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Maternal and perinatal outcomes with covid-19: lesson learned from the tertiary hospital

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ABSTRACT

Background: The COVID-19 pandemic has led to global health crisis. Most studies have focused on evaluating the effects of COVID-19 on the general population, and there is still insufficient data on its impact on vulnerable populations, such as pregnant women. The study evaluates maternal and perinatal outcomes on pregnant women with COVID-19 in Kariadi as tertiary hospital in Central Java.

Methods: We prospectively collected and analyzed data for a cohort of 45 pregnant patients with COVID-19 between March 31st and September 23th 2020 in Kariadi hospital.

Results: A total of 45 pregnant women with COVID-19 delivered 46 babies including one twin pregnancy. The symptoms ranged from asymptomatic (28.9%), mild (26.6%), moderate (8.8%), severe (2.2%), and critical (6.6%). Gestational age was 22 to 41 weeks. Cesarean section was the most mode of delivery (86.7 %). Diabetes in pregnancy and HIV were the most common comorbidities found in this study, there were also seven patients came with preeclampsia. There were three maternal mortalities, we reported one maternal death (2.2 %) caused by severe respiratory disease COVID-19 in second trimester. The other two death cases were pregnancy complicated with severe preeclampsia with hyperthyroid and preeclampsia with diabetes in pregnancy. Perinatal outcomes were intrauterine fetal death (8.7%), stillbirth (2.2%), and severe asphyxia (2.2%).

Conclusion: Although we obtain mostly maternal and perinatal outcomes in good outcomes, it is urgent to analyze potential high-risk maternal death with COVID 19.

Keywords: Coronavirus, COVID-19, perinatal, pregnancy.

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INTRODUCTION

First time found on December 31st 2019, in Wuhan China, novel coronavirus caused Coronavirus disease (COVID-19), had become a pandemic disease.[1] This infection spread rapidly, with total world case more than 35.1 million in October 1st 2020, and more than one million death case, this disease is a worldwide public health emergency.[2] First case of COVID-19 in Indonesia was reported on March 2nd 2020.[3] The case spreads and increasing rapidly throughout Indonesia. Until October 1st 287.000 cases were identified, 215.000 healed, and 10.740 died due to COVID-19 in Indonesia.[2]

Patients with infection may be asymptomatic or may experience mild symptoms like fever, malaise, dry cough, and severe illness, including pneumonia, respiratory failure, and death.[4,5] Most cohort studies have focused on evaluating the effects of COVID-19 on the general population and there are insufficient data on its impact on vulnerable populations, such as pregnant women.[5]

Physiologic maternal adaptations to pregnancy predispose pregnant women to a more severe infection course, with subsequently higher maternal and fetal morbidity and mortality.[1] Anatomical changes such as an increase in the transverse diameter of the thoracic cage and an elevated level of the diaphragm, decrease maternal tolerance to hypoxia. Lung volume changes and vasodilation can lead to mucosal edema and increased secretions in the upper respiratory tract. Also, alterations in cell-mediated immunity contribute to the increased susceptibility of pregnant women to be infected by intracellular organisms like viruses.[6,7]

The risks of morbidity with severe lower respiratory tract infections are not limited to maternal outcomes because there is a known increased occurrence of preterm birth, fetal demise, and delivery of low birth weight infants with nearly all maternal severe lower respiratory tract viral infections. With regard to the fetus and the new-born, the immaturity of the innate and adaptive immune systems makes them highly susceptible to infections.[6,7]

In a case series of 118 pregnant women with COVID-19 in Wuhan Province, 92 % of women have mild disease, 8% had

