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Prevention of Preeclampsia

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Abstract

Preeclampsia is an obstetric disorder that affects 3–8% of pregnant women and remains a leading cause of short- and long-term neonatal and maternal morbidity and mortality. Professional societies recommend the use of low dose aspirin to prevent preeclampsia in high-risk women. However, interest in prevention of this disease and better understanding of its pathophysiology have led to growing research on other agents. This review focuses on the main therapeutic agents evaluated or in use for preeclampsia prevention.

Keywords

Preeclampsia; Aspirin; Statin; Metformin; Esomeprazole; Pregnancy

Introduction, Epidemiology, and Risk Factors

Preeclampsia is a multisystem disorder that affects 3–8% of pregnancies in the US and 1.5 and 16.7% worldwide, and results in 60,000 maternal deaths and >500,000 preterm birth worldwide each year. Geographic, social, economic, and racial differences may explain the different rates of preeclampsia seen in different populations. Worldwide, preeclampsia is the second leading cause of maternal death, with estimates of at least 16% among low-middle income countries up to more than 25% in certain countries in Latin America[1–3].

Preeclampsia is characterized by new-onset hypertension which usually occurs after 20 weeks' gestation, and evidence of end-organ dysfunction[3]. The end-organ disease resulting from the preeclampsia is varied, and can include proteinuria, acute kidney injury, hepatic dysfunction, hemolysis, thrombocytopenia, and – less frequently – liver rupture, seizures (eclampsia), stroke, and death[4]. There are a number of risk factors for developing preeclampsia such as history of preeclampsia in a prior pregnancy, diabetes, hypertension, obesity, and multiple pregnancy[3]. The reported incidence of preeclampsia for twin gestation ranges from 8–20% and for triplets' ranges from 12–34%, however if the index pregnancy affected by preeclampsia was a multiple gestation, the risk of recurrence in a subsequent pregnancy is lower than if the index pregnancy was a singleton (6.8% vs. 14.1%, $p < 0.001$)[5,6].

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Preeclampsia remains a major cause of maternal mortality and morbidity including seizures, acute kidney injury, pulmonary edema, severe hypertension, cerebrovascular events, and liver injury[3]. However, the consequences of preeclampsia are long-arching, and preeclampsia has been associated with an increased risk of future maternal cardiovascular, metabolic, and cerebrovascular diseases and premature mortality[7]. Preeclampsia is also associated with adverse neonatal outcomes, usually secondary to iatrogenic preterm delivery and increased risk of fetal growth restriction and placental abruption. These include respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, neonatal intensive care units (NICU) admission, neurodevelopmental delay, and fetal or neonatal death[8].

The adverse intrauterine environment associated with preeclampsia is thought to contribute to the association between maternal preeclampsia and childhood and adult chronic disease in the offspring, such as obesity, diabetes, hypertension, and neurodevelopmental abnormalities [9,10]. Due to the above adverse outcomes, preeclampsia adds a substantial financial burden on the health care system in the United States, estimated more than $1.03 billion in maternal costs and $1.15 billion in infant costs, in the first year after delivery [11].

The only current cure for preeclampsia is delivery of the placenta and fetus, however this is commonly associated with iatrogenic preterm delivery. In an effort to prevent that and improve outcomes for mothers, children and adult offspring, research efforts are currently focused not only on treatment of preeclampsia, but on ways to prevent preeclampsia from occurring. Recent advances in understanding the pathogenesis of preeclampsia and need to reduce its short- and long-term morbidities, led to research in novel agents for either the prevention or treatment of preeclampsia. These include agents such as anti-digoxin antibodies, antithrombin, relaxin, proton pump inhibitors, 3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibitors (statins), use of apheresis and others. Discussion of all these therapeutics is beyond the scope of this paper, which will review the most promising therapeutics aimed at prevention of preeclampsia, including aspirin, statins, metformin, and esomeprazole.

Pathophysiology of Preeclampsia

While not fully understood, the pathophysiology of preeclampsia is likely a multifactorial combination of genetic and environmental factors, and abnormal placentation[3,12]. The genetic and environmental components to the disease are evident by epidemiological studies suggesting a hereditary component to preeclampsia, and an apparent contribution of risk factors such as low socioeconomic status, maternal obesity and geographical variations to the risk of preeclampsia. [1,3,13].

