Article

Pathophysiology of Preeclamsia

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A B S T R A C T

The uncertainty of the etiology and underlying mechanisms of the pathophysiology of this disease makes causal structuring and primary prevention of preeclampsia impossible, making it difficult to control morbidity and mortality, both maternal and perinatal. From the many theories on preeclampsia, the disease can be classified into Placental preeclampsia, maternal preeclampsia, and Vascular Disorders of Pregnancy (VDP). Increased inflammatory response to placental factors, excessive inflammatory response to placental factors, and primary vascular disorders are the basis of distinction and also the basis of pathophysiology among the three forms of preeclampsia.

I. INTRODUCTION

Preeclampsia is defined as new-onset hypertension and proteinuria or other end-organ damage that occurs after 20 weeks of pregnancy (Phipp,s et al., 2019). Many theories have been put forward by experts about preeclampsia, so this disease is also called the disease of theories; however, the uncertainty of the etiology and underlying mechanisms underlying the pathophysiology of this disease makes causal structuring and primary prevention of preeclampsia impossible, so that morbidity and mortality are difficult to control, both maternal and perinatal (Christopher, et al., 2020).

Preeclampsia is worldwide, affecting 5-8%(Gathiram, et al., 2016; Belay and Wudad, 2019), and is responsible for 70,000 maternal deaths and 500,000 fetal deaths worldwide each year (Rana, et al., 2019). Hospital-based reports in Indonesia before the BPJS policy was implemented, especially from teaching hospitals showed the incidence of preeclampsia varied between 7.1-16.6% (Karmia, 2019).

II. DISCUSSION

II.1 Pathogenesis

Although many theories have been put forward by experts, the mechanism of pathogenesis of preeclampsia has narrowed down to the 'two-stage model' (Rana, et al., 2019; Abbas, et al., 2021), as shown in (Figure 1):

1. The first stage is abnormal placentation, which occurs in the early 1st trimester. This stage is asymptomatic, characterized by abnormal placental formation and the release of placental factors (soluble toxic factors) into the maternal circulation, leading to inflammation, endothelial dysfunction and maternal systemic disease. Failure of tropoblast invasion occurs at this stage. The uteroplacental ischemia that occurs at this stage promotes hypertension and multiorgan failure seen at the maternal syndrome stage.

2. The second stage is maternal syndrome, which occurs later in the 2nd trimester and 3rd trimester. This stage is symptomatic, causing hypertension and proteinuria, with angiospasm in the brain leading to the onset of eclampsia. This stage is found to be anti-angiogenic in excess.
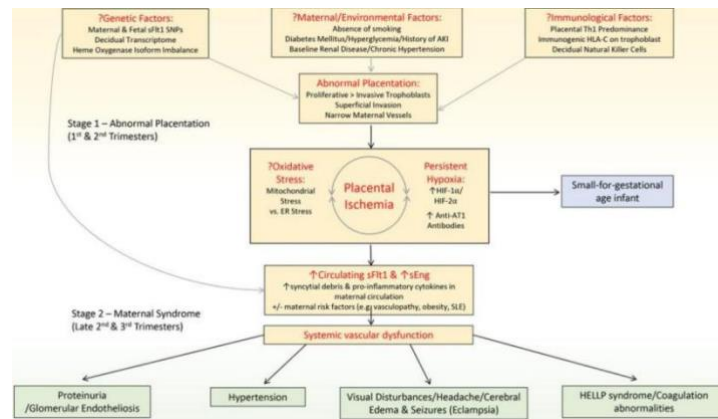

Fig 1: (Schematic of Preeclampsia Pathogenesis (Rana, et al., 2019))

From fig 1 it can be seen that whatever factors are associated with preeclampsia (genetic, environmental, immunologic), they all play a role through failure of tropoblast invasion (resulting in abnormal placentation), which occurs long before some women know they are pregnant, and long before clinical manifestations become apparent. The endothelial dysfunction that occurs is caused by circulating factors of fetal origin from the placenta (soluble toxic factors) (Christopher, et al., 2020). The clinical syndrome starts from abnormal placentation which further releases antiangiogenic markers, mediated by soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng). High levels of sFlt-1 and sEng cause endothelial dysfunction, vasoconstriction, and immune dysregulation, which negatively affect every maternal and fetal organ system (Christopher, et al., 2020).

