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Paper 1

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A Promising Effect of Pravastatin for Reducing Preeclamsia Incidence in High Risk Pregnant Women

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ABSTRACT

Preeclamsia is still a threat in obstetrics because it is the leading cause of maternal death (15-20% in developing countries). Globally, preeclampsia causes 70,000-80,000 pregnant women to die and 500,000 babies die annually (Brennan, 2014), with increased morbidity such as prematurity and fetal growth disturbance (Sibai, 2012). The exact cause of preeclampsia is still not clearly known (also called "The disease of theory"), but recent studies shows that the imbalance of pro-angiogenic (VEGF, PlGF) and anti-angiogenic factors (sFlt-1, s-Eng) plays an important role in the pathogenesis preeclampsia. The presence of general maternal endothelial dysfunction induced by an imbalance of these factors is a major phenomenon in preeclampsia, which results in placental hypoxia / ischemia, resulting in vasoconstriction resulting in hypertension (Brennan, 2014). Termination of pregnancy is still as a definitive therapy for preeclamsia. Therefore, early prevention is necessary in the management of preeclampsia. In 2013, ACOG recommended the administration of low-dose aspirin and calcium 1 gram / day to patients in pregnant women with high risk of preeclamsia (ACOG, 2013). However, low-dose aspirin is less useful in preventing preeclampsia in patients with a history of previous chronic hypertension and not reduce the incidence of term preeclampsia (the incidence of preeclampsia at gestational age above 37 weeks) (Rolnik et all, 2017; Roberge et all, 2017). This weakness of low-dose aspirin has led to recent research focusing on the prevention of preeclampsia. The similarity between the pathogenesis mechanism of preeclampsia and cardiovascular disease makes pravastatin (a protective therapy in cardiovascular disease before) as a potential agent for preventing preeclampsia (Constantine et all, 2016). Therefore, the role of pravastatin for reducing preeclampsia incidence in high risk pregnant women will be discussed in this article.

Introduction

The incidence of preeclampsia ranges from 3-10% of pregnant women worldwide. Based on data from the East Java Provincial Health Office, the maternal mortality rate in East Java in 2016 was 91 / 100,000 live - the maternal mortality rate in East Java in 2016 was 91 / 100,000 live births with the highest cause was preeclampsia / eclampsia by 30.90% (165 people) with a trend that tends to increase in the last three years (East Java Province Health Office, 2016).

Preeclampsia is hypertension, specifically related to pregnancy with multisystem involvement, at gestational age after 20 weeks, and can overlap with other type of hypertension (superimposed). Preeclampsia is defined as hypertension that has just occurred (new onset) and proteinuria or hypertension and significant end organ dysfunction with or without proteinuria after 20 weeks of pregnancy in women which was previously normotensive. This is different from the old definition of preeclampsia which lists proteinuria as a mandatory criteria for preeclampsia (ACOG, 2013). In high-risk pregnant women, ACOG recommended low-dose aspirin and calcium 1 gram / day to prevent preeclampsia (ACOG, 2013). However, the studies showed that low-dose aspirin does not reduce the incidence of preeclampsia at gestational age more than 37 weeks (Rolnik et all, 2017; Roberge et all, 2017). Similarly, other studies, state that low-dose aspirin is not useful for preventing preeclampsia in patients with chronic hypertension (Constantine et all, 2016). Therefore, several recent studies, add pravastatin as an agent other than low-dose aspirin to prevent preeclampsia. Pravastatin was chosen because the basis of the pathogenesis of preeclampsia has a similarity to cardiovascular disease, which is the presence of systemic endothelial dysfunction (Katsi et all, 2019).

Preeclamsia

Diagnosis of Preeklamsia

Preeclampsia is a specific syndrome related to pregnancy which is marked by systolic blood pressure > 140 mmHg and or diastolic blood pressure> 90 mmHg at two measurements with intervals of at least 4 hours, which occurs at 20 weeks of gestation, in women previously known to have normal blood pressure, accompanied by proteinuria (protein levels kadar 300 mg / 24 hours). In situations which proteinuria is not obtained, ACOG defines preeclampsia as a state of hypertension accompanied by: thrombocytopenia (platelets <100,000 / mL), an increase in serum transaminases up to 2 times the normal value, renal insufficiency (serum creatinine > 1.1 mg / dL or more than 2-fold increase of serum creatinine in the absence of other kidney diseases), pulmonary edema and visual or cerebral disorders (ACOG, 2013).

