissue as well as in neonate nasopharyngeal swabs [27]. Various factors such as viral load, time between onset of illness and delivery, and stage of pregnancy can influence the vertical transmission of SARS-CoV-2 [5].

Table 3: Differences in antibody detection of infants with and without COVID-19

ECLIA	COVID-19 (+) n = 4	COVID-19 (−) n = 29	p-value
Reactive (+), n = 4	0	4 (12.1)	1.000
Reactive (−), n = 29	4 (12.1)	25 (75.8)	

ECLIA: Electro-Chemiluminescence immunoassay.

Komine-Aizawa *et al*. explained several possibilities of COVID-19 transmission between mother and fetuses which include direct infection of the syncytiotrophoblast layer through the synchronous layer through ACE2 and the fc receptor, maternal circulation to extravillous trophoblasts or other placental cells, maternal immune cells, and ascending infection through the mother's vaginal tract [28]. Transmission during vaginal delivery is another possible pathway for SARS-CoV-2 infection in neonates, although uncommon [29] and associated with a lower risk of intrapartum transmission of SARS-CoV-2 [30].

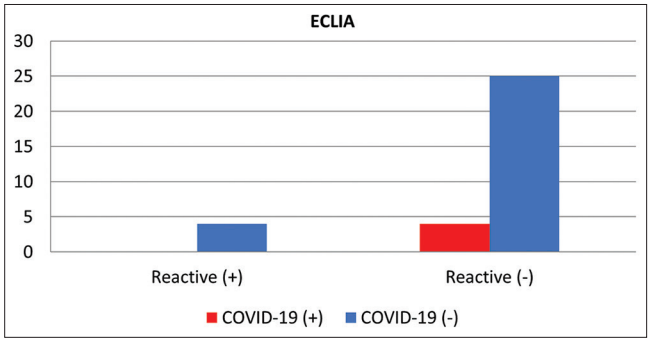

Figure 1: Distribution of antibodies in infants with and without COVID-19

This study found that the age and D-dimer level of mothers who gave birth to COVID-19 (+) infants were higher than the group of mothers with COVID-19 (−) infants. Turan *et al*. reported that maternal age with obesity and combined elevated D-dimer and interleukin-6 levels was predictors of poor pregnancy outcome in COVID-19 [31]. Jardine and Morris. found that obesity, age over 35 years, from the low socioeconomic background, and women increased the risk of COVID-19 disease severity [32]. The weight of infants with confirmed COVID-19 was lower than infants without COVID-19 (2792.5 ± 660.97 g), and one in

4 (25%) infants with confirmed COVID-19 had asphyxia at birth. Yang *et al*., described that the mean birth weight of the seven infants born to COVID-19 infected mothers was 2096 ± 660 g [33]. Juan *et al*. also reported similar results of eight neonates with a birth weight <2500 g born to pregnant women with COVID-19 who had given birth between 28 and 41-weeks' gestation [34]. However, Yang *et al*. concluded no statistical differences in low birth weight, neonatal asphyxia, and premature rupture of membranes between mothers with and without COVID-19 [33].

In this study, the average Apgar scores in the 1st and 5th min in 33 neonates born to mothers with confirmed COVID-19 infection are within the normal range (normal score 7–10). These data are consistent with the research of Dong *et al*., and a systematic review by Kasraeian *et al*., which showed that the overall average Apgar score of neonates born to COVID-19-positive mothers in the 1st and 5th min did not deviate from the normal value [35], [36].

Our results showed that, of 33 infants who were undergone RT-PCR and COVID-19 serologic examination, 4 infants (12.1%) showed negative PCR results but positive formation of SARS-CoV-2 antibodies. Another 4 newborns (12.1%) showed positive PCR results but no formation of SARS-CoV-2 antibodies. The remaining 25 babies (75.8%) showed negative PCR and negative serologic results. This finding was similar to those reported by Zeng *et al*., where six babies with negative COVID-19 infection showed positive SARS-CoV-2 antibodies. Similar result was also reported by Dong *et al*., who found one neonate had an increase of anti-SARS-CoV-2 IgM and IgG antibodies within 2 h of birth. At the late second semester of pregnancy, IgG is passively transferred across the placenta from mother to fetus and reaches high levels at birth [14]. When the baby is born, the level of IgG antibodies in the infant's serum is similar to that of the mother's, both of which are strongly positive. However, infant IgG antibodies decline rapidly and become negative after approximately 100 days, whereas maternal IgG antibodies remain at high levels [37]. In this cohort study, maternal IgG antibodies to SARS-CoV-2 were transferred across the placenta during pregnancy after asymptomatic infection. Cord blood antibody concentrations correlated with maternal antibody concentrations and with the duration between infection onset and delivery as well. Flannery *et al*. stated that maternally derived SARS-CoV-2-specific antibodies may provide protection for the newborn from COVID-19 infection. This is important because maternally derived antibodies are a key element of neonatal immunity. The presence of antibodies in infants who were negative COVID-19, and are born to mothers with COVID-19 indicate the possibility of transplacental immunity (natural passive immunity) [38]. However, further study is warranted to determine the type of antibody that has increased.

Our study also found 4 infants (12.1%) that showed positive PCR results, though the transmission route was unclear. Moreover, no SARS-CoV-2 antibodies detected in these infants' blood. Possible explanation was the sampling time factor which is ≤14 days post-symptom onset in COVID-19 patients may be the reason that SARS-CoV-2 antibodies cannot be detected. This is in accordance with the findings of Tan-Lim and Burog. who stated that the sensitivity of ECLIA to detect the presence of antibodies to SARS-CoV-2 varied depending on the time of sampling. ECLIA has a high specificity of 99.8% and a sensitivity of 37.6% when used ≤ 14 days from the onset of symptoms. The sensitivity is 82.4% when used for at least 14 days from the onset of symptoms [39]. The immune system in neonatal is also immature and continue to develop during the 1st years of their life. The microbiome composition of mother is also affecting infant's immune system development [40].

Conclusion

Negative result of COVID-19 RT-PCR on amniotic fluid and placenta suggested that no evidence of in utero mother-to-child transmission found in this study. However, further studies are needed as no definite results can be drawn due to the low number of analyzed cases. Therefore, vertical transmission, although uncommon, should be taken into consideration in the management of COVID-19 pregnant women. Infants born to infected mothers must be carefully tested and clinically monitored.

Keypoints

- At present, there is not enough evidence to support intrauterine transmission of COVID-19 between mother and newborn.
- Clinical and laboratory data in infants born from COVID-19-positive mother should be carefully interpreted.
- Further study on placenta, amniotic fluid, and cord blood needed to evaluate the possibility of vertical transmission of COVID-19.

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