COVID-19 Infection and the Preeclampsia in Pregnant Women

Infeksi COVID-19 dengan Preeklamsia pada Ibu Hamil

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Abstract

Objective: To determine the relationship between COVID-19 infection and preeclampsia in pregnant women at RSD dr. Soebandi Jember.

Methods: This study used cross-sctional study with simple random sampling. The data is secondary data from medical records of 118 pregnant women who checked their pregnancies from March 2020 to December 2021 at RSD dr. Soebandi Jember and analyzed with chi-square test and logistic regression test.

Results: Multivariate analysis showed that there were a relationship between COVID-19 infection with preeclampsia. COVID-19 is the most risky variable with an OR of 4.045 (95% CI 1.595 – 10.259). This condition happens because COVID-19 infection triggers down-regulation of RAS which make the failure of spiral artery remodelling and preeclampsia.

Conclusion: There is a relationship between COVID-19 infection and the incidence of preeclampsia in RSD dr. Soebandi Jember.

Keywords: COVID-19, preeclampsia, renin-angiotensin system (RAS), SARS-CoV-2.

Abstrak

Tujuan: *Untuk mengetahui hubungan antara infeksi COVID-19 dengan kejadian preeklamsia pada ibu hamil di RSD dr. Soebandi Jember.*

Metode: *Penelitian ini merupakan studi potong lintang dengan pengambilan sampel menggunakan simple random sampling. Penelitian ini menggunakan data sekunder rekam medis 118 ibu hamil yang memeriksakan kehamilannya mulai Maret 2020 hingga Desember 2021 di RSD dr. Soebandi Jember dan dianalisis dengan uji statistik Chi-square dan uji regresi logistik.*

Hasil: *Analisis statistik menunjukkan terdapat hubungan antara infeksi COVID-19, usia, dan obesitas dengan kejadian preeklamsia di RSD dr. Soebandi Jember. Variabel COVID-19 merupakan variabel yang paling berisiko terhadap terjadinya preeklampsia dengan OR 4,045 (95% CI 1,595 – 10,259). Hal ini terjadi karena infeksi COVID-19 memicu down-regulasi pada RAS yang mengakibatkan kegagalan remodelling arteri spiralis dan preeklamsia*

Kesimpulan: *Terdapat hubungan antara infeksi COVID-19 dengan kejadian preeklamsia di RSD dr. Soebandi Jember.*

Kata kunci: *COVID-19, preeklamsia, renin-angiotensin system (RAS), SARS-CoV-2.*

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INTRODUCTION

Coronavirus Disease 2019 or COVID-19 is caused by SARS-CoV-2 virus. WHO designated COVID-19 as a world pandemic on March 11, 2020. SARS-CoV-2 spread to almost all countries, including Indonesia.[1] Based on data from the Indonesian Ministry of Health, as of January 3, 2022 there were 4,263,433 confirmed cases of COVID-19 in Indonesia. Pregnant women are a group who vulnerable being infected by COVID-19 due to physiological changes during pregnancy.[2] Pregnant women with COVID-19 infection also have worse clinical outcomes than non-pregnant women with COVID-19 infection.3 Based on data from the Indonesian Ministry of Health on July 30, 2021, there were 2,179 pregnant women died and 18% of them died because of COVID-19.

Pregnant women with COVID-19 are at risk of developing preeclampsia, fetal death, and premature birth.[3] and preeclampsia being a significant contributor to perinatal and maternal mortality.[4] Although the exact cause of preeclampsia remains uncertain, the theory of endothelial dysfunction plays a crucial role in its development. Endothelial dysfunction has also been observed in COVID-19 patients.[5] Both endothelial dysfunction occured in COVID-19 and preeclampsia. Previous research indicates that pregnant women with severe COVID-19 face a fivefold higher risk of developing preeclampsia compared to those with asymptomatic COVID-19. However, the existing academic literature on the connection between COVID-19 infection and preeclampsia in pregnant women is limited, and the World Health Organization (WHO) has not provided specific guidance on managing pregnant women with COVID-19.[6] Identifying the relationship between COVID-19 infection and preeclampsia in pregnant women is of paramount importance for determining appropriate treatment and reducing the mortality rate. There have been 29 reported cases of pregnant women with both COVID-19 and preeclampsia at RSD dr. Soebandi Jember from March 2020 to December 2021. Considering of these conditions, we are interested in researching this study.