Table 1. Summary statistical analyses and outcome measures

Variable	frequency	%	Mean ± SD	Median (min-max)
Descriptive Statistics				
Age			32.02 ± 5.69	32 (23 – 48)
20 – 35	32	72.1		
> 35	13	28.9		
Gestational age at presentation				
Second Trimester (14-28 weeks)	2	4.3		
Third Trimester (> 28 weeks)	43	93.5		
Symptomatic on presentation				
Fever	6	13.3		
Cough	12	26.7		
Dyspnea	11	24.4		
Fatigue/malaise	2	4.4		
Sore throat	0	0		
Nasal congestion	2	4.4		
Diarrhea	1	2.2		
Severity of disease				
Asymptomatic	25	54.3		
Mild	12	26.6		
Moderate	4	8.8		
Severe	1	2.2		
Critical	3	6.6		
Referral system				
Referral	35		Form other hospitals (33) Public health center (1) Mayor's official residence as isolation place (1) Come by themself (10)	
A nasopharyngeal swab is taken in Kariadi hospital	38		Other hospitals (6) Mayor's official residence as isolation place (1)	
Maternal Investigation				
Lymphocyte			14.50 ± 7.12	15 (2 – 33)
Lymphopenia (< 20)	33			
NLR (Neutrophil lymphocyte Ratio)			9.28 ± 10.64	5.06 (1.87 – 48.5)
NLR > 5,8	18			
Pneumonia found on X-Ray	21		No X-ray in 2 patients	
CRP			3.92 ± 6.21	1.23 (0.08 – 26)
CRP > 0,3	30		No data in 8 patients	
Procalcitonin			0.61 ± 2.46	0.7 (0.01 – 11.62)
Procalcitonin > 0.5	2		No data in 22 patients	
Maternal Outcome				
Gestation at delivery			37.08 ± 3.96	38 (22.14 – 41.29)
Aterm	28	62.2		
Preterm	17	37.8		
Mode of delivery				
Vaginal	6	13.3		
Caesarian section	39	86.7		
Pregnancy comorbidities				
DM in pregnancy	3			
Obesity	2			
HIV	3			
Toxoplasmosis with neurological deficit	1			
Azotemia	2			
Anemia	2			

Variable	frequency	%	Mean ± SD	Median (min-max)
Graves disease	1			
Adverse pregnancy outcome				
Preterm	17	37.8		
Aterm	28	62.2		
IUGR	2	4.4		
PPROM	2	4.4		
Fetal distress	2	4.4		
ICU admission	3	6.7		
Need for mechanical ventilation	3	6.7		
Maternal death	3	6.7		
Perinatal Outcomes				
Birthweight (mean, SD)			2808.9 ± 704.8	2840 (900 – 4200)
Birthweight <2500 gr	10			
APGAR recorded	46	100		
APGAR 1 min			7.67 ± 2.84	9 (0 – 9)
APGAR < 7 at 1min	1			
APGAR 5 min			8.51 ± 2.94	10 (0 – 10)
APGAR < 7 at 5 min	1			
NICU admission	2			
IUFD	4		1 twin	
Stillbirth	1			
Perinatal mortality	6			

Abbreviation; Intrauterine fetal death (IUFD); neonatal intensive care unit (NICU); intensive care unit (ICU); preterm premature rupture of membrane (PPROM), human immune virus (HIV); diabetes mellitus (DM); neutrophil to lymphocyte ratio (NLR); c-reactive protein (CRP).

severe disease (defined as hypoxemia), and one woman had critical illness (defined as requiring mechanical ventilation); there were no deaths.[12] This severity of disease breakdown has been similarly reported in New York City. A preceding systematic review and meta-analysis of outcomes of coronavirus infections during pregnancy reported on 18 studies that included 79 women and found higher rates of miscarriage, preterm birth, preeclampsia, cesarean birth, and perinatal death in the setting of COVID-19.[14]

Until now, there is a lack of data in the literature about the effect of COVID-19 infections during pregnancy in Indonesia. This study's objective was to evaluate maternal and perinatal outcomes on pregnant women with COVID-19 in Indonesia.

METHODS

This prospective cohort study of pregnant women with SARS-CoV-2 infection was admitted and delivered at Kariadi Hospital Semarang Indonesia, from March 31st 2020 to September 23th 2020. Pregnant women with laboratory-confirmed COVID-19 were included, defined by a positive result on a reverse transcriptase-polymerase chain reaction (RT-PCR) assay for SARS- CoV-2.

We collected data about age, presenting signs and symptoms, and medical comorbidities. Obstetric outcomes, maternal complications, disease severity, and perinatal outcomes were also obtained.

Positive cases defined as women with confirmed SARS-CoV-2 infection on an RT-PCR assay performed on a nasopharyngeal swab before or during hospitalization.

