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Screening Preeclampsia and the Role of Low Dose Aspirin for the Prevention of Preeclampsia

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Abstract

Preeclampsia is one of the leading causes of maternal morbidity and can affect fetal conditions such as inhibition of intrauterine growth, premature labor, placental abruption, fetal distress, and, worst of all, intrauterine fetal death. In contrast to the decreasing incidence of pregnancies with infection, preeclampsia did not decrease significantly during the past two decades. Prevention of preeclampsia is an effort that is currently being intensively carried out to reduce morbidity and mortality of pregnant women. Prophylactic administration of low-dose aspirin (81 mg/day) is recommended in women with a high risk of preeclampsia. It should be started between 12 weeks of gestation to 18 weeks (optimal before 16 weeks). Aspirin has been shown to be safe for the mother and the fetus during pregnancy. Treatment with aspirin also did not increase the risk of developing congenital malformations and had no adverse effect on fetal development or bleeding complications during the neonatal period.

Introduction

Preeclampsia is one of the leading causes of maternal morbidity and can affect fetal conditions such as inhibition of intrauterine growth, premature labor, fetal distress, placental abruption, and worst of all, intrauterine fetal death. The prevalence of preeclampsia to date has not changed significantly [1]. The World Health Organization (WHO) estimated that preeclampsia is seven times more prevalent in developing countries than in developed countries, with a prevalence of 1.8–18% versus 1.3–6% in developing versus developed countries, respectively. A study in Indonesia reported that the incidence of preeclampsia in Indonesia was 128,273/year, or around 5.3%. Preeclampsia did not decrease significantly during the past two decades. In contrast, the incidence of pregnancy with infection is decreasing [1], [2].

Prevention of preeclampsia is an effort that is currently being intensively carried out to reduce morbidity and mortality for pregnant women. The most important prevention principle in preeclampsia is to carry out primary prevention and secondary prevention. Primary prevention is by knowing the signs and symptoms of the causes of preeclampsia, such as screening for risk factors, while secondary prevention is by limiting salt consumption during pregnancy, use of low-dose aspirin, calcium supplementation at least 1 g/day. Cause of preeclampsia in pregnant women is not known with certainty so that the primary prevention is to control the risk factors of preeclampsia. Several risk factors for preeclampsia include extremes of maternal age (adolescents and women older than 40 years old), preexisting hypertension, diagnosis of preeclampsia in a previous pregnancy, obesity, diabetes, renal disease, nulliparity, multiple gestations, and preexisting autoimmune diseases, such as antiphospholipid antibody syndrome and systemic lupus erythematosus [2], [3].

Early identification of pregnancy with preeclampsia is very important by health workers at the primary healthcare level to prevent morbidity and mortality. Screening for preeclampsia risk is crucial for pregnant women from the beginning of pregnancy. Most prospective studies using maternal clinical risk factors to predict preeclampsia show relatively low performance, with only about one-third of cases predictable. In recent years, acetylsalicylic acid or aspirin has been widely reported as a regimen to prevent the onset of preeclampsia [4]. Meta-analyses have shown that early (before the 16th week of gestation) use of aspirin in low doses has reduced the risk of preeclampsia [5], [6].

Table 1: Classification of preeclampsia risks assessed at antenatal visit [2].

High risk
History of preeclampsia
Multiple pregnancy
Chronic hypertension
Type 1 or 2 diabetes mellitus
Renal Disease
Autoimmune disease (ex., systemic lupus erythematosus, antiphospholipid syndrome)
Moderate risk
Nulliparity
Obesity (body mass index >30 kg/m^2
History of preeclampsia on mother or sister
Age ≥35 years
Patient-specific history (pregnancy interval >10 years)

Screening Preeclampsia

Several recent studies have found that the combination of maternal risk factors, biochemical and ultrasound markers has the potential to predict cases of preeclampsia with higher sensitivity and specificity. According to The International Federation of Gynecology and Obstetrics (FIGO), the combination of maternal risk factors, serum placental growth factor (PlGF), mean arterial pressure (MAP), and uterine artery pulsatility index (UTPI) is the best combination that can be used to screen for preeclampsia [5], [6].