sFlt-1 is believed to be the underlying mechanism of preeclampsia. sFlt-1 binds to and simultaneously reduces levels of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), which are very important mediators for endothelial cell function, especially in fenestrated endothelium (brain, liver, glomeruli). Meanwhile, sEng is a kind of cell surface co-receptor that binds to and simultaneously reduces the levels of transforming growth factor (TGF)-β, which normally induces cell migration and proliferation. These factors mediate downstream effects that result in endothelial dysfunction, vasoconstrictive conditions, oxidative stress, and microemboli that play a role in various organ systems and at the same time as the clinical picture of preeclampsia (Christopher, et al., 2020).

II.2 Pathophysiology

As mentioned earlier, although the causative factors of preeclampsia are different, the pathogenesis is the same and boils down to dysfunction and damage to the endothelium lining the vasculature (Cunningham, et al., 2014). Possomato-Viera and Khalil summarized the pathogenesis and pathophysiology of preeclampsia in one scheme as shown in Figure 2 below (Possomato-Viera and Khalil, 2016):
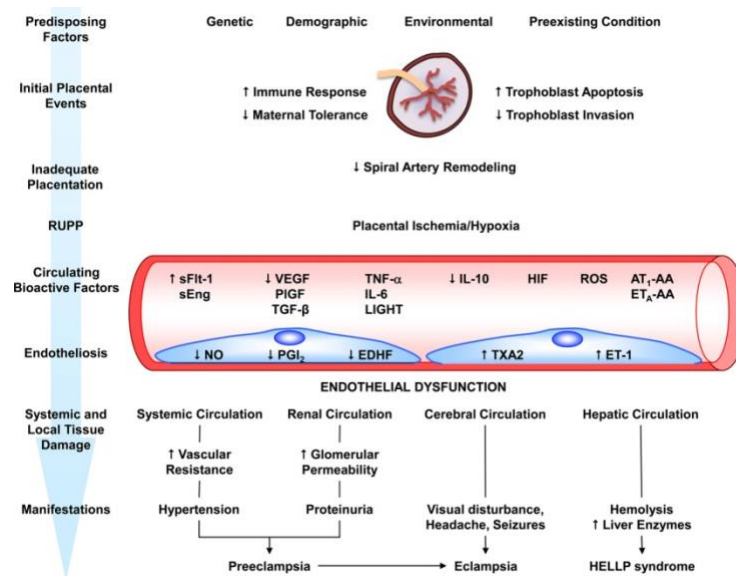

Fig 2: (Pathogenesis and Pathophysiology of Preeclampsia (Possomato-Viera and Khalil, 2016))

Genetic factors, demographic factors, environmental factors and pre-existing conditions lead to reduced maternal tolerance, increased immunologic response, increased trophoblast apoptosis, reduced trophoblast invasion, inadequate placentation (impaired spiral artery remodeling), reduced uterine perfusion pressure (RUPP) and placental ischemia or hypoxia. RUPP causes the occurrence of:

1. imbalance between antiangiogenic factors (soluble fms-like tyrose kinase-1/SFlit-1 and soluble endoglin/SEng) and proangiogenic factors (vascular endothelial growth factor/VEGF and placental growth factor/PlGF), or
2. stimulated release of circulating bioactive factors such as cytokines, hypoxia inducible factor-1/HIF-1, reactive oxygen species/ROS, angiotensin AT1 receptor agonistic autoantibodies/AT1-AA and others. These circulating bioactive factors reach the vascular endothelium and cause complete endothelial dysfunction.

Endothelial dysfunction in the systemic circulation leads to hypertension, endothelial dysfunction in the renal circulation leads to increased glomerular permeability resulting in proteinuria, endothelial dysfunction in the cerebral circulation leads to headaches, visual disturbances, and seizures, and endothelial dysfunction in the hepatic circulation leads to hemolysis and elevated liver enzymes/HELLP syndrome (Possomato-Viera and Khalil, 2016).

