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## SPECIAL ARTICLE

# Potential of Pravastatin for the Prevention and Treatment of Preeclampsia

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## ABSTRACT

Preeclampsia (PE) is a severe pregnancy complication affecting 5–10% of pregnancies worldwide and remains a leading cause of maternal and neonatal morbidity and mortality. Although low-dose aspirin is widely used for prevention, its efficacy is limited, necessitating the development of novel therapeutic strategies. This review examines the potential of pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, as a preventive and therapeutic agent for PE.

Pravastatin exerts pleiotropic effects, including upregulation of placental growth factor, suppression of soluble fms-like tyrosine kinase-1, and anti-inflammatory and antioxidative properties. Preclinical studies demonstrate its ability to mitigate PE-like symptoms in animal models, whereas clinical studies suggest its potential to reduce the incidence of severe PE in high-risk pregnancies. However, its effectiveness is limited when administered after 35 weeks of gestation, and its optimal dosage remains undetermined.

Building on existing clinical evidence, well-designed large-scale randomized controlled trials are crucial to establish the safety and efficacy of pravastatin in PE prevention. Further research is needed to evaluate its potential for reducing long-term cardiovascular risk in women with a history of PE. An ongoing clinical trial in Japan (jRCTs031230067) aims to address these gaps and contribute to future PE prevention strategies.

**Keywords:** preeclampsia, pravastatin, angiogenic factors, cardiovascular risk, randomized controlled trial.

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# Introduction

Preeclampsia (PE) is a multisystem pregnancy complication characterized by new-onset hypertension, proteinuria, and organ dysfunction after 20 weeks of gestation. It can result in severe maternal and fetal complications, affecting multiple organ systems, including the liver, kidneys, cardiovascular system, and coagulation pathways. In severe cases, PE may progress to eclampsia, a life-threatening condition characterized by seizures, or to hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, further increasing maternal and perinatal risks.

Globally, PE affects approximately 5%–10% of pregnancies and remains a leading cause of maternal and perinatal mortality and morbidity. Each year, it is associated with an estimated 50,000 maternal and more than 500,000 perinatal deaths worldwide[1, 2]. Early-onset PE, occurring before 34 weeks of gestation, poses a particularly high risk of adverse neonatal outcomes due to prematurity and fetal growth restriction (FGR). It is also associated with an increased risk of stillbirth and long-term neurodevelopmental impairment in surviving infants[3]. Late-onset PE, occurring after 34 weeks of gestation, significantly contributes to maternal complications such as stroke, placental abruption, and postpartum hemorrhage[3]. These severe maternal and neonatal outcomes underscore the urgent need for effective preventive and therapeutic interventions.

Despite decades of research, delivery of the placenta remains the only definitive treatment for PE, which presents challenges when the condition occurs preterm. Premature delivery is associated with an increased risk of neonatal complications, including respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC), often necessitating specialized neonatal intensive care[4]. Additionally, women with a history of PE have a significantly higher lifetime risk of cardiovascular disease (CVD), stroke, and metabolic syndrome, suggesting shared pathophysiological mechanisms between hypertensive pregnancy disorders and long-term cardiovascular dysfunction[5]. Emerging evidence also suggests that offspring born to mothers with PE may have an increased predisposition to hypertension and metabolic disorders in adulthood, with intergenerational health implications[6].

In this paper, we provide an overview of the risk factors for PE, current understanding of its pathophysiology, and the preventive role of low-dose aspirin. Furthermore, we focus on the potential use of pravastatin as a novel and promising strategy for PE prevention. Given its pleiotropic effects, including endothelial protection, anti-inflammatory properties, and improvement of placental function, pravastatin has gained attention as a potential intervention to modify the disease course. We examine the current evidence supporting pravastatin use for PE prevention and discuss its future clinical implications.

