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VASCULAR CELL ADHESION MOLECULE-1 (VCAM-1) AND BLOOD PRESSURE ON PREECLAMSIA PATIENTS

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Abstract: *Preeclampsia refers to a systemic syndrome characterized by extensive maternal endothelial dysfunction clinically accompanied by hypertension, edema, and proteinuria during pregnancy. It occurs in about 3% to 5% of pregnant women, usually in the last trimester and is more common in primiparas (women who are pregnant for the first time. Some of these women progress to convulsions (eclampsia). Other complications stem from systemic endothelial dysfunction include acute renal failure and pulmonary edema.About 10% of women with severe preeclampsia have hemolysis, elevated liver enzymes, and low platelets, which is called hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP syndrome). Pregnancy can trigger hypertension in women who were previously normotensive or can exacerbate the disease in women who previously had hypertension. The cause of both cases is unknown. Generalized edema, proteinuria, or both often accompany hypertension precipitated or exacerbated by pregnancy. This hypertension can be accompanied by seizures, especially if ignored [1]. Hypertensive disorders that complicate pregnancy are common and are one of the elements that cause a large number of maternal deaths in the United States in addition to bleeding and infection, which continue to be. Most of the poor pregnancy outcomes associated with hypertension can be prevented with good prenatal monitoring and treatment if needed. Pregnancy hypertension is clinically pregnancy-induced hypertension. it was found that the correlation between maternal age and VCAM-1 levels did not have a correlation. These results were obtained by controlling for independent variables (systolic blood pressure and diastolic blood pressure) and intermediate variables (number of pregnancies). When statistical tests were carried out without controlling for systolic blood pressure, while other variables were controlled, there was a significant correlation between maternal age and VCAM-1 levels. Then the statistical test was carried out again by controlling only the systolic blood pressure variable and the other variables were not, then the obtained correlation was also not significant from maternal age and VCAM-1 levels.*

Keywords - ***vascular cell adhesion, VCAM-1, blood pressure, preeclamsia patient***

I. INTRODUCTION

Preeclampsia refers to a systemic syndrome characterized by extensive maternal endothelial dysfunction clinically accompanied by hypertension, edema, and proteinuria during pregnancy. It occurs in about 3% to 5% of pregnant women, usually in the last trimester and is more common in primiparas (women

who are pregnant for the first time. Some of these women progress to convulsions (eclampsia). Other complications stem from systemic endothelial dysfunction include acute renal failure and pulmonary edema.About 10% of women with severe preeclampsia have hemolysis, elevated liver enzymes, and low platelets, which is called hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP syndrome).

The endothelium is a layer of cells lining the vascular wall that faces the lumen and is attached to a subendothelial network consisting of collagen and various glycosaminoglycans including fibronectin. Previously it was thought that the function of the endothelium was as a structural barrier between the circulation and the surrounding tissue, but now it is known that the endothelium functions to regulate vascular tone, prevent thrombosis, regulate the activity of the fibrinolytic system, prevent leukocyte attachment and regulate vascular growth. Adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) play a central role in endothelial cell–leukocyte adherence and white blood cell migration to the subsequent perivascular tissue. Cellular adhesion molecules mediate specific steps of leukocyte endothelial cell interactions, and have been implicated in the pathophysiology of preeclampsia. The soluble form of the molecule can be detected in plasma, and its concentration is thought to reveal the degree of activation of certain cell types. Increased soluble form of VCAM-1 indicates endothelial cell activation/dysfunction.

II. PREGNANCY HYPERTENSION

Pregnancy can trigger hypertension in women who were previously normotensive or can exacerbate the disease in women who previously had hypertension. The cause of both cases is unknown. Generalized edema, proteinuria, or both often accompany hypertension precipitated or exacerbated by pregnancy. This hypertension can be accompanied by seizures, especially if ignored [1]. Hypertensive disorders that complicate pregnancy are common and are one of the elements that cause a large number of maternal deaths in the United States in addition to bleeding and infection, which continue to be. Most of the poor pregnancy outcomes associated with hypertension can be prevented with good prenatal monitoring and treatment if needed. Pregnancy hypertension is clinically pregnancy-induced hypertension [2]. Hypertension of pregnancy is characterized by an increase in systolic blood pressure of more than 140 mmHg and diastolic blood pressure of more than 90 mmHg at gestational age of more than 20 weeks without a history of previous hypertension and without proteinuria. Preeclampsia (PE) is a collection of symptoms or syndromes that affect pregnant women with gestational age above 20 weeks with the main signs of hypertension and proteinuria with a worldwide prevalence of around 5-8%. Edema is no longer a criterion because it is a common symptom in pregnancy[3].