Asymptomatic were defined for those who reported being in usual health with no signs or symptoms of COVID-19. Mild COVID-19 was defined as symptoms requiring no additional oxygen supplementation beyond standard labor and delivery care. Severe COVID-19 was defined as dyspnea (patient-reported), respiratory rate 30 breaths per minute or higher, oxygen saturation 93% or less on room air, or findings consistent with pneumonia on chest X-ray, or a combination of these. Critical COVID-19 was defined as any or all of the following: respiratory failure (need for intubation and invasive ventilation), septic shock, and multiple organ dysfunction or failure.[5,9,10]

RESULT

A total of 163 patients suspected COVID-19 came to Kariadi Hospital, Semarang, Central Java during March 31st 2020 to September 23rd 2020, nasopharyngeal samples for RT- PCR for SARS-CoV-2 nucleic acid were taken to make the diagnosis. A total of 45 (27.6%) patients had confirmed COVID-19 infection based on the RT-PCT test on their second and third trimesters.

Most cases found were asymptomatic 25/45 (55.6%), mild symptoms were found in 12 /45 (24.4%), 4/45 (8.8 %) with moderate symptoms, 1/45 (2.2%) patient had severe symptoms, and 3/45 (6.6%) had acute symptoms (Table 1). Among the symptomatic women, 26,7 % complained cough, 24.4 % dyspnea, 13.3 % fever, nasal congestion and malaise about 4.4%, and 2.2 % diarrhea.

Based on the table, 43 patients had chest X-rays, and 21/43 (48,8 %) showed pneumonia on X-ray. Most of these patients came to Kariadi Hospital as a referral from another hospital (77.7%), some of them came by themself due to obstetrical complain (22,2 %). 84.4 % patients had nasopharyngeal swabs and diagnosed as positive COVID-19 in Kariadi hospital.

MATERNAL AND PERINATAL OUTCOMES

Mean age of patients was 32 years old (ranged from 23 to 48 years) with 93.5% came in their third trimester. Gestational age ranged from 22 to 41 weeks. Some pregnant women came with a number of comorbidities or complications in their pregnancy, 3 patients had diabetes in pregnancy, 3 with HIV, 2 patients with obesity, one patient toxoplasmosis with neurological deficit, 2 patients with azotemia, 2 patients with severe anemia, and 1 patient with hyperthyroid. Seven women came with preeclampsia.

Cesarian section was the most mode of delivery (86.7%), 6 of 45 women had vaginal delivery. 17 of 45 women had preterm delivery (37.8%), 62.2 % had term delivery. Lymphocytopenia was reported in 33 of 45 cases (73.3 %), NLR (Neutrophil Lymphocyte Ratio) >5.8 was found in 18 patients (40%), and elevated C-reactive protein concentration (>0.3 mg/dl) was found in 30 of 38 patients (8 patients had no CRP data).

Our study had 45 women, 43 women in their third trimester, delivered 44 babies, two patients were in their second trimester.

We reported three maternal mortalities (6.6%), all the three of them were admitted to the Intensive Care Unit and required mechanical ventilation. The first case was a woman with severe septic due to pneumonia COVID-19, she had diabetes in pregnancy, severe preeclampsia and azotemia. She came with fever, dyspnea, cough, 25 weeks pregnancy, intrauterine fetal death, delivered vaginally on the fourth day of treatment, and 1500 gr baby. On the fifth day of treatment, she was intubated and had SIMV ventilator due to the worsening of the disease, she died on tenth day of treatment.

The second case was woman came with a one-week fever, and dyspnea, she was referred to Kariadi hospital due to worsening of dyspnea, she got ARDS due to COVID-19, the dyspnea gets worsen and the baby died intrauterine on sixth day of treatment and delivered vaginally, and the mother died soon after that.

The third case was 30 weeks pregnant woman who came with dyspnea, serious disease, and severe preeclampsia, on sixth day of treatment, she had acute pulmonary edema, and eclampsia, the baby was fetal distress, emergency caesarian section was held, and the 2000 gr baby was born stillbirth, the mother was intubated using mechanical ventilation and died on fourteenth day of treatment.