## Risk factors

Although substantial progress has been made in recent years, the precise pathophysiological mechanisms underlying PE remain unclear. However, several maternal risk factors have been identified, including advanced maternal age, nulliparity, twin pregnancy, assisted reproductive technologies such as in vitro fertilization (IVF), obesity, pre-existing hypertension, type 1 and type 2 diabetes mellitus, chronic kidney disease, and autoimmune diseases such as systemic lupus erythematosus and antiphospholipid syndrome, and a family history of PE[7-12]. Additionally, lifestyle factors such as excessive gestational weight gain, poor diet, and physical inactivity have been implicated in increasing PE risk[13]. Genetic predisposition, epigenetic modifications[14], and environmental influences are believed to contribute to the heterogeneity of PE phenotypes, further complicating prevention and treatment strategies[15].

Despite these advances, effective disease-modifying therapies remain limited, and the search for novel pharmacological interventions to improve

maternal and fetal outcomes remains a major research priority. In parallel with research on PE risk factors, studies on PE prediction have also advanced. Notably, early-onset PE has a high detection rate when biomarker assessments are incorporated[16-18].

## Pathophysiology of PE

### *Pathophysiology of PE and the role of angiogenic factors*

PE and its related condition, FGR, have been associated with the placenta-derived circulating factor soluble fms-like tyrosine kinase-1 (sFlt-1), also known as soluble vascular endothelial growth factor receptor-1. Vascular endothelial growth factor (VEGF) receptors include VEGF receptor-1 (Flt-1), which mediates angiogenic signaling, and sFlt-1, which functions as an antagonist by inhibiting VEGF signaling.

In 2003, researchs led by Maynard and Karumanchi, and, led by Kaori Koga and Minoru Osuga, independently reported that maternal serum sFlt-1 levels are associated with hypertensive disorders of pregnancy (HDP)[19, 20]. The following year, Karumanchi et al. published a study demonstrating longitudinal changes in maternal sFlt-1 levels during pregnancy in normotensive and preeclamptic women[21]. Given its critical role as a bottleneck factor in PE development, sFlt-1 is considered a key regulator in the final stage of the disease, which results from a multifactorial interplay involving maternal and fetal immunity, genetics, and other contributing factors.

### *The two-step theory of PE pathogenesis*

The "Two-Step Theory" is widely accepted as a unifying hypothesis explaining PE pathogenesis, encompassing both early placental malformation and later dysregulation of angiogenic factors[22] (Fig. 1).

1. Early placental malformation: During early placentation, failure of extravillous trophoblast (EVT) invasion into the uterine myometrium and inadequate remodeling of the spiral arteries result in insufficient vascular expansion. Consequently, reduced maternal blood flow to the intervillous space creates a hypoxic environment.

2. Vascular dysfunction in mid-to-late pregnancy: In response to hypoxic stress, the placenta overproduces angiogenesis inhibitors such as soluble endoglin and sFlt-1, which circulate in the maternal bloodstream. These factors impair maternal endothelial function, leading to hypertension and proteinuria—hallmarks of PE.

Furthermore, in 2013, Nakashima and Saito from the University of Toyama demonstrated that under physiological oxygen conditions in early pregnancy, autophagy deficiency leads to impaired EVT invasion, contributing to poor spiral artery remodeling[23]. These findings provide critical insights into early pathogenic mechanisms underlying PE and enhance understanding of its pathogenesis.

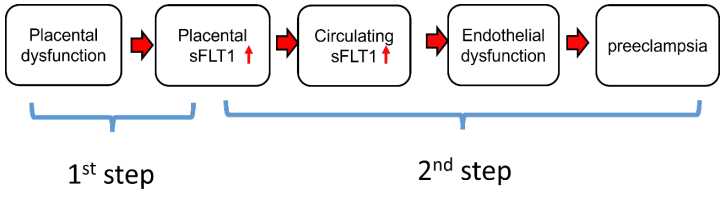


**Fig. 1.** Two-step theory of preeclampsia.

### *Role of placental growth factor (PlGF) and the sFlt-1/PlGF ratio*

PlGF, a key proangiogenic factor primarily produced by the placenta, plays a critical role in pregnancy. Low maternal circulating PlGF levels are associated with PE. The balance between proangiogenic factors, such as PlGF, and antiangiogenic factors, such as sFlt-1, is essential

for maintaining a healthy pregnancy. Studies indicate that maternal PlGF and sFlt-1 levels differ significantly between normotensive and preeclamptic pregnancies throughout gestation[21].