The identified risk factors can assist in assessing the risk of pregnancy at the initial antenatal visit. Based on the results of research and the latest international guidelines, the PNPK of Preeclampsia published by POGI divides the major risk factors for preeclampsia into two, namely high risk and moderate risk (Table 1) [2].

The presence of one high-risk factor or the presence of two or more moderate risk factors can be used to assist in guiding the prophylactic administration of aspirin, which is effective in reducing the risk of preeclampsia. Uterine artery Doppler ultrasound is a non-invasive method to detect changes in the early stages of decreased uteroplacental circulation. On this examination, it can be seen clearly the direction of flow in the uterine, arcuate, radial and spiral arteries around the trophoblast tissue so that various indices can be measured as needed [3], [4].

In a normal pregnancy, the systolic/diastolic ratio (S/D), pulsatility index (PI), and resistance index (RI) will decrease after 24–26 weeks of gestation, until a steady picture is achieved, namely a high and almost flat diastolic velocity picture. In the first trimester of pregnancy, the uterine artery waveform has a diastolic notch that disappears after 24 weeks of gestation. The appearance of a high impedance in the resistance index (RI > 0.58) of the uterine arteries occurs at 16–24 weeks of gestation, which is sometimes accompanied by notching at the beginning of diastole, indicates high uterine artery resistance due to vasoconstriction of uteroplacental blood vessels. If this curvature persists and the S/D, PI, RI values remain high after 24–26 weeks of gestation, it means that the pressure at the end of the uterine arteries is elevated, which usually accompanies preeclampsia or restricted fetal growth (Figure 1) [7], [8], [9].

Several research data showed that the mean uterine artery PI in early-onset severe preeclampsia and normotensive pregnancy showed significant differences. Aardema *et al*. (2004) conducted a Doppler examination to determine PI in 531 nulliparous women at 22 weeks of gestation, and the results differed significantly between pregnant women with preeclampsia or hypertension with uncomplicated pregnancies, where the PI results were increased in pregnant women with early preeclampsia in pregnancy followed by poor pregnancy outcome before 35 weeks [10]. Soares *et al*. (2007) conducted a study to determine uterine artery Doppler results during the first trimester of pregnancy. Uterine artery Doppler examination is performed at ll–14 weeks of gestation in singleton pregnant women at the University of St. George's Fetomaternal Unit in London. Soares found the mean PI in preeclampsia before 34 weeks was 1.56, while in preeclampsia after 34 weeks, it was 1.42 with a standard deviation of 0.24 [11].

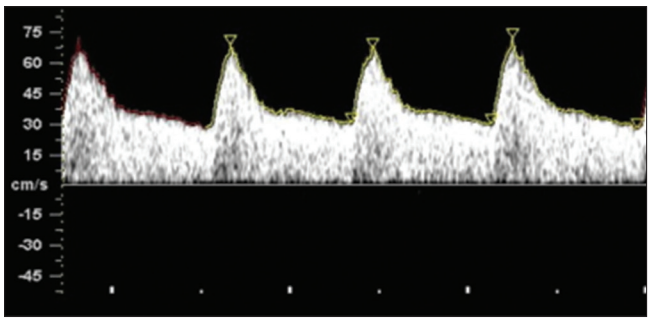

Figure 1: Normal uterine artery Doppler waves in the first trimester [9]

The findings of this study are consistent with previous studies where high uterine artery resistance in early-onset severe preeclampsia is associated with the pathogenesis of preeclampsia itself, namely the presence of abnormal trophoblast invasion in the spiral arteries and changes in the subplacental arteries blood flow (Figure 2). Whereas in normotensive pregnancies it is associated with normal uterine Doppler artery velocimetry images because there is no disruption of placental blood flow [12].

