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The Role of Aspirin in the Prevention of Preeclampsia (A Mini Review)

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ABSTRACT
Preeclampsia is a severe pregnancy complication characterized by hypertension and proteinuria after 20 weeks of gestation. It is a leading cause of maternal and neonatal morbidity and mortality worldwide. Low-dose aspirin has been widely studied as a preventive measure for pre-eclampsia in high-risk women. This paper explores the role of aspirin in preventing preeclampsia, its mechanisms of action, and the effectiveness of different dosages and administration times. Studies have shown that aspirin, when taken before 16 weeks of gestation at a dosage of at least 100 mg per day, significantly reduces the risk of severe and early-onset preeclampsia. However, adherence to aspirin therapy remains a challenge, particularly among socioeconomically disadvantaged women. Increased education and healthcare access are crucial to optimizing the benefits of aspirin in preventing preeclampsia.
Keyword: Preeclampsia, Hypertension, Proteinuria, Aspirin

ABSTRAK
Preeklampsia adalah komplikasi kehamilan yang serius yang ditandai dengan hipertensi dan proteinuria setelah usia kehamilan 20 minggu. Kondisi ini merupakan salah satu penyebab utama morbiditas dan mortalitas ibu serta bayi di seluruh dunia. Aspirin dosis rendah telah banyak diteliti sebagai tindakan pencegahan preeklamsia pada wanita berisiko tinggi. Artikel ini membahas peran aspirin dalam pencegahan preeklampsia, mekanisme kerjanya, serta efektivitas dosis dan waktu pemberian yang berbeda. Penelitian menunjukkan bahwa aspirin yang dikonsumsi sebelum usia kehamilan 16 minggu dengan dosis minimal 100 mg per hari secara signifikan menurunkan risiko preeklampsia berat dan dini. Namun, kepatuhan terhadap terapi aspirin masih menjadi tantangan, terutama di kalangan wanita dengan kondisi sosial ekonomi rendah. Peningkatan edukasi dan akses layanan kesehatan sangat penting untuk mengoptimalkan manfaat aspirin dalam pencegahan preeklampsia.
Kata kunci: *Preeklampsia, Hipertensi, Proteinuria, Aspirin*

Preeclampsia is one of the serious complications in pregnancy characterized by hypertension and the presence of protein in the urine after 20 weeks of gestation [1]. This condition can cause severe complications for the mother and fetus, including eclampsia, HELLP syndrome [2], fetal growth disorders, and maternal and infant mortality [3], [4]. According to WHO data, preeclampsia contributes to more than 70,000 maternal deaths and 500,000 infant deaths worldwide every year.

One of the strategies to prevent preeclampsia that has been extensively researched is the use of low-dose aspirin [5]. Aspirin has antiplatelet and anti-inflammatory properties that are believed to improve placental function and reduce the risk of preeclampsia in mothers with high risk factors. Several clinical studies and meta-analyses have shown that aspirin is effective in lowering the incidence of preeclampsia if administered at the right time at the appropriate dose [6], [7], [8].

Although many studies have confirmed the effectiveness of aspirin in preventing preeclampsia, there are still some gaps in research that need to be explored further. One of them is the difference in response to aspirin therapy based on genetic factors, maternal health conditions before pregnancy, and the influence of optimal dose in different populations. In addition, the constraints in patient compliance, especially in groups with limited access to health services, are a major challenge that has not been fully resolved [9], [10], [11]. Therefore, more research is needed to develop more effective strategies in improving patient adherence to aspirin therapy, including better educational approaches and more accessible distribution systems for communities with socioeconomic limitations [6].

2. The mechanism of action of aspirin

Low-dose aspirin has been recommended as a preventive therapy for preeclampsia for high-risk pregnant women [8]. The mechanism of action of aspirin in preventing preeclampsia is related to its pharmacological properties as an antiplatelet, anti-inflammatory, and placental perfusion enhancer agent [4], [8].The following is a more detailed description of this mechanism:

Antiplatelet effects

Preeclampsia is often associated with endothelial dysfunction and platelet hyperactivity, leading to increased blood coagulation as well as impaired circulation to the placenta [12]. Low-dose aspirin works as an antiplatelet by inhibiting the enzyme cyclooxygenase-1 (COX-1), which is responsible for the production of thromboxane A2 (TXA2) [8], [13]. Thromboxane A2 is a mediator that causes vasoconstriction and platelet aggregation [8], [11]. Aspirin inhibits COX-1 irreversibly, thereby decreasing the production of TXA2 [8]. As a result, there is a decrease in platelet aggregation and increased vasodilation, which helps prevent the formation of blood clots and improves blood flow to the placenta [8], [10]. This effect is especially important in pregnant women at risk of preeclampsia because this condition is often associated with blood hypercoagulability which can worsen placental hypoxia [7], [10].