In women who later develop PE, maternal PlGF levels progressively decline from mid-pregnancy onward, whereas sFlt-1 levels increase relative to normotensive controls. Leveraging this biomarker imbalance, a 2016 European multicenter study reported that the sFlt-1/PlGF ratio serves as a reliable predictor of PE onset in high-risk pregnant women[24]. A previous study also found that sFlt-1/PlGF ratio at 16-18 weeks of gestation in elderly gravida has a high sensitivity for predicting preeclampsia, especially early onset preeclampsia[25]. This biomarker is now widely used in clinical practice for early detection and risk stratification of PE. Subsequent validation studies in Asia have reported similar findings[26, 27].

## Current preventive strategies for PE

### *Low-dose aspirin for PE prevention*

Aspirin remains the most widely accepted preventive measure for PE. The Aspirin for Evidence-Based PE Prevention (ASPRE) trial, a multicenter, double-blind, placebo-controlled study, demonstrated that daily administration of 150 mg aspirin during early pregnancy reduced the incidence of PE before 37 weeks by 62%[28]. However, the overall effectiveness of aspirin remains limited, necessitating the development of alternative preventive strategies.

Several international guidelines currently recommend low-dose aspirin (81 mg/day) for high-risk women, including those issued by the American College of Obstetricians and Gynecologists[29], the World Health Organization, the International Society for the Study of Hypertension in Pregnancy[30], and the U S Preventive Services Task Force[31].

### *Need for novel preventive and therapeutic approaches*

A simulation study estimated that universal aspirin use among pregnant women in the United States could prevent approximately 13% of PE cases[32]. Although this represents a significant advancement, it underscores the need for additional preventive and therapeutic strategies. Among emerging candidates, pravastatin has gained increasing attention for its potential role in PE prevention and treatment.

## Pravastatin as a novel approach for PE prevention and treatment

### *Classification and pharmacological properties of statins*[33]

Statins are classified based on their potency as either standard or strong statins:

- Standard statins, including pravastatin, simvastatin, and fluvastatin, lower serum low-density lipoprotein (LDL) cholesterol levels by approximately 15%.
- Strong statins, such as atorvastatin, pitavastatin, and rosuvastatin, reduce LDL cholesterol levels by approximately 30%.

Statins are also categorized based on solubility into water-soluble and lipophilic statins. Among the six currently marketed statins, only pravastatin and rosuvastatin are water-soluble. Unlike lipophilic statins, which undergo hepatic metabolism, water-soluble statins exhibit minimal hepatic metabolism, making them a suitable option for patients with hepatic impairment.

### *Why Is pravastatin the preferred statin for PE?*

Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are lipid-lowering agents that inhibit HMG-CoA reductase, a key enzyme in cholesterol biosynthesis. The first statin, mevastatin, was discovered in 1973 by Akira Endo in Japan[34], marking a major breakthrough in cardiovascular pharmacotherapy. Although mevastatin was never commercialized, subsequent research led to the development of eight statins, six of which remain in clinical use. Pravastatin was one of the statins

developed in Japan[35]. During pregnancy, physiological hypercholesterolemia occurs to support fetal and placental growth, necessitating an increased lipid supply[36]. If statin therapy is considered during pregnancy, standard statins may be preferable to strong statins due to their milder cholesterol-lowering effects. Furthermore, PE is often associated with hepatic dysfunction, raising concerns regarding drug metabolism and potential hepatotoxicity. Water-soluble statins, which can be administered to patients with hepatic impairment, offer a distinct advantage. Among the available statins, pravastatin uniquely meets both of these criteria (Table 1).