Based on the onset, preeclampsia is classified into two: early type preeclampsia (early onset) and late type (late onset). Early and late onset of preeeclampsia are suspected have different clinical etiologies and manifestations. Early onset of preeclampsia occurs at less than 34 weeks' gestation. Early onset of preeclampsia is uncommon, with a prevalence of 0.38%, but it gives more severe manifestations and complications for the mother and fetus than late onset. Late onset of preeclampsia occurs after 34 weeks' gestation, and constitute 88% of all incidence of preeclampsia[10]. Placental abnormality is the main etiopathogenesis mechanism of early onset of preeclampsia, whereas predisposing to maternal cardiovascular or metabolic risk factors for endothelial dysfunction, as part of an excessive systemic inflammatory response is an etiopathogenesis mechanism from late onset of preeclampsia. This theory has been supported by pathological findings and analysis of factors circulating in blood vessels (Ornaghi et all, 2013).

Several risk factors have been identified that can increase the incidence of preeclampsia (Steegers, 2010). Risk factors that have consistently been associated with the incidence of preeclampsia are age, parity, history of preeclampsia in previous pregnancies, family history of preeclampsia, twin pregnancies and maternal medical conditions that already exist before (such as diabetes, obesity, chronic hypertension, kidney disease, thrombophilia and auto-immune diseases). The identification of risk factors is carried out at the first visit of the antenatal examination (Thangaratinam, 2011).

Pathogenesis of Preeklamsia

Preeclampsia is the end result of various possible factors including a number of factors in the mother, placenta and fetus. Etiology of preeclampsia is not definitely clearly known. Several mechanisms have been proposed to explain the cause but abnormal placentation, imbalance of angiogenic factors and endothelial dysfunction are thought to play a major role in the pathogenesis of preeclampsia (Wang et all, 2013).

According to Redman et al in 2009[1], the pathogenesis of preeclampsia consists of two stages. The first stage is abnormal placentation (occurs in trimesters one and two). Abnormal placentation can be caused by interference with cell protective factors: reduced levels of nitritoxide, reduced hemeoxygenase (HO), as well as due to oxidative stress, genetic, environmental and immunological factors, which in turn cause disturbances in the remodeling of the spiral arteries, and result in decreased maternal and fetal blood flow. Abnormal placentation will also cause decreased placental perfusion, and the result is placental ischemia. This condition causes the release of placental factors (sFlt-1, sEng, PIGF and VEGF) into the maternal circulation and cause the second stage (occurs in the third trimester). The release of these placental factors in the form of an imbalance of angiogenic factors results in a complete maternal vascular endothelial dysfunction. Endothelial dysfunction that occurs in the maternal systemic circulation cause manifestation of preeclampsia's signs and symptoms. A systemic vasoconstriction process occurs in various maternal organs. It can be said that endothelial dysfunction contributes to the overall major symptoms in preeclampsia (hypertension, edema, proteinuria and inappropriate platelet aggregation) (Phipps et all, 2016).

Management of Preeklamsia

Medical treatment for preeclampsia is still focused on clinical management in the form of management of maternal hypertension, prevention of seizures by administering magnesium sulfate and obstetric management (pregnancy termination). The termination of pregnancy becomes a new problem if the symptoms of preeclampsia appear at a gestational age that is far from term with all the morbidity and mortality. Therefore, prevention of preeclampsia incidence in high-risk pregnant women is the main focus in reducing maternal and neonatal morbidity and mortality due to preeclampsia. Early detection and screening of preeclampsia in all pregnant women through history taking, physical examination and doppler ultrasound can determine pregnant women who are at high risk for preeclampsia. For these high-risk mothers, ACOG recommends administering low doses of aspirin and calcium to prevent preeclampsia. Low-dose aspirin given to pregnant women who are at high risk of preeclampsia can reduce the incidence of preeclampsia by 10-24%, decrease the incidence of IUGR by

20%, and premature labor by 14% (Henderson et all, 2017). However, recent study states that low-dose aspirin does not reduce the incidence of preeclampsia in the term preeclampsia (gestational age> 37 weeks) and less useful in preventing preeclampsia in patients with chronic hypertension.

