

# How Preeclampsia Occurs and Potential Therapies for Curing Preeclampsia

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**Abstract:** As a relatively common pregnancy disorder associated with hypertension, preeclampsia originates within the placenta and can cause a variety of maternal and fetal problems. In some cases, it potentially threatens both mother and baby's lives. Based on recent works, this review paper mainly focuses on the painstaking mechanism of preeclampsia to have it better understood, followed by the possible and feasible therapies we proposed.

## 1. Introduction

Preeclampsia (PE) is a multisystem illness caused by pregnancy. [1]. It's a multifactorial condition marked by the hypertension occurs after 20 weeks of pregnancy. There are two subtypes, one is early type (delivery before 34 weeks) and another late type (delivery beyond 34 weeks) diagnosis [2]. PE is a pregnancy complication on high frequency. Based on data provided by the National Health Portal of India, preeclampsia affects eight to ten percent of pregnant women [1]. PE can have serious consequences both for mothers and infants. Intrauterine growth restriction, premature delivery, placental abruption, foetal discomfort, and fetal mortality are all related with the syndrome, which is one of the primary led to maternal death. [3]. In utero exposure to hypertensive illnesses during pregnancy has been linked to significant long-term cardiovascular repercussions in offspring, containing early an increased risk of ischemic heart disease and stroke and onset hypertension, according to a growing body of research. [4]. Delivery is widely accepted as the only definitive treatment [5]. Additionally, it is essential to observe clinical changes closely and monitor inflammation indicators to help identify infections early, diagnose them in a timely manner, and implement the appropriate antibiotics in a timely manner, in order to improve outcomes [6].

## 2. Main body

### 2.1. Distribution characteristics of PE

*Geographical* A high number of maternal deaths are reported annually in developing countries. Preeclampsia monitoring is limited due to insufficient prenatal care. [7].

*Age-related* Preeclampsia risk increases with maternal age over 35 years old, according to a population-based study conducted in Ecuador.

*Altitude* The chances of developing preeclampsia are significantly elevated at high altitudes [8].

### 2.2 signaling cascades involved

#### 2.2.1 Angiogenic factors' function in preeclampsia

We made progress in figuring out how to treat preeclampsia last year, and we discovered that angiogenic had something to do with it. Several angiogenic isoforms have been identified; however, sFlt1 appears to be the most common protein linked to preeclampsia.

The mechanism via which sFlt1 influences preeclampsia performance is not completely understood. However, because the placenta is so important in preeclampsia, researchers have been looking into how early abnormalities in placental vascular remodeling may contribute to the disease.

Early in normal placental development, extra-villous cytotrophoblasts of fetal origin penetrate the uterine spiral arteries of the decidua and myometrium. Invasive cytotrophoblasts replace the endothelial layer of the maternal spiral arteries, transforming them from tiny, high-resistance vessels to big, capacitance vessels (Figure 1) capable of supplying enough placental perfusion to maintain the developing fetus. In preeclampsia, this transition is not complete. The myometrial segments remain thin, and invasion of the spiral arteries by cytotrophoblasts is limited to the superficial decidua. Fisher et al. discovered that during normal conditions, cytotrophoblasts adopt an endothelial phenotype by downregulating the expression of adhesion molecules specific to their epithelial cell origin and adopting an endothelial cell surface adhesion phenotype, a practice called as pseudo-vasculogenesis or vascular mimicry. Because cytotrophoblasts do not switch cell-surface molecules in preeclampsia, they are not able to enter the myometrial spiral arteries adequately. [9]