Redman in 1999 proposed a theory that divided preeclampsia into two parts, namely placental preeclampsia and maternal preeclampsia. This division refers to the maternal systemic inflammatory response. Maternal preeclampsia arises as a result of an excessive maternal systemic inflammatory response to placental factors (antiangiogenic factors and proinflammatory factors) that are still within normal limits. This occurs when there are chronic inflammatory conditions, such as Diabetes Mellitus, obesity, chronic hypertension, and some autoimmune conditions. In placental preeclampsia, the maternal systemic inflammatory response arises as a reaction to and is equivalent to excessive levels of placental factors. Both forms of maternal response lead to activation and complete maternal endothelial dysfunction (Staff, 2019). Maternal preeclampsia usually occurs at later gestational age, while placental preeclampsia usually occurs at an earlier gestational age. This can be seen schematically in Figure 3 below.
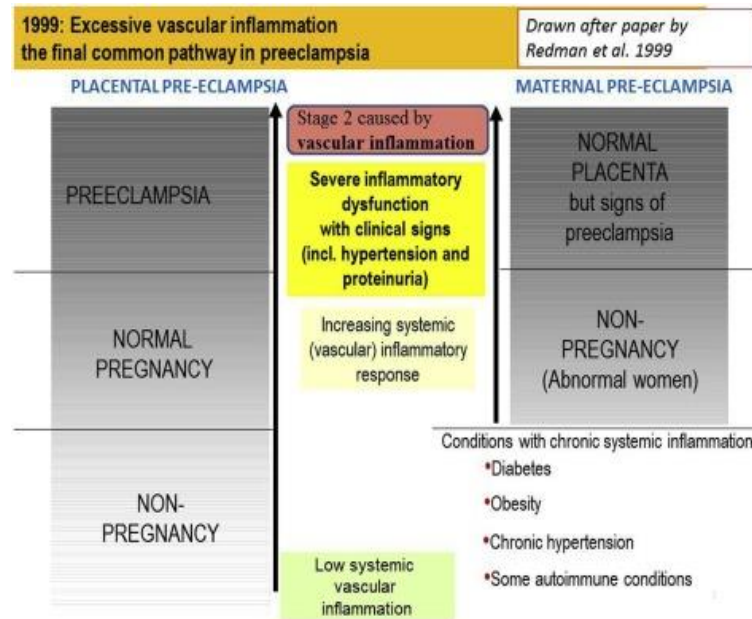

Fig 3: (Excessive vascular inflammatory response to pregnancy (Staff, 2019))

In addition, it turns out that endothelial dysfunction that occurs due to primary disorders/abnormalities within the endothelium itself (Dharmashankar and Widlansky, 2010) has the potential to cause hypertension. Hypertension due to this primary endothelial dysfunction can manifest in pregnancy and is called "vascular disorder of pregnancy" (VDP), or pregnancy vascular disorders (Michita, et al., 2018). According to Berhan, the term VDP (vascular disorders of pregnancy) is more relevant and inclusive of the underlying pathology of this disease that affects all organs and systems (Berhan, 2016). Berhan strongly believes that vascular factors are the main cause of preeclampsia, and writes that: "No Hypertensive Disorder of Pregnancy; No Preeclampsia-eclampsia; No Gestational Hypertension; No Hellp Syndrome. Vascular Disorder of Pregnancy Speaks for All" (No hypertension of pregnancy, no preeclampsia-eclampsia, no gestational hypertension, no HELLP syndrome. They are all vascular disorders of pregnancy).

Based on what Redman and Berhan stated, it can be concluded that there are three situations lead to general vasospasm (hypertension) and which further underlie the emergence of preeclampsia syndrome, namely:

1. vasoconstrictor release by placenta (endothelin, thromboxane A2, angiotensin-II and ROS) in placental preeclampsia (Staff, 2019),

2. Maternal vascular hyperresponsiveness to vasoconstrictors in maternal preeclampsia (Staff, 2019),
3. relative reduction of vasodilators (nitric oxide/NO, prostacyclin and prostaglandin E2) in VDP (Berhan, 2016).

