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NOVEL INTERVENTIONS FOR THE PREVENTION OF PREECLAMPSIA

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Abstract

Purpose of Review—To review the rational, biological plausibility, and discuss the current research on novel interventions for the prevention of preeclampsia.

Recent Findings—Preeclampsia affects up to 8% of pregnancies worldwide and remains a major cause of maternal and neonatal morbidity and mortality. Multiple medications have been investigated or repurposed as potential effective interventions for preeclampsia prevention. Aspirin is currently the only drug for which there is some evidence of benefit for preeclampsia prevention, and its use is recommended by professional societies for pregnancies at risk. Statins have shown promise for prevention of preeclampsia in animal models and human pilot studies, without any trend or concerns for safety signals or teratogenicity. The use of metformin has also gained popularity in experimental studies but observations from randomized clinical trials were not consistent on its utility as a possible intervention for preeclampsia prevention. While initial studies evaluating esomeprazole were promising, randomized trials failed to show benefit.

Summary—Contemporary research shows exciting new opportunities for prophylactic treatment for preeclampsia, to prevent this debilitating and life-threatening disease.

Keywords

Preeclampsia; Aspirin; Pravastatin; Metformin; Esomeprazole; Pregnancy

Introduction

Preeclampsia (PE) is a multisystem progressive disorder affecting up to 5–8% of all pregnancies and is part of the spectrum of hypertensive disorders of pregnancy [1,2]. It is a morbid obstetric complication characterized by new-onset hypertension – typically after 20 weeks' gestation – with evidence of end-organ damage, which can range from renal injury, liver injury, hemolytic effects, neurological injury including seizures (eclampsia), stroke, and

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death [2,3]. PE is the third leading cause of maternal mortality worldwide [4,5]. The WHO estimates that 76,000 maternal deaths are caused annually by PE, accounting for 16% of global maternal mortality, most of which occur in low and mid-income countries [4,5]. In developed countries, PE represents the most frequently cited indication for provider-initiated preterm birth [6], and in the United States, approximately 20% of pregnancy-related maternal mortality, and a more than a third of iatrogenic preterm births, are attributable to PE [7].

At present, the only definitive cure for PE is delivery, however, this practice is usually associated with premature delivery and increases the risk of neonatal morbidities. Recent advances in understanding its pathogenesis led to interest in novel agents to treat or prevent PE. While discussion of all of these agents is beyond the scope of this manuscript, we will limit our review to specific interventions, including novel controversies about aspirin, statins, metformin, and proton pump inhibitors. A cure for PE other than delivery would result in a significant reduction in maternal and neonatal morbidity and mortality.

Pathophysiology of Preeclampsia

The exact pathological mechanisms resulting in PE are unknown, and PE is more of a syndrome with different subtypes rather than a single disease. The pathogenesis is proposed to be multifactorial, resulting from an interaction of genetic and environmental factors, and abnormal placentation [2,8]. The genetic etiology of PE is evident by the added risk of the disease in patients with a family history of the disease, with current epidemiologic evidence of both maternal and paternal origins [9], and environmental influences are apparent by contribution of variables such as socioeconomic status, weight, and geography to the risk of the disease [2,10]. The impact of genetic predisposition and environmental factors associated with PE are beyond the scope of this review and are discussed elsewhere [2,9,10].

PE is considered by many as a two-step disease with the first step occurring early in pregnancy and characterized by abnormal invasion of trophoblasts and remodeling of the uterine spiral arteries [11,12]. The abnormal placentation, in turn, results in an abnormal maternal vascular response, resulting in an imbalance of angiogenic and antiangiogenic factors, an enhanced immune and inflammatory maternal response to trophoblasts, increased vascular resistance, enhanced platelet aggregation, activation of the coagulation system, and endothelial cell dysfunction [2,3,8,13,14]. It is hypothesized that poor placentation results in placental ischemia, which causes increased levels of anti-angiogenic factors in the maternal serum such as soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng) [15–20]. This leads to maternal vasoconstriction, which is postulated to increase maternal blood pressure in an effort to improve placental perfusion [16,17]. Poor placental perfusion also results in lower levels of placental factors in the maternal serum, including placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), likely as a consequence of the anti-angiogenic effects of sFlt-1 and sEng [15,17,21]. The above is further supported by experiments in animal models, where induced overexpression of sFlt-1 and/or sEng results in the typical phenotypic features of PE, including elevated blood pressure, proteinuria, hemolysis, liver transaminitis, thrombocytopenia, and fetal growth restriction [19,22,23].

