Analysis of Preeclampsia in Pregnant Women Reviewing from Vascular Disorders due to Endothelial Dysfunction

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ABSTRACT

Preeclampsia is a multisythemic disorder in pregnancy. Some theories reveal that PE is a result of imuune and hormonal response disorders during pregnancy. In the preeclampsia there is a endothelial dysfunction in the controlling vascular function to respond to blood composition and function disorder as a physical barrier to the exchange of fluid, ion proteins and cells from the blood through the vasculer wall. In addition, there is a decrease in angiogenesis and vasodilatation of blood vessels in response to oxygen pressure and mechanical stress like shear stress. Analyzing the incidence of preeclampsia in pregnant women in terms of vascular disorders doe to endothelial dysfunction. Design : observational, a cross sectional approach. Probability sampling using random sampling. Statistical analysis logistic regression. Data processing Hosmer and Lemeshow Test. Assumption of the amount of influence a summary model. PE incidence of pregnant woman 94 (6.15%), 53 people (56.4%) PE, 41 (43.6%) PEB. Trombocytes test: sig= $0.002 < p=0.05$, leukocytes value: sig $0.033 > p=0.05$, neutrophil value: sig $0.040 > p=0.05$. Based on statistic level platelets, leukocytes and neutrophil affect PE incidence.

Keywords: leukocyt, neutrophil, preeclampsia, thrombocyt

BACKGROUND

Preeclampsia is a multisythemic disorder that occurs in pregnancy characterized by the presence of hypertension, edema and protrinuria. It usually happened at over 20 weeks at gestational or in the third quarter of pregnancy. Most often happens by 37 weeks of gestation, also can happen after labor.(Diana Christine Lalenoh, 2018).

Until recently etiology of preeclampsia is not known. But some theories reveal that PE is a result of imuune and hormonal response disorders during pregnancy, so make the remodeling disorder of uterin blood and endothelial dysfunction.It was thought that the endothelial function was a structural barrier between circulation and the surrounding tissues, but is presently known that the endothel functions the vascular tonus, prevent thrombosis, set up of the activity of the fibrinolysis system, prevent leukocyte progression and regulate vascular growth.(Darwin, Fithra and Elvira, 2018).

Endothelial dysfunction in PE happened to systemically, characterized by an increase in factor VIII, fibronectin total and cellular, thrombomodulin, endotheline, growth factor activity and tPA/PAI-1 disorders and the prostacyclin/thromboxane-A2 balancing. On the placenta PE there is no trophoblasts invasion that results in reduced blood flows so as to causing the placental hypoxia. Hypoxia modulates the increase in VEGF which is an angiogenic factors in the placenta.

The endothel plays a role in the of angiogenesis process by regulating the balance of angiogenic factors through several processes including proliferation and cell migration, vascular formation, synthesis and release of pro-angiogenic factors including VEGF. In PE there is an inbalance of the angiogenic factors where is the decrease in pro-angiogenic factors such as: VEGF, placental growth factor (PIGF), adenosine, NO, Ang-I and Ang-II, angiopietin tyrosine kinase (Tie2) and EPC; and an increase in anti-angiogenic factors such as: sFlt-1 and soluble endoglin receptor (sEnd). (González, 2014).

According to the World Health Organization (WHO), preeclampsia is estimated to account for 70,000 maternal deaths and 500,000 infant deaths annually. Preeclampsia cases that incidence in Indonesia are 128,273 per year with a percentage of 5.3% (Nuraini, Abimanyu and Rosida, 2020). Data from the World Bank State that since 2000, AKI is rating in Indonesia has declined, citing a rate of 177 per 100,000 for the birth of life in 2017. But it is still far from the target of the sustainable development goals (SDGS) of 70 per 100,000 life births by 2030 (Amalia, Harfiani and Chairani, 2020).

East Java health profile shows that the three highest causes of maternal death in 2019 are 31.15 percent pre elamsi (162), 24.23% hemorrhage, other 23.1% causes or (120).(Dinas Kesehatan Provinsi Jawa Timur, 2020). And according to the health profiles of the district's unfortunate, early 2016 maternal mortality rates number 41,537 or (72.22 per 100,000 live births) of pregnant mothers number 6 mothers (20 %), birth mothers number 7 mothers (23.3 %), mother nifas 17 (56.6%). The causes of maternal death include 17 cases (56.7%), 11 cases of bleeding (36.7%), sepsis 1 case (3.3%) and amniotic embolism 1 case (3.3%). (RENCANA KERJA DINAS KESEHATAN KABUPATEN MALANG TAHUN 2018, 2018).