Anti-inflammatory effects

Excessive systemic inflammation in pregnancy can contribute to the development of preeclampsia. Low-dose aspirin has anti-inflammatory properties that play a role in reducing inflammation that occurs during pregnancy. Aspirin inhibits cyclooxygenase-2 (COX-2), which is responsible for the production of pro-inflammatory prostaglandins [7]. By reducing pro-inflammatory prostaglandins such as prostaglandin E2 (PGE2), aspirin can reduce systemic inflammation and prevent endothelial dysfunction that triggers preeclampsia [10]. Aspirin also increases the production of lipoxin and resolvin, which are anti-inflammatory compounds that help regulate the body's immune response to inflammation [7]. High inflammation during pregnancy can lead to disturbances in endothelial function and increased blood pressure, which is characteristic of preeclampsia. By reducing inflammation, aspirin can help maintain vascular balance and reduce the risk of complications [13].

Increased Placental Perfusion

Disruption of blood circulation to the placenta is one of the main causes of preeclampsia. Aspirin can increase placental perfusion through several mechanisms, including: Vasodilation and Prostasykline Regulation. In addition to inhibiting A2 thromboxanth, aspirin also increases the production of prostacline (PGI2), which is a powerful vasodilator [8], [11]. Increased prostacycline helps dilate blood vessels and increases blood flow to the placenta [7]. Thus, aspirin helps prevent placental ischemia, which is one of the main factors in the pathogenesis of preeclampsia [8]. Increased Angiogenesis (Formation of Blood Vessels). Aspirin plays a role in increasing levels of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), which play a role in placental angiogenesis [10], [13]. Good angiogenesis is essential to ensure optimal placental development and adequate delivery of nutrients and oxygen to the fetus [10]. Angiogenesis disorders often occur in mothers at risk of preeclampsia, so the effect of aspirin in increasing blood vessel formation is very beneficial [14]. Reduction of Endothelial Dysfunction. Preeclampsia is often caused by impaired endothelial function, leading to an imbalance between the vasodilator (prostacycline) and vasoconstrictor (thromboxane A2) [8]. By lowering A2 thromboxan and increasing prostacycline, aspirin improves endothelial function and reduces maternal blood pressure [8], [11]. Better endothelial function also helps prevent hypertension that occurs due to preeclampsia [8], [14].

Studies have shown that the timing of aspirin administration greatly affects its effectiveness in preventing preeclampsia. Before 16 weeks of pregnancy, aspirin is more effective when given early, because in the first trimester there is a process of remodeling the blood vessels of the placenta [10]. Aspirin helps prevent placental insufficiency early in pregnancy development [15]. Studies show that aspirin reduces the risk of premature and severe preeclampsia by up to 40% if taken before 16 weeks of pregnancy at a dose of at least 100 mg per day [15]. After 16 weeks of pregnancy, the effectiveness of aspirin is reduced if given late because

the process of forming placental blood vessels is almost complete [9]. However, aspirin may still provide benefits for women with high risk factors, especially in preventing mild to moderate preeclampsia [16], [17].

3. Aspirin Dosage and Time of Administration

The effectiveness of aspirin is highly dependent on the timing of its administration. Based on recent research, aspirin should be given before 16 weeks of pregnancy, because during this period the formation of placental blood vessels is still ongoing [8]. If given after 16 weeks, its effectiveness in preventing preeclampsia decreases significantly. The recommended dosage varies between 75 to 150 mg per day, depending on the guidelines of each country. Studies show that ≥ doses of 100 mg per day are more effective in lowering the risk of severe preeclampsia than lower doses [9].

Some factors that can influence the success of aspirin in preventing preeclampsia include the effectiveness of aspirin depends on regular daily consumption [10]. Low-dose aspirin that is less than 100 mg per day may be less effective [11]. Women with low socioeconomic status tend to have more limited access to health, which can affect optimal aspirin use [3], [7]. Studies indicate that aspirin taken at night has a greater effect on reducing the risk of preeclampsia than morning administration. Platelet aggregation activity is higher in the early morning, taking aspirin at night may better inhibit thromboxane production [18].