Contemporary evidence suggests that preeclampsia is a two-stage disease. The first stage is an early pregnancy asymptomatic stage, resulting from poor placentation due to abnormal trophoblast invasion and spiral artery remodeling. This results in the second stage of the disease, characterized by a placental ischemia/reperfusion injury and a maternal immune-mediated response. Consequently, there is a release of anti-angiogenic factors and placental debris into the maternal circulation and an inadequate release of pro-angiogenic factors. This

leads to an angiogenic imbalance, immune-mediated exaggerated inflammatory response, and endothelial cell dysfunction which result in enhanced platelet aggregation, abnormal activation of the coagulation system, and increased systemic vascular. The overall consequence of this cascade is the clinical manifestations such as elevated blood pressure, proteinuria and other end-organ injury [3,12,14,15]. The poor placentation results in abnormal fetal perfusion, which is evident by abnormal uterine artery blood flow and a 22.2% incidence of fetal growth restriction in pregnancies affected by preeclampsia, especially among preterm gestations [16,17]. This abnormal perfusion is often seen on uterine artery Doppler evaluation as notching. However, the utility of this finding to predict preeclampsia is limited[17].

The placental anti-angiogenic factors most commonly studied and thought to contribute to the disease are soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng)[18,19]. These molecules cause maternal vasoconstriction and hypertension, possibly in an effort to improve placental perfusion[20]. The pro-angiogenic placental factors inhibited in the disease process include placental growth factor (PlGF) and vascular endothelial growth factor (VEGF). This inhibition is likely due to a combination of placental ischemia and the anti-angiogenic inhibitory effects of sFlt-1 and sEng[18,21].

The inflammatory response resulting from preeclampsia activates cyclooxygenase (COX)[22], which increases thromboxane A2 (TxA2) levels and reduces endothelial cell prostacyclin levels (PGI2)[22,23]. TxA2 increases platelet aggregation and causes vasoconstriction, and PGI2 counteracts these effects[24]. The inflammatory response is therefore also a contributor to the disease phenotype. (Figure)

Aspirin

Aspirin is a non-steroidal anti-inflammatory drug, which acts by non-selectively and irreversibly inhibiting COX, resulting in anti-platelet and anti-inflammatory effects by preventing the conversion of arachidonic acid to thromboxane and prostaglandins, including TxA2 and PGI2[23,25]. PGI2, unlike TxA2, is rapidly repleted, and the overall net effect of aspirin is therefore a preferential inhibition of TxA2[23,26]. Aspirin also inhibits hypoxia-induced sFlt-1 overexpression by inhibiting COX-1 as an added mechanism of counteracting preeclampsia [27,28]. (Figure)

Aspirin is currently the only medication recommended for the prevention of preeclampsia. Studies on aspirin use for preeclampsia prevention date back to 1979, and have used doses ranging from 50 to 150mg daily starting at various gestational ages in low- and high-risk women[29]. Although the results are mixed, more recent systematic reviews and meta-analyses suggest that this may be due to variations in aspirin dosing and timing of drug initiation in the individual studies, with the most beneficial effects seen when aspirin is started before 16 weeks' gestation[29,30]. Currently, both the U.S. Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists (ACOG) recommend aspirin use for preeclampsia prevention for women at high risk for developing the disease (e.g. those with chronic hypertension, pre-gestational diabetes mellitus, multifetal gestation, renal disease, and autoimmune disease, etc), and to be started between 12 and 28 weeks' gestation

and continued until delivery[3,31]. In the U.S. aspirin is available as 81-mg formulation; thus, this is the dose most commonly recommended and clinically used. In addition, there are no studies comparing the effects of different doses of aspirin and none of the studies suggesting the benefit from a higher dose were conducted in the US. Moreover, fetal and long-term children safety data of high-dose aspirin use during gestation are limited.