Generally these pregnant women do not show signs of vascular abnormalities or hypertension before. This syndrome usually appears at the end of the second to third trimester of pregnancy. In Indonesia, preeclampsia and eclampsia are one of the main causes of maternal and perinatal death [4]. Many factors increase the incidence of preeclampsia/eclampsia, one of the risk factors for preeclampsia is teenage pregnancy or less than 20 years and advanced pregnancy or more than 34 years. A study in Norway, of 6619 singleton pregnancies found 33.4% were advanced pregnancies. Then data from Taiwan showed that the proportion of women with advanced pregnancies increased from 11.4 to 19.1% in 2010. In the UK, advanced pregnancies constituted 18.2% of all pregnancies. It can be concluded that delaying pregnancy, which is one of the risk factors for preeclampsia, has become a worldwide trend. Physiology of pregnancy requires proper oxygenation of the placenta [5]. However, Reactive Oxygen Species (ROS) derived from these high oxygen flows, are involved and required for cell replication, proliferation and maturation, embryonic development and maintenance of pregnancy. In addition, the increase in oxygen concentration led to the emergence of markers of oxidative stress[6].

III. PATHOGENESIS OF PREECLAMSIA

Early events in the pathogenesis of preeclampsia are abnormal trophoblast implantation and lack of development of adequate placental perfusion. In normal pregnancy, fetal extravillous trophoblastic cells (trophoblastic cells unassociated with chorionic villi) at the implantation site invade blood vessels and damage blood vessels, destroying vascular smooth muscle and replacing maternal endothelial cells with fetal trophoblast

cells (forming a feto-maternal hybrid). blood vessel) [7]. This process converts decidual spiral arteries from small-caliber resistance vessels to large-capacity uteroplacental vessels lacking smooth muscle walls [8].

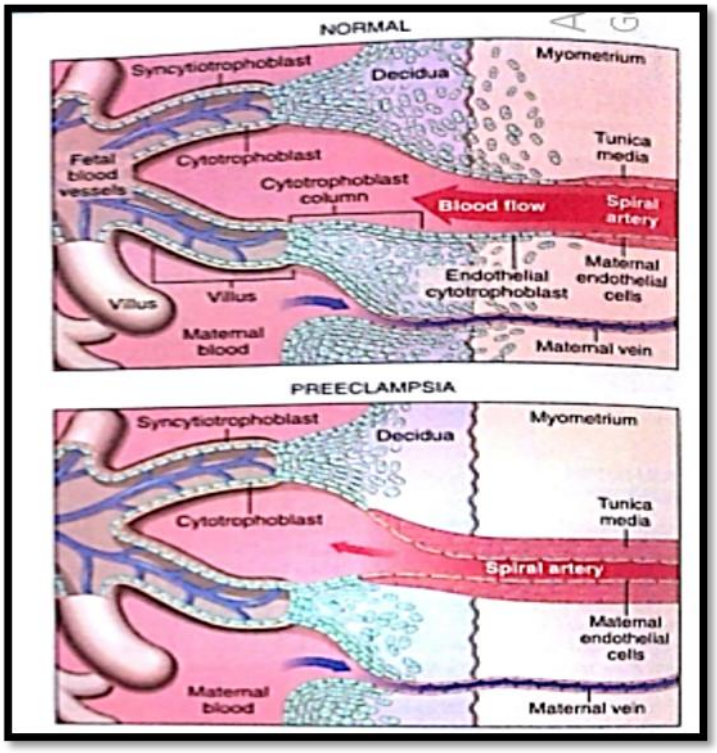

Figure 1. Physiological changes in uterine spiral arteries and remodeling failure in preeclampsia [8]

An imbalance of angiogenic (vascular endothelial growth factor/VEGF and placental growth factor/PGF) and anti-angiogenic factors (soluble FMs-like tyrosine kinase 1/sFlt-1 or soluble endoglin/sEng) that is responsible for placental vasculogenesis is also present in recent years. thought to play a role in causing endothelial injury due to hypoxia [9].

