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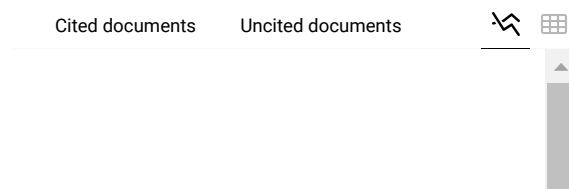
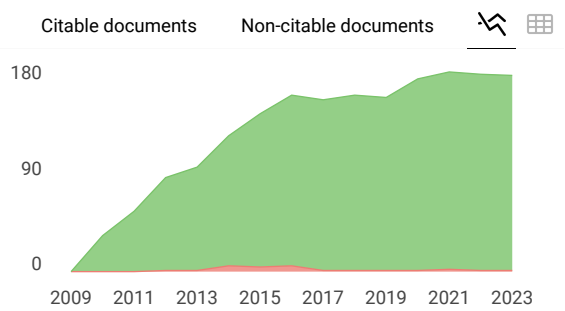
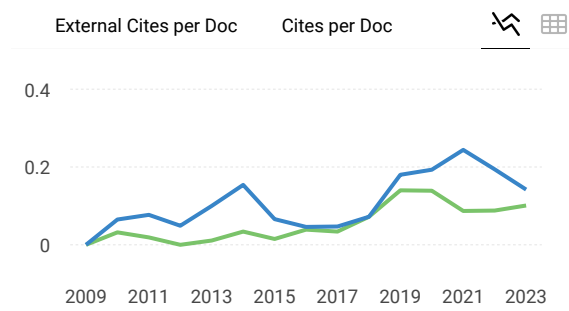
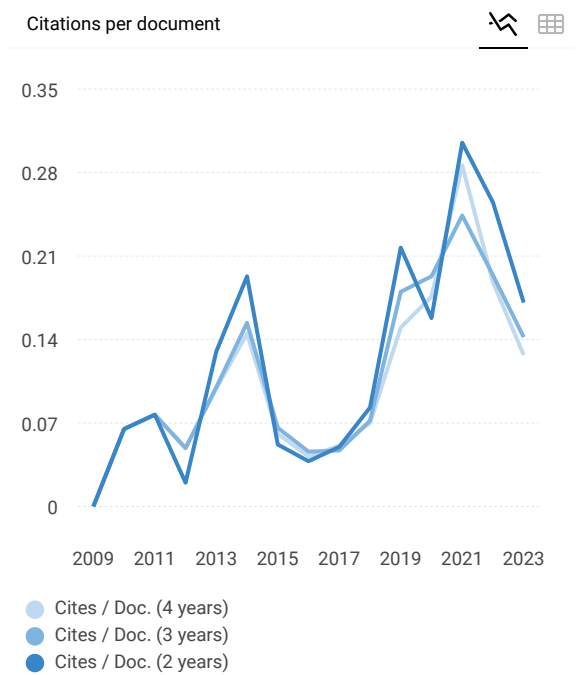
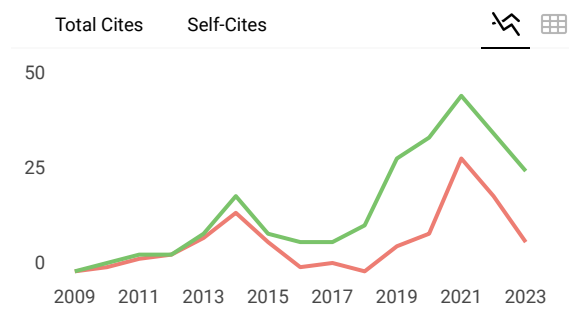
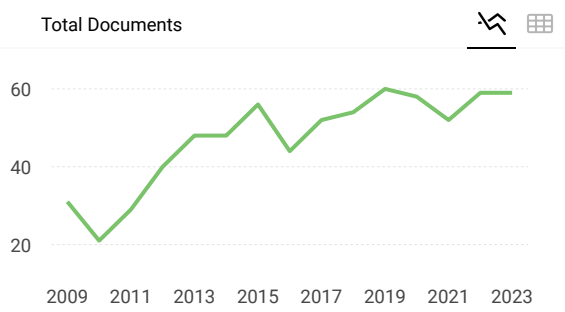
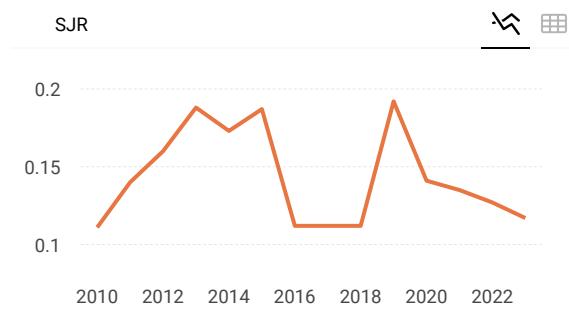
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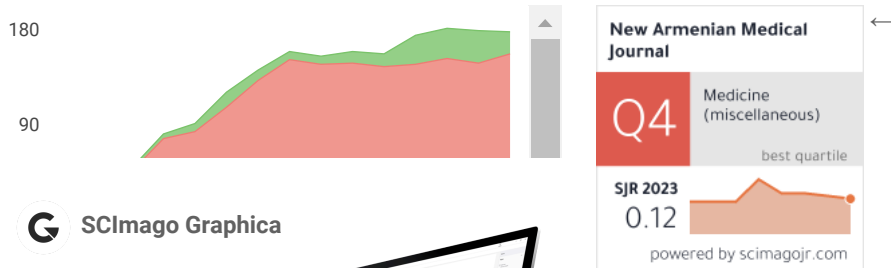
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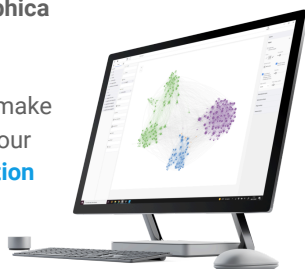
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MATERNAL AND PERINATAL OUTCOME OF COVID-19 IN OBSTETRIC CASES: 9 MONTHS EXPERIENCE FROM EAST JAVA TERTIARY REFERRAL HOSPITAL