METHODS

This study is a cross-sectional design and involves pregnant women who underwent pregnancy check-ups at RSD dr. Soebandi Jember between March 2020 and December 2021. The samples were selected using a simple random sampling method, resulting in the inclusion of 118 medical records of pregnant women who met the specified exclusion and inclusion criteria.

The inclusion criteria encompassed pregnant women with both COVID-19 infection and preeclampsia in pregnancies beyond 20 weeks of gestation, provided that complete medical records were available. Pregnant women with COVID-19 infection who had a prior history of hypertension, kidney failure, nephrotic syndrome, anasarca edema, eclampsia, or stroke were excluded from the study. Data analysis was conducted using SPSS version 24.

After 118 samples were collected, bivariate analysis is performed by chi-square test. There are nine variables to be analyzed, namely COVID-19, age, education, work, delivery method, gravida, history of diabetes mellitus, obesity, and baby birth weight. The COVID-19 variable is divided into two criteria, yes and no. The age variable is divided into two criteria, high risk (>35 years) and low risk (≤35 years). Education variable is divided into two criteria, incomplete (junior high school, elementary, no school) and complete (college, senior high school). Work variable is divided into two criteria, yes and no. The gravida variable is divided into two criteria, primigravida and multigravida. The variable history of diabetes mellitus is divided into two criteria, yes and no. Obesity variable is divided into two criteria, yes and no. Variable baby birth weight is divided into two criteria, low (<2500 grams) and normal (≥2500 grams). After the bivariate analysis, the variables with p value < 0.25 would be re-analyzed in multivariate analysis to find the most risky factor for preeclampsia. Multivariate analysis was performed using backward LR method of logistic regression test. This study has passed the ethical coincidence test by the Ethics Commission of Medical Faculty, Jember University, as certified under the ethic No: 1575/H25.1.11/KE/2022.

RESULTS

Table 1. Characteristics of Samples

Variable	Preeclampsia				Normal				Total	
	COVID-19		Normal		COVID-19		Normal			
	N	%	N	%	N	%	N	%	N	%
Age (y o)										
<20	0	0	0	0	0	0	1	0.85	1	0.85
20-35	19	16.1	8	6.78	30	25.42	24	20.34	81	68.64
>35	10	8.47	10	8.47	0	0	16	13.57	36	30.51
Education										
College	0	0	2	1.69	0	0	4	3.39	6	5.08
Senior High School	19	16.1	4	3.39	8	6.78	20	16.95	51	43.22
Junior High School	5	4.24	7	5.92	15	12.71	11	9.32	38	32.20
Elementary School	4	3.39	5	4.24	7	5.93	6	5.09	22	18.65
No Education	1	0.85	0	0	0	0	0	0	1	0.85
Work										
Yes	2	1.69	2	1.69	6	5.08	2	1.69	12	10.17
No	27	22.88	16	13.57	24	20.34	39	33.05	106	89.83
Delivery method										
Vaginal	14	11.86	10	8.47	5	4.24	25	21.19	54	45.76
Abdominal	15	12.71	8	6.78	25	21.19	16	13.56	64	54.24
Gravida										
Multigravida	8	6.78	8	6.78	25	21.19	23	19.5	64	54.24
Primigravida	21	17.8	10	8.47	5	4.24	18	15.25	54	45.76
History of Diabetes Mellitus										
No	13	11.02	8	6.78	25	21.19	30	25.42	76	64.4
Yes	16	13.56	10	8.47	5	4.24	11	9.32	42	35.6
Obesity										
No	7	5.93	8	6.78	25	21.19	18	15.25	58	49.15
Yes	22	18.64	10	8.47	5	4.24	23	19.5	60	50.85
Baby birth weight (gram)										
>3500	1	0.85	0	0	4	3.39	3	2.54	8	6.78
2500-3500	12	10.17	8	6.78	21	17.8	29	24.58	70	59.32
<2500	16	13.56	10	8.47	5	4.24	9	7.62	40	33.9