One mechanism of endothelial dysfunction involves the release of the tyrosine protein sflt-1 (such as tyrosine kinase or sVEGFR1), which is a circulating anti-angiogenic protein and inhibitor of endogenous vascular endothelial growth factor (VEGF), which acts by increasing endothelial dysfunction causing oxidative stress, ROS. and damage [1]. VEGF is key in the process of new blood vessel growth and in the overall maintenance and health of endothelial cells[10]. The level of sFlt-1 is known to be elevated in PE, and this increase precedes the manifestation of the disorder. High levels of these VEGF inhibitors, leading to disruption of VEGF by adhering to endothelial cell Flt-1 receptors, are found on membranes. sFlt-1 is the truncated form of the Flt1 receptor. sFlt-1 when secreted, in contrast to VEGF and placental growth factor (PlGF), promotes endothelial dysfunction. Several studies have shown that VEGF and PlGF are upregulated in PE by sFlt-1[11].

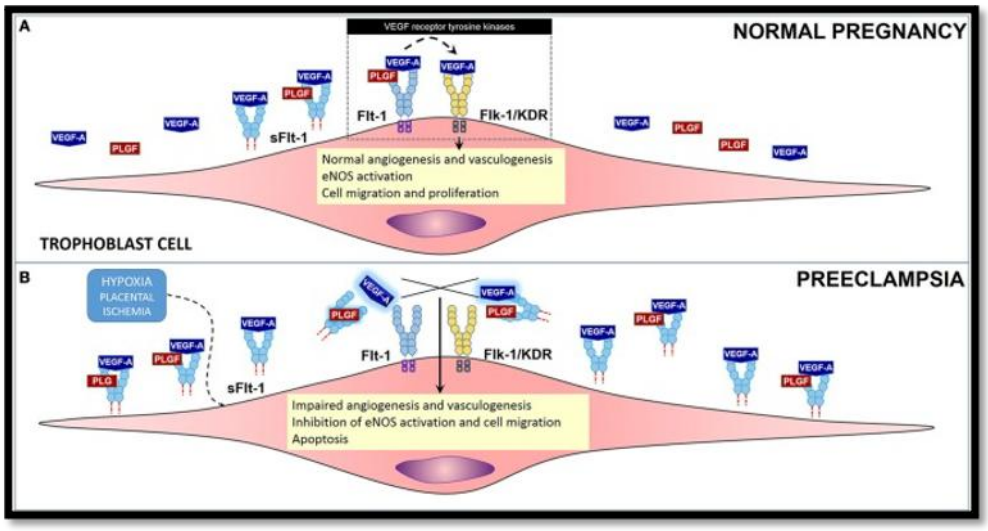

Figure 2. The role of the anti-angiogenic factor sFlt-1 in preeclampsia [11]

Preeclampsia is associated with a hypercoagulable state. Arteriolar and capillary thrombosis can occur throughout the body, particularly in the liver, kidneys, brain, and pituitary. This hypercoagulation is probably related to decreased endothelial production of PGI2, a potent antithrombotic factor, and increased release of procoagulant factors [2]. PGI2 production is stimulated by VEGF and TGF-β, and women with preeclampsia have been shown to have decreased endothelial PGI2 production [13].

During normal pregnancy, renal blood flow and glomerular filtration rate are markedly increased. With the development of preeclampsia, renal perfusion and glomerular filtration decrease. Plasma uric acid concentrations are usually elevated, especially in women with more severe disease[14]. In the majority of preeclamptic women, a slightly reduced glomerular filtration usually results from a decrease in plasma volume, which causes the plasma creatinine value to approximately double that expected in a normal pregnancy of about 0.5 mg/dL [3]. In some cases of severe preeclampsia. However, renal involvement is profound, and plasma creatinine may increase several times the normal nonpregnant value or up to 2 to 3 mg/dL. After delivery, in the absence of underlying chronic renovascular disease, complete restoration of renal function can usually be anticipated [15].

