

# New Pharmacological Opportunities for Prevention of Preeclampsia

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## Abstract

Preeclampsia (PE) is a disorder in the pregnancy, with a worldwide prevalence of 5 to 8%. Is one of the leading causes of maternal and perinatal morbidity and mortality? Actually exist different diagnostic criteria, however due to the complexity of PE and signs and symptoms that make up this syndrome could be not clearly evident. It has recently been postulated pathophysiology of PE in three pathophysiologic processes: inadequate uterine remodeling, placental dysfunction and maternal endothelial dysfunction. Despite advances in the treatment of PE and decades of research, the results of medical interventions have failed to significantly decrease the morbidity and mortality of this disease. The main reason for this is perhaps the multifactorial origin of pathogenic processes that lead to the development of PE. That is why the approach to patient management has been present PE prevent or its inception happening late in pregnancy.

The key to prevention is knowledge of the factors that trigger pathophysiological processes that culminate in the presentation of the PE. However, efforts to determine the origin of these processes are still poorly or incompletely understood, on the one hand, because the approach to research in this population may be unethical compared to other diseases of women in non - pregnant population, the multifactorial origin and the difficulty of carrying out studies in the early stages of pregnancy because they can endanger both mother and as the product.

**Keywords:** Preeclampsia; Eclampsia; Hypertension induced pregnancy

## Introduction

Preeclampsia (PE) involves dysfunction in pregnancy, with consequences of morbidity and mortality worldwide. The prevalence of PE is 5% to 8%. PE is characterized by systolic blood pressure (SBP)  $\geq$  140 mmHg or diastolic blood pressure (DBP)  $\geq$  90 mmHg as assessed on two occasions at least 4 hours apart. Additionally, PE is also characterized as the presence of proteinuria of  $>$ 300 mg per 24 hours or when urinary dipstick proteinuria is  $\geq$  1, after 20 weeks of pregnancy, or in the absence of proteinuria, the first appearance of thrombocytopenia [1,2]. PE is one of the major causes of maternal mortality, resulting in 50,000 to 60,000 deaths annually worldwide. This disease also increases the risk of complications in the mother and development of cardiovascular disease in later life in the newborn and the mother [2].

PE is a multisystem, unique human syndrome because it is not naturally present in animals. PE is specific to pregnancy because once the placenta is removed, the clinical findings disappear. These features make it difficult to research because experimental animals do not provide data that can be properly extrapolated. The fact that PE is only present in pregnancy hampers investigations because of ethical considerations involving the mother and fetus that could jeopardize the healthy progression of the pregnancy. There are multiple genetic and environmental factors involved in the development of the pathogenesis of PE. These factors are still not clearly understood. Additionally, despite the knowledge of the pathophysiology of PE, there are still no available drugs for preventing or curing PE. However, the recommendation for protecting the life of the mother is termination of pregnancy. Therefore, more research on this topic is required to provide as much information as possible to facilitate decision-making. The best time to stop pregnancy and the best interventions to prolong the safety of the woman and her fetus [1].

This review summarizes current recommendations on the management of PE. New findings on the pathogenesis of this disease are discussed, as well as new opportunities to improve identification of patients at risk and potential therapeutic targets. These targets could be the focus of attention in future years as drug targets to prevent PE.

## Definition of PE

PE is the result of high endothelial dysfunction secondary to inadequate trophoblastic invasion that occurs in the second half of pregnancy. PEE is defined as the presence of hypertension after 20 weeks of gestation accompanied by new onset of proteinuria. In the absence of proteinuria, signs and symptoms of organ damage, including visual disturbances, headache, epigastric pain and/or edema of rapid development, indicate PE [1,2].

## Diagnostic criteria of PE

Because of the complexity of PE, and despite the systemic damage caused by endothelial dysfunction, many of the signs and symptoms that comprise this syndrome are not clearly evident. The elevation of the blood pressure is the known sign of PE. The diagnostic criteria for PE have evolved over time to achieve a timely and specific diagnosis.

Diagnosis of PE includes the development of hypertension after 20 weeks of gestation in a woman with previously normal blood pressure (Table 1). Hypertension is not the only criterion for diagnosing PE. In many cases, PE is associated with new onset of proteinuria. However, in the absence of proteinuria in the diagnostic range, a diagnosis can be established with new onset of thrombocytopenia, pulmonary edema, or visual or neurological disorders, among others [1,2].