Differences in pathophysiology have implications for differences in clinical and laboratory features, as well as differences in management and prognosis.

a. Placental Preeclampsia

The concept adopted for placenta preeclampsia is that the placenta plays a central role in the pathogenesis of preeclampsia, and the reduction in uteroplacental perfusion arising from abnormal trophoblast invasion of the spiral artery triggers a cascade of events leading to maternal distress. Schematically, the concept is shown in the following figure.
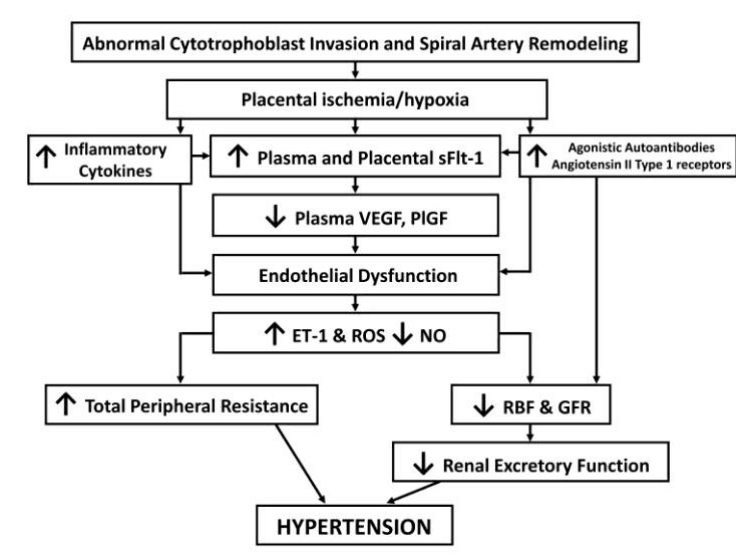

Fig 4: (Hypothetical scheme of pathophysiology of preeclampsia (Jeyabalan, et al., 2015))

Placental ischemia is thought to cause extensive maternal vascular endothelial activation/dysfunction leading to accelerated endothelin and superoxide formation, increased vascular sensitivity to angiotensin II, and reduced formation of vasodilators such as NO. These endothelial abnormalities cause hypertension through inhibition of renal-pressure natriuresis and through increased total peripheral resistance. Based on this theory, placental expulsion (termination of pregnancy) is the therapy for preeclampsia

b. Maternal Preeclampsia

In maternal preeclampsia, increased vascular tone (hypertension) may occur as part of syndrome-X. Schematically, this concept looks like in the following figure.
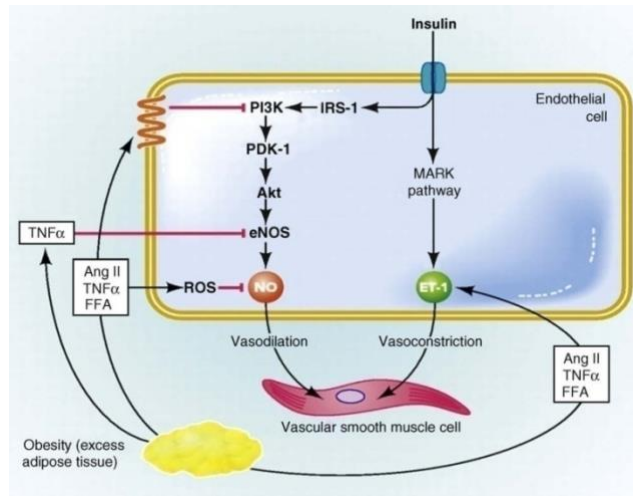

Fig 5: (Mechanism of insulin-mediated nitric oxide (*NO*) and endothelin 1 (ET-1) induced vasodilation and vasoconstriction (Jeyabalan, et al., 2015))

Excessive adipose tissue especially in visceral fat triggers an increase in adiponectin, which disrupts endothelial stability, resulting in impaired vascular tone regulation. In addition, adipose tissue activates Angiotensin II, TNF-α and FFA. All three affect two insulin-dependent pathways in endothelial cells, namely stimulating the mitogen-activated protein kinase (MAPK) pathway (which has the effect of stimulating vascular smooth muscle contraction) and suppressing the phosphatidylinositol kinase (PI3K) pathway (which has the effect of stimulating vascular smooth muscle relaxation). As a result, blood pressure increases and is followed by preeclampsia syndrome (Jeyabalan, et al., 2015).