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Abstract

Background: Covid-19 infection in vulnerable obstetric patients still requires a lot of research, especially in developing countries to help determine the best policy to manage it.

Objective: To analyze the characteristic of Covid-19 infection in obstetric patients.

Methods: In an East Java tertiary Covid-19 referral hospital, a case control analysis was conducted using medical records on obstetric cases of Covid-19 infection from March until November 2021.

Results: Covid-19 was identified in 109 cases (9.3%) from 1170 patients who came to our obstetric room. Majority came in pregnancy state with 76% and had delivered 93.6%. Most patients were asymptomatic (68.8%) with minimal contact history (2.8%). Comorbidity found in 41.3% cases, obesity and hypertension in pregnancy dominated the cases. Symptomatic cases were associated with lower gestational age ($p=0,005$) and birthweight ($p=0,015$), low lymphocyte count ($p=0,006$), abnormal chest X-Ray ($p<0,001$), intensive care admission ($p=0,002$) and maternal death ($p<0,001$), while asymptomatic cases were associated with more reactive antibody test ($p=0,002$).

Conclusion: There were a high number of Covid-19 obstetric cases with the majority asymptomatic and came for delivery. Significantly higher reactive antibody tests in asymptomatic cases may aid Covid-19 identification. Covid-19 symptoms should be given more consideration, because they are linked to a lower gestational age, birth weight, poor clinical parameters, the need for intensive care, and maternal mortality.

KEYWORDS: . COVID-19, pregnancy, perinatal outcome, obstetrics complications, maternal mortality.