Table 2. The Relationship between COVID-19 and Preeclampsia

Variable	Preeclampsia		Normal		Total		*P-value*	OR	CI 95%	
	N	%	N	%	N	%			Lower	Upper
COVID-19										
Normal	18	15.25	41	34.75	59	50		1.000	Reference	
COVID-19	29	24.58	30	25.42	59	50	0.039	2.202	1.037	4.677

Table 3. Relationship between Risk Factors and Preeclampsia

Variable	Preeclampsia		Normal		Total		P-value	OR	CI 95%	
	N	%	N	%	N	%			Lower	Upper
Age (y o)										
≤35	27	22.88	55	46.61	82	69.49		1.000	Reference	
>35	20	16.95	16	13.56	36	30.51	0.021	2.546	1.141	5.682
Education										
Complete	25	21.19	32	27.12	57	48.31		1.000	Reference	
Incomplete	22	18.64	39	33.05	61	51.69	0.387	0.722	0.345	1.513
Work										
Yes	4	3.39	8	6.78	12	10.17		1.000	Reference	
No	43	36.44	63	53.39	106	89.83	0.628	1.365	0.387	4.819
Delivery Method										
Vaginal	24	20.43	30	25.42	54	45.76		1.000	Reference	
Abdominal	23	19.49	41	34.75	64	54.24	0.347	0.701	0.334	1.471
Gravida										
Multigravida	16	13.56	48	40.68	64	54.24		1.000	Reference	
Primigravida	31	26.27	23	19.49	54	45.76	0.000	4.043	1.850	8.836
History of Diabetes Mellitus										
No	21	17.8	55	46.61	76	64.4		1.000	Reference	
Yes	26	22.03	16	13.56	42	35.6	0.000	4.256	1.912	9.475
Obesity										
No	15	12.71	43	36.44	58	49.15		1.000	Reference	
Yes	32	27.12	28	23.73	60	50.85	0.002	3.276	1.507	7.121
Baby Birth Weight (gram)										
≥2500	21	17.8	57	48.31	78	66.1		1.000	Reference	
<2500	26	22.03	14	11.86	40	33.9	0.000	5.041	2.220	11.446

Table 4. Multivariate Analysis of Factors Influencing Preeclampsia

	Variable	P-value	OR	CI 95%	
				Lower	Upper
Step 1	COVID-19	0.027	3.110	1.140	8.483
	Age	0.346	2.057	0.459	9.208
	Gravida	0.621	1.490	0.307	7.235
	DM	0.999	0.000	0.000	
	Obesity	0.362	1.788	0.513	6.230
	BBW	0.999	0.001	0.000	
Step 2	COVID-19	0.017	3.302	1.235	8.827
	Age	0.163	2.508	0.690	9.125
	DM	0.999	0.000	0.000	
	Obesity	0248	1.990	0.619	6.394
	BBW	0.999	0.001	0.000	
Step 3	COVID-19	0.016	3.343	1.250	8.941
	Age	0.221	2.207	0.621	7.845
	Obesity	0.230	2.047	0.636	6.593
	BBW	0.311	2.091	0.501	8.719
Step 4	COVID-19	0.003	4.045	1.595	10.259
	Age	0.019	3.306	1.215	8.991
	Obesity	0.009	3.110	1.332	7.261

These result support previous research that any relationship between COVID-19 infection and the incidence of preeclampsia.[7]

DISCUSSION

The results of bivariate analysis showed that COVID-19, age, gravida, history of diabetes mellitus, obesity, and baby birth weight had significant relationship with preeclampsia. Meanwhile, education (p = 0.387), occupation (p = 0.628), and delivery method (p = 0.347) did not have a relationship with preeclampsia. The results of the multivariate analysis indicate that the COVID-19 variable (p = 0.003) has the most significant influence on the occurrence of preeclampsia at RSD dr. Soebandi Jember, with an odds ratio (OR) of 4.045. In conclusion, pregnant women who contract COVID-19 have a 4.045 times higher risk of developing preeclampsia compared to pregnant women without a COVID-19 infection.