Spiral Artery Abnormal Changes

In normal pregnancy, trophoblasts invade the muscle layer of the spiral arteries, which causes degeneration of the muscle layer resulting in dilatation of the spiral arteries. Several theories are considered related to the incidence of preeclampsia, such as placental ischemia, vasospasm, hemostatic disorder followed by coagulation system activation, damage of vascular endothelial, and nitric oxide (NO) and lipid metabolism abnormalities [5]. In hypertension in

pregnancy, trophoblast cell invasion does not occur in the muscle layer of the spiral arteries and surrounding tissues. The spiral muscle layer remains rigid so that the lumen of the spiral arteries does not distend and vasodilate. As a result, the spiral arteries are relatively constricted and spiral artery remodeling fails, resulting in decreased uteroplacental blood flow, placental hypoxia, and ischemia [5], [6].

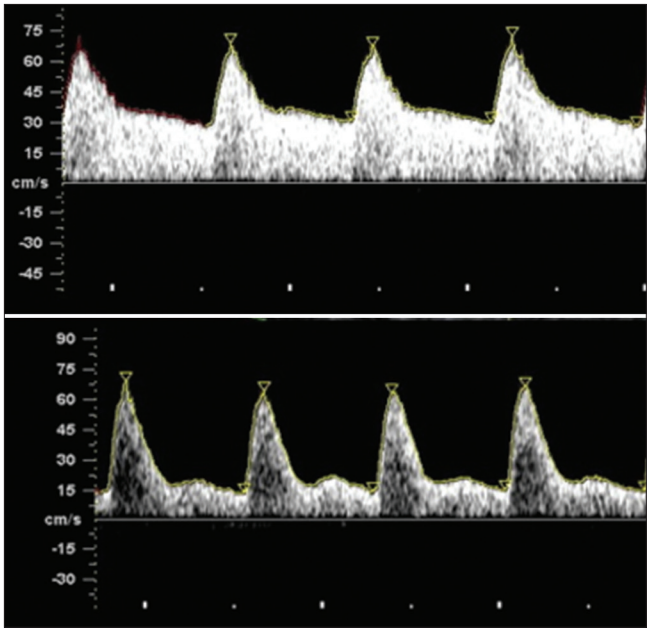

Figure 2: Abnormal uterine artery Doppler view with notch [9]

The incident of placental ischemia that causes clinical symptoms of preeclampsia is related to the production of placental factors entering the maternal circulation and therefore causing endothelial cell dysfunction. The placenta produces a protein, soluble FMS-like tyrosine kinase 1 (sFlt-1). This protein works by binding to receptors for vascular endothelial growth factor (VEGF) and placental-like growth factor (PLGF). If the levels of these proteins increase in the maternal circulation, then the levels of free VEGF and PLFG will decrease. This causes endothelial cell dysfunction. Usually, sFlt-1 levels are elevated in maternal serum and placenta in preeclamptic pregnancies than in normal pregnancies. Increased levels of sFlt-1 have also been reported to be associated with the degree of disease that occurs [5], [6].

This sustained placental ischemia will liberate toxic substances such as cytokines, free radicals in the form of lipid peroxidase in the maternal blood circulation and cause oxidative stress, a condition where the number of free radicals is more dominant than antioxidants. In the next stage, oxidative stress that occurs along with the circulation of toxic substances can stimulate endothelial dysfunction on all endothelial surfaces of blood vessels in the organs of preeclampsia patients (Figure 3) [6].

Based on the disease onset, preeclampsia is divided into two subtypes: early-onset preeclampsia, occurring before 34 weeks of gestation, and late-onset preeclampsia, occurring at 34 weeks or more. Early-onset preeclampsia is believed to have a strong association with placental dysfunction, while late-onset preeclampsia is a maternal disease. Therefore, the risk of early-onset preeclampsia is closely related to stunted fetal growth. Early-onset preeclampsia affects 2% of pregnancies and significantly contributes to maternal and perinatal morbidity and mortality [7], [8].