INTRODUCTION

On December 31, 2019, Wuhan received the first notice of a new form of pneumonia case [Adhikari SP et al., 2020]. Since then, the disease, which is officially named Coronavirus Disease (Covid-19) by WHO on February 11, 2020, has become a major threat around the world which currently contributes to around half a million new cases every day [WHO Coronavirus Disease 2020]. Indonesia as a developing country is also not immune from the impact of this outbreak. WHO de-

clared the novel coronavirus outbreak as a public health emergency of international concern since 30 January 2020 [WHO. Timeline 2019], while the notification of the Covid-19 case for the first time in Indonesia was announced 1 month later on March 1, 2020 for two patients who had contact with foreign citizens [Setiawaty V et al., 2020].

The rapid spread of the Covid-19 pandemic will affect people at all levels of society, and pregnant women are among the most vulnerable [Rasmussen SA et al., 2019]. Physiological changes in the form of decreased maternal immunity occurred to avoid rejection of the fetus so that pregnancy is associated with an increased risk of infection [Robinson DP, Klein SL 2012]. Several studies regarding pregnant women infected with Covid-19 have been

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carried out, but conditions in some areas can give different and inconsistent results. Publication on pregnancy with Covid-19 in developing countries like Indonesia is still rare, so that our 9 months of experience from the main referral hospital for Covid-19 located in East Java area which is became one of the Covid-19 hotspots with the second highest number of cases and the highest number of deaths in Indonesia [Covid-19 STP] is very important to determine local policies in the handling of pregnant women in the midst of an pandemic.

MATERIAL AND METHODS

We performed the retrospective cross sectional design study using medical records at Obstetrics and Gynecology Department of Academic Soetomo General Hospital, in Surabaya, Indonesia which serves as the main East Java tertiary hospital and also Covid-19 referral hospital. This study was conducted for 9 months from March (first Covid-19 cases identified in Indonesia) until November 2020. All obstetric cases with Covid-19 infection confirmed with molecular laboratory examination using real time reverse transcription polymerase chain reaction (real time RT-PCR) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were included in our study. The Abbott m2000 with Abbott RealTime SARS-CoV-2 assay was used for the qualitative detection of nucleic acids from SARS-CoV-2, results were reported positive when RdRp or N-gene tested positive.

The data collected in this study were basic maternal data (maternal age, gestational weeks, parity, referral status, pregnancy plan and maternal death), delivery data (Mode of delivery, birth weight, Apgar Score and Perinatal mortality) and Covid-19 infection related data (comorbidity, symptoms, Intensive Care Admission, contact history, hematological laboratory examination, chest X-Ray examination and rapid antibody test result). Covid-19 symptoms were divided into asymptomatic, mild (symptomatic patients with-

out evidence of viral pneumonia or hypoxia), moderate (clinical sign of pneumonia, ex: fever, cough and dyspnea or fast breathing without sign of severe pneumonia saturation of hemoglobin as measured by pulse oximetry (SpO_2) >90%), severe (clinical sign of pneumonia with central cyanosis or SpO_2 <90%; severe respiratory distress, ex: fast breathing, grunting, very severe chest indrawing; general danger sign; lethargy or unconsciousness or convulsion) [WHO. Clinical management 2020]. Lymphocytopenia is indicated by lymphocyte count $< 1 \times 10^9/L$ [Huang C et al., 2020], abnormal chest X-Ray is concluded based on pictorial review of Jacobi study [Jacobi A et al., 2020]. Rapid antibody tests were conducted using immunochromatographic assay with lateral flow method in detecting qualitative SARS-CoV-2 IgG/IgM antibody (Wondfo One Step Covid-19). Ethical approval was obtained from the Academic Soetomo General Hospital.

Categorical variables were expressed as numbers (percentage) whereas continuous variables were expressed as means (Standard Deviation / SD) or medians (interquartile ranges /IQRs). For statistical analysis, SPSS version 24.0 software for windows (IBM Corp., Armonk. N.Y., USA) was used. To compare the difference in categorical variables, Chi-Square and Fisher Exact Test were used as alternatives; Independent T-Test and Mann-Whitney Test were used as alternatives for continuous variables. Statistical significance was described as a p value of less than 0.05.