A preliminary study by the author in the medical room of Wava Husada Hospital stands for 39 cases of preeclampsia (6.18%). It stands at 41,02% (16 people) peb and (23 people = 58.97%) PE. Of the 16 cases of expectant mothers with preeclampsia a normal thrombocyte 15 (93.75%), 1 person tall thrombocytes (6.25%). Leukocytes value on pregnant mothers with heavy preeclampsia 8 persons (50%) with normal leukocytes value, and 8 persons (50%) the rest leukocytes high. The lab results of neutrophil 9 people (56.25%) normal and 7 people (43.75%) high.

Results of the laboratory 23 pregnancy with a mild preeclampsia show normal thrombocytes 20 (86.96%), 2 persons (8.7%) and a low of 1 (4.35). Leukocytes are 15 persons

(65.22%) and leukocytes normal 8 persons (34.78%), high neutrophil scores are found in 16 expectant mothers (69.57%) and as normal as 7 people (30.43%).

Based on the above data, the author wants to do an analysis of preeclampsia in the pregnant woman based on vasculer disorder due to endothelial dysfunction at the Wava Husada Hospital Kepanjen Malang Regency.

METHODS

This research metods is quantitative study. With observational research design, which is researchers only observe, without providing intervention on the variables to be studied. As for the approach used sectionals. Sampling retrieval is chosen randomly sampling using the method of random sampling. Uses data is a secondary data from medical records Wava Husada Hospital. Population 105, respondent sample is 94. Statistic test using logistic regression. Data processing uses Hosmer and Lemeshow Tests. The general assumption of impact using Model Summary and simultane tests using Omnibus Test of Models Coefficients.

RESULTS

Tabel 1. Cross-tabulation of platelet and preeclampsia and severe preeclampsia

Trombosit		Preeclampsia		Total
		PE	PEB	
Rendah (< 150)	Count	3	1	4
	% within thrombosit	75.0%	25.0%	100.0%
	% within preeklampsia	5.7%	2.4%	4.3%
	% Of Total	3.2%	1.1%	4.3%
Normal (< 150-400)	Count	49	33	82
	% within thrombosit	59.8%	40.2%	100.0%
	% within preeklampsia	92.5%	80.5%	87.2%
	% Of Total	52.1%	35.1%	87.2%
Tinggi (> 400)	Count	1	7	8
	% within thrombosit	12.5%	87.5%	100.0%
	% within preeklampsia	1.9%	17.1%	8.5%
	% Of Total	1.1%	7.4%	8.5%
Total	Count	53	41	94
	% within thrombosit	56.4%	43.6%	100.0%
	% within preeklampsia	100.0%	100.0%	100.0%
	% Of Total	56.4%	43.6%	100.0%

1. Base on crosstabs platelets based on preeclampsia are obtained platelets in preeclampsia in pregnant woman are most often within normal range. A total of 82 respondents (87.2%) by 49 respondents (52.1%) in PE pregnant woman and 33 (35.1%) in pregnant woman with severe PE. As for the thrombocyst drop and increase in platelets from normal levels, there is 1% in both PE and severe PE respectively.

Tabel 2. Cross-tabulation of Leukosit and preeclampsia and severe preeclampsia

Leukosit		Preeclampsia		Total
		PE	PEB	
Rendah (< 4)	Count	1	0	1
	% within Leukosit	100.0%	.0%	100.0%
	% within preeklampsia	1.9%	.0%	1.1%
	% Of Total	1.1%	.0%	1.1%
Normal (4-10)	Count	19	18	37
	% within Leukosit	51.4%	48.6%	100.0%
	% within preeklampsia	35.8%	43.9%	39.4%
	% Of Total	20.2%	19.1%	39.4%
Tinggi (> 10)	Count	33	23	56
	% within Leukosit	58.9%	41.1%	100.0%
	% within preeklampsia	62.3%	56.1%	59.6%
	% Of Total	35.1%	24.5%	59.6%
Total	Count	53	41	94
	% within Leukosit	56.4%	43.6%	100.0%
	% within preeklampsia	100.0%	100.0%	100.0%
	% Of Total	56.4%	43.6%	100.0%

2. Results of cross-tabulation of leukocyte levels on the incidence of preeclampsia in pregnant women is 59.6% of preeclampsia pregnant women experienced an increase in leukocyte levels in the blood in pregnant women PE is 35.1% and in severe PE is 56.1%. For low leukocyte levels in pregnant women PE is 1% and no in severe PE pregnant women have lower leukocytes levels.