During normal pregnancy, there is a balance between platelet thromboxane A2 (TXA2) as a platelet activator and vasoconstrictor, and endothelial prostacyclin. This balance accounts for platelet aggregation and peripheral vasoreactivity regulation during pregnancy and maintains uteroplacental blood flow [7]. In preeclampsia, platelet TXA2 levels significantly increase, whereas prostacyclin levels are markedly decreased. This imbalance appears from 13 weeks of gestation in high-risk patients. TXA2/PGI2 imbalance can be treated with low-dose aspirin [6], [7].

Aspirin

Aspirin or acetylsalicylic acid inhibits the platelet cyclooxygenase (COX)-1 enzyme irreversibly, acts to suppress TXA2 formation, and is a potent activator of vasoconstriction and platelet aggregation. Aspirin can interfere with platelet aggregation by irreversibly inactivating the platelet cyclooxygenase (COX) enzyme. The presence of TXA2 activation can be mediated through COX-1. Aspirin is able to inhibit COX-1, so it can improve the balance of thromboxane A2/prostacyclin. COX-2 is also involved in increased sensitivity to angiotensin II, immune system activation, and increased oxidative stress during preeclampsia.

Aspirin also has anticoagulant and anti-inflammatory properties that play a role in preventing preeclampsia. If given at the beginning of the second trimester (<16 weeks of gestation), low-dose aspirin inhibits platelet aggregation and promotes vasodilation. This pharmacological property results in increased uteroplacental blood flow. The debate over indications of aspirin in the prevention of preeclampsia was rediscussed in 2014 by the US Preventive Services Task Force (USPSTF). It aims to update the guidelines of the American Congress of Obstetricians and Gynecologists (ACOG) 2002 [7], [8]. The efficacy of low-dose aspirin administration in preeclampsia prevention in high-risk patients and in reducing adverse events during the perinatal period was revisited to update clinical practice guidelines and prescribing in obstetrics. The recommendations are based primarily on a recent meta-analysis. The USPSTF recommends that prophylactic low-dose aspirin be considered for women with more than one moderate preeclampsia risk factors [8], [13].

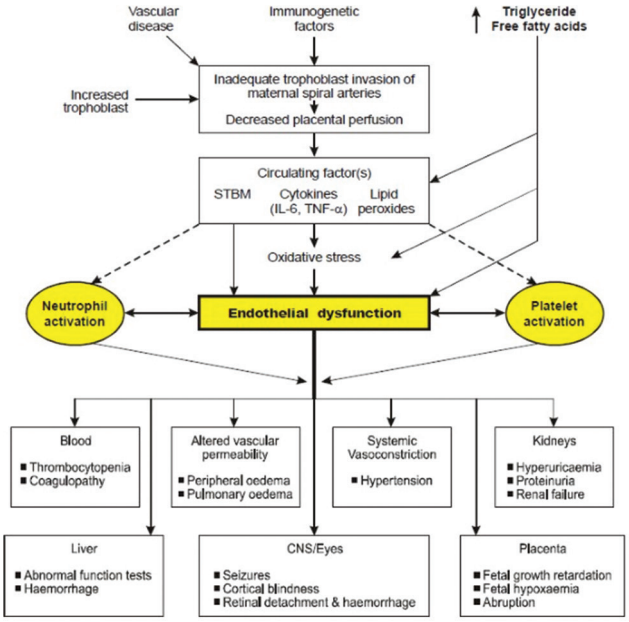

Figure 3: Organ dysfunction in preeclampsia [6]

Based on the National Guidelines of Medical Service (PNPK) on the diagnosis and management of preeclampsia, published by the Indonesian Obstetrics and Gynecology Association (POGI), several conclusions were obtained in the use of aspirin, namely [2]:

1. Low-dose aspirin use for primary prevention is associated with a reduced risk of preeclampsia, preterm delivery, and fetal, neonatal, or small infant death during pregnancy. In contrast, its use for secondary prevention reduces the risk of preeclampsia, preterm delivery <37 weeks, and birth weight <2500 g.
2. Preventive effect of aspirin was more pronounced in the high-risk group.
3. There are no data showing any difference between aspirin administration before and after 20 weeks.
4. Administration of high-dose aspirin is better at reducing the risk of preeclampsia, but the resulting risk is also higher.