RESULTS

During our first 9 months study, there were 109 Covid-19 confirmed cases from 1170 obstetric patients admitted to our emergency obstetric room (9.3%) can be seen in Figure 1. We did not do universal PCR testing to all patients admitted, testing is only carried out if there is a suspicion or positive in Covid-19 screening result. Of all the patients who came to our obstetric emergency room, 293 cases were suspected or had a positive initial Covid-19 screening. From each of these cases, a SARS-CoV-2 examination was implemented by PCR and 37.2% (109/293) were confirmed positive. The detailed number of patients who had positive Covid-19 screening and confirmed Covid-19 patients (PCR +) every month can be seen in Fig-



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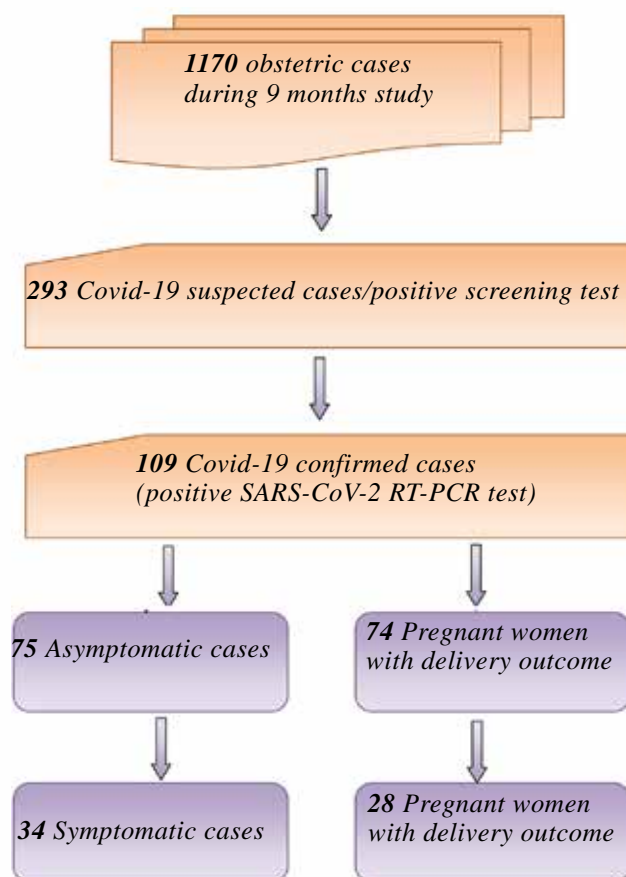


FIGURE 1. Study Population Description

ure 2. The highest number of cases of pregnancy with Covid-19 occurred in June (42 cases; 21.5% from 158 patients admitted).

From 109 SARS-CoV-2 PCR confirmed cases included in our study, we had 2 patients who presented in postpartum condition and out of 107 cases of pregnancy, the majority (102 cases; 93.6%) had delivery. There were 11 severe cases, all of which required intensive treatment and there

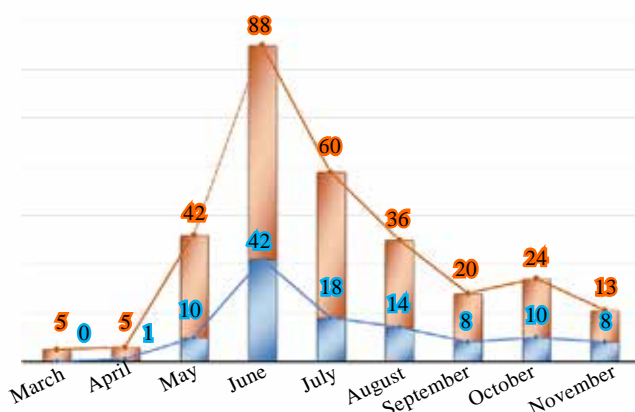


FIGURE 2. Number of Positive Covid-19 Screening Patients and Covid-19 Confirmed Patients (PCR+) Every Months. Patients with PCR (+) (top columns) and positive screening (lower columns)

were 7 maternal deaths and 8 perinatal deaths during our study. All patient characteristics in this study can be seen in Table 1.