According to ACOG and USPSTF , aspirin is recommended for high-risk mothers, namely is history of preeclampsia in previous pregnancies, twin pregnancies, chronic diseases such as hypertension, diabetes mellitus, or kidney disease, autoimmune diseases such as lupus or antiphospholipid syndrome, body mass index (BMI) ≥30 kg/m². In addition, mothers at moderate risk, such as primigravida or age ≥35 years, may also consider taking aspirin if there is more than one risk factor [19].

4. Pathophysiology of Preeclampsia

The pathophysiology of preeclampsia involves a variety of complex mechanisms, especially placental dysfunction and vascular system disorders. Here are the main stages of the pathophysiology of preeclampsia. In normal pregnancy, the cells of the placental trophoblasts will invade the mother's spiral artery, causing vasodilation and increased blood flow to the placenta [8]. However, in preeclampsia occurs incomplete trophoblastic invasion cause the spiral artery remains narrow and undergoes remodeling [8], [20], [21]. Placental ischemia and hypoxia cause the release of pro-inflammatory and antiangiogenic factors [8].

As a result of placental hypoxia, there is an increase in the release of factors that disrupt the balance of angiogenesis. And then sFlt-1 (soluble fms-like tyrosine kinase-1) inhibit VEGF (Vascular Endothelial Growth Factor) and PlGF (Placental Growth Factor), causing endothelial dysfunction [13], [16]. Endothelin-1 acting as systemic vasoconstriction that increases blood pressure [16]. Pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) cause immune cell activation and oxidative stress [13], [14]. As a result of the imbalance of angiogenic factors, occurs systemic vasoconstriction increased peripheral vascular resistance causing hypertension [8]. Endometrial dysfunction cause capillary leakage leading to proteinuria and edema [10], [16]. Platelet activation and coagulation an increased risk of thrombosis and HELLP syndrome (Hemolysis, Elevated Liver Enzymes, Low Platelets) [2], [10], [12].

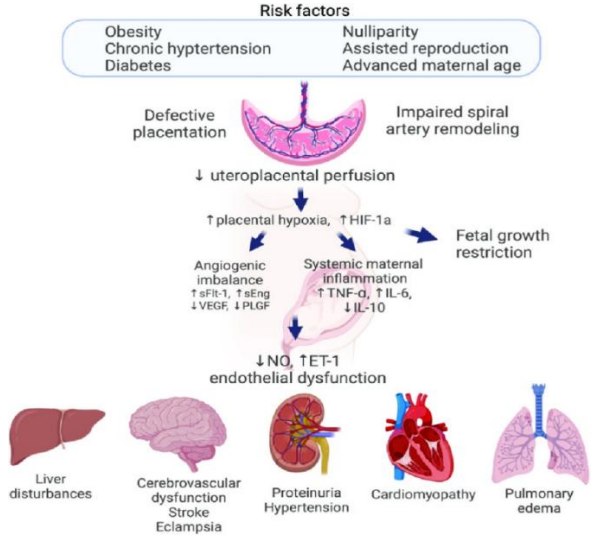

Figure 1. Schematic of pathways leading to the development of preeclampsia [22]

The effects of hypertension and endothelial dysfunction cause various complications in the organ. In the kidney occurs glomerular endotheliosis cause proteinuria and kidney failure [10]. In the liver occurs periportal necrosis cause epigastric pain and increased liver enzymes [10]. In the brain occurs cerebral edema cause headaches, visual impairment, and eclampsia (seizures) [12], [13], [17]. In the heart occurs increased afterload cause risk of heart failure [4], [15] (See Fig.1).

5. The Role of Aspirin in the Prevention of Preeclampsia

Low-dose aspirin (typically 75–150 mg per day) has been recommended by various health organizations, including the American College of Obstetricians and Gynecologists (ACOG) and the WHO, for women at high risk of preeclampsia [3], [7], [14], [23]. Initiation between 12–16 weeks of gestation (ideally before 16 weeks). Discontinuation around 36 weeks of gestation or before delivery to minimize the risk of postpartum hemorrhage [24].