Based on these conclusions, POGI recommends the use of aspirin in the following patients [2]:

1. Low-dose aspirin (75 mg/day) is recommended for preeclampsia prevention in high-risk women (Level evidence II, Grade A recommendation).
2. Low-dose aspirin should be initiated before 20 weeks gestational age (Level evidence III, Grade C recommendation).

The Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE), a double-blind, randomized, placebo-controlled trial, identified patients at high risk of preeclampsia at 11–14 gestational weeks using the Fetal Medicine Foundation (FMF) screening test. Comparisons were made between aspirin (150 mg/day at bedtime) and placebo in high-risk patients from 11–14 to 36 gestational weeks. The results showed a significant decrease of 62% in the incidence of premature preeclampsia [4], [5].

Aspirin use during pregnancy is likely safe for both the mother and fetus. Treatment with aspirin has not been shown to increase the risk of developing congenital malformations and has neither adverse effects on fetal development nor cause bleeding complications in the neonates [14]. Although adverse effects, such as vaginal bleeding and gastrointestinal symptoms, are reported in a small subset of patients (10%), there is no evidence of an increased risk of bleeding in the mother, and unrelated to the incidence of placental abruption [4]. There have also never been reports regarding premature closure of the fetal arterial canal.

Research conducted by Rachmi (2016) examined the effect of giving aspirin 125 mg/day, namely 500 mg Acetosal tablets divided into four parts (available at the puskesmas) on decreasing uterine artery vascular resistance in pregnant women. Ultrasound Doppler velocimetry of abnormal uterine arteries at the gestational age of 16–24 weeks [13]. The results showed that ultrasound Doppler velocimetry of the uterine arteries after giving aspirin 125 mg/day for 4 weeks in pregnant women. The results obtained were 76 subjects with uterine artery Doppler ultrasound which became normal and 23 subjects remained with abnormal ultrasound results (20 level I and 3 pregnant women level III). This study showed that low-dose aspirin could significantly reduce uterine artery resistance, with $p = 0.0001$ ($p < 0,05$) and is effective for reducing abnormal uterine artery resistance in pregnant women aged 16–24 weeks [13], [15].

A recent meta-analysis report by Van Doorn *et al*. (2021) evaluated the effect of aspirin dose on preeclampsia incidence at all ages. In premature preeclampsia, women who were assigned to a 150 mg dose randomly, had a significantly reduced risk of preeclampsia by 62% (RR = 0.38; 95% CI: 0.20–0.72; $p = 0.011$). Aspirin doses of <150 mg did not significantly reduce the risk of preeclampsia. The number needed to treat (NNT) with 150 mg aspirin was reported to be 39 (95% CI: 23–100). There is a maximum 30% reduction in preeclampsia risk at all gestational ages and with all aspirin doses [16].

Conclusion

Preeclampsia is one major cause of maternal and perinatal morbidity and mortality. Early diagnosis during routine antenatal and natal examinations and prompt, appropriate management are essential to prevent morbidity and mortality. Screening is carried out on every pregnant woman to classify patients with high-risk and moderate-risk of preeclampsia. Low-dose aspirin administration has been widely reported

as a preventive measure in patients at high risk of preeclampsia. The use of aspirin is safe for the mother and fetus during pregnancy. The US Preventive Services Task Force (USPSTF) and ACOG recommended low-dose aspirin (81 mg/day) for high-risk women, initiated between 12 and 28 weeks of gestation (optimally before 16 weeks) and continued daily until delivery. Recent studies published that aspirin 150 mg/day can reduce early-onset preeclampsia incidence by more than 50%.

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