Covid-19-related comorbidities occurred in 41.3% of patients, obesity (29.4%) and hypertension in pregnancy (19.3%) were the most frequent. The majority of patients were asymptomatic. Lymphopenia occurred in 21 cases, the majority of cases had normal chest X-rays while reactive rapid antibody (77.1%) dominated 94 patients who underwent this examination.

This study also conducted an analysis between symptomatic and asymptomatic cases (Table 2). It was found that gestational age ($p < 0,001$) and birth weight ($p < 0,05$) were significantly lower in symptomatic cases. On examination of the patients, there was a lower lymphocyte count ($p < 0,01$), more abnormal chest X-rays ($p < 0,001$) and fewer reactive antibody test results ($p < 0,01$) in symptomatic cases.

DISCUSSION

The first Covid-19 case notification in Indonesia was detected in early March, so we started this research in the same month. In the first two months of study, because the transmission was still not very much identified at that time in line with the limited capacity of the SARS-CoV-2 RT-PCR examination laboratory, our center carried out a very strict screening protocol for all obstetric patients who entered the emergency room. Diagnostic RT-PCR testing was only reserved on suspicion of pneumonia or contact with Covid-19 cases. This initial strategy proved difficult enough to identify obstetric cases with Covid-19 so that only 1 case was found.

We all know that the majority of patients come to the obstetric emergency room for delivery purposes so that it will be difficult to find patients who have Covid-19 symptoms. 93.6% of our Covid-19 patients came for delivery. Other studies also show the same result, a systematic review of 108 cases of Covid-19 in pregnancy showed that the majority were found in the 3rd trimester and delivery occurred in 80% of cases [Zaigham M, Andersson O, 2020]. This condition is also indicated by the collected cases, the majority of which are asymptomatic, and if we add mild symptoms cases that are sometimes difficult to identify, it

reaches approximately 79.8% of cases. This is in line with several studies such as Igbinsosa which carried out universal screening in all patients where the proportion of asymptomatic patients was 63% [Igbinsosa I et al., 2020]. In contrast, the

Vouga study which showed the proportion of asymptomatic was only in 31.9% of cases [Vouga M et al., 2020] and Kayem's research which shows a symptomatic proportion of up to 80.6%, but this can occur due to differences in the strategy of

TABLE 1.