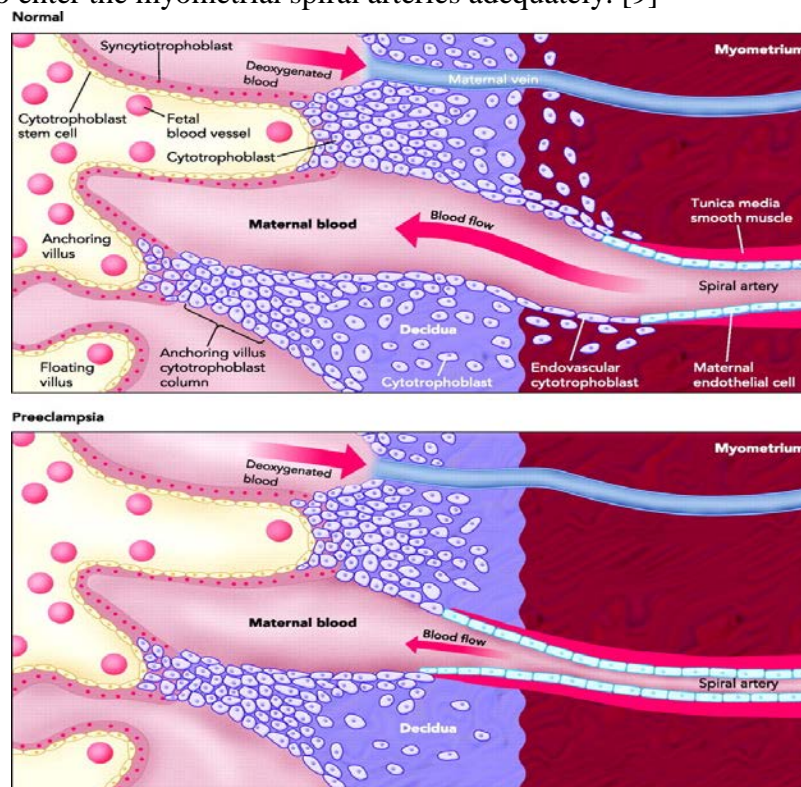


Figure 1. Preeclampsia causes abnormal placentation. In normal circumstances, fetal cytotrophoblasts enter the maternal spiral arteries and convert them from small-caliber resistance channels to large-caliber capacitance vessels. The fetus will receive adequate nutrition as a result of this process. In preeclampsia, cytotrophoblasts are unable to penetrate the spiral arteries, which is a source of debate. We can see that small-caliber vessels maintain the original type

The levels of circulating sFlt1 in women with preeclampsia are significantly higher before the onset of clinical symptoms. As plasma sFlt1 concentrations rise in preeclampsia, the free concentrations of the ligands—VEGF and PlGF—fall. In the mouse model, deleting sFlt1 or introducing exogenous VEGF can offset the antiangiogenic effects of preeclamptic plasma. In genetically altered animals, we also showed that reducing VEGF expression in the glomeruli by 50% produces proteinuria and glomerular endothelial damage akin to preeclampsia. If we lower the level of sFlt1, we can expect the level of VEGF in the maternal vasculature to return to normal. Preeclampsia could be avoided as a result. [10]

### 2.2.2 ET-1

This section aimed to show whether ET-1 production is elevated in PE. The factors responsible for elevated ET-1 in preeclamptic women are unknown. To test if AT1-AA is responsible for increased ET-1 production, researchers retro-orbitally administered IgG from NT pregnant women (NT-IgG) or preeclamptic women (PE-IgG) into pregnant mice during gestation days thirteen and fourteen. It is

extremely difficult to detect due to its short  $t_{1/2}$ , tiny blood volume collection, and high-affinity interaction with its receptor. As a result, we used the levels of preproET-1 mRNA as a proxy for ET-1 production instead. At gestational day 18, kidneys and placentas were collected, and expression levels of ET-1 mRNA were measured by the use of quantitative RT-PCR technology. The expression of preproET-1 mRNA in the kidneys of pregnant mice injected with PE-IgG was found to be 80 percent greater than in the kidneys of animals which treated with NT-IgG. (Figure 2A). Then, in the placentas of pregnant mice injected with PE-IgG, we see a fifty percent increase in the expression of preproET-1 mRNA compared to NT-IgG-injected pregnant mice (Figure 2B).