Tabel 3. Cross-tabulation of Neutrophil and preeclampsia and severe preeclampsia

Neutrophil		Preeclampsia		Total
		PE	PEB	
Rendah (< 1.50)	Count	1	0	1
	% within Neutrophil	100.0%	.0%	100.0%
	% within preeklampsia	1.9%	.0%	1.1%
	% Of Total	1.1%	.0%	1.1%
Normal (1.50-7)	Count	19	18	37
	% within Neutrophil	51.4%	48.6%	100.0%
	% within preeklampsia	35.8%	43.9%	39.4%
	% Of Total	20.2%	19.1%	39.4%
Tinggi (> 7)	Count	33	23	56
	% within Neutrophil	58.9%	41.1%	100.0%
	% within preeklampsia	62.3%	56.1%	59.6%
	% Of Total	35.1%	24.5%	59.6%

Total	Count	53	41	94
	% within Neutrophil	56.4%	43.6%	100.0%
	% within preeklampsia	100.0%	100.0%	100.0%
	% Of Total	56.4%	43.6%	100.0%

3. The neutrophil level of the pregnant woman with preeclampsia is at most high, 59.6% of the neutrophil preeclampsia in pregnant woman being at the top of the 35.1% of the PE pregnant woman and 24.5% of the severe PE in pregnant woman. For low neutrophil levels, only at 1% of PE pregnant woman, and no severe PE pregnant woman have had lower neutrophil levels.

Statistical Analysis

Statistical analysis in this study used Logistic Regression, data processing using the Hosmer and Lemeshow Test. The results of processing data, obtained the sig value. 0.141 > 0.05 so that the data used is appropriate if read using Logistic Regression.

The Summary model shows a Nagelkerke R Square value of 0.240 which means that the magnitude of influence together of the three variables x (platelets, leukocytes and neutrophils) against the variable y (preeclampsia) by 24%. So there is still an open possibility of 76% of other variables affecting the incidence of preeclampsia that were not included in this study. On Omnibus Tests of Model Coefficients got the value of chi square count 18,513 > chi square table of 7,814. It could be argued that in the same way the three x variables affect the y variable.

On the Variabel in The Equation got a variable platelet value a sig value. 0.002 < p= 0.05, the means a platelet levels is affecting preeclampsia in pregnant woman. An exp (b) platelet count is 1,013. Meaning that if the platelet levels increases, 1,013 times over in incidence of preeclampsia. Leukocytes variables have a sig. 0.033 > p= 0.05 that means leukocyte increase in the preeclampsia of the pregnant woman, when leukocytes high will cause a preeclampsia event in the pregnant woman by 33%. And the neutrophil's variables have a sig. 040 > p= 0.05 which means that the rise in neutrophils affects preeclampsia in pregnant woman, when high neutrophils will cause a 40% preeclampsia incidence in pregnant woman.

DISCUSSION

1. Identification of the incidence of preeclampsia in pregnant women at Wava Husada Hospital Kepanjen

Based on the results of the tabulation in this reserach, the incidence of preeclampsia in pregnant women for the January - September 2021 period was 94 events (6.15%) of all pregnant women treated in the delivery room of Wava Husada Kepanjen Hospital as many as 1528 people, with details of 53 people (56.4%) pregnant women with PE and 41 people (43.6%) severe PE. According to the Pedoman Nasional Pelayanan Kedokteran (PNPK) the incidence of according to the Pedoman Nasional Pelayanan Kedokteran (PNPK) the incidence of preeclampsia in Indonesia is 128,273/year or about 5.3%. (Djamil et al., 2015). According to the World Health Organization (WHO), preeclampsia cases that occur in Indonesia are 128,273 per year with a percentage of 5.3% (Nuraini, Abimanyu and Rosida, 2020).

Efforts by the government to reducing the MMR/CBR have been made through strict surveillance of expectant mothers. The monitoring of pregnancies through the ANC (Ante Natal Care) is made at least 6 times during pregnancy and at least 2 visits by Obstetrician. One of can the early detection for abnormality pregnancy is preeclampsia. WHO recommends that when an ANC, pregnancies are also given calcium tablets, the recommended daily dose for pregnant women is 1.5 - 2.0 gr peroral to reduce the risk of pre-eclampsia and sulfas ferrosus tablets as well as folic acid to prevent or reduce the risk of anemia in pregnant women.