Data Characteristic of SARS-CoV-2 Confirmed Infection in Obstetric Patient

Obstetric Variables	SARS-CoV-2 Confirmed Infection in Obstetric Patients (n=109)	Covid-19 infection Related Data	SARS-CoV-2 Confirmed Infection in Obstetric Patients (n=109)
Basic Maternal Data		Comorbidity-no (%)	
Maternal Age		No Comorbidity	64 (58.7%)
Mean±SD y.o.	29.1±5.6	With Comorbidity	45 (41.3%)
Gestational Classification-no (%)		Lung TB	1 (0.9%)
< 20 weeks	4(3.7%)	Obesity	32 (29.4%)
Preterm	27 (24.8%)	Autoimmune	1 (0.9%)
Aterm	76 (69.7%)	Diabetes in Pregnancy	1 (0.9%)
Postpartum	2 (1.8%)	Hypertension in Pregnancy	21 (19.3%)
Gestational Age		Symptom-n(%)	
Mean ± SD y.o.	36.3±6	Asymptomatic	75 (68.8%)
Parity-no (%)		Symptomatic	34 (31.2%)
Nulipara	45 (41.3%)	Cough	19 (17.4%)
Multipara	64 (58.8%)	Febrile	12 (11.0%)
Referral Status-no(%)		Dyspnea	21 (19.3%)
Not Referred	34 (31.2%)	Anosmia	2 (1.8%)
Rejected by other hospital	30 (27.5%)	Symptom Classification-n(%)	
Referred	45 (41.3%)	Mild	12 (11.0%)
Pregnancy Plan-o(%)		Intermediate	11 (10.1%)
Pregnancy state	107 (98.2%)	Severe	11 (10.1%)
Conservative Treatment	3 (2.8%)	Intensive Care Admission-n(%)	
Pregnancy Termination	2 (1.8%)	No	98 (89.9%)
Delivery	102 (93.6%)	Yes	11 (10.1%)
Maternal Death-no(%)		Covid-19 Contact History-n(%)	
no	102 (93.6%)	No	106 (97.2%)
yes	7 (6.4%)	Yes	3 (2.8%)
Delivery Data		Hematological Laboratory Result	
Mode of Delivery-	No(%)	Hemoglobin g/dl	10.9±1.9
All Delivery	102 (93.6%)	Hematocyte %	33.2±5.6
Spontaneous Vaginal Delivery	48 (44.0%)	Platelet / μ l	286357.8±100908.7
Assisted Vaginal Delivery	2 (1.8%)	WBC / μ l	12618.1±4250.5
Cesarean Delivery	52 (47.7%)	Neutrophyl / μ l	10809.7±7436.5
Birthweight		Lymphocyte / μ l	1570.6±559.8
Mean ±SD grams	2959.8±687.2	NLR	7.2±4.5
Apgar Score-no(%)		Lymphocytopenia-n(%)	21 (19.3%)
All delivery	102 (93.6%)	Chest X-Ray--n(%)	
0	5 (4.6%)	normal	65 (59.6%)
1-3	7 (6.4%)	abnormal	44 (40.4%)
4-6	19 (17.4%)	Rapid Antibody Test-n(%)	
7-10	71 (65.1%)	The number tested	94 (86.2%)
Prenatal Mortality-no(%)		Non reactive	10 (9.2%)
No	94 (86.2%)	reactive	84 (77.1%)
Yes	8 (7.8%)		

Analysis of Maternal and Perinatal Outcome based on the Presence of Covid-19 Symptom

Maternal and Perinatal Outcomes	SARS-CoV-2 Confirmed Infection in Obstetric Patients		P
	Asymptomatic (n=75)	Symptomatic (n=34)	
Maternal Age			
Mean±SD y.o.	29.4±5.6	27.8±5.8	0.395
Gestational Age			
Median (IQR) y.o.	38(2)	37(4.7)	0.005
Comorbidity-n(%)			
Any	31 (41.3%)	14 (41.2%)	0.988
Obesity	22(29.3%)	10 (29.4%)	0.993
Hypertension in Pregnancy	14 (18.7%)	7 (20.6%)	0.814
Hematological Laboratory Results – Median (IQR)			
Platelet /μL	277000 (123000)	285500 (110000)	0.943
WBC /μL	11670 (5015)	10610 (7200)	0.671
Neutrophyl /μL	9173 (5237.5)	8735 (6647.7)	0.886
Lymphocyte / μL	1701.5 (809.5)	1185 (678.5)	0.006
NLR	5.1(4.4)	7.6 (6.1%)	0.159
Lymphocytopenia–n(%)	11 (14.7%)	10 (29.4%)	0.071
Chest X-Ray–n(%)			
abnormal	21(28%)	23 (67.6%)	0.000
Rapid Antibody Test–n(%)			
reactive	65(95.6%)	19 (73.1%)	0.002
Intensive Care Admission–n(%)			
Yes	0 (0%)	11 (32.4%)	0.000
Maternal Death–n(%)			
Yes	0 (0%)	7 (20.6%)	0.000
Mode of Delivery–n(%)			
spontaneous vaginal delivery	37 (50%)	11 (39.3%)	
assisted vaginal delivery	2 (2.7%)	0 (0%)	0.374
cesarean delivery	35 (47.3%)	17 (60.7%)	
Birthweight			
Median (IQR) grams	3100 (712.5)	2775 (1025)	0.015
Perinatal Mortality–n(%)			
yes	4 (5.4%)	4 (14.3%)	0.137