While ACOG and USPSTF utilize risk factors based on history and clinical characteristics to identify women at risk for developing preeclampsia, more recent studies have investigated the use of first-trimester screening tests which include assessment of serum PlGF concentration, uterine artery doppler studies, and other maternal parameters to identify patients at highest risk for developing preeclampsia who would benefit from prophylactic aspirin use[32]. However, in randomized clinical trials, these screening tests underperformed due to low positive predictive value. In addition, preeclampsia prevention was limited to small number of preterm preeclampsia, and most screen-positive patients would not benefit from interventions. Due to their under-performance and lack of data form the U.S., first trimester screening using biomarkers and ultrasonography remains investigational and is not endorsed by professional societies in the US [33]. However, some experts have advocated for universal aspirin use during pregnancy, due to its low cost of approximately $5 throughout pregnancy, its well-studied maternal and neonatal safety profile, and the potential for it to reduce the burden of preeclampsia, improve maternal and fetal outcomes, and reduce healthcare cost[34,35]. This approach has not been endorsed by professional societies in the U.S.

Lastly, aspirin use appears to be safe during pregnancy as there have been multiple studies that failed to identify an association between low-dose aspirin use during pregnancy and higher risk of placental abruption, postpartum hemorrhage, spinal hematoma, congenital anomalies, persistent pulmonary hypertension in the neonate, premature closure of the ductus arteriosus, or neonatal bleeding complications or intracranial hemorrhage[36]. There have also been no notable adverse neonatal or childhood outcomes following in-utero aspirin exposure, with follow-up to 18 years of age[31].

Statins

Statins are competitive inhibitors of the enzyme 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which converts HMG-CoA to mevalonic acid[37]. Recently, there is growing interest in the role of statins to prevent preeclampsia due to increasing number of studies demonstrating strong biological plausibility to reverse or ameliorate several pathophysiological pathways associated with preeclampsia. Animal models suggest that statins increase the production of PlGF, and reduce sFlt and TxA2[38]. Additional pleiotropic actions of statins include enhanced trophoblastic invasion and improved placental blood flow, anti-inflammatory and antioxidant effects, endometrial protection, inhibition of platelet adhesion, and anticoagulant effects[39]. These properties are thought to counteract the pathophysiological pathways of preeclampsia, and may result in a protective effect against it or amelioration of its manifestations on maternal, fetal and neonatal wellbeing[40]. (Figure)

Studies into the use of statins for preeclampsia have evaluated it using a therapeutic approach for patients who develop preeclampsia, and a prophylactic approach for women at high-risk for developing the disease. In animal models of preeclampsia, statins were shown to resolve the clinical manifestations of preeclampsia, and prevent associated fetal growth restriction[41,42]. Other findings include increased nitric oxide production in the vasculature, reversing angiogenic imbalance, and anti-inflammatory and oxidative actions[43]. Initial data from case reports demonstrated that, when given to women with preterm preeclampsia, pravastatin use was associated with improvement in blood pressure and reduction in sFlt-1 serum concentrations, and improved pregnancy outcomes[44]. Other reports demonstrated that pravastatin prevented fetal demise in patient with massive perivillous fibrin deposition in the placenta and improved angiogenic profile[45]. A pilot multicenter, randomized, placebo-controlled trial enrolled high-risk women with a history of preeclampsia that required delivery before 34 weeks in a prior pregnancy. These women were randomized between 12- and 16-weeks' gestation to receive either pravastatin 10 mg daily or placebo. Findings from the study demonstrated no identifiable maternal or fetal/neonatal safety risk signals associated with pravastatin therapy. In addition, clinical outcomes including the rates of preeclampsia and indicated preterm delivery tended to be lower, and the angiogenic imbalance reversed in subjects receiving pravastatin[46].

However, results from other human studies especially those where pravastatin was used after the development of preeclampsia, are mixed[43]. In a prospective cohort of women with antiphospholipid syndrome and poor obstetrical history, addition of pravastatin to standard of care in women who developed preeclampsia or intrauterine uterine growth restriction, led to improved pregnancy and neonatal outcomes. On the other hand, a recent randomized double-blinded placebo-controlled proof of concept trial (Statins to Ameliorate early onset Preeclampsia (StAmP) trial) did not show a benefit in using pravastatin in patients who develop early preeclampsia, with no evidence of improved angiogenic biomarkers or lower preeclampsia rates[47]. Despite the imitations of the study which included small sample size, slow recruitment, overoptimistic sample size assumptions, and lack of power to identify differences in clinical outcomes, the StAmP trial supported the safety of pravastatin as there were no maternal serious adverse events and extremely low drug concentrations in the cord. The latter finding is similar to the pilot randomized trial in the US, which showed that the majority of fetuses exposed to pravastatin, had drug concentration in their cord blood below or close to the detection limit of the assay[46].