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<b>Blood pressure</b>	SBP $\geq$ 140 or DBP $\geq$ 90 mmHg on two occasions within 4 h after 20 WG in a woman with previously normal blood pressure. If SBP $\geq$ 160 or DBP $\geq$ 110 mmHg, hypertension can be confirmed in a short time interval (minutes) to facilitate the initiation of antihypertensive therapy.
<b>Plus</b>	
<b>Proteinuria</b>	$\geq$ 300 mg in 24 h urine (can be extrapolated to the time of collection). Ratio protein / creatinine $\geq$ 0.3 mg / dL. Strip 1+ (used only if there are no other quantitative method).
<b>Or in the absence of proteinuria, new onset hypertension with new onset of any of the following:</b>	
<b>Central Nervous System</b>	<sup>1</sup> Headache / visual disturbances. <sup>2</sup> Eclampsia. RPLS. cortical blindness or retinal detachment. Glasgow $<$ 13. stroke. TIA. Reversible ischemic neurological deficit.
<b>Cardio respiratory</b>	<sup>1</sup> Chest pain. SatO <sub>2</sub> $<$ 97%. <sup>2</sup> Severe uncontrolled hypertension over a period of 12 hours despite the use of 3 antihypertensive drugs. SatO <sub>2</sub> $<$ 90%. Intubation. Pulmonary edema. Need for positive inotropic support.
<b>Hematologic</b>	<sup>1</sup> Leukocytosis. Elevation of INR or PT. Thrombocytopenia. <sup>2</sup> Platelet count $<$ 50 $\times$ 10 <sup>9</sup> / L. Transfusion.
<b>Renal</b>	<sup>1</sup> Elevated serum creatinine, serum uric acid elevation. <sup>2</sup> Acute kidney damage. New indication for dialysis appearance
<b>Hepatic</b>	<sup>1</sup> Nausea. Threw up. Epigastric pain right upper quadrant pain. Elevated liver enzymes, bilirubin or LDH. Hypoalbuminemia. <sup>2</sup> Liver failure. Bruising or hepatic rupture
<b>Feto-placental</b>	<sup>1</sup> Abnormal FHR. Oligohydramnios. <sup>2</sup> Abruptio placentae with maternal or fetal compromise. Birth of a dead product.
1 Warning signs. 2 Complications. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MmHg: Millimeters of Mercury; WG: Weeks of Gestation; RPLS: Reversible Posterior Leukoencephalopathy Syndrome; TIA: Transient Ischemic Attack; SatO <sub>2</sub> : Oxygen Saturation; INR: International Normalized Ratio; TPT: Thromboplastin Time; LDH: Lactate Dehydrogenase; FHR: Fetal Heart Rate	

**Table 1:** Diagnostic Criteria for PE.

## Classification of PE

PE is classified on moderate and severe. In moderate PE, hypertension is present with sustained SBP values of 140-159 mmHg or DBP values of 90-109 mmHg and proteinuria is present, or there is one or more of the warning signs and symptoms shown in Table 1. In severe PE, SBP is  $>$ 160 mmHg or DBP is  $>$ 110 mm and proteinuria is present, or there is one or more complications (Table 1) [2].

There are several guidelines with different diagnostic criteria of PE, but all of them agree on the evidence of signs and symptoms of target organ damage as a substitute for proteinuria when this is accompanied by hypertension.

## Current treatment of PE

The first consideration in the management of PE is to maintain the safety of the mother and fetus. The second consideration is to ensure delivery of a mature newborn who does not require prolonged intensive care [1,2]. Once PE is diagnosed, subsequent management will depend on the following: the results of maternal and fetal assessment, gestational age, and presence of labor or rupture of the membranes, vaginal bleeding, and the wishes of the mother.

In medical practice, in a woman with PE with constant SBP  $<$ 160 mmHg and DBP  $<$ 110 mmHg, treatment without pharmacological intervention is preferred. However, this practice has been in decline based on new information that the use of drug therapy has a greater benefit. However, antihypertensive treatment in this group is limited to methyldopa, labetalol, and nifedipine. These interventions reduce the risk of severe hypertension, but do not diminish the progression of PE [2].

In women with severe PE who present before fetal viability, maternal stabilization is recommended after interruption of pregnancy. This is performed in an intensive care unit and parenteral treatment is combined with labetalol, hydralazine, and even nitroglycerin or

nitroprusside in addition, magnesium sulfate can be used for prevention of seizure activity, but not for its hypotensive effect [2].

Once treatment is established, close monitoring is required to identify the presence of serious complications of PE, which can be divided into maternal and fetal complications. Maternal complications include eclampsia, reversible posterior leukoencephalopathy syndrome, cortical blindness or retinal detachment, transient ischemic attack, uncontrolled severe hypertension, pulmonary edema, myocardial ischemia or infarction, thrombocytopenia, acute renal damage, liver dysfunction, placental abruption, and maternal death. Fetal complications include still birth, intrauterine growth restriction, low birth weight, and prematurity [2].

Despite efforts to treat PE, treatment is symptom-based and focused on controlling blood pressure. With regard to the time of delivery, gestational age should be the maximum feasible. However, in severe PE, in addition to antihypertensive treatment, termination of pregnancy is recommended if it is greater than 34 weeks. If the pregnancy is less than 34 weeks and the mother and product are stable, the pregnancy should be continued with administration of corticosteroids [1].