The next step was to determine if autoantibody-induced increases in preproET-1 mRNA expression in the mouse kidney and placenta were caused by AT1R activation. Losartan, an AT1R blocker, or a 7-aa epitope peptide that neutralizes autoantibodies were coinjected into pregnant mice. The preproET-1 mRNA level in the placentas and kidneys decreases in the PE+losartan group, as shown in the figure. As a result, PE- IgG is responsible for the increase of preproET-1 mRNA expression in pregnant mice's kidneys and placentas. In response to PE-IgG, only alterations in AT1R activation were detected in the placentas and kidneys, with no significant changes in AT1R expression. [11]

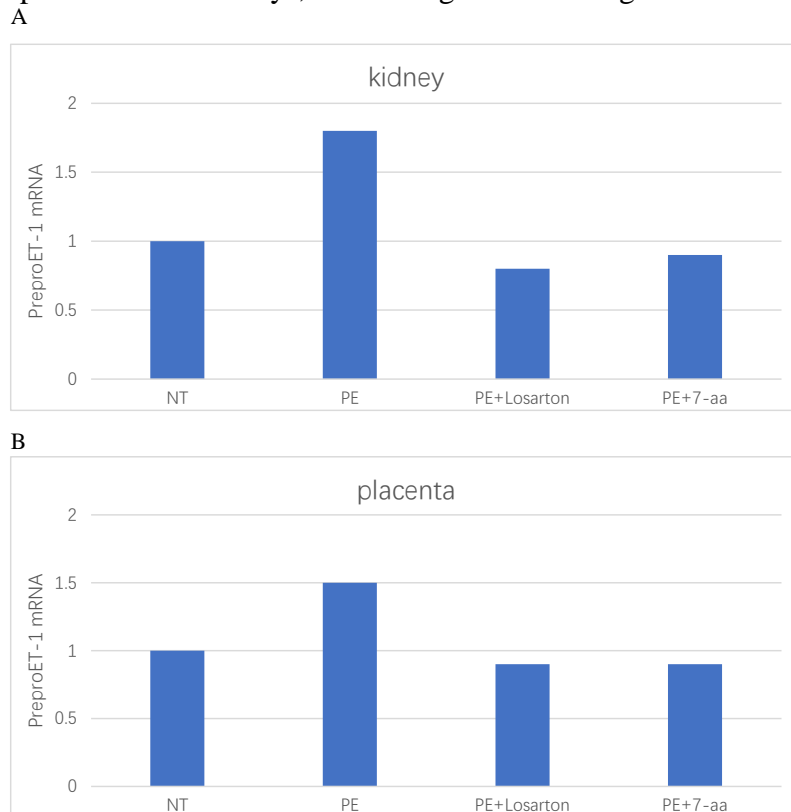


Figure 2. PreproET-1 m is a protein that is produced in the body before it is PE-IgG–injected pregnant mice had higher RNA levels in their kidneys and placentas, while NT-IgG–injected pregnant mice did not. When Losartan or a 7-aa epitope peptide that neutralizes autoantibodies can be given simultaneously, PE-IgG–injected pregnant mice had lower amounts in their kidneys and placentas, while NT-IgG–injected pregnant mice have no significant reduction

### 2.2.3 Relaxin

The ovary's corpus luteum produces relaxin. In pregnancy, the hormone luteinizing hormone, which circulates throughout the luteal phase of the menstrual cycle, starts to rise. Human chorionic gonadotrophin is a main inducer of relaxin production in pregnant women, and it is generated by the placenta.

At comparable gestational ages, circulation levels of immunoreactive H2 relaxin were shown to be identical in women with preeclampsia and normal pregnancy. However, it's unclear if circulating relaxin bioactivity is low under this condition. The LGR8 and LGR7 relaxin receptors were not discovered until recently. Their effect on blood arteries is little understood. Similar to other systems of

receptors, only fewer receptors, raised expression of non-active receptors, or dissoluble receptors could hamper relaxin signaling pathway to the vasculature, decreasing renal vasodilation in pregnancy. Due to the vascular gelatinase activity of relaxin raised represents a proximal stage in the pregnancy's vasodilatory signaling pathway, aberrant MMP-2 activity could ledto preeclampsia's poor renal function. The relaxin-induced vasodilation pathway may be overpowered if the ET, ETA, or ETB receptor is overexpressed on the smooth muscle of renal arterioles' vascular walls. Reduced ETB receptor or endothelial NO synthase activity may increase the risk of preeclampsia in a woman by reducing trophoblast invasion and affecting maternal endothelium function. In a cryptic fashion, much previous work has hinted at comparable possibilities.