In addition, poor placentation results in an inflammatory response, which activates cyclooxygenase (COX) [24]. This results in an increase in thromboxane A2 (TxA2) levels and a reduction in endothelial cell prostacyclin levels (PGI2) [24,25]. TxA2 is associated with increased platelet aggregation and vasoconstriction, and PGI2 counteracts these effects [26]. This imbalance, therefore, is a major contributor to the clinical spectrum of PE, and reductions in PGI2 levels have been identified months prior to the clinical onset of the disease [27].

In the following sections, we will discuss some of the currently used and potential agents for the prevention of preeclampsia.

Aspirin

Background and Mechanism of Action

Aspirin is a non-selective and irreversible cyclooxygenase inhibitor with anti-platelet and anti-inflammatory properties, and acts as an inhibitor of both COX isoforms, COX-1 and COX-2 [28]. Normally COX produces prostaglandins, most of which are pro-inflammatory, and thromboxanes, which promote clotting [29]. Aspirin prevents the conversion of arachidonic acid to thromboxane and prostaglandins, including TxA2 and PGI2 [25,28,29].

PGI2 is synthesized by endothelial cells lining the cardiovascular system [30]. It is a potent vasodilator, inhibitor of platelet aggregation, and is rapidly repleted by endothelial cells [25,30]. TxA2 is produced by activated platelets during hemostasis [26,31]. It has prothrombotic properties, and stimulates the activation of new platelets and increases platelet aggregation [26,31]. It is not as readily repleted by anuclear platelets, and therefore aspirin has the overall effect of preferentially inhibiting TxA2 synthesis [25]. Inhibiting the effects of TxA2, which include vasoconstriction and increased platelet aggregation, have made aspirin an attractive choice to prevent PE [26,32]. In addition, by inhibiting COX-1, aspirin inhibits the overexpression of sFlt-1 resulting from hypoxic changes in the placenta, further contributing to its mechanism of counteracting PE [33,34].

Clinical Data and Implications

The use of aspirin as a medication for PE prevention was first described in 1979 [35]. Studies using 50–150 mg of daily aspirin showed mixed results in the reduction of PE [28,36–39]. Consequently, in 2014, U.S. Preventive Services Task Force (USPSTF) concluded that there was adequate evidence of a reduction in risk for PE, in women at increased risk for PE who received low-dose aspirin, thus demonstrating substantial benefit [40]. They reported that low-dose aspirin (range 60mg to 150mg daily) reduced the risk for PE by 24% in clinical trials [40]. In the U.S., aspirin is available as 81mg formulation, thus this is the dose most commonly recommended and used in clincial practice. However, some meta-analyses and systematic reviews have suggested a dose response effect of aspirin in PE prevention and a significant reduction in prevalence of preterm PE [41,42]. This reduction occurred when aspirin was initiated before 16 weeks of gestation and at a daily dose of at least 100mg [39]. However, there were 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.

More recently, there has been interest in first-trimester screening tests to predict women at risk for developing PE and to stratify based on risk of who would benefit from aspirin prophylaxis during their pregnancy [43–45]. In the first trimester of pregnancy, it has been reported that a combination of low maternal serum concentrations of PlGF, high uterine artery pulsatility index, and other maternal parameters, identified 93.1% of patients who would develop PE requiring delivery before 34 weeks of gestation [46]. Unfortunately, in a randomized trial this screening algorithm underperformed [47]. At present time, biomarkers and ultrasonography cannot accurately predict PE and should remain investigational.

The American College of Obstetricians and Gynecologists (ACOG) released a practice bulletin in 2019, recommending that women with any of the high-risk factors for PE (previous pregnancy with PE, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes mellitus, and chronic hypertension) and those with more than one of the moderate-risk factors (first pregnancy, maternal age of 35 years or older, a body mass index of more than 30, family history of PE, sociodemographic characteristics, and personal history factors) should receive low-dose (81 mg/day) of aspirin for PE prophylaxis, initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks of gestation) and continued until delivery [2].

In contrast to limiting aspirin use for screen positive high risk women, others have advocated for universal aspirin for all pregnant women, due to the substantial proportion of American women who now qualify for, and could benefit from, prophylactic aspirin administration, based on ACOG recommendations [48–50]. The arguments for this include its low cost [50], favorable maternal and neonatal safety profile and the clinical effectiveness of aspirin in reducing significant burden of PE, as well as overall healthcare cost reduction. However, this practice has not been advocated by professional societies in the US.