A specific feature of endothelial dysfunction in preeclampsia (either soluble placental factors or adiponectin-induced) is reduced NO bioability. Endothelial dysfunction can lead to nitroso-redox imbalance (ROS vs NO). This state is characterized by reduced endothelium-dependent vasorelaxation (NO) (Treuer and Gonzalez, 2015). Oxidative stress can induce lekocyte and platelet adhesion to the endothelium as well as the release of cytokines and antiangiogenic factors. Adhesion of blood cells and endothelial cells is an important inflammatory process in the pathogenesis of preeclampsia. The result of this inflammatory process is vasoconstriction and increased vascular resistance (increased blood pressure) (Matsubara, et al., 2015).

c. VDP

One of the primary abnormalities in the vascular endothelium that is closely related to the incidence of VDP is the NOS3 enzyme gene polymorphism. NOS3 enzyme plays a role in NO production, where NO acts as a vasodilator, prevents platelet adherence and aggregation, reduces lekocyte adherence to the endothelium and suppresses vascular muscle cells (Matsubara et al., 2015). NOS3 enzyme controls NO production through regulation of expression or activity by NOS3 enzyme so that NO availability is maintained. Sensitivity to various vascular diseases is thought to be related to the NOS3 enzyme gene, so this gene is referred to as a "susceptibility gene". Various polymorphisms have been found in the promoters, exons and introns of the NOS3 gene. It is suspected that these

polymorphisms cause imbalances in the functions of various regulatory regions of the NOS3 gene (Salimi, 2015).

NOS3 gene polymorphisms result in downregulation of the NOS3 enzyme, resulting in reduced NO production (Salimi, 2015; Zeng, et al., 2016). SNPs of the NOS3 enzyme gene that have been intensively studied are G894T (guanine/thymine substitution at position 894 which causes the change of glutamate to aspartate at position 298 in exon 8) which results in disruption of the enzyme proteins, T-786C (thymine/cytosine substitution at position 786 of the 5'-flanking region of the promoter) which results in decreased promoter action, and VNTR (variable number of tandem repeats 4b/a polymorphism) (Salimi, 2015; Zeng, et al., 2016).

NOS3 gene SNP T-786C is the most important NOS3 gene polymorphism associated with preeclampsia (OR = 3.06 for recessive model, CC vs TC + TT), and may predispose to more severe complications such as HELLP syndrome and eclampsia (Leonardo, et al., 2015). NO production in preeclampsia is lower than that in normal pregnancy. Inhibition of NO synthesis for a long time causes conditions such as hypertension, proteinuria, thrombocytopenia and stunted fetal growth (Zeng et al., 2016). Karmia found that the NOS3 gene promoter polymorphism G-649A was more prevalent (60%) in preeclampsia whose blood pressure improved within 24 hours after the placenta was delivered (Karmia, 2019). This finding suggests that it is possible that the NOS3 G-649A gene mutant strengthens the arginine/NO pathway, so that NO production is maintained and blood pressure can recover faster.