2.   Identified platelet levels in preeclampsia's pregnant woman.

The results of this study are found that platelets in preeclampsia are more than normal. Cross-tabulation between platelets and 94 samples obtained 87.2% of pregnant woman's platelets with preeclampsia is normal levels (52.1% in PE pregnant woman and 35.1% in severe PE). A platelet level is high 8.5% (1.1% in PE pregnant woman and 7.4% in severe PE). And 4.3% preeclampsia pregnant woman have low platelets (3.2% in PE pregnant woman and 1.1% in severe PE). Kartika, Serudji and Obstetri (2015) states that in normal physiological conditions, circulating platelets are at stuck.

A healthy endotheline will be release the several mediators such as nitrit oxide (NO) and an adenosine that blocks platelet adhesion activity to the endotel.
Endothelial inflamasion make the production of this protective mediator to decrease. Instead, NO metabolic levels and adenosine increased in preeclampsia patients in a parallel to significant platelet activity compared with normotensive pregnancies. NO concentration increases in the feto-placental circulation in preeclampsia. Increased levels of NO are further compensation for platelets activation in preeclampsia. (Kartika, Serudji and Obstetri, 2015).

In preeclampsia a hypercoagulation occurs in the maternal or placental circulation which results in a decrease in cuagulation and platelet factors. In pregnant women with hypertension it causes a megakaryocytes drop in the fetus make a thromboytin (megakaryocytic stimulating factor) not to increase causing a thrombocytopeni. Hypertension make intravascular dehydration and make a vasospasme so that there is tissue dehydration that causes of endothelial damage, coagulation/hypercoagulation increases so that thrombocytopenes occur, decreased fibrinogen levels, intravasculer hemorrhage and DIC. The longer the disease process and the longer the time between the preeclampsia/eclampsia and the labor process can make platelet levels lower. Thrombocytopenia occurs due to increased platelet activation and platelet coagulation due to the wounded for blood vessels (Fortuna Maudy Sintya *et al.*, 2021).

Research by Fortuna Maudy Sintya et al., (2021) obtained the results of patients with preeclampsia having a minimum platelet level of 301,000/mm3, a maximum of 415,000/mm3, and an average of 351,733.33/mm3 with a standard deviation of 33,552.66/mm3. Patients with eclampsia have a minimum platelet level of 122,000/mm3, a maximum of 281,000/mm3, and an average of 209,200/mm3 with a standard deviation of 42,465.45/mm3. There is a significant difference between platelet levels in preeclampsia and eclampsia patients.(Fortuna Maudy Sintya et al., 2021). Syahputra, Lumbanraja dan Edianto (2019) in his research states that Systemic vascular inflammation make the endothelial damage which will increase the activation of the coagulation system and increase the consumption and platelets production. Increased thrombopoiesis will produce young platelets that are larger in size than more maturing platelets. The results of this study did not find significant differences in PLR and MPV values between preeclampsia and normal pregnancy (p = 0.584 and 0.573) (Syahputra, Lumbanraja and Edianto, 2019).

In the Kibas research 2021, the pathophysiology of thrombocytopenia in preeclampsia is related to inflammatory processes in the endothelium, the release of thromboxane A2 is followed by an increase in the thromboxan/prostacyclin ratio. Thromboxan A2 triggers of vasospasm, induces platelet aggregation and endothelial damage as a cause of platelet dysfunction and causes activation, aggregation, microangiopathic platelet hemolysis which further triggers increasingly severe vasospasm so that thrombocytopenia occurs as an important indicator in preeclampsia (Kibas, Latuconsina and Maelissa, 2021).

Research by Yusrianty, et al, 2014 Yusrianty, et al, 2014 concluded that hemoglobin levels and platelet levels did not get a meaningful difference. (Yusrianty, Lukas and Tahir, 2014). In the reaserch by Monteiro (2014), concluded that platelet is lowering in the preeclampsia patient. Research by Widyastiti and Setianingrum (2019) there is no difference

between normal pregnancy with preeclampsia. Normal pregnancy with severe preeclampsia and preeclampsia with severe preeclampsia.(Widyastiti and Setianingrum, 2019).

Giving supplements in the tablets of sulfas ferrosus and folic acid to pregnant women aims to prevent anemia or treatment in anemias pregnant women. One of the functions of folic acid is to help the absorption of iron by the body, so that the combination of folic acid and tablets of sulfas ferrosus is expected to be able to increase hemoglobin levels in the pregnant women blood.