Preeclampsia is a pregnancy-specific condition characterized by placental dysfunction and maternal response to systemic inflammation with endothelial activation and coagulation. The diagnosis of preeclampsia is based on the presence of specific hypertension caused by pregnancy accompanied by other organ system disorders at gestational age above 20 weeks [16]. Preeclampsia, previously always defined by the presence of hypertension and proteinuria that just occurred in pregnancy (new onset hypertension with proteinuria) [17]. Although these two criteria are still the classic definition of preeclampsia, several other women present with hypertension with other multisystem disorders that indicate the presence of severe preeclampsia even though the patient does not have proteinuria. Meanwhile, edema is no longer used as a diagnostic criterion because it is very common in women with normal pregnancies [18].

Hypertension usually occurs before other signs. To make the diagnosis of preeclampsia, the increase in systolic pressure should be 30 mmHg or more above the pressure normally found, or 140 mmHg or more [19]. An increase in diastolic pressure is actually more reliable. When the pressure If the diastolic rises by 15 mmHg or more, or to 90 mmHg or more, the diagnosis of hypertension can be made. Determination of blood pressure is carried out at least 2 times with an interval of 6 hours at rest. The definition of severe hypertension is an increase in blood pressure of at least 160 mmHg systolic or 110 mmHg diastolic. a sphygmomanometer should use a mercury sphygmomanometer, but if it is not available, you can use a needle sphygmomanometer or a validated automatic sphygmomanometer [20]. Recent reports have shown that measuring blood pressure using automated tools often gives lower results [21].

Edema is a generalized and excessive accumulation of fluid in body tissues, and can usually be detected by weight gain and swelling of the feet, fingers, and face [22]. Mild pretibial edema is common in normal pregnancy, so it is of little significance for the diagnosis of preeclampsia. Weight gain of 1/2 kg per week in pregnancy can still be considered normal, but if the increase of 1 kg a week several times, this needs to raise awareness of the onset of preeclampsia [23]. Prateinuria means protein concentration in urine that exceeds 0.3 g/liter in 24-hour urine or qualitative examination shows 1 or 2+ or 1 g/liter or more in catheterized urine or midstream taken at least 2 times with 6 hours interval. Usually proteinuria develops later than hypertension and weight gain, and should therefore be considered a fairly serious sign [24].

IV. VASCULAR CELL ADHESION MOLECULE-1 (VCAM-1)

VCAM-1 is a group of immunoglobulin adhesion molecule which is a protein receptor, vascular adhesion molecule in humans has a weight of 100-110 kDa, consists of 715 amino acids (aa) type 1 transmembrane glycoprotein with characteristics of the presence of seven types of immunoglobulin C2. VCAM-1 can be identified through examination of blood, joint fluid or examination of cerebrospinal fluid [25].

Under normal conditions VCAM-1 is expressed in low levels which is induced by several cytokines (IL-1, TNF , IL-4 and IL-13). When induced VCAM-1 plays an important role in the migration of leukocytes that will express VLA-4, however the role of VCAM-1 depends on the expression status and activation of all adhesion molecules [26]. VCAM-1 is a member of the immunoglobulin (Ig) protein superfamily. VCAM-1 consists of several extracellular Ig-like domains containing a pure-associated loop, a single-type transmembrane domain, and an amino-amino-carboxyl-endus cytoplasmic domain [27].