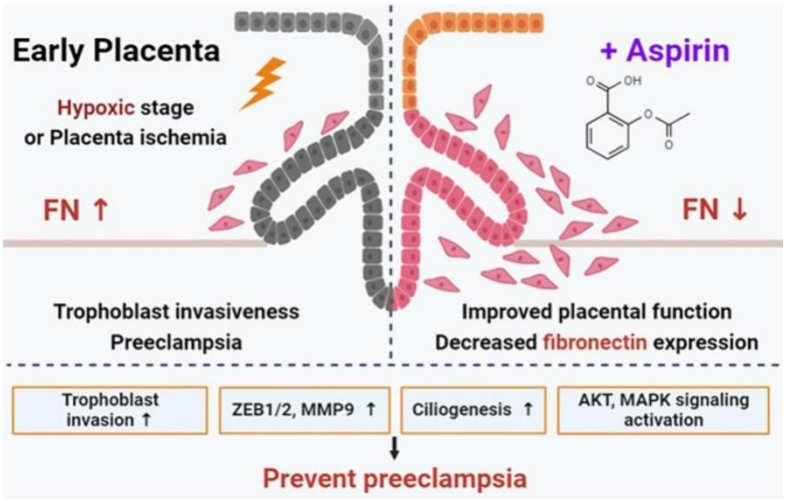

Figure 2. Aspirin's Mechanism in Preventing Preeclampsia [25].

Fibronectin, especially total fibronectin (tFN) and plasma fibronectin (pFN), saw a significant increase in women with preeclampsia compared to normal pregnancies. An increase in fibronectin is related to endothelial dysfunction, which leads to vascular leakage and edema. Inflammation of the placenta, which triggers increased synthesis of fibronectin. Invasive disorders of trophoblasts, which inhibit the remodeling of spiral arteries. An increase in fibronectin is also associated with increased proteinuria and systemic vascular disorders, making it one of the indicators of severe preeclampsia [26] (See Fig.2).

Aspirin inhibits the enzymes cyclooxygenase-1 (COX-1) and COX-2, which causes decreased production of vasoconstrictor thrombosan A2 (TXA2) and platelet proaggregation. Increased prostacycline (PGI2) which is a vasodilator and anti-platelet aggregation The imbalance between TXA2 and PGI2 contributes to increased expression fibronectin in preeclampsia. By reducing TXA2 and increasing PGI2, aspirin helps maintain endothelial function and suppresses fibronectin expression [27].

Aspirin has an anti-inflammatory effect that helps reduce endothelial activation and oxidative stress, which is a major factor in the increase in fibronectin. Aspirin works with inhibits transcription factor NF-κB, which reduces the expression of proinflammatory cytokines such as TNF-α and IL-6. Reduces the production of reactive oxygen species (ROS) that trigger endothelial damage and increases fibronectin [28]. By suppressing inflammation, aspirin decreases the expression of fibronectin induced by inflammatory cytokines.

Preeclampsia is associated with impaired angiogenesis, which leads to an inadequate invasion of trophoblasts into the spiral arteries. Aspirin increases angiogenic factors such as VEGF and PlGF, which improves spiral artery remodeling. Reduces placental hypoxia, which is a trigger for increased fibronectin. Restores vascular homeostasis and reduces the release of fibronectin into the maternal circulation [29]. Aspirin strengthens the function of the endothelial barrier by increasing the production of nitric oxide (NO) and prostasiclin, which reduces vascular permeability. Inhibits the release of fibronectin due to endothelial dysfunction. Lowers the risk of proteinuria and edema which is often associated with increased fibronectin [30].

6. Recent Research Results

Population-based studies in France show that aspirin can reduce the risk of severe and premature preeclampsia by 40%, especially if given before 16 weeks of pregnancy at a dose of ≥ 100 mg per day [2], [13]. However, adherence to aspirin use remains a challenge, especially in communities with limited access to health services.

7. Conclusion

Low-dose aspirin is an effective preventive therapy for preeclampsia, especially for women with high risk factors. Aspirin administration before 16 weeks of pregnancy at a dose of ≥ 100 mg per day has been shown to significantly reduce the risk of severe and premature preeclampsia. However, the success of this therapy depends on patient compliance as well as access to adequate health services. Therefore, education to medical personnel and pregnant women about the importance of using aspirin in the prevention of preeclampsia needs to be increased to reduce the incidence and adverse effects of preeclampsia.

Further studies are needed to explore other biomarkers that can more accurately predict responses to aspirin, in addition to fibronectin. More research is needed to evaluate whether personalized dosage (based on weight or genetic factors) can be more effective in preventing preeclampsia. Further studies are needed to understand how aspirin interacts with maternal metabolism, insulin resistance, and autoimmune diseases, which also contribute to the pathogenesis of preeclampsia. The combination of aspirin with other therapies, such as low-dose heparin or nutritional supplements (arginine, antioxidants), needs to be further researched to optimize the prevention of preeclampsia.

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