### **3. Future perspectives**

#### **3.1 Antihypertensive Therapies**

Because hypertension is the most prevalent medical problem seen during the period of pregnancy, it is calculated that 6–8% of pregnancies will have it. It is quite essential for us to know if it possible to find a feasible therapy by investigating the hypertension.

The use of methyldopa, beta blockers (not the same as atenolol), labetalol, and nifedipine which is release slow is recommended. For emergency preeclampsia treatment, we can utilize labetalol, IV hydralazine, and oral nifedipine. Methylenedopa and labetalol, as well as beta blockers, are recommended as first-line treatments in the ACOG Practice Bulletins. Angiotensin-converting enzyme inhibitors, we believe, are not the best option. Few hypertension is defined as BP 160 mm Hg systolic, DBP 105 mm Hg diastolic, or all of them in preeclampsia. There are also a few more treatments that are suggested. Hydralazine can be given intravenously (IV) at a dosage of 10 milligram or at a dose of 5 milligram (IM). As needed, a dose of five to ten mg can be given with twenty minutes' intervals. Another medicine should be explored if blood pressure does not respond to 20 mg IV or 30 mg IM. In this case, a bolus dose of labetalol 20 mg IV can be given, followed by a follow-up dose of 40 mg 10 minutes later if necessary, and two more doses of 80 mg 10 minutes apart for a total of 220 mg. A substitute agent can be employed if the blood response pressure is not attained. Start with 10 mg of long-acting nifedipine and increase if necessary after 30 minutes. When none of these three medications are functioning or there is proof of hypertensive encephalopathy, we can give at a rate of 0.25 g/kg/minute and up to 5 g/kg/minute sodium nitroprusside. If continue to use it over 4 hours, fetal cyanide poisoning can develop.

#### **3.2 Low-dose aspirin or may be some calcium**

Many researches extensively studied in women to prove that low-dose aspirin is one of the potential method to cure preeclampsia. Low-dose aspirin lowers the risk of preeclampsia by 17%, fetal or neonatal death by 14%, and the relative risk of preterm birth by 8%. Women with a high risk of preeclampsia (hypertension in a previous pregnancy, chronic kidney disease, autoimmune diseases such as systemic lupus erythematosus and antiphospholipid syndrome, type 1 or 2 diabetes, or chronic hypertension) or more than one moderate risk factor for preeclampsia (first pregnancy, age >40 years, pregnancy interval >10 years, BMI >35 kg/m<sup>2</sup> at first visit, family history of preeclampsia. Women with at least two intermediate risk factors (as described above) or at least one high risk factor (as listed above) for preeclampsia should take aspirin as a dose of 75 milligram every day for the same period of time, according to the UK NICE guidelines. [12]

In studies, calcium supplementation for hypertensive illnesses during pregnancy reduced the risk of preeclampsia by 50%, as well as the risk of premature birth and the uncommon occurrence of the composite outcome "death or substantial morbidity." These women were provided a low-calcium diet in these experiments. Meanwhile they also intake 1 g of calcium at least every day as an additional.

Although the proof for calcium supplementation in the stopping of hypertensive diseases is mixed, it is really deserve a further research since it's may be useful.

### **3.3 Endothelium may be a target**

ET-1 is largely produced by endothelial cells, but it is produced in the placenta by the syncytiotrophoblast as well. ET-1 regulates vascular tone and stimulates cell proliferation, differentiation, and also hormone synthesis.

ET receptor antagonists are being utilized to treat a variety of cardiovascular disorders, including congestive heart failure, hypertension, myocardial infarction, vascular restenosis and atherosclerosis, malignancy, renal failure, and cerebrovascular disease. ETA receptor blockers have been shown to alleviate maternal hypertension in a variety of pregnant hypertensive animal models (sFlt-1 infusion, RUPP, AT1-AA infusion models, TNF- $\alpha$  infusion). Despite the fact that blocking the endothelin system during the preeclamptic state appears to be a useful pharmacological intervention, research has found that it is not beneficial to fetal development. ET-1 was discovered to be necessary for appropriate embryonic development in genetically engineered animals. Animals that lack both the ETA receptor and ET-1 exhibit craniofacial abnormalities or cardiovascular, nevertheless knocking out the ETB receptor results in a phenotype that resembles human megacolon (Hirschsprung's disease). Antagonists of endothelin receptors, on the other hand, may still be a viable treatment option for preeclampsia.