Some adverse pregnancy outcomes found in this study, two patients gave birth 2 IUGR babies, first case was women with neurological deficit due to toxoplasmosis, she got decrease of consciousness, three times seizures due to toxoplasmosis, she came to emergency room with fever and dyspnea, diagnosed with pneumonia due to COVID-19 from X-ray and nasopharyngeal swab, she was 38 weeks pregnancy, gave birth to 1600 gr baby by caesarian section, with good Apgar score. The second case was 30 weeks women came with fever, cough, dyspnea, severe preeclampsia, the baby was fetal distress, and had end-diastolic flow, an emergency caesarian section was held, 900 gr baby was born with APGAR score 1-5-6 and admitted to NICU.

There were two cases of PPROM (Preterm Premature Rupture of Membrane), first case was 35 weeks women with HIV, came with fever and cough, gave birth 2100 gr baby with caesarian section, with good APGAR score, the second one was 30 weeks women went to the emergency department with no symptom of COVID-19 and had vaginal birth of 1490 gr baby, with APGAR score 7-8-9.

In terms of perinatal outcomes, the majority did not require resuscitation within 1 min Apgar score of 8-9 and 5 min Apgar score of 9-10. In our study only one baby weighed 2714 gr found with severe asphyxia with 1 min Apgar score of 3-4, the baby was resuscitated and referred to NICU, and died on fourth day of treatment. This study's mean birth weight was 2808 gram, ten babies (21%) was weighed < 2500 gram.

We discovered total of six perinatal mortalities (4 IUFD including one set of twins, one stillbirth, and one severe asphyxia). One twin set with IUFD was delivered on 36 weeks, weighed 2700 gr and 1400 gr, the mother was referred from other hospitals due to twin pregnancy and IUFD, morbid obesity, and preeclampsia, she complained of fever and cough and a nasopharyngeal swab was taken, with positive result.

In our study 5 newborns tested were confirmed positive for COVID-19. From these findings, vertical maternal-fetal transmission cannot be ruled out.

DISCUSSION

We report 45 women with laboratory-confirmed COVID-19 infection during delivery hospitalization in Kariadi hospital. Among pregnant women with COVID-19 disease, 54.3 % were asymptomatic. This is a high number, with implications for infection prevention and control.[8] Among symptomatic women, the most commonly reported symptom was cough (26.7 %), similar to previous reports, followed by dyspnea (24.4 %) and fever (13.3 %). COVID-19 as pandemic which spread rapidly and the high risk of exposure and transmission on labor and delivery units, universal testing for COVID-19 at the time of antepartum and delivery admission when possible is essential to facilitate appropriate infection prevention and to give necessary medical care while protecting staff, other patients, family members, and newborns.[8]

Immune function is relatively suppressed during pregnancy. At the same time, during pregnancy, women undergo physiological changes that increase their susceptibility to severe respiratory infections and subsequent respiratory failure, a key concern in relation to COVID-19 infections.[11] It is reported in the literature that pregnant patients infected with SARS-CoV and

MERS-CoV indeed have more adverse outcomes (spontaneous miscarriage, intrauterine growth restriction and premature delivery); the mortality rate of pregnant patients is as high as 25 % compared to 10 % in ordinary infected people. Recently, Chen et al. and Zhu et al. reported that the perinatal infection COVID-19 might have adverse effects on newborns, but the adverse mother-to-child outcomes are fewer compared with SARS-CoV.[1,12]

Our study on pregnant patients infected with COVID-19 in their second and third trimester seems to bear these. Most cases had asymptomatic manifestation (54.3%), one patient was found with severe cases (2.2 %), and 3 patients with critical cases (6.6 %).

Chest x-ray examination showed pneumonia in 21/45 (46.6 %) of the patients. 73.3 % of our sample were lymphopenia.

