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Clinical Overview in Pregnancy with COVID-19 at prof. Dr. I.G.N.G. Ngoerah Hospital Period of April 2020-March 2021

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Abstract

BACKGROUND: Pregnant women are one of the populations that are susceptible to coronavirus disease 2019 (COVID-19) infection due to physiological changes during pregnancy that is an adaptive response to pregnancy such as diaphragmatic elevation, increased oxygen consumption, and airway mucosal edema which can also make pregnant women more intolerant of hypoxia. In addition to being vulnerable, COVID-19 in pregnant women may have a different clinical course from the general population.

AIM: This study aims to determine the demographic and clinical characteristics in pregnancy with COVID-19 at Prof. Dr. I.G.N.G. Ngoerah Hospital, Bali, Indonesia.

METHODS: This study was a cross-sectional descriptive study using secondary data derived from patient medical records and carried out in the delivery room and medical record installation at Prof. Dr. I.G.N.G. Ngoerah Hospital, Bali, Indonesia, for the period of April 1, 2020–March 31, 2021.

RESULTS: Of the 275 patients, most were in the age range of 26–30 years (46.55%), in the third trimester (81.45%), and patients came alone (54.18%). Most of the patients came without symptoms with reactive rapid antibody results (60.97%). Of the 197 patients who delivered, 84.77% had CS and 66.55% without oxygen therapy. About 69.69% of patients experienced complications and the mortality rate was 1.09%. The highest birth weight was >2500 g by 76.8%, with the good neonatal outcome (82.92%) and negative swab results (89.45%). Inflammatory markers tend to increase as symptoms increase. Neutrophil-to-lymphocyte ratio, procalcitonin, and ferritin were markedly increased from moderate symptoms to severe-critical symptoms. The same was true for ferritin levels, where there was a sharp rise in significant symptoms. Meanwhile, procalcitonin levels have started to increase quite strikingly from moderate symptoms to the highest in severe symptoms.

CONCLUSION: It is hoped that this demographic and clinical picture would further our understanding of COVID-19 and help us develop methods to lessen the disease's severity and spread to enhance maternal and newborn outcomes.

Introduction

Coronavirus disease 2019 (COVID-19) incidence has been increasing in waves. Globally, the peak incidence was on December 2020 until January 2021 then increased again on April and August 2021. Global mortality rate was up to 2.02%; meanwhile, Indonesia had higher mortality rate up to 3.38% [1]. Older age was associated with increased mortality risk. Case fatality rate (CFR) on ≥80-year-old patients was 14.8%, higher than the general population that was 2.3% [2].

Pregnant and postpartum woman is a population with higher risk for COVID-19 morbidity and mortality. Physiological changes such as immunology response, respiration, and coagulation may affect the disease severity on pregnancy [3]. Clinical manifestation found on pregnant woman who does not have significant difference with the general population including fever (68%), cough (34%), dyspnea (12%), malaise (12%), and diarrhea (6%) [4]. According to the severity, 8% had severe symptoms and 1% had critical condition [5]. Some studies had shown bad outcome on pregnancy with COVID-19 such as preeclampsia, premature labor, neonatal death, gestational diabetes, and low birth weight [6]. The studies for vertical transmission during pregnancy are still limited but it could happen with a risk of 16 out of 1000 live birth [7].

COVID-19 infection has the potential to cause severe inflammatory response. The inflammatory response then causes various changes in inflammatory protein levels in the patient. Several inflammatory markers (C-reactive protein [CRP], procalcitonin, ESR, IL-6, and IL-10) showed a significant increase in these markers. These markers were also found to be associated with the severity of symptoms [8]. In pregnancy, there tends to be a more severe clinical course so that there is a possibility of changes in inflammatory markers that are different from the general population [3]. Based on this review, COVID-19 in pregnancy and postpartum woman has a significant clinical and laboratory impact. In addition to clinical effects, these infections also have the potential to affect the neonate either due to vertical transmission

or the disease process in the mother. Therefore, in this study, we investigated COVID-19 in pregnancy.