In summary, the hypothetical scheme of pathogenesis and pathophysiology of preeclampsia can be seen as in the following figure:
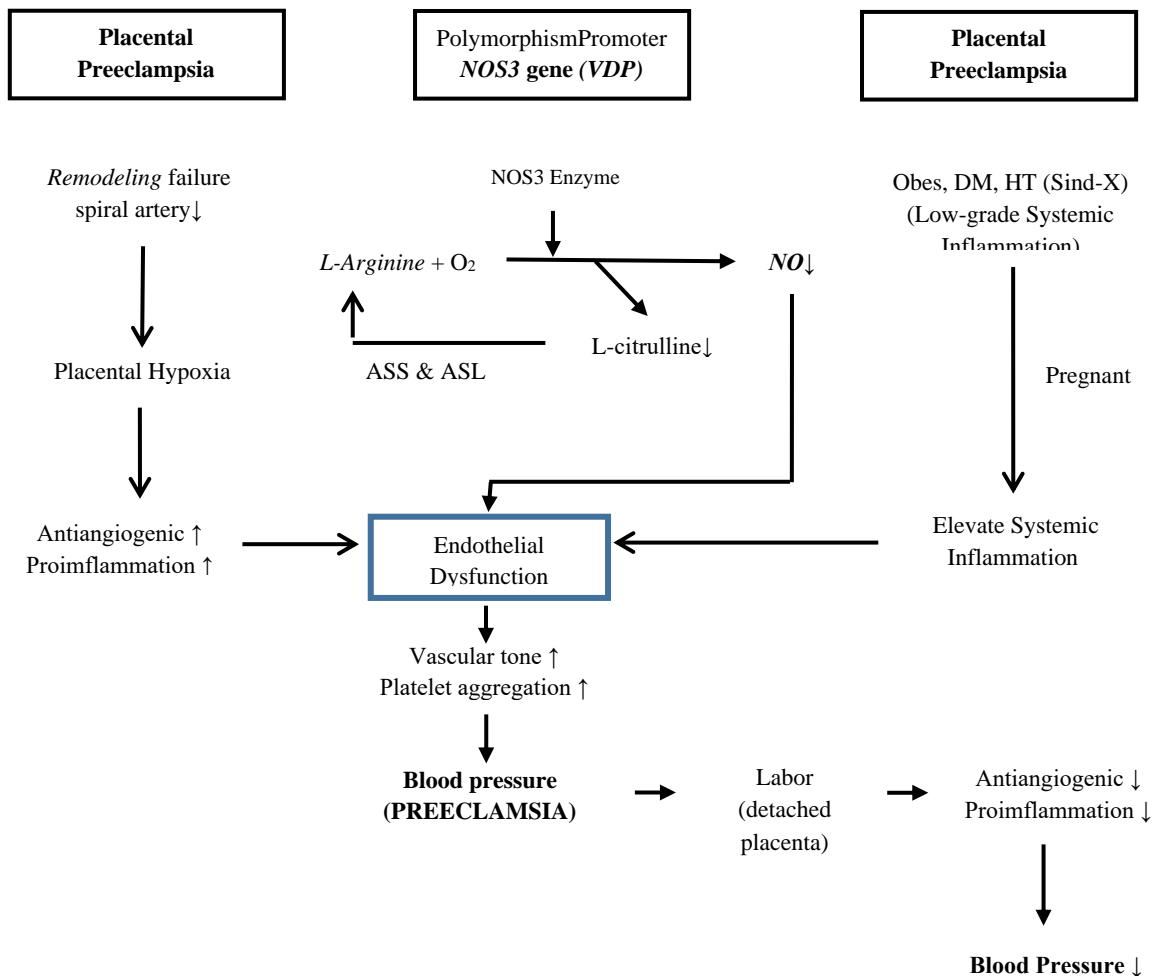
Note   ASS = argininosuccinate synthase
        ASL = argininosuccinate lyase

Fig 6: (Hypothetical scheme of pathogenesis and pathophysiology of preeclampsia)

III. CONCLUSION

The current pathogenesis of preeclampsia is the 'two-stage model', where the first stage (abnormal placentation stage) is accompanied by the release of placental factors (soluble toxic factors) into the maternal circulation, leading to inflammation, endothelial dysfunction and maternal systemic disease (hypertension and multiorgan failure) in the second stage. The second stage is maternal syndrome, which is symptomatic, causing hypertension and proteinuria, and eclampsia. At this stage there is anti-angiogenic overload.

Three situations that lead to generalized vasospasm (hypertension) and which further underlie the emergence of preeclampsia syndrome are: placental release of vasoconstrictors (endothelin, thromboxane A2, angiotensin-II and ROS) in placental preeclampsia, maternal vascular hyperresponsiveness to vasoconstrictors in maternal preeclampsia, and relative reduction of vasodilators (nitric oxide/NO, prostacyclin and prostaglandin E2) in VDPyer.

Differences in pathophysiology have implications for differences in clinical and laboratory features, as well as differences in management and prognosis.

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