3. Identifying of leukocyte levels in pregnant women with preeclampsia

The results of this study found that leukocyte levels in preclampsias pregnant women is 59.6% (56 respondents) increased consisting of 33 respondents (35.1%) in preeclampsia pregnant women and 23 respondents (24.5%) severe preeclampsia pregnant women. 39.4% of preeclampsia pregnant women with leukocyte levels within normal limits, consisting of 20.2% (19 respondents) of PE pregnant women and as many as 18 respondents (19.1%) of severe PE pregnant women. And only 1 respondent of PE pregnant women experienced a decrease in leukocyte levels. This means that there is to increase leukocytes in pregnant women with preeclampsia.

In patients of preeclampsia there is an increase in oxidative stress so that the trophoblast debris and necrotic trophoblast products also increase. This condition make the inflammation response are a large to. The inflammatory response will endothelial cells activation and larger macagogue/granulocyte cells, resulting in an inflammatory reaction.(Darwin, Fithra and Elvira, 2018).

Leukocytes or commonly called White blood cells act as an immune system or kill germs and diseases that are in the human bloods. In normal of leukocytes levels amounts to 3200-10000 mm, based on the morphological form consists of five types, is lymphocytes, monocytes, neutrophils, eosinophils, and basophils. Of the five types of morphological forms of leukocytes, these have different functions and features. Leukocytes are the main function for the body's defenses. Leukocytes serve for protection or as a defense of the body against infections as well as killing cells that mutations.(Giyartika and Keman, 2020).

The results of a study by Yusrianty, et al (2014) found that serum levels of P38 MAPK in severe preeclampsia patients were higher than in normal pregnancy, and leukocyte levels in severe preeclampsia patients were higher than normal pregnancy, while hemoglobin levels and platelet levels did not get a meaningful difference, it was also found that serum levels of P38 MAPK were positively correlated with leukocyte levels in severe preeclampsia patients ($p<0.05$ r = 0.471). The role of Leukocytes is protecting or as a defense of the body in fighting infections and killing cells that undergo mutations will naturally be produced by the body when cells in the body or other parts of inflammation, either due to inflammation by bacteria or inflammation caused by disturbances. In pregnant women with preeclampsia there is a metabolic disorder due to endothelial dysfunction so that there is an increase of leukocytes. Although not all pregnant women with preeclampsia metabolism experienced an increase in leukocyte levels, but in this study more preeclampsia pregnant women experienced an increase in leukocyte levels. The increase in leukocyte levels is a series initiated by placental hypoxia that triggers activation and an increase in P38 MAPK levels so make incidence of inflammatory response. This increase triggers an inbalancing between angiogenic and antiangiogenic factors, which then occurs endothelial dysfunction which causes an increase in vascular permeability resulting in vasoconstriction of blood vessels and finally preeclampsia occurs.

4. Identifying neutrophil levels in pregnant women with preeclampsia

The results of this study found that neutrophil levels in preeclampsia pregnant women is 69.1% (65 respondents) increased, consisting of 38 respondents (40.4%) in pregnant women with PE and 27 respondents (28.7%) pregnant women with severe PE.

Leukocyte levels, especially neutrophils, increase because they describe the inflammatory process that occurs in preeclampsia/eclampsia. Elevated neutrophil levels may also describe the severity of the inflammatory response in severe preeclampsia. (Fortuna Maudy Sintya et al., 2021).

Neutrophils are one of the parts of leukocytes that is the first line of the body's defenses in the fight against infections. There are studies that state that neutrophils also infiltrate systemic vascular tissue in women with preeclampsia which causes systemic vascular inflammation that will cause endothelial damage, which can increase the activation of the coagulation system as well as increase consumption and production of platelets.(Syahputra, Lumbanraja and Edianto, 2019). The same with Giyartika and Keman (2020) they are stated that in pregnant women with preeclampsia, an increase in neutrophil levels was obtained. This could have happened given neutrophils as part of leukocytes which are considered the body's first line of resistance to infection. The most numerous leukocytes are neutrophils. The main function of neutrophils is to fight bacterial infections and inflammatory disorders. In tissue damage related to noninfective diseases, neutrophils have an important role. (Giyartika and Keman, 2020).