Methods

This was a descriptive, cross-sectional study using secondary data source collected from medical records of pregnant patients with COVID-19 infection at RSUP Prof. Dr. I.G.N.G. Ngoerah, Denpasar, Bali, from April 1, 2020, until March 31, 2021, a single center, 1-year study. Patients with a history of pregnancy on the first, second, and third trimester were included with total sampling. Diagnosis of COVID-19 was made with positive *polymerase chain reaction* (PCR) nasopharyngeal swab of SARS-CoV-2.

Some outcomes were taken from the medical record including patient's age, medical referral origin (hospital or primary health center or else), history of live birth parturition, gestational age from abdominal ultrasonography or the 1st day of last menstruation, severity of clinical symptoms, rapid test of SARS-CoV-2 serology antibody or antigen performed as screening tool for pregnant patients before entering the ward, chest X-ray examination, delivery method (cesarean or vaginal delivery), oxygen therapy modalities, maternal complication, birth weight, neonate real-time PCR of nasopharyngeal/oropharyngeal swab, newborn condition (asphyxia or vigorous baby), neutrophil-to-lymphocyte ratio (NLR), ferritin, procalcitonin, d-dimer, and CRP. Then, the data were recorded in the data collection sheet for further analysis. Data analysis was conducted with Microsoft Excel and IBM SPSS version 25. The result was presented with consideration of the data types, categorical data were presented with frequency and percentage distribution. Numerical data with normal distribution presented using mean and standard deviation, numerical data with abnormal distribution presented using median and range.

Results

From April 1, 2020, to March 31, 2021, a total of 275 subjects were eligible and included in the study. The majority of the specimens age range was 26–30 years old (n = 128; 46.55%), third trimester (n = 224; 81.45%), none parturition history (n = 106; 38.55%), and mostly came not by referral (n = 149; 54.8%), described further on Table 1. Based on the severity, patients are divided into asymptomatic, mild symptoms, moderate symptoms, severe symptoms, and critical symptoms. The highest proportion was asymptomatic patients, namely, 32.36%, meanwhile, for mild, moderate, severe, and critical symptoms, respectively, 25.09%, 16.00%, 18.91%, and 7.64%, respectively.

Table 1: Characteristics of samples

Characteristics	n	%
Range of age (years)		
15–20	6	2.18
21–25	55	20.00
26–30	128	46.55
31–35	52	18.91
36–45	34	12.36
Total	275	100.00
Gestation age		
Trimester 1	8	2.91
Trimester 2	43	15.64
Trimester 3	224	81.45
Total	275	100.00
Referred from		
Not by referral	149	54.18
Regional public hospital	42	15.27
Private hospital	63	22.91
University Hospital of Udayana	4	1.45
Midwife	4	1.45
Public health office	3	1.09
Primary Health Centre	4	1.45
Obstetrics and gynecologist	1	0.36
University hospital posts	1	0.36
University hospital	3	1.09
Clinic	1	0.36
Total	275	100.00
Parturition history		
0	106	38.55
1	96	34.91
2	50	18.18
3	17	6.18
≥4	6	2.18
Total	275	100.00
Severity		
Asymptomatic	89	32.36
Mild	69	25.09
Moderate	44	16.00
Severe	52	18.91
Critical	21	7.64
Total	275	100.00
Delivery method		
Vaginal delivery	30	15.23
Cesarean section	167	84.77
Total	197	100.00
Oxygen therapy		
Mechanical ventilator	26	9.45
HFNC	11	4.00
NRM	26	9.45
Nasal cannula	29	10.55
Room air	183	66.55
Total	275	100.00
Specific treatment		
Remdesivir	54	19.64
Favipiravir	9	3.27
Azithromycin	39	14.18
Hydroxychloroquine	4	1.45
Enoxaparin	68	24.73
Dexamethasone	75	27.27
Vitamin D	13	4.73
IVIG	1	0.36
Convalescent plasma	3	1.09
Total	266	100.00

HFNC: High-flow nasal cannula, NRM: Non-rebreathing mask, IVIG: Intravenous immunoglobulin.