Currently, there are multiple criteria for better management of PE, but the only cure for PE is termination of pregnancy. This results in a difficult decision for the physician and the mother because of the psychological burden, and the social and economic morbidity.

## Strategies for prevention of PE

Despite advances in the treatment of PE and decades of research, the results of medical interventions have failed to significantly decrease the morbidity and mortality of PE. The main reason for this failure could be the multifactorial origin of pathogenic processes that lead to the development of PE. Therefore, the approach for management patients with PE is preventing its late occurrence in pregnancy. The key to prevention of PE is knowledge of the factors that trigger

pathophysiological processes that culminate in the presentation of the PE. However, efforts to understand the origin of these processes are still poorly or incompletely understood. There is a lack of knowledge because the approach to study this population may be unethical compared with diseases of nonpregnant women. The multifactorial origin of PE and difficulty in carrying out an investigation in the early stage of pregnancy because it can endanger the mother and fetus has made research difficult [3]. Understanding the developmental characteristics of the placenta in pregnancy at high risk for PE is essential for understanding the pathophysiology and developing strategies for prevention. Generally, the pathophysiological process of PE can be divided into three stages.

### **Inadequate uterine remodeling**

In the PE invasion of interstitial part of the uterus it is relatively preserved, but in the invasion endo- and perivascular uterine artery, the invasion of the decidual arteries by extrafuzziness, the cytotrophoblasts decreases 56% and the invasion of the arteries in the myometrium on 76-18%. Endothelial cells are not replaced by trophoblasts and the layer of smooth muscle cells is not affected. Therefore, the uterine arteries have a smaller diameter and retain their vasoconstrictor potential. This vasoconstrictor potential is the source of placental hypoxia, maladaptation of blood flow, and the phenomenon of ischemia – reperfusion [3,4].

Inadequate trophoblastic invasion produces an imbalance between angiogenic factors that include vascular endothelial growth factor (VEGF) and platelet growth factor, as well as antiangiogenic factors, such as VEGF-1 receptor, also called soluble fms-like tyrosine kinase-1 (sFlt-1 or sVEGFR-1) Levels of sFlt-1 are elevated during the first 10 weeks of gestation. Levels of sFlt-1 are more elevated in pregnant women with PE than in those without PE, with a second peak between gestational weeks 26 to 29. This suggests that blocking VEGF action results in poor formation of the placental vascular bed [5].

Another event that occurs early in the onset of symptoms of PE is elevation of certain inflammatory cytokines, such as tumor necrosis factor-alpha and the interleukins (IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, and IL-8). Women with PE may initially have lower plasma IL levels compared with healthy pregnant women, but as pregnancy progresses, cytokines become elevated. The activation of macrophages and natural killer cells leads to lysis trophoblastic decidual cells [5]. Additionally, women who are predisposed to PE are thought to have changes in the vascular bed. These changes include generalized disruption of uterine spiral arteries, even before the start of trophoblast invasion [3].

### **Placental dysfunction**

Inadequate placental trophoblast invasion occurs dysfunction, in which several elements produced by the placenta are released into the maternal circulation. In pregnancy there is a physiological state of hypoxia is second to tenth week of pregnancy, when an increase of oxygen occurs by the spiral arteries. However, in pregnancies with PE, hypoxia remains throughout pregnancy. This situation is indicated by permanently high levels of hypoxia-induced factor-1. The state of hypoxia increases gene expression of fetal hemoglobin, which is linked to the pathogenesis of PE. Several studies [3,6] have shown increased expression and accumulation of free fetal hemoglobin in the placenta with PE due to oxidative damage to the placental barrier. Free hemoglobin and its metabolites are toxic in several ways as follows. Ferrous hemoglobin ( $Fe^{2+}$ ) binds strongly to the vasodilator nitric oxide (NO) and reduces the availability of free NO, resulting in vasoconstriction. Hemoglobin ( $Fe^{2+}$ ) with attached oxygen generates oxygen-free radicals spontaneously. Heme creates

an inflammatory response via activation of neutrophils and cytokine production [3,6].

The phenomenon of hypoxia/re-oxygenation, which occurs during oxidative stress, induces placental dysfunction in the placenta. Cellular stress includes alterations in the redox state in maturation of proteins, leading to accumulation of misfolded proteins in the lumen of the endoplasmic reticulum (ER). This produces stress called „endoplasmic reticulum stress“, which triggers an adaptive response called the unfolded protein response. This response reduces the amount of protein in the ER lumen. ER stress is associated with PE of the placenta and intrauterine growth retardation. Misfolded proteins can also be detected in urine as a potential biomarker for the Congo red test [6,7].