ies had different results, such as from the Breslin study where a contact history could be found in approximately 34.5% of cases [Breslin N et al., 2020]. This suggests our local characteristic where it is more difficult to find this information. Negative stigma and fear of isolation in Covid-19 make evaluating this history more difficult.

The first confirmed obstetric case with Covid-19 was only obtained at the end of April where asymptomatic case referral and no contact history were obtained. The patient was tested for an RT-PCR examination due to a reactive rapid antibody examination at the referral hospital. Since then our department has revamped and expanded its Covid-19 screening to be able to do more testing. Testing is carried out not only based on symptoms and contact history of Covid-19, but also if abnormalities are found on laboratory tests, chest X-ray images and also a reactive rapid antibody test. By implementing this strategy, the identification of Covid-19 cases in our center is increasing. The peak occurred in June with 42 Covid-19 cases in 1 month or more than a fifth of patient visits to the obstetric emergency room. This condition can be caused by a sudden increase in cases accompanied by overloading the capacity of the hospitals around our center, from our study it was found that up to 27.5% of cases were rejected by other hospitals because there was no longer obstetric care capacity in that place.

Although severe symptoms were present in only 10.1% of cases, all required intensive care. In line with this study, some data showed that the severe condition in pregnancy cases with Covid-19 reaches 8-11% [Vouga M et al., 2020]. Hall's research from May to October of 34 patients also received 8.6% of maternal covid cases requiring critical care [Hall M et al., 2020]. The majority of these severe conditions (7 of 11 cases) resulted in death (6.4% of total Covid-19 cases). 6 cases of death were closely related to respiratory failure caused by Covid-19 pneumonia, while 1 other case

identifying cases where examination is only carried out on cases with suspicion of Covid-19 [Kayem G et al., 2020] (14).

Besides that, the contact history of the Covid-19 case is very difficult to identify by the patient, it is evident from our data that only 3 cases felt that they had close contact, although in Indonesia at the time this article was written there were more than 100,000 active cases [Covid-19 STP]. Other stud-

was a case of cardiogenic shock due to cardiomyopathy which also experienced Covid-19 infection. Hence, we need to pay more attention to symptomatic Covid-19 cases because the need for intensive care and death is clearly in this group. Although many studies have reported that Covid-19 does not increase the risk of death, for example in the Vouga study, which only experienced 0.6% of maternal deaths from a total population of 926 pregnancies with Covid-19, several studies have shown that the mortality rate can reach 4-15% [Rasmussen SA et al., 2019]. Other studies in developing countries do different things, such as the study from Iran which reported 7 out of 9 cases that ended in maternal death [Hantoushzadeh S et al., 2020]. By all means, the differences in health facilities will greatly affect the handling of obstetric cases with Covid-19, especially in cases with severe symptoms.

We get a fairly large number of cases in one hospital alone, around 109 cases with an incidence of about 9.3% of visits to emergency obstetric rooms. Other studies show something different. The Igbinsa Study had only proportion of 2.5% positive cases [Igbinsa I et al., 2020], whereas a higher proportion was shown by the Vintzielos study of 19.9% and also the Sutton study of 15.3% [Sutton D et al., 2020; Vintzielos WS et al., 2020]. The difference in incidence of course really depends on the testing strategy applied by each hospital. Comorbidity occurred in 45% of cases in our center, the majority was due to obesity and hypertension in pregnancy, and however the presence of these comorbidities was not associated with the presence of symptoms or not in the Covid-19 cases. Research from Vouga showed the opposite, where there is a relationship between comorbids but is slightly different from this study because Vouga compares it with severe symptoms of Covid-19 [Vouga M et al., 2020]. The association between comorbidity and Covid-19 in pregnancy clearly requires further research.