A total of 197 patients gave birth while treated, with details of 15.23% by vaginal delivery and 84.77% by cesarean section. According to the oxygen therapy given, as many as 66.55% were without oxygen therapy, while the rest required oxygen therapy with a nasal cannula (10.55%), NRM (9.45%), HFNC (4.00%), and intubation with a mechanical ventilator (9.45%). Specific therapy that is often given to patients is remdesivir (19.64%), azithromycin (14.18%), enoxaparin (24.73%), and dexamethasone (27.27%).

Additional examination characteristics in this study were based on the results of rapid tests for both antibodies and antigens and chest X-ray examination, as shown in Table 2. Overall, 44.36% of pregnant women did not undergo rapid examination, because it is no longer

Table 2: Additional examination of samples

Additional exam	n	%
COVID-19 serologic rapid test		
Reactive IgG	26	9.45
Reactive IgM	8	2.91
Reactive IgG and IgM	47	17.09
Non-reactive	19	6.92
Not examined	122	44.36
Positive antigen	50	18.18
Negative antigen	3	1.09
Total	275	100.00
Rapid test of asymptomatic patients		
Reactive	63	70.79
Non-reactive	1	1.12
Not examined	20	22.47
Positive antigen	5	5.62
Negative antigen	0	0.00
Total	89	100.00
Rapid test of patients with symptoms		
Reactive	18	9.68
Non-reactive	18	9.68
Not examined	102	54.84
Positive antigen	45	24.19
Negative antigen	3	1.61
Total	186	100.00
Chest X-ray findings		
Pneumonia	136	49.45
Pleural effusion and pneumonia	13	4.73
Pleural effusion	2	0.73
Normal	70	25.45
Not examined	54	19.64
Total	275	100.00

a mandatory examination in accordance with the 2021 edition of the COVID-19 Management Guidelines. In patients undergoing rapid antibodies, in 9.45% only IgG is reactive, in 2.91% only IgM is reactive, in 17.09% there are reactive IgG and IgM, and 6.92% were non-reactive. Meanwhile, in patients who underwent rapid antigen, as many as 18.18% had positive antigen and 1.09% had negative antigen. However, when presented specifically to patients who were subjected to antigen examination, as many as 50 of the 53 examinations (94.34%) were positive.

According to the presence or absence of symptoms, 22.47% of asymptomatic patients were not tested, and most of them had reactive rapid antibody results (60.79%). A small percentage of 5.62% showed positive antigen test results. However, all patients (100%) who underwent rapid antigen test showed positive results. Meanwhile, in patients with symptoms, most (54.84%) did not undergo a rapid examination. Each 9.68%, 9.68%, 5.62%, and 0.00% showed the results of rapid reactive antibody examination, non-reactive antibody, positive antigen, and negative antigen respectively. On antigen examination, as many as 45 of 48 (93.75%) showed positive results.

On chest X-ray examination, the dominant (49.45%) showed a picture of pneumonia, while the other chest X-ray images showed pleural effusion and pneumonia in 4.73%, pleural effusion in only 0.73%, normal in 25.45%, and no chest X-ray examination in 19.64% as shown in Table 2.

Based on Table 3, as many as 30.31% of subjects are without complications and 69.69% with complications. Several complications with a fairly high proportion were prematurity (13.18%), premature rupture of membranes (21.09%), anemia (16.73%), and pre-eclampsia (5.45%). Meanwhile, the maternal mortality rate is 1.09%. The CFR is calculated based

Table 3: Maternal outcome

Maternal outcome	n	%
Complication		
No complication	85	30.31
Incomplete abortion	2	0.73
Prematurity	38	13.18
Gestational hypertension	3	1.09
Chronic hypertension	1	0.36
Pre-eclampsia	15	5.45
Eclampsia	1	0.36
PROM	58	21.09
Anemia	46	16.73
Thrombocytopenia	13	4.73
PPCM	2	0.73
Postpartum hemorrhage	2	0.73
Fetal distress	4	1.45
Antepartum hemorrhage	3	1.09
Hyperemesis gravidarum	2	0.73
Total	275	100.00
Mortality		
Demise	3	1.09
Alive	272	98.91
Total	275	100.00

PROM: Premature rupture of membrane, PPCM: Peripartum cardiomyopathy.

on the number of pregnant women who died due to COVID-19 divided by the total number of pregnant women infected with COVID-19 at Prof. Dr. I.G.N.G. Ngoerah Denpasar on April 1, 2020, until March 31, 2021, then multiplied by 100%.