Safety Data

Aspirin is safe to use in pregnancy. Multiple studies have failed to show an association between aspirin and placental abruption, postpartum hemorrhage, or estimated blood loss [51]. Low-dose aspirin is not a contraindications in a patients receiving regional anesthesia, and does not increase the risk of spinal hematomas [52]. Multiple studies have failed to show an association between aspirin and congenital anomalies, premature closure of the ductus arteriosus, persistent pulmonary hypertension of the newborn, neonatal intracranial hemorrhage or neonatal bleeding complications [51,53–55]. Moreover, there is an abundance of robust data to support the safety of aspirin beyond the first trimester. A systematic review from the US Preventative Services Task Force in 2014 concluded that aspirin usage was not associated with maternal or neonatal harm, with normal follow-up to an 18-year period [40].

Statins

Background and Mechanism of Action

5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is an enzyme that converts HMG-CoA to mevalonic acid [56]. Statins are HMG-CoA reductase inhibitors and act as competitive inhibitors of the enzyme [56]. Studies in animal models show that statins, specifically pravastatin, may increase the production of PlGF and inhibit the production of sFlt-1, thereby reversing the imbalance in angiogenic and anti-angiogenic factors which contributes to PE [57–60]. Pravastatin has also been also shown to stimulate trophoblast invasion, improve placental blood flow to reduce placental ischemia, act as anti-inflammatory agents and antioxidants, protect the endometrium, and act as anticoagulants [61–64]. Statins also decrease the production of TxA2 and inhibit platelet adhesion [65]. All these effects combined, target and counteract the biological mechanisms that result in the PE phenotype. Animal studies also suggest that pravastatin may counteract long-term adverse effects of PE on maternal and fetal health [66].

Clinical Data and Implications

Results from human studies, which are currently limited to small series, pilot studies, and case reports are promising [67–70]. Brownfoot et al reported that pravastatin stabilized the blood pressure and reduced the concentrations of sFlt-1 in four patients with preterm preeclampsia (less than 30 weeks gestation) [69]. Costantine et al, for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Units Network, showed in a pilot multicenter, double-blind, placebo-controlled, randomized trial, that pravastatin reduced the rate of PE and preterm delivery in women with history of preeclampsia that required delivery before 34 weeks, compared with placebo. The authors found no identifiable maternal or fetal/neonatal safety risks associated with pravastatin therapy during pregnancy (started between 12 and 16 weeks gestation and continued till delivery) [70]. Lastly, Lefkou et al., reported a prospective cohort of 21 women with antiphospholipid syndrome and poor obstetrical history, that adding pravastatin (to low dose aspirin and low molecular weight heparin) prolonged pregnancy by almost 10 weeks, improved birthweight and neonatal outcomes, and ameliorated uterine artery Doppler velocimetry [68]. There are at least four current prospective humans studies at various trial stages investigating the role of pravastatin in preventing or treating PE [71–74].

Safety Data

Short-term use of statins can be associated with statin-associated muscle symptoms (SAMS) in 0.1–0.2% of users, and include myalgias and muscle weakness, and typically affect the thighs, calves, buttocks and back muscles [75]. Extremely rarely, they can be associated with drug-induced liver injury (DILI), with an incidence of approximately 1 per 100,000 [75]. On the other hand, statins were initially classified as pregnancy category X by the FDA due to theoretical concern for teratogenic effects. However, many of these studies were poorly designed, small and retrospective, and ultimately were a limiting factor in the conduction of research into the role of statins as a potential agent for PE prevention [65]. Later studies, including systematic reviews and meta-analyses, failed to show a significant increase in

teratogenicity in pregnancies with statin use, as well as no increased risk of stillbirth or spontaneous abortions [65,76]. Also, while statins do decrease maternal cholesterol levels, a pilot human study did not show an effect on fetal cholesterol levels or fetal weight [70].

Moreover, most of the animal and pilot human studies have used pravastatin one of the most hydrophilic and hepatoselective statin, and the least potent inhibitors of HMG-CoA reducatse [77–79].

Metformin

Background and Mechanism of Action

Metformin is a biguanide, and is also known as dimethyl-biguanide hydrochloride [80]. It is used mainly as an anti-diabetic agent, and exerts its anti-diabetic effects by inhibiting hepatic gluconeogenesis, both directly and by promoting insulin-mediated suppression, as well as by reducing gastrointestinal glucose absorption and increasing glucose uptake by peripheral tissues [80]. It has been suggested that metformin may prevent PE by improving cardiovascular function, improving insulin sensitivity, and limiting gestational weight gain [81]. Additionally, metformin was also found to have a dose-dependent reduction in sFlt-1 and sEng and counteracts sFlt-1-mediated inhibition of vasculogenesis [82]. These effects may counteract the poor placental perfusion and angiogenic/anti-angiogenic imbalance resulting in the clinical PE spectrum, making metformin a potential candidate for use as a medication for PE prevention.