**Table 1.** Currently used statins.

| statin | strong/standard | Water/fat soluble |
|---|---|---|
| Rosuvastatin | strong | Water soluble |
| Pitavastatin | strong | Fat soluble |
| Atorvastatin | strong | Fat soluble |
| Fluvastatin | standard | Fat soluble |
| Simvastatin | standard | Fat soluble |
| Pravastatin | standard | Water soluble |

## Considerations for statin use during pregnancy

***Can pravastatin be used during pregnancy?***

Over the past decade, various animal models and clinical reports have investigated pravastatin use in pregnant women. However, randomized controlled trials (RCTs) have been limited, primarily due to the classification of statins as Category X by the United States Food and Drug Administration (FDA) for use during pregnancy. Consequently, pravastatin use for PE prevention in pregnant women has faced significant regulatory barriers.

Nevertheless, accumulating evidence suggests that pravastatin does not exhibit strong teratogenic potential[37]. Additionally, retrospective studies have reported that infants born to women who inadvertently received pravastatin during early pregnancy did not show an increased risk of congenital abnormalities[38-40].

Given the promising findings from animal models demonstrating the potential of pravastatin for PE prevention and treatment, as well as the low likelihood of teratogenicity in humans, pravastatin has been evaluated as a therapeutic option for PE. In 2021, the FDA issued a statement removing contraindications for statin use during pregnancy.

## Pravastatin as an affordable PE treatment

Another key advantage of pravastatin is its cost-effectiveness, making it an accessible treatment even in resource-limited settings. Given the global burden of PE and its associated maternal and fetal complications, the affordability and safety profile of pravastatin may facilitate widespread adoption in both high-income and developing countries.

## Mechanisms in PE prevention

Regulation of Angiogenic Factors: Pravastatin upregulates PlGF and downregulates sFlt-1, thereby improving placental blood flow[41, 42].

Anti-inflammatory Effects: Pravastatin reduces inflammatory cytokine production, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), mitigating maternal vascular inflammation[43].

Reduction of Oxidative Stress: Pravastatin suppresses oxidative stress-induced placental damage, supporting its protective role during pregnancy[44].

## Preclinical evidence

Elucidating PE pathogenesis is crucial for developing effective therapeutic strategies. Animal models play a key role in understanding disease mechanisms and evaluating potential treatments. A pregnancy-induced hypertensive mouse model was previously established through placenta-specific overexpression of sFlt-1 (Fig. 2)[41].

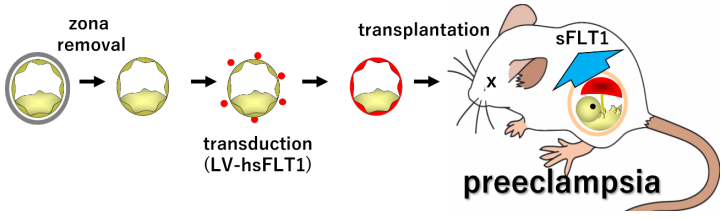


**Fig. 2.** Establishment of a preeclampsia mouse model.

Despite sFlt-1 overexpression, implantation and live birth rates remained unaffected. However, these transgenic mice exhibited elevated blood pressure, proteinuria, and intrauterine FGR, closely resembling the clinical manifestations of PE. Additionally, both blood pressure and proteinuria normalized postpartum, further supporting this model as representative of human PE.

Using this model, we explored potential therapeutic interventions. As discussed earlier, pravastatin has been reported to exert effects beyond cholesterol-lowering, including roles in angiogenesis. Notably, pravastatin inhibits angiogenesis at high concentrations but promotes angiogenesis at low concentrations in vitro[45].

### Evaluation of pravastatin in a PE mouse model

Based on these findings, we investigated the effects of pravastatin in a mouse model of PE. The dosage was adjusted according to body weight to ensure it remained within clinically relevant levels for humans. Pravastatin administration successfully prevented the onset of PE symptoms. Although post-onset administration did not result in statistically significant therapeutic effects, a trend toward reduced blood pressure elevation was observed.