Based on Table 4, the outputs parameter recorded in neonates include birth weight, clinical conditions (asphyxia or vigorous baby), and results of reverse transcription polymerase chain reaction (RT PCR) examination. According to birth weight, birth weight <1500 g was in 5.53%, 1500–2500 g was in 17.59%, and >2500 g was in 76.8%. The clinical condition neonates were found to be vigorous baby (82.92%), moderate asphyxia (12.56%), severe asphyxia (4.52%), and IUFD (1.00%). Finally, according to the results of the RT PCR examination, the neonate obtained a positive swab result (2.01%), negative swab result (89.45%), and no swab (8.54%). Not all babies are examined by RT PCR because it is not mandatory according to the 2021 edition of the COVID-19 guidelines and according to the decision of a pediatrician.

Table 4: Neonatal outcome

Neonatal outcome	n	%
Birth weight		
<1500 g	11	5.53
1500–2500 g	35	17.59
>2500 g	153	76.88
Total	199**	100.00
Clinical condition		
Vigorous baby	163	82.92
Moderate asphyxia	25	12.56
Severe asphyxia	9	4.52
IUFD	2	1.00
Total	199**	100.00
COVID-19 RT-PCR		
Positive swab	4	2.01
Negative swab	178	89.45
Not performed	17	8.54
Total	199**	100.00

**275 included subjects with COVID-19 infection, 197 were giving birth, and two of them were twins (a total of seven gemelli cases), IUFD: Intrauterine fetal demise.

Based on the results of the examination of inflammatory markers as shown in Table 5, in general, there is an upward trend of the inflammatory markers median results as the severity of the disease increases. There are several markers in this study, namely, NLR, procalcitonin, ferritin, D-dimer, and CRP. In NLR, there is a significant difference between

Table 5: Inflammation markers result based on clinical severity

Clinical severity	NLR (median)	NLR (range)
Asymptomatic	4.42	0.48–17.41
Mild	3.94	0.19–13.87
Moderate	4.84	0.14–9.14
Severe	7.45	2.10–17.95
Critical	11.41	6.10–90.18
Clinical severity	Ferritin (median)	Ferritin (range)
Asymptomatic	52.06	10.36–400.70
Mild	87.18	17.03–551.10
Moderate	83.03	6.16–620.50
Severe	126.1	76.06–494.34
Critical	174.7	2.34–333.70
Clinical severity	Procalcitonin (median)	Procalcitonin (range)
Asymptomatic	0.09	0.02–0.79
Mild	0.07	0.02–0.56
Moderate	0.12	0.01–2.56
Severe	0.21	0.08–1.50
Critical	0.415	0.08–4.24
Clinical severity	D-dimer (median)	D-dimer (range)
Asymptomatic	1.57	0.45–9.50
Mild	1.56	0.03–6.10
Moderate	1.08	0.40–3.03
Severe	1.41	0.27–23.80
Critical	2.19	0.44–14.73
Clinical severity	CRP (median)	CRP (range)
Asymptomatic	14.32	0.49–152.01
Mild	19.20	1.38–123.00
Moderate	39.56	5.83–95.44
Severe	93.56	9.78–79.50
Critical	80.31	40.07–197.64

NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein.

the NLR median value of moderate-asymptomatic symptoms (3.94–4.84) with severe symptoms (7.45) and critical symptoms (11.41). Ferritin levels also had a high difference between asymptomatic to moderate symptoms (52.06–83.03 mcg/L) with severe symptoms (126.10 mcg/L) and critical symptoms (174.70 mcg/L). Median procalcitonin also increased significantly from asymptomatic-moderate symptoms (0.07–0.12 ng/mL) to severe symptoms (0.21 ng/mL) and critical symptoms (0.42 ng/mL), while the levels of D-dimer only shown a slightly upward trend. The lowest median levels of D dimer were found in moderate (1.08 g/mL) and severe (1.41 g/mL) symptoms, and the highest in critical symptoms (2.19 g/mL). CRP levels had a significant increase from mild asymptomatic symptoms (14.32–19.20 mg/L) to moderate symptoms (39.56–93.56 mg/L). The highest CRP was in severe symptoms (93.56 mg/L).