Statins were initially classified as Category X by the FDA. This was due to poorly designed, small, retrospective studies that suggested an increase in teratogenic effects with statin use[39], in addition to the absence of any indications to use statins in pregnancy. More contemporary studies and systematic reviews suggest that statins, and in particular pravastatin, do not demonstrate increased risk in fetal malformations, stillbirth, spontaneous abortions, or effects on fetal cholesterol levels or fetal weight[39,46]. These findings could be expected by the unique pharmacokinetic and properties of pravastatin. Pravastatin is among the most hepatoselective and hydrophilic statins with limited transplacental transfer, as demonstrated in placental transfer studies and from the observed cord blood drug concentrations in the two clinical trials described above[46–48].

Metformin

Metformin, or dimethyl-biguanide hydrochloride, is a biguanide used mainly as an anti-diabetic agent[49]. Its mechanisms of action include inhibition of hepatic gluconeogenesis, reducing gastrointestinal glucose absorption, and increasing glucose absorption by peripheral tissues[49]. By inhibiting sFlt-1 and sEng, metformin counteracts their antiangiogenic effects[50]. This may overall reverse the placental perfusion and imbalance of angiogenic and antiangiogenic factors in the clinical preeclampsia spectrum. However, clinical data on the effectiveness of metformin as a prophylactic agent for preeclampsia prevention are varied[51]. In a recent randomized, double blind, placebo-controlled trial of pregnant women with a BMI >35 without diabetes, the use of metformin resulted in a 75% reduction in the incidence of preeclampsia[52]. However, a recent meta-analysis of five randomized trials concluded that metformin use did not result in a significant reduction in the incidence of preeclampsia[51].

The safety profile of metformin use in pregnancy is well-established. The most common maternal side effect is transient gastrointestinal symptoms in up to 25% of women[53]. Although metformin freely crosses the placenta, it is poorly metabolized by the fetus, and multiple studies have shown no evidence of teratogenicity or adverse fetal or neonatal effects, however long-term data on neurodevelopmental or metabolic outcomes associated with its use are limited[54–57].

Esomeprazole

The use of proton pump inhibitors including esomeprazole is safe in pregnancy, and has not been found to be associated with fetal teratogenicity, miscarriage or preterm birth[58]. In preclinical studies, esomeprazole was associated with an inhibition of sFlt-1 and sEng production, with associated vasodilation and a reduction in endothelial dysfunction[59]. In an sFlt-1 overexpression animal model, esomeprazole was able to counteract preeclampsia symptoms[59].

However, human studies using esomeprazole have been less promising. In a randomized, placebo-controlled study, there was no apparent pregnancy prolongation or reduction in sFlt-1 with using 40mg of esomeprazole daily[60]. Further research is needed to evaluate the use of higher doses of esomeprazole and using the medication as a prophylactic agent for preeclampsia prevention.

Conclusion

Contemporary research into prophylactic and therapeutic interventions for preeclampsia are providing novel and promising modalities. Research into this topic remains a major endeavor, and as our understanding of the disease is evolving, studies will continue to pave the way for new effective therapeutics for preeclampsia.