The fetal trophoblast is considered an alloantigen and the mother reacts to this and mounts an immune response. quarter It is known that the uterus-fetal perfusion begins towards the end of the first quarter while high levels of microparticles of microvilli of the syncytiotrophoblast (STMBs) in the maternal circulation are detected during the second and third quarters. Oxidative stress increases the release of STMBs and other debris in the maternal circulation; on PE a secondary inflammatory response could be due to STMBs [3,5].

### **Maternal endothelial dysfunction**

It corresponds to the alteration of endothelial function, characterized by an increase in the concentration of vasopressor agents and platelet aggregating as thromboxane A2 and endothelin-1 (TX A2), and a decrease of the vasodilator and antiplatelet substances such as NO and PG2. This imbalance of vasoactive substances, with increased sensitivity to angiotensin II, determined a state of vasoconstriction. This results in increased peripheral vascular resistance, and thus causes an increase in blood pressure. To this increased, endothelial permeability is associated [8].

NO, the main vasodilator in the placenta is involved in regulation of the fetoplacental unit, vascular reactivity, placental vascular resistance, trophoblast invasion, apoptosis, and adhesion and aggregation of platelets in the intervillous space. Furthermore, asymmetric dimethylarginine (ADMA) is recognized as a biomarker of endothelial disorders, cardiovascular disorders, hypercholesterolemia, and stroke. ADMA precursor formed NO, L-arginine, in the presence of oxygen and the cofactor tetrahydrobiopterin, with production of L-citrulline. ADMA is formed when arginine residues in proteins are methylated by the action of the arginine proteins methyltransferase types I and II. ADMA is a competitive inhibitor of L-arginine for three NO synthase isoforms [9].

In early pregnancy, a reduction in ADMA levels and a concomitant increase in NO can lead to hemodynamic adaptation in response to an increased need for organ perfusion in pregnancy. Uterine relaxation then allows intrauterine growth without disturbance to the fetus. At the end of pregnancy, increasing ADMA levels physiologically prepares the uterine muscle fibers for greater contractile activity, which is required to counteract the uterine relaxation induced by NO [9,10].

Recent studies have suggested that plasma ADMA concentrations may serve as a biomarker of risk for endothelial dysfunction. Decreasing ADMA levels are observed in normal pregnancy with a further increase correlated with gestational age. In pregnancy at high risk of PE, ADMA levels increase to higher levels than observed in normal pregnancy. Holden et al. showed that the mean plasma ADMA concentrations in women with PE in the third quarter were 1.17  $\mu$ mol/L, which were significantly higher than those in controls [9,10].

TXA 2 is an arachidonic acid metabolite prostaglandin H synthase derivative (PGHS) which is produced in platelets and endothelial cells. Constrictor effects of TXA 2 in vascular smooth muscle are mediated by the TXA 2 receptor (TP), a member of the family of heterotrimeric prostanoid receptors coupled to protein. TXA 2 is regarded as a vasoconstrictor, which is increased in women at high risk of PE. Circulating levels of TXB 2 (a TAA 2 metabolite) are significantly increased in pregnancies with PE. The vasoconstrictive effects of TXA 2 in PE are amplified by their ability to potentiate the vasoconstrictor effects of angiotensin II and endothelin-1. NO and prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) inhibit prostaglandin TXA 2 actions through TXA 2 receptor desensitization. However, pregnancies with PE, NO production and PGI<sub>2</sub> are affected. DNA methylation of omental arteries shows that the gene thromboxane synthase is hypomethylated frequently in the vessels of women with PE than in those of women without PE. This finding is also associated with increased expression of thromboxane synthase in the omental arteries of women with PE. Taken together, these data suggest that, in PE, there is an imbalance in production of vasoconstrictors (TXA 2) and vasodilator prostanoids (PGI<sub>2</sub>), which are modulated by epigenetic modifications [11].

Autoantibodies against angiotensin receptor 1 are present in pregnancy. These autoantibodies have a pharmacological effect similar to that of angiotensin II agonists. Stimulation of the angiotensin receptor 1 receptor by these circulating autoantibodies could also be responsible for hypertensive symptoms of PE because concentrations of these circulating autoantibodies increase after 20 weeks of gestation [5,12].

## Prevention of PE

### Identifying high-risk patients

The pathogenic process of PE begins during the first quarter, long before clinical signs are evident. Therefore, identifying early biomarkers is difficult. Although there is no ideal method of predicting development of PE, distinguishing between women who are at a high risk of PE and those with a low risk is possible.

The most important factors for development of PE are as follows [13,14]:

1. PE in previous pregnancies is a risk factor for development of PE. Women who have PE in the first pregnancy have a seven times risk of PE in the second pregnancy Risk ratio (RR 7.19; 5.85 to 8.83).
2. Hypertension in pregnancy is a factor involved in development of PE. The prevalence of chronic hypertension in women who develop PE is 