Cesarean Section (CS) delivery was performed in half of the delivery cases (50.9%), the presence of symptoms did not show a significant difference in the mode of delivery. This report is lower than studies elsewhere such as the GESTACOVID multicenter study [Olivia Hernández B et al., 2020] which reported 54% of the 661 cases which were

delivered by CS (20). Some systematic reviews even get a very high proportion of SC (91%) [Yang Z et al., 2020], different types of referral cases as well as protocols from each hospital can influence this proportion.

Although the majority of babies born had a good Apgar score, perinatal mortality was still obtained in 8 cases. Symptomatic cases are associated with a lower gestational age, thus in line with significantly lower fetal weight. This is possible because of the faster termination of symptomatic Covid-19 cases. However, it should be emphasized that these two groups are still within the range of term gestational age and normal birth weight so that the symptoms are not associated with an increase in perinatal mortality. Liu's study also showed no differences in birth weight, fetal distress and neonatal asphyxia between patients with and without Covid-19 [Zhang L et al., 2020]. Kayem's study shows low neonatal death is only 0.2% [Kayem G et al., 2020], This naturally can be due to differences in the severity of the obstetric case that came and also the ability to care for critical babies for each hospital.

Lymphocytopenia was found in 19.3% of cases, the presence of symptoms was associated with a significant decrease in the number of lymphocytes, other studies showed the same thing, Liu's study showed lymphocytopenia as the most hematological problem [Liu D et al., 2020]. Rasmussen even showed that lymphopenia can be obtained up to 65-85% [Rasmussen SA et al., 2019]. About 40% of abnormal chest X-Ray images were obtained and the majority of the rapid antibody test results were reactive. When compared to the presence of symptoms, abnormal X-rays were found to be significantly higher in symptomatic patients, which of course correspond to the clinical condition of the pneumonia cases. Another study from Ortiz showed the same thing where abnormal X-Ray images were obtained in all cases of Covid-19, but this condition was obtained from all cases with severe symptoms [Ortiz EI et al., 2020].

It is interesting to find that our study results showed the rapid antibody test gives more reactive results in asymptomatic cases, this showed that this examination can help to screen for asymptomatic patients in order to get an indication for RT-PCR testing. Mild symptomatic or maybe post symptom-

atic conditions that already produce antibodies can also be filtered out by this examination so that we can avoid unidentified Covid-19 cases that have these characteristics. Indirectly, Covid-19 can be suspected if an immune response is obtained that may not show clinical symptoms or only have mild symptoms [Sethuraman N et al., 2020]. Fabre's study shows the positive predictive value of this serology test is 60% [Fabre M et al. 2020].

The advantage of this study is that the number of cases is large enough for analysis and this study was conducted in one hospital so as to avoid biased identification and handling strategies for Covid-19 cases which can be very different in every hospital. The limitation is that RT-PCR testing is not carried out on all the patients who come to our hospital so that the possibility of an unidentified Covid-19 case is still unavoidable. Moreover this study did not compare with negative patients and most of the patients were in the 3rd trimester who required de-

livery. However, the conditions in this study represent the conditions faced by tertiary referral hospitals for maternal Covid-19 cases.

CONCLUSION

This study showed the high number of Covid-19 obstetric cases from all patients who came to the obstetric emergency room, the majority of patients were asymptomatic and came for delivery so that identification of this asymptomatic condition is important. Significantly higher reactive antibody tests in asymptomatic cases may aid this identification. Meanwhile, the presence of Covid-19 symptoms requires more special attention because it was associated with lower gestational age and birth weight, with worse laboratory parameters through low lymphocyte counts, high abnormal X-Ray images, the need for intensive care and also maternal mortality.

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