Conflicts of Interest & Funding Source:

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Practice points:

- Aspirin is recommended for the prevention of preeclampsia in high-risk women
- First trimester screening for preeclampsia is not recommended in the US

Research directions:

- The optimal dose of aspirin in preeclampsia prevention, and the cohort of women who will benefit from higher dose
- The effectiveness of statins in preventing preeclampsia
- The role of statin in managing pregnancies complicated by early onset preeclampsia

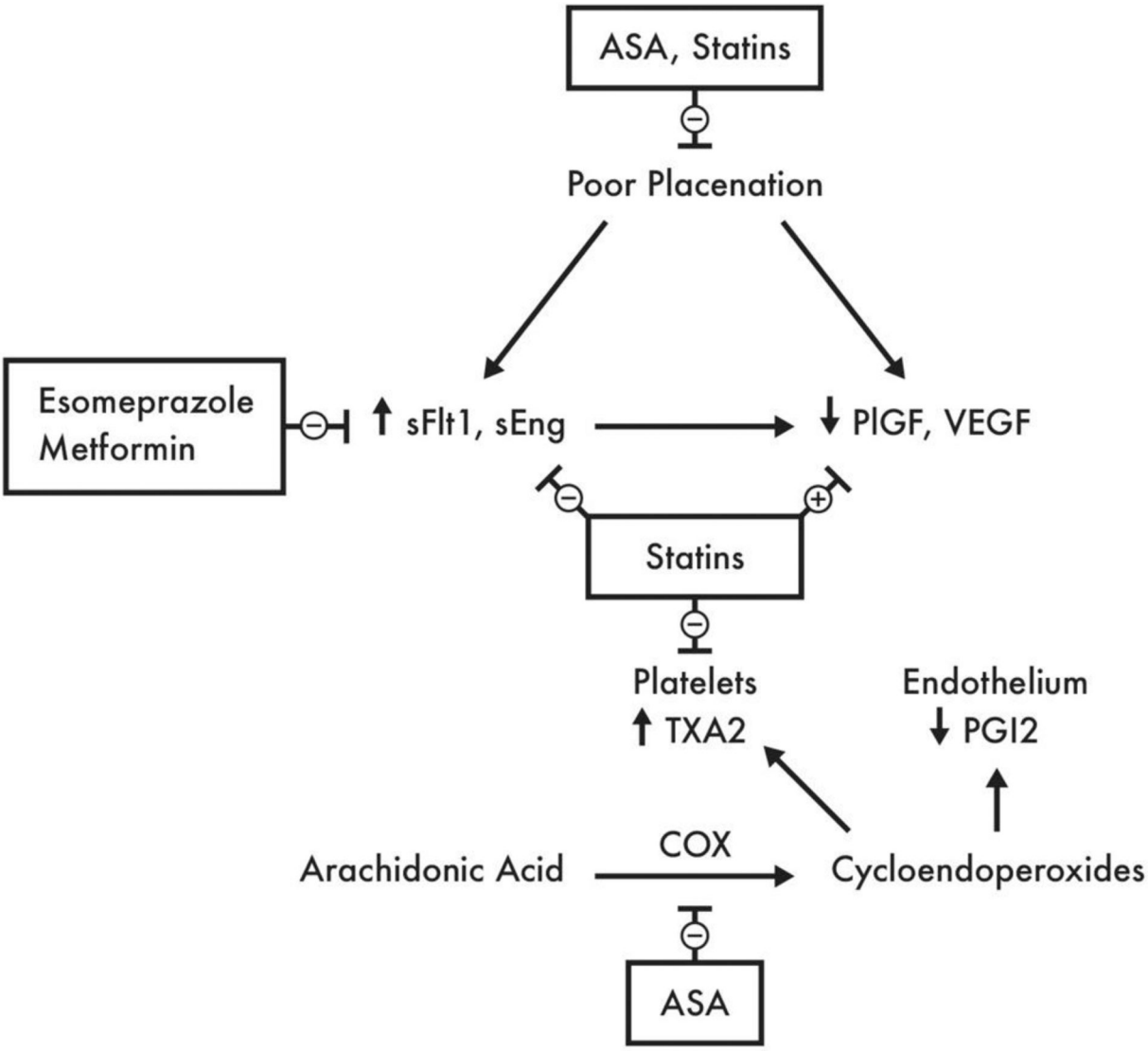

Figure:

Pathophysiology of Preeclampsia and Proposed Mechanisms of Actions of Preventive Agents

ASA, Aspirin; COX, cyclooxygenase; sEng, soluble endoglin; sFlt1, soluble fms-like tyrosine kinase 1; PGI2, prostaglandin I2 (prostacyclin); PlGF, placental growth factor; TXA2, thromboxane A2; VEGF, vascular endothelial growth factor