Discussion

Demographic

Similar studies by Ko *et al*. (2021) and Saimin *et al*. (2021) had higher and lower number of participants than this study. This might be affected by the level of local spread of the disease, the protocol for treating COVID-19, and the place where the study was conducted (hospital types: Primary, secondary, or tertiary hospitals) [9], [10]. The participants age distribution in this study (mostly 26–30 years old) correlates with other studies with median age 29 years old [9] and 31 years old [11]. It happened mostly on the third trimester similar with other studies, but this study has lower referral rate. This might be because difference of each referral system and hospital types and location [11], [12], [13], [14], [15], [16], [17]. Parturition history and participants with first pregnancy have higher prevalence for COVID-19 infection [11], [18].

Clinical symptoms and severity

When compared with the general population, the number of symptomatic patients and severe-critical diseases such as multiple organ failure, septic shock, and respiratory failure is higher in pregnant women [19]. The severity of symptoms in pregnant women can be influenced by age because the age of pregnant women is generally young, while in the general population, severe symptoms are more common in old age. There is no difference between general population and pregnant woman clinical symptoms [4].

Clinical symptoms that tend to be more severe in pregnant women may be explained in several ways. First from the immunological aspect, there is a change in the response to viral infection. The shift in the CD4+ T-cell population, dominant in Th2 cells over Th1 cells, causes the humoral immune response to be more dominant than the cellular response. This decrease in Th1 response causes changes in the pattern and rate of clearance of infected cells. It is also thought to be associated with a higher risk of severe symptoms in pregnancy [3]. In pregnancy, the study of Tanacan *et al*. (2021) showed that inflammatory markers tended to be higher in pregnancies with COVID-19 compared to those without infection [20]. Changes in the balance of cytokines such as TNF-, IL-1, IL-10, and IFN-γ due to COVID-19 cause adverse outcomes in pregnancy [21]. Second, from the aspect of respiration, there is a decrease in respiratory function due to the elevation of the diaphragm which is pushed by the enlarged uterus. These changes cause a decrease in tidal volume, a decrease in functional residual capacity, end-expiratory volume, and residual volume. Third, from the coagulation aspect, pregnancy is a prothrombotic condition when experiencing COVID-19, the tendency for thrombosis will increase. The study in 184 critical cases found that 24–31% had thromboembolism. This is due to the activation of the coagulation pathway which causes hypercoagulation and thrombocytopenia [3].

Chest X-ray examination can give several kinds of results such as peripheral infiltrates leading to pneumonia, consolidation, normal, pleural effusion, and nodules, from the most frequent to the rare [17], [22]. There is a progressive pattern in which the area of the lung that is first affected is the basal part and then spreads to the apex and periphery of the lung [23].

Based on the results of this study and other studies conducted in Indonesia [24] compared to studies in other countries such as America [25], [26], it was found that the frequency of SC in Indonesia higher up to 86.7% compared to other countries 47% or without an increase in SC compared to the general population.

During pregnancy, the target maternal peripheral oxygen saturation (SpO_2) should be 95% to maintain the oxygen demand of the fetus. If SpO_2 falls below 95%, arterial blood gas analysis is necessary to measure the partial pressure of oxygen (PaO_2): Maternal PaO_2 >70 mmHg is required to maintain a diffusion gradient of oxygen from the mother to the fetus [2].

Pregnant women with COVID-19 also need to be assessed for the possibility of venous thromboembolism (VTE). COVID-19 can cause coagulopathy, so the advantages and disadvantages of giving anticoagulants such as bleeding need to be considered. Antepartum VTE prophylaxis for those who will soon give birth and are not severe or critically ill can be given unfractionated heparin 5000 units subcutaneously every 12 h. Higher dose does not significantly improve efficacy but may increase the bleeding rate [2], [27].