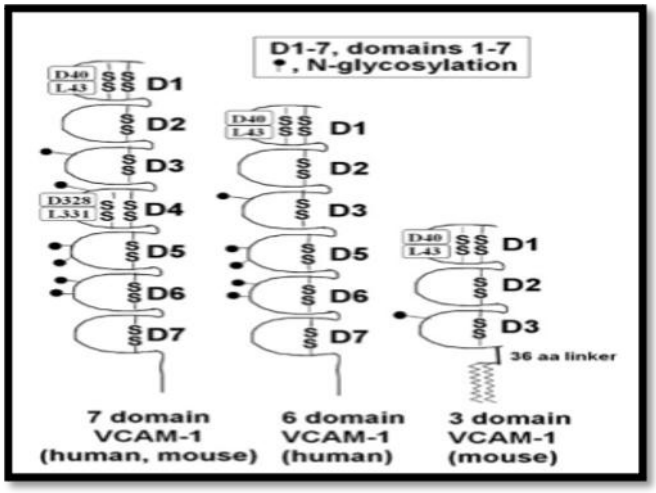

Figure 3. VCAM-1 . connector variations [27].

Human VCAM-1 has two linker variations containing six or seven immunoglobulin-like domains with disulfation linkages. The six-domain form of human VCAM-1 has no domain 4. The mouse VCAM-1 has a seven-domain form and a unique three-domain form. The three-domain form is associated with glycophosphatidylinositol via a 36-amino acid glycophosphatidyl-linker. In VCAM-1, domains 1 and 4 contain binding sites for integrins. VCAM-1 is also N-glycosylated. VCAM-1, vascular cell adhesion molecule-1 [28].

Integrin binding to VCAM-1 is regulated by the integrin activation state. a4b1 integrins bind readily to domain 1 but require higher affirmation activation to bind to domain 4. These integrins that bind to domains 1 and 4 require amino acids D40 and L43, or D328 and L331, respectively [22]. a4b7-integrin also binds to VCAM-1 (dotted arrow) but with lower affinity than its binding to other adhesion molecules, mucosal addresses on cell adhesion molecules (1 not shown). Galectin 3 binds to the N-glycosylation site on VCAM-1. VCAM-1 has six N-glycosylation sites that can participate in galectin 3 binding. VCAM-1 also coimmunoprecipitates with ezrin and moesin. Cell surface expression of VCAM-1 requires CD151 or CD9-associated tetraspanins. The long extracellular cycle of tetraspanin (LEL) is required for its binding to members of the immunoglobulin superfamily. This LEL contains CCG and CC motifs. VCAM-1 can also be cut from the cell surface by

ADAM17. ADAM8, and ADAM9. Solid arrow, major ligand binding site [24]. Dotted arrow, ligand binding requires higher integrin activation. Large gloved arrow, galectin3 binds to the N-glycosylation site. ADAM, disintegrants and metalloproteases. The mechanism by which placental ischemia leads to the clinical syndrome of preeclampsia is thought to be related to the production of placental factors that enter the maternal circulation resulting in endothelial cell dysfunction [21]. The soluble protein tyrosine kinase 1 (sFlt-1) is a protein produced by the placenta. It acts by binding to the vascular endothelial growth factor receptor (VEGF) binding domain, and also binding to placental-like growth factor (PLGF). Increased levels of these proteins in the maternal circulation result in decreased levels of free VEGF and free PLGF, with the resultant endothelial cell dysfunction. Serum and placenta levels of pregnant women are elevated in pregnancies complicated by preeclampsia above values seen during normal pregnancy[22]. Maynard and coworkers demonstrated that placental-derived VEGF receptor (sFlt1), and VEGF and PLGF antagonists, are not regulated in preeclampsia, leading to elevated systemic sflt1 levels that fall after delivery[28].

V. Conclusion

From the results of the review, it was found that the correlation between maternal age and VCAM-1 levels did not have a correlation. These results were obtained by controlling for independent variables (systolic blood pressure and diastolic blood pressure) and intermediate variables (number of pregnancies). When statistical tests were carried out without controlling for systolic blood pressure, while other variables were controlled, there was a significant correlation between maternal age and VCAM-1 levels. Then the statistical test was carried out again by controlling only the systolic blood pressure variable and the other variables were not, then the obtained correlation was also not significant from maternal age and VCAM-1 levels. These results indicate that maternal age does not affect blood pressure, both systolic and diastolic, with an increase in VCAM-1 levels in patients with preeclampsia because maternal age can only increase VCAM-1 levels if it is influenced by systolic blood pressure, not vice versa where age affects blood pressure. This causes an increase in VCAM-1 levels.

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