Research by Singgih et al (2020) shows that NLR values can be used to predict the incidence of preeclampsia in later life in pregnant women. However, it should be noted that there are many other factors that also affect the value of the NLR, not only from the state of preeclampsia. (Singgih, Firmansyah and Dewi, 2020). Research by Sachan et al.(2017) in India showed that preeclampsia women obtained higher NLR values compared to the group of normal pregnant women (Sachan et al., 2017). Another study conducted by Abd-Alazim et al. in 2018 found that NLR values were higher in preeclampsia pregnant women compared to normal pregnant women and increased significantly in the group of pregnant women with severe preeclampsia (p = 0.042). (Abd-Alazim et al., 2018). Research was also by Gogoi et.al. in 2018, compared to 67 preeclampsia pregnant women and another group of normal pregnant women it was found that NLR was higher in women with preeclampsia compared to the control group (6.8 ± 7.6 vs 3.0 ± 0.98; P=0.001). (Priyanka Gogoi,Pallavi Sinha and Priyanka Firmal, 2018). Prasmusinto et al (2017) also conducted a study to compare NLR values by involving 134 pregnant women with preeclampsia and 118 normal pregnant women. From this study, results were obtained that preeclampsia pregnant women showed higher NLR values with an average value of 4.41 (95% CI 1.41-32.54, p<0.001), but the onset of preeclampsia did not affect the NLR value. In the ROC analysis curve, NLR is an important marker of preeclampsia with a sensitivity value of 80.1% and a specificity of 87.3% (95% CI 0.85-0.93, a cut-point value of 3.295). (Prasmusinto, Jono and Lisnawati, 2017).

An increase in leukocyte levels is followed by an increase in neutrophil levels, couse that neutrophils are part of leukocytes that function to provide protection to the body when inflammation occurs, both due to bacterial or systemic inflammation. Increasing the knowledge and awareness of pregnant women about the importance of maintaining nutritional intake during pregnancy is very important. The Medician, especially Midwives and Obgyn Specialists who are in direct contact with pregnant women and reproductive women, must intervension more in the form of counseling both individuals or groups on them so that nutritional intake with balanced nutrition in order to increase the body's resistance to the possibility of inflammation. Monitoring of pregnant women by medician assisted by health cadres is also a very decisive factor in improving the nutritional status of pregnant women.

5. Analyzing the effect of platelet levels on the incidence of preeclampsia in pregnant women

The results of cross-tabulation between platelet levels and the incidence of preeclampsia in pregnant women found that platelet levels in preeclampsia pregnant women were at most within normal limits. A total of 82 respondents (87.2%) with a division of 49 respondents (52.1%) in preeclampsia pregnant women and 33 respondents (35.1%) in severe

preeclampsia pregnant women. The increase in platelets above normal levels was 7 respondents (7.4%) in severe PE pregnant women and only 1 respondent (1.1%) in the preeclampsia pregnant women. The decline occurred in respondents of PE pregnant women is 3 respondents (3.2%) and 1 respondent (1.1%) severe preeclampsia pregnant women. The results of statistical analysis obtained a value of sig = 0.002 < p = 0.05. This can be interpreted to mean that platelet levels affect the incidence of preeclampsia in pregnant women with preeclampsia, both mild and severe preeclampsia.

Fortuna Maudy Sintya et al (2021) in theys study, placentath abnormalities are considered responsible for the release of microparticles and antiangiogenic factors into the maternal systemic circulation. These soluble factors starting platelet activation, produce inflammatory cytokines, and vascular endothelial dysfunction. Although the circulating platelets are in a resting state, when exposed to soluble mediators or microparticles in inflammatory blood vessels such as in preeclampsia, platelets are activated by the binding of the mediator to the mediator's surface receptors. After activation, platelets release various dissolved and adhesion molecules such as CD40L and platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31). As soluble mediators release into the inflammatory environment they trigger interactions between platelets, leukocytes, and endothelial cells (ECs). This interaction between platelets and leukocytes stimulates the migration of neutrophils to the inflammatory site by forming platelet-leukocyte aggregates. This bond between platelets and leukocytes causes an increase in endothelial permeability and induces the production of inflammatory cytokines and causing morphological amplification and molecular inflammatory responses.(Fortuna Maudy Sintya et al., 2021).

Research by Yusrianty, et al, 2014 concluded that hemoglobin levels and platelet levels did not obtain significant differences (Yusrianty, Lukas and Tahir, 2014). And Monteiro (2014) in his research stated that platelets have decreased in preeclampsia patients. Research by Widyastiti and Setianingrum (2019) there was no difference between normal pregnancy with preeclampsia, normal pregnancy with severe preeclampsia and middle preeclampsia with severe preeclampsia. (Widyastiti and Setianingrum, 2019).

ANC (Ante Natal Care) is carried out as an effort to monitor the development of the condition of pregnant women and the welfare of the fetus, so that it can be detected immediately when abnormalities are found in both the mother and fetus. One of the abnormalities that can be detected during the ANC is preeclampsia. Because when the ANC is carried out a blood pressure check which is the first indicator of the presence of preeclampsia. Close monitoring of pregnant women is expected to be able to suppress the incidence of preeclampsia while reducing complications that can occur due to the occurrence of preeclampsia in pregnant women. An integrated ANC carried out in the form of a laboratory examination of blood is very important if the indication of preeclampsia can be reviewed from vascular disorders.