Clinical Data and Implications

Clinical data on whether metformin can decrease the risk of PE is varied [83]. In a large trial comparing metformin to placebo in obese pregnant women (body mass index >35) without diabetes, there appeared to be a 75% reduction in the incidence of PE [84]. Conversely, a recent meta-analysis of five randomized controlled trials comparing metformin treatment with placebo, showed no benefit of pravastatin in reducing the risk of PE [83].

Safety Data

The most common side-effects of metformin in pregnancy are transient gastrointestinal symptoms in up to 25% of patients, including nausea, vomiting, and diarrhea, and a metallic taste after ingestion [85–87]. Metformin may also be associated with Vitamin B12 deficiency with long-term use [85]. An extremely rare but more serious side effect is lactic acidosis [85].

Metformin freely crosses the placenta and is poorly metabolized by the fetus [88,89]. Despite this, multiple studies have shown that metformin has no apparent teratogenic effects on the fetus [90,91]. A prospective study which followed offspring of mothers who took metformin during pregnancy up to 2 years of age determined that the use of metformin is not associated with fetal, neonatal or childhood neurodevelopmental adverse outcomes [92]. Not surprisingly, the use of metformin in pregnancies complicated by diabetes is associated with an improved fetal body fat distribution in the offspring [93]. By 7–9 years of age, offspring

of women taking metformin had similar body fat percentages, and similar serum metabolic panels [94].

Esomeprazole

Background and Mechanism of Action

Esomeprazole is a proton pump inhibitor, typically used for the management and treatment of gastroesophageal reflux disease and peptic ulcer disease [95]. Preclinical studies showed that esomeprazole can inhibit the production of sFlt-1 and sEng, have a vasodilatory effect, and decrease endothelial dysfunction, thereby counteracting some of the proposed mechanisms contributing to the PE phenotype [96,97]. Esomeprazole was also able to counteract the PE symptoms resulting from induced sFlt-1 overexpression in animal models [97]. The sFlt-1 inhibitory effects were accentuated when metformin was added to esomeprazole in preclinical studies [98].

Clinical Data and Implications

In a randomized placebo-controlled study of 119 women diagnosed with preterm PE, the use of 40mg of esomeprazole daily did not prolong pregnancy and was not associated with a reduction in sFlt-1 levels [99]. However, this may be attributed to the low dose of esomeprazole used. Also, the women included in the study were between 26 weeks' and 31 weeks' gestation at randomization, and the beneficial effects of esomeprazole may not be seen if started later in pregnancy. Further studies are needed to evaluate the effectiveness of and safety of higher doses of esomeprazole in the treatment of PE.

Safety Data

Proton pump inhibitors are generally very safe with a low side-effect profile. Adverse effects associated with their use are typically more related to long-term consumption. These can include acute and chronic kidney disease, hypomagnesemia, community-acquired pneumonia, bone fractures, and *Clostridium difficile* infections [100]. Proton pump inhibitors are safe to use in pregnancy and are not associated with teratogenicity, added miscarriage risk or preterm delivery [101,102].

Future Directions

There are many other agents being studied as potential candidates for prevention and even treatment of PE. These include COX-2 inhibitors, sulfasalazine, azathioprine, antithrombin, human relaxin-2, anti-digoxin antibodies, recombinant human-activated protein C, melatonin, and others [103]. Despite initial optimism about the potential role for sildenafil in PE prevention, a Dutch study raised concerns about the safety of the medication in humans [104,105]. Another innovation in PE prevention and treatment, is short interfering RNA (siRNA) modulation to silence sFlt-1 production in the placenta [106,107]. Studies in mouse and baboon models showed an amelioration of the clinical signs and symptoms of PE using siRNA [106]. However, several prior attempts to prevent PE based on pathophysiological pathways have failed. Therefore, before any therapy becomes widely used, properly powered studies with well-designed maternal and children follow-up evaluations, are needed to

determine the safety and efficacy of these interventions, as animal models of preeclampsia do not represent the entire phenotype of the disease.

Conclusion

Although PE remains a major cause of worldwide morbidity and mortality, contemporary research into novel agents for PE prevention and treatment offer exciting new opportunities for preventing and curing this debilitating and life-threatening disease. Research into this topic is still needed, to better understand the pathology of the disease to develop targeted therapies that may ameliorate the disease with a limited side-effect profile.

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