These results support previous research that any relationship between COVID-19 infection and the incidence of preeclampsia. COVID-19 infection can trigger down-regulation of the Renin-Angiotensin System (RAS) due to binding of SARS-CoV-2 to the ACE2 receptor.[7] ACE2 or Angiotensin Converting Enzyme-2 is an enzyme which converts angiotensin II to angiotensin 1-7.[8] Down-regulation of the Renin-Angiotensin System (RAS) is characterized by decreased levels of angiotensin 1-7, angiotensin which acts as a vasodilator. This decrease of angiotensin 1-7 levels triggers an increase in the systemic arterial vasoconstrictive effect of angiotensin II, including spiral artery vasoconstriction.[9] This condition can lead to failure of spiral artery remodelling. The failed spiral artery remodelling leads to placental ischemia and increased oxidative stress. Oxidative stress can cause angiogenic imbalance by increasing the expression of sFlt-1 as an antiangiogenic protein. The angiogenic imbalance triggers endothelial dysfunction which later causes preeclampsia.[10]

The results also support previous research which stated that COVID-19 infection can trigger preeclampsia through increased coagulation cascade activity. Increased activity of coagulation cascade is characterized by changes in PT (prothrombin time), BT (bleeding time), a PTT (activated Partial Thromboplastin Time), CT (clotting time).[11] The other research also stated that COVID-19 infection is known to increase the inflammatory response which is characterized by an increase in the value of CRP (C-reactive protein), D-dimer, and NLR (neutrophil lymphocyte ratio) which in turn triggers occurrence of preeclampsia.[12]

Multivariate analysis in Table 4 shows that age is associated with preeclampsia. Pregnant women >35 years have a 3,306 times risk of developing preeclampsia compared to pregnant women ≤35 years. The results support previous research which states that ages > 35 years are more at risk of developing preeclampsia because of vascular degeneration. This degeneration of blood vessels occurs due to decrease in nitric oxide and increase in oxidative stress with age.[13] Vascular degeneration can cause endothelial dysfunction through platelet aggregation and impaired prostaglandin metabolism.[14] This condition triggers vasoconstriction and can potentially lead to cardiovascular and nephrological disorders.[15]

Multivariate analysis in Table 4 also shows that obesity is associated with preeclampsia. Obese pregnant women have a risk of 3,110 times of developing preeclampsia compared to normal or non-obese pregnant women. The results supports previous research which states that obese pregnant women are more at risk of developing preeclampsia because lipids can be found in the placenta and can interfere placental invasion.[16] In addition, the complement system also has an important role in increasing the risk of preeclampsia in obese pregnant women. Complement system can be activated locally, by adipose tissue, and systemically, by the liver or other organs. The complement system functions to protect the body from pathogens and plays a role in physiological processes, such as regulating the humoral immune response. The complement system must be lowered to allow adequate placentation because the embryo has paternal and maternal antigens, but is simultaneously activated to protect fetus and mother from pathogens. In obesity, there is an increase of the complement system activation due to the high amount of adipose tissue. The increase of complement system can trigger placentation disorders which lead to preeclampsia.[17]

CONCLUSION

The COVID-19 variable shows a significant relationship with preeclampsia. Pregnant women with COVID-19 have a 4.045 times higher risk of developing preeclampsia compared to pregnant women without a COVID-19 infection at RSD dr. Soebandi Jember.

LIMITATION OF STUDY

This study did not examine the relationship between the severity of COVID-19 and the degree of preeclampsia in pregnant women.

FUTHER RESEARCH RECOMMENDATION

Future researchers can use a larger number of samples and use different research methods, such as cohorts, to minimize research bias. Future researchers are also expected to be able to deepen this research topic by analyzing the relationship between the severity of COVID-19 and the degree of preeclampsia in pregnant women.

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