6. Analyzing the effect of leukocyte levels on the incidence of preeclampsia in pregnant women

The results of cross-tabulation of leukocyte levels on the incidence of preeclampsia in pregnant women as many as 59.6% of preeclampsia pregnant women experienced an increase in leukocyte levels in the blood in preeclampsia pregnant women as much as 35.1% and in severe preeclampsia as much as 56.1%. For low leukocyte levels in preeclampsia pregnant women as much as 1% and no severe preeclampsia pregnant women experienced a decrease in leukocyte levels. The results of statistical analysis obtained the Sig value. 0.033 > 0.05 which means that an increase in leukocyte levels affects the incidence of preeclampsia in pregnant women, when high leukocyte levels will cause an incidence of preeclampsia in pregnant women by 33%.

Metabolic disorders such as preeclampsia and eclampsia, hematologic changes caused by hypovolemia caused by vasospasm, hypoalbuminemia hemolysis microangiopathic due to

arterioles spasm and hemolysis due to damage to the arteriole endothelium. Such changes can be in the form of an increase in hematocrit due to hypovolemia, an increase in blood viscosity, thrombocytopenia, and symptoms of mycoangiopathic hemolysis. Metabolic disorders also result in inflammation, so the number of leukocytes, especially neutrophils is increases or leukocytosis. (Kibas, Latuconsina and Maelissa, 2021).

The results of the study by Yusrianty, et al (2014) found that serum levels of P38 MAPK in severe preeclampsia patients were higher than in normal pregnancy, and leukocyte levels in severe preeclampsia patients were higher than normal pregnancy, and hemoglobin levels and platelet levels did not get a meaningful difference, it was also found that serum levels of P38 MAPK were positively correlated with leukocyte levels in severe preeclampsia patients (p<0.05 r = 0.471). Any increase in serum P38 MAPK levels will have an impact on increasing leukocyte levels in severe preeclampsia (Yusrianty, Lukas and Tahir, 2014). Research conducted by Halenur Bodag, et al in 2018 on The Predictive Value Of Total Leukocyte Count and Leukocyte Differential for Severe Preeclampsia found that there was no significant difference in leukocyte levels between preeclampsia patients and healthy pregnant women. (Kibas, Latuconsina and Maelissa, 2021).

The increase in leukocyte levels can be understood as a series starting by placental hypoxia that triggers activation and increase in P38 MAPK levels so that an inflammatory response occurs. This increase triggers an imbalance between angiogenic and antiangiogenic factors, which then occurs endothelial dysfunction which causes an increase in vascular permeability resulting in vasoconstriction of blood vessels and finally preeclampsia incidence

7. Analyzing the effect of neutrophil levels on the incidence of preeclampsia in pregnant women

The results of cross-tabulation between neutrophil levels in pregnant women and the incidence of preeclampsia increased the most, as much as 59.6% of neutrophil levels of preeclampsia pregnant women were within high limits of 35.1% in preeclampsia pregnant women and 24.5% in severe preeclampsia pregnant women. For low neutrophil levels, only 1% of preeclampsia pregnant women and no in severe preeclampsia pregnant women have decreased neutrophil levels. Statistical analysis results obtained Sig values. 0.040 > 0.05 which means that an increase in neutrophil levels affects the incidence of preeclampsia in pregnant women, when neutrophil levels are high it will cause an incidence of preeclampsia in pregnant women by 40%.

According to Giyartika and Keman (2020) in preeclampsia pregnant women, an increase in neutrophil levels was obtained. This could have happened given neutrophils as part of leukocytes which are considered the body's first line of resistance to infection. The most numerous leukocytes are neutrophils. The main function of neutrophils is to fight bacterial infections and inflammatory disorders. In tissue damage related to noninfective diseases, neutrophils have an important role (Giyartika and Keman, 2020).

Result of The research by Nofrienis et al in 2021, based on various cut off point values that were determined to be analyzed in the study, the lowest cut off point value for the diagnosis of NLR 3.08 and the highest 8.1.6–8 The higher the NLR cut off point value, the lower the percentage of patients both in EOP (Early Onset Preeclampsia) and LOP (Late Onset Preeclampsia) which has the NLR value. The analysis based on the cut off point value also did not differ significantly between EOP and LOP. (Nofrienis et al., 2021).