Pravastatin for Preventing Preeklamsia

Preeclampsia has many similarities in pathogenesis with cardiovascular disease. Both are related in the process of endothelial dysfunction, inflammatory processes and oxidative stress (Constantine et all, 2013). Both share many risk factors (such as obesity, hypertension, dyslipidemia). In addition, pregnant women who experience preeclampsia have a risk of future cardiovascular disease such as hypertension, heart disease, ischemic stroke and chronic kidney disorders[19 20]. Statins have been used as protective agents for cardiovascular disease. Because of this similarity and the ability of statin to reserve endothelial dysfunction, it has been proposed that statins can be considered as potential candidates in the prevention of preeclampsia.

Mechanism of Action

Statins are a group of lipid lowering drugs used mainly in the treatment of hypercholesterolemia. The main action of these drugs is inhibiting enzyme 3-hydroxy-3- methylglutaryl coenzyme-A-reductase, thereby decreasing cholesterol synthesis in the liver, leading to a decrease in plasma cholesterol level. They also reduce circulating LDL-cholesterol level by increasing the expression of low-density lipoprotein receptors. Beside of their action on lipid dependent effects, Statins also has a biological effect which is lipid independent. Statins could represent a new class of possible useful drugs in the management of preeclampsia based on their pleiotropic effects: statins exert a protective effect on vascular endothelial cells, induce the expression of HO-1 and inhibit cytokine mediated release of sFlt-1 in cultured placental explants. Expression of HO-1 or direct exposure to CO reduce VEGF-E-stimulated sFlt-1 release from human umbilical vein endothelial cells (HUVEC), while siRNA mediated HO-1 knockdown increases sFlt-1 release. Since serum sFlt-1 levels closely associated with severity of preeclampsia, stain use can be expected to reduce the clinical severity of preeclampsia (Cudmore, 2007; Ramma, 2014).

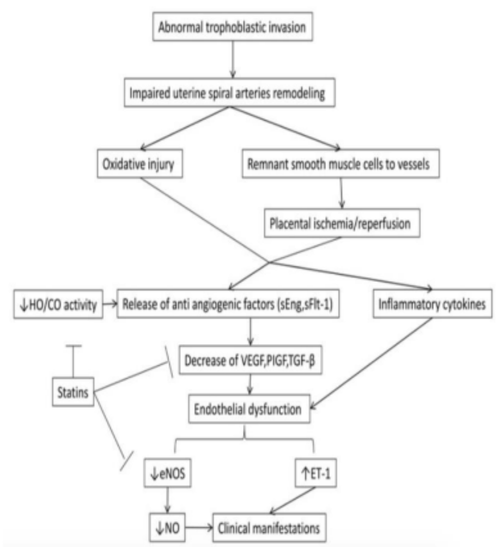

Figure 1. Action of Pravastatin for Preventing Preeclamsia (Constantine et all, 2016).

In recent studies, pravastatin was chosen as one of statin group to prevent preeclamsia because of its hydrophilic type. In animal studies, pravastatin, was shown to lower blood pressure, promote the release of VEGF, PlGF and suppress production of sFlt-1 and sEng. This mechanism cause reversing the angiogenic imbalance in preeclampsia[24]. Pravastatin also has another pleiotropic action that also help their mechanism to prevent preeclamsia such as vascular reactivity modulation, antiinflammatory effect (reducing Th1/Th2 ratio), antioxidant and antithrombotic. This process causes the protection and stabilization effect on endothel, so clinical manifestation of preeclamsia related to endothelial dysfunction can be prevented. In animal model of preeclamsia, pravastatin also shown reducing the incidence of IUGR and improving maternal outcome related to hypertension and proteinuria (Kumasawa et all, 2011; Singh et all, 2011). All biological effects of pravastatin can restore maternal endothelial dysfunction so maternal vascular reactivity can be reduced. It can prevent maternal systemic vasoconstriction so blood pressure will not be raised.