Caesarian birth was the mode of delivery in 86.7 %, which is high compared with the reported cesarean birth rates in Indonesia. Similarly, the preterm birth rate at less than 37 weeks of gestation in our study was higher than that in the general population. Preeclampsia was also found on 7 patients (15.5 %). These results were consistent with previous studies.[1,11]

Some perinatal morbidities and mortalities found in this study, two babies had IUGR, 2 fetal distress, one stillbirth, 4 intrauterine fetal death and severe asphyxia, one mechanism implicated in this is related to the pre placental hypoxia which can occur as result of maternal respiratory compromise with pneumonia/ pneumonitis. This can perpetuate a cascade of anti-angiogenic and pro-inflammatory factors promoting endothelial dysfunction, end-organ damage, and placental insufficiency; thereby contributing to relative fetal hypoxemia and eventually hypoxia, there were maternal comorbidities that made the outcome worse.[11] One stillbirth baby at 30 weeks pregnancy was born from mother who came with severe disease, eclampsia and COVID-19 with pulmonary edema, 2 babies born IUFD from mother with ARDS due to COVID-19 and from a mother with COVID -19 with diabetes in pregnancy, azotemia, and preeclampsia. Twin babies with IUFD were born from a mother with COVID-19 and preeclampsia, with morbid obesity.

We found that COVID-19 infection can evolve in disease manifestation and severity during delivery hospitalization. For women with COVID-19 infection we must be aware for rapid progression of symptoms (in the form of fever, shortness of breath, hypoxia, or a combination of these) and worsening clinical status. The question of why some individuals remain asymptomatic or have mild COVID-19 compared with severe or critical disease remains unanswered. The published literature to date suggests that the most prevalent comorbidities associated with COVID-19 severity in the non-pregnant population are hypertension and diabetes, followed by cardiovascular disease and respiratory diseases.[8]

With respect to maternal ICU admissions and mortality rates during COVID-19, the available data appears reassuring. In contrast, SARS and MERS respectively had 15–18% and 25– 27% mortality rates; 30% and 60% ICU admission rates, and a requirement for mechanical ventilation in 35% and 41% of women.[11] We found three maternal mortality cases. The first case was due to ARDS COVID-19. The second case was COVID-19 with diabetes in pregnancy, azotemia, preeclampsia, and the last one due to COVID-19, pulmonary edema, eclampsia and grave disease, all of them were admitted to ICU and had mechanical ventilation.

This is different from other studies such as a case series of 118 pregnant women with COVID-19 in Wuhan Province, 92 % of women had mild disease, 8% had severe disease (defined as hypoxemia), and one woman had critical illness (defined as requiring mechanical ventilation) but there were no deaths.[6] In a review Mehreen et al. in Scandinavia 108 pregnant women with confirmed COVID-19 showed three cases of maternal intensive care admission (3%) but no confirmed fatalities.[6]

There were two babies admitted to NICU due to severe asphyxia, weighed 2715 gr and 900gr. This is different from other studies by Zhu et al. (n = 10) where 60% of the neonates were born premature and required respiratory support.[11]

Vertical transmission of COVID-19 infection from mother to fetus is beyond the scope of this report. We report initial new-born testing but not a detailed analysis of the testing or comprehensive evaluation of the extent of vertical transmission.

STRENGTH AND LIMITATION

We acknowledge that our study is limited by the small sample, however, our research has some strengths. Only pregnant women with laboratory-verified SARS-CoV-2 infection were included in our review. Thus, the clinical manifestations and maternal-neonatal outcomes are representative of the disease and our findings are essential for understanding the characteristics of the disease in pregnant patients and their infants.

CONCLUSION

Although we obtain mostly maternal and perinatal in good outcome, it is urgent in-depth analysis potential high-risk maternal death with COVID 19. Our study suggests the possibility of severe maternal morbidity, maternal mortality, and perinatal death with COVID-19 infection in pregnancy. There is also a higher rate of preterm birth, preeclampsia, and C-section patient with COVID-19.

CONFLICT OF INTEREST

All author declares there is no conflict of interest regarding publication of this report.

ETHICAL APPROVAL

Ethical Committee Faculty have approved this study protocol of Medicine, Universitas Diponegoro with ethical clearance references number 531/EC/KEPK-RSDK/2020. All study protocol in accordance by Helsinki Declaration of human rights.

CONFLICTS OF INTEREST

There is no conflict of interest in this study.

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AUTHOR CONTRIBUTION

All authors had contributed equally in writing the original draft and agreed for final version of the manuscript for publication.

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