Neutrophils as one of the parts of leukocytes have a very important role in the body's defense functions. In pregnant women with preeclampsia there is inflammation caused by metabolic disorders due to endothelial dysfunction. Each inflammatory event forces the body to produce leukocytes in which neutrophils become part of the body's defense system. One of the things that can be done as an effort to prevent inflammation is closely related to increasing the body's resistance through improving the nutritional of pregnant women.

CONCLUSION

Based on the results of the tabulation of this study, the incidence of preeclampsia in pregnant women for the January - September 2021 period was 94 events (6.15%) of all pregnant women treated in the delivery room of Wava Husada Kepanjen Hospital as many as 1528 people, with details of 53 people (56.4%) pregnant women with preeclampsia and 41 people (43.6%) severe preeclampsia.

In this study, platelet levels in pregnant women with preeclampsia were more within normal limits. Cross-tabulation between platelet levels and the incidence of preeclampsia from 94 samples of pregnant women with preeclampsia consisting of 53 people (56.4%) preeclampsia pregnant women and 41 people (43.6%) in the severe preeclmpsia, obtained 87.2% platelet levels of pregnant women with preeclampsia within normal limits (52.1% in preeclampsia pregnant women and 35.1% in severe preeclampsia pregnant women). Platelet levels above the normal limit were 8.5% (1.1% in preeclampsia pregnant women and 7.4% in severe preeclampsia pregnant women). And 4.3% of preeclampsia pregnant women have low platelet levels (3.2% in preeclampsia pregnant women and 1.1% in severe preeclampsia pregnant women).

Leukocyte levels in preclampsia pregnant women is 59.6% (56 respondents) increased consisting of 33 respondents (35.1%) in preeclampsia pregnant women and 23 respondents (24.5%) severe preeclampsia pregnant women. 39.4% of preeclampsia pregnant women with leukocyte levels within normal limits, consisting of 20.2% (19 respondents) of preeclampsia pregnant women and as many as 18 respondents (19.1%) of severe preeclampsia pregnant women. And only 1 respondent of preeclampsia pregnant women experienced a decrease in leukocyte levels. This means that there is a tendency to increase leukocytes in pregnant women with preeclampsia.

Neutrophil levels in preclampsia pregnant women is 69.1% (65 respondents) increased, consisting of 38 respondents (40.4%) in preeclampsia pregnant women and 27 respondents (28.7%) severe preeclampsia pregnant women.

Cross-tabulation between platelet levels and the incidence of preeclampsia in pregnant women obtained the results of platelet levels in preeclampsia pregnant women were at most within normal limits. A total of 82 respondents (87.2%) with a division of 49 respondents (52.1%) in PE pregnant women and 33 respondents (35.1%) in pregnant women with PEB. The increase in platelets above normal levels was 7 respondents (7.4%) in PEB pregnant women and only 1 respondent (1.1%). The decline occurred in respondents of PE pregnant women as many as 3 respondents (3.2%) and 1 respondent (1.1%) peb pregnant women. Statistical analysis obtained a sig value = 0.002 < p = 0.05. This can be interpreted to mean that platelet levels affect the incidence of preeclampsia in pregnant women with preeclampsia, both mild and severe preeclampsia.

The results of cross-tabulation of leukocyte levels on the incidence of preeclampsia in pregnant women as many as 59.6% of preeclampsia pregnant women experienced an increase in leukocyte levels in the blood with a division in preeclampsia pregnant women as much as 35.1% and in severe preeclampsia as much as 56.1%. For low leukocyte levels in preeclampsia pregnant women as much as 1% and no severe preeclampsia pregnant women experienced a decrease in leukocyte levels. The results of statistical analysis obtained the Sig value. 0.033 > 0.05 which means that an increase in leukocyte levels affects the incidence of preeclampsia in pregnant women, when high leukocyte levels will cause an incidence of preeclampsia in pregnant women by 33%.

The results of cross-tabulation between neutrophil levels in pregnant women and the incidence of preeclampsia increased the most, as much as 59.6% of neutrophil levels of preeclampsia pregnant women were within high limits with a division of 35.1% in

preeclampsia pregnant women and 24.5% in severe preeclampsia pregnant women. For low neutrophil levels, only 1% of preeclampsia pregnant women and no severe preeclampsia pregnant women have decreased neutrophil levels. The results of statistical analysis obtained the Sig value. 0.040 > 0.05 which means that an increase in neutrophil levels affects the incidence of preeclampsia in pregnant women, when neutrophil levels are high it will cause an incidence of preeclampsia in pregnant women by 40%.

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