Safety Use of Pravastatin in Pregnancy

Pravastatin was chosen from various other statin drugs because of its hydrophilic nature. Its protein binding is the lowest so that drug interactions is also minimal (Lecarpentier et all, 2012). Absorption in oral administration is about 40-75%, passing the first metabolic rate at liver. Pravastatin excretion in intact form through the liver, and renal (secretion in tubules). The average absorption time is 2.4 hours with 18% bioavailability. Time to achieve maximum concentration in plasma is average an hour after oral administration. Half-life ranges from 1-3 hours (Hatanaka, 2000; Katzung et all, 2012). Because protein binding capacity of pravastatin is very low and there is no need metabolism for its elimination, so pravastatin interaction with other drugs is very minimal (Hatanaka, 2000). Only a small portion of pravastatin passes through the placental barrier, due to its hydrophilic nature, making it difficult penetrate the cell membrane. Pravastatin penetrates the placenta through active transport system, and expelled from the placenta into the maternal circulation also through active transport system which transport mechanism from fetal to maternal is faster. As much 18 ± 4% pravastatin is transferred from the maternal circulation to the fetus, then equal 13% will be returned to the maternal circulation. Ratio of fetal and maternal concentrations of 0.2. The plasma protein binding capacity for pravastatin is the lowest compared to other statins, so the increasing of synthesis protein binding in pregnancy does not affect the distribution of Pravastatin (Lecarpentier et all, 2012).

Statin are currently still categorized as X by The Food and Drug Administration (FDA), which mean this group of drugs are deemed to be contraindicated during pregnancy. These FDA recommendations were based on 2004 report in New England Journal of Medicine; a report of 178 cases, identifying 31 fetal malformations among 70 reported statin exposed pregnancies (Edison & Muenke, 2004). However, this report did not find a consistent pattern of congenital malformations in relations to the degree of lipophilic characteristics of the various statins. Importantly, the report lacked a reliable denominator of the total number of exposed cases to allow calculation of increased risk, since the report was based on retrospective studies in pregnancies resulting in neonates with congenital anomalies (Zarek & Koren, 2014). A Canadian study provided data on the risk of congenital anomalies associated with statin use during pregnancy; the study consisted of 288 pregnant women, divided into 3 groups: group A: women prescribed statins in first trimester, group B: women prescribed fibrate/nicotinic acid during first trimester, and group C: women exposed to statin between 1 year and 1 month before conception, but not during pregnancy. Among women with a live birth, the rate of congenital anomalies was 3/64 (4.69%) in group A, 3/14 (21.43%) in group B, and 7/67 (10.45%) in group C. The adjusted OR for congenital anomalies in group A compared with group C was 0.36. This study concluded no pattern of fetal congenital anomalies or evidence of an increased risk in the live born infants of women exposed to statins in first trimester[32]. The newly published systematic review and meta-analysis about pregnancy outcome following first trimester exposure to statins (review all studies until 2013), also came to reassuring conclusions: with a total of more than 800 patients (from 6 studies), the result showed no increased risk of birth defects in the statins exposed pregnancies compared with the control subject (RR 1.15; 95% CI 0.75 to 1.76). The relative risk of miscarriage was increased in the statin exposed group compared to control subjects (RR 1.35; 95% CI 1.04 to 1.75) (Zarek & Koren, 2014).

Study of Pravastatin in Pregnancy

Brownfoot and colleagues reported their experience with four patients with preterm preeclampsia (<30 week gestation) who were treated with pravastatin. The authors reported that the use of pravastatin stabilized patients' blood pressure and lowered serum sFlt-1 concentrations (Brownfoot et al, 2015). Clinical trial of pravastatin during pregnancy by Constantine showed there was potential effect of pravastatin to prevent preeclamsia. There was 20 pregnant women with high risk of preeclamsia who were divided into 2 groups: the control group who received placebo and the treatment group who received pravastatin. From the results of the study, four people became preeclampsia and 3 people became severe preeclampsia in the control group. In the treatment group that received pravastatin there was no subject became preeclampsia and only one patient had gestational hypertension (Constantine et al, 2016).

Conclusion

Preeclamsia is the most challenging obstetric complication because of its high rate of morbidity and mortality in maternal and neonatal. Many researches were done how to prevent preeclamsia in high risk women. Based on clinical trial that has been done before, there is a potential effect of pravastatin to prevent preeclamsia. But there is still important concern about long term effect of statin if it is during pregnancy because of its categorization as X category by FDA, which mean this group of drugs are deemed to be contraindicated during pregnancy. On contrary with this category, a systematic review and other trials studies about pravastatin effect in pregnancy show no increased risk of congenital abnormality. It can be believed because of hydrophilic nature of pravastatin markedly reduces its ability to cross the placenta. Although pravastatin is still a promising candidate for preventing preeclamsia in high risk women, more research is still needed to be applied worldwide.

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