Further experiments using both a PE mouse model and human umbilical vein endothelial cells demonstrated that pravastatin induces the expression of PlGF, an essential angiogenic factor. Additionally, pravastatin treatment reduced circulating sFlt-1 levels in PE mice. In this PE model, where placenta-specific overexpression of sFlt-1 led to FGR, pravastatin administration improved FGR[41]. Subsequently, other research groups have reported that statin treatment increases VEGF and PlGF levels in animal models[46], further supporting these findings.

In our experiments, pravastatin administration did not affect live birth rates. However, FGR was observed, with fetal weights approximately 15% lower than those in the control group. No gross morphological abnormalities were detected in the fetuses, and both male and female offspring exhibited normal reproductive capacity postnatally. Additionally, no studies have reported an increased incidence of fetal malformations in statin-treated mouse models.

## Clinical evidence

Several clinical studies have reported promising results regarding the potential benefits of pravastatin in the prevention and treatment of PE.

Lefkou et al reported that adding pravastatin to low-dose aspirin and low-molecular-weight heparin prolonged pregnancy, improved birth weight, and enhanced neonatal outcomes in women with antiphospholipid syndrome and a poor obstetric history[47]. Costantine et al conducted two small randomized placebo-controlled trials and demonstrated

that pravastatin use reduced the incidence of PE[42, 48]. Döbert et al found that pravastatin administration after 35 weeks of gestation did not prevent PE, highlighting the importance of early intervention[49]. From an Asian perspective, the INOVASIA study reported favorable outcomes in the secondary prevention of PE, demonstrating significantly lower rates of preterm delivery and neonatal morbidity, as well as improved birth weight and Apgar scores among pravastatin-treated mothers[50].

Recent meta-analyses further support the potential role of pravastatin in preventing PE. A systematic review of 14 studies involving 1,570 pregnant women found that pravastatin notably reduced the incidence of PE by 61%, preterm birth by 45%, intrauterine growth restriction by 45%, and neonatal intensive care unit admissions by 77%[51]. Additionally, randomized trials have demonstrated that pravastatin improves angiogenic balance by increasing PlGF levels and reducing sFlt-1, key mediators of endothelial dysfunction in PE. Furthermore, a clinical study (jRCTs031230067) was recently initiated in Japan to evaluate the efficacy of pravastatin in preventing PE recurrence in women with a history of HDP.

### Regulatory considerations and future directions

Despite these promising results, research on pravastatin use during pregnancy faces regulatory challenges. The U.S. FDA previously classified statins as Category X in pregnancy due to concerns regarding fetal harm. However, accumulating clinical and epidemiological data indicate that pravastatin is not teratogenic.

In July 2021, the FDA revised its stance, removing strong contraindications for statin use during pregnancy, particularly for women with significant cardiovascular risk factors. This regulatory shift has paved the way for larger RCTs to further evaluate the safety and efficacy of pravastatin in PE prevention.

Collectively, these findings support pravastatin as a promising therapeutic option for PE. Future research should focus on large multicenter trials to optimize dosing strategies, determine the ideal timing for intervention, and assess long-term maternal and neonatal outcomes.

## Conclusion and future perspectives

Current evidence strongly suggests that pravastatin is a promising therapeutic option for PE but also highlights certain limitations.

Although pravastatin has preventive effects, its efficacy in the treatment of post-onset PE remains unclear. Administration during the late stages of pregnancy (after 35 weeks) does not provide a preventive benefit. However, the optimal dosage and administration regimens remain to be determined. Large-scale RCTs with long-term follow-up are essential to establish the efficacy and safety of pravastatin in PE prevention, particularly in high-risk populations. From a long-term perspective, pravastatin may also play a role in reducing future cardiovascular risk in women with a history of PE. Additionally, pravastatin is a low-cost medication, as its patent has expired, making it an economically feasible option for widespread clinical use. Given its potentially high efficacy in PE prevention, pravastatin could have a significant impact on healthcare economics by reducing maternal and neonatal complications, lowering hospitalization costs, and improving long-term health outcomes.

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## Potential conflicts of interest

The author declares no competing interests.

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