Maternal outcome

A total of 69.69% of maternal participants in this study had complications such as PROM (21.09%), prematurity (13.18%), and pre-eclampsia (5.45%). Premature delivery is 1.59 times to 1.82 times higher in patients with COVID-19. Pre-eclampsia also has a higher risk in patients with COVID-19 with an RR of 1.76 (95% CI: 1.27–2.43) [24]. However, in another study with a smaller sample, there was no difference in the risk of pre-eclampsia and PROM in patients with COVID-19 compared to the general population [28]. Mortality of pregnant women with COVID-19 is higher from 2-fold to 22.3-fold depending on many factors such as access to health services [24], [29], [30].

Neonatal outcome

There is no significant relationship between neonatal birth weight and maternal COVID-19 infection [31], [32]. This can be explained because COVID-19 appears as an acute infection, if it occurs close to delivery, it is unlikely to have an impact on birth weight. However, for infections occurring early in pregnancy and for women suffering from hypoxia due to sequelae, growth follow-up is recommended to assess the risk of fetal growth retardation. However, another study found that mothers with COVID-19 had a risk of giving birth to low birth weight due to premature birth, with increased risk in patients with COVID-19 [33].

Most of the neonates clinical condition were vigorous baby (82.92%), while the other outcomes were; moderate asphyxia (12.56%), severe asphyxia (4.52%), and IUFD (1.00%). Research by Marin Gabriel *et al*. (2020) showed that as many as 10.5% required advanced neonatal resuscitation (positive pressure ventilation until intubation and vasoactivity) [34]. Wiyati *et al*. (2020) reported a lower outcome, only 2.2% experienced severe asphyxia [17]. Worse outcomes were found in meta-analytical studies, namely, as many as 30% of cases of fetal death. Neonatal outcomes may be influenced by underlying maternal characteristics such as preterm delivery and severity of symptoms [35]. Meanwhile, in this study, 13.18% of premature births were found, 18.91% of severe symptoms, and 7.64% of critical symptoms.

In this study, the results of the COVID-19 RT PCR naso/oropharyngeal swab in neonates were positive at 2.02%; compared to other studies of 4.4% [34]. The positive result is still unclear due to vertical transmission or through respiratory droplets during labor. The evidence for vertical transmission of COVID-19 is still unclear. The incidence of vertical transmission was 2% until 5.8% [7], [36], [37].

Inflammation markers

The previous studies have shown that inflammatory markers increase significantly with the severity of COVID-19 symptoms [8], [38]. In this study, several inflammatory markers will be discussed including NLR, ferritin, procalcitonin, D-dimer, and CRP. The higher the NLR [39], ferritin [40], [41], CRP [38], [42], and procalcitonin [8], [38] then show an increasing severity of the disease. The NLR value in pregnant woman is higher than non-pregnant COVID-19 patients [43]. Ferritin has a role as an acute-phase reactant and as an immune-regulated mediator in severe and critical COVID-19 symptoms [44], [45]. CRP is a systemic marker for acute inflammatory response, infection, and tissue damage so that it can be used as an indicator of inflammation [38]. This explanation is in accordance with the results of this study where there was an increase in NLR, ferritin, and procalcitonin, especially in pregnant patients with severe and critical symptoms; elevated CRP in moderate to critical symptoms.

D-dimer levels, a marker of coagulopathy, in pregnant women can increase even though they are not suffering from COVID-19 [46]. Therefore, determining the incidence of COVID-19 VTE in pregnant women is challenging. The measurement threshold for the D-dimer value is >1000 ng/mL if it does not meet the clinical criteria for pulmonary embolism and <500 ng/mL if it meets the symptoms of pulmonary embolism [47].

The limitation in this study might be the limited number of participants found even with total sampling. There are not many descriptive studies based on Indonesia, and Bali is also an international tourist spot with high density which may lead to high local transmission or even multinational transmission.

Conclusion

This study illustrates the characteristics of pregnant COVID-19 patients on Bali, Indonesia, with

adescription of demographic, clinical severity, laboratory examinations, and maternal/neonate outcomes. It is hoped that this demographic and clinical picture would further our understanding of COVID-19 and help us develop methods to lessen the disease's severity and spread to enhance maternal and newborn outcomes.

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