## **4. Other diseases associated with preeclampsia**

### **4.1 The Association between Arterial Stiffness and Preeclampsia**

The pulse wave velocity can be calculated using ultrasound to evaluate arterial stiffness (PWV). Women who have high PWVs have been found to have a higher chance of developing preeclampsia. Greater PWV (and hence raised vascular stiffness) is a key hallmark of preeclampsia, according to a meta-analysis. There was a trend toward higher cardiac to brachial PWV in a research of women with preeclampsia 16 months after delivery.

With additional central measurements of PWV (heart to femoral and heart to carotid) not being significantly higher, this shows that vascular stiffness may linger after a preeclamptic pregnancy, impacting mostly the smaller arteries. Reported by Yinon et al. backs up this claim. He discovered that women with early onset preeclampsia in the past, who were six to twenty four months post-partum at the time of the study, had raised arterial stiffness ( $p = 0.0105$ ) using the index of radial augmentation (a measure of arterial stiffness derived in the same way to PWV). The tendency toward higher arterial stiffness among women with late-onset preeclampsia was not significant statistically ( $p = 0.08$ ). [13]

### **4.2 The relationship between Insulin Resistance or Gestational Hyperlipidemia and Preeclampsia**

Normal pregnant hyperlipidemia is defined as a 3-fold increase in triglyceride levels and a 50% raise in terms of total cholesterol, primarily low-density lipoprotein (LDL) and phospholipids, which normally recover to normal standard six to ten weeks after delivery. In Hubel et al research. that contain gestationally matched preeclamptic and normal pregnant women, the LDL cholesterol: apolipoprotein B ratio was shown to be lower in preeclamptic women, whereas triglyceride levels were higher. In preeclampsia, the quantities of soluble vascular cell adhesion molecule-1 in the serum were substantially greater. The levels of total cholesterol, free fatty acids, apolipoprotein B, and LDL cholesterol all rose. Predominance of smaller, denser LDL, Pre-eclampsia is characterized by a potential contributor to endothelial cell dysfunction, according to this study. These findings are also corroborated by Sattar et al findings from a comparable study. In these women, aberrant lipid indicators may have a role in the risk of cardiovascular disease.

Insulin sensitivity is reduced during pregnancy to allow for greater glucose transport to the fetus. Preeclampsia, in other words, causes insulin resistance to be increased for a period of up to three months following delivery. Diabetes mellitus risk is about 2-fold greater following a preeclamptic pregnancy, according to research.

### 4.3 The impact between Peripheral Vascular Disease or Stroke and Pre-Eclampsia

Fewer research has looked at the link with the risk of stroke or peripheral vascular disease later in life and preeclampsia. Firstly, a report of World Health Organization recognized gestational hypertension exclusively in females who used the oral contraceptive pill as a thromboembolic illness risk factor. Pre-eclampsia has been thought as a danger factor for stroke in the Study of Stroke Prevention in Young Women. Female with a history of pre-eclampsia had a higher risk of stroke death (adjusted RR: 3.59; 95 percent CI: 1.04 to 12.4) than women with normotensive pregnancies, according to this study (adjusted RR: 3.59; 95 percent CI: 1.04 to 12.4). Even after taking into account established risk variables, Women who had hypertension during pregnancy had a higher risk of stroke, which remained substantial. In the Family Blood Pressure Programme study (HR: 2.10; 95 percent CI: 1.19 to 3.71) and the previously discussed Taiwanese population-based cohort study (HR: 14.5; 95 percent CI: 1.3 to 165.1) with up to 6.8 years of follow-up. [14]

## 5. Conclusions

As all details described above, the mechanism of how preeclampsia occurs, the distribution of it and possible methods to cure it is becoming clearly than before. This review is aiming to conclude some aspects of this attracting disease from other people's paper. And after completing this review we think we should give more attention to the hypertension to cure this disease because it's a common symptom when fall this disease. And also we deem that angiogenic is also a key factor associated with preeclampsia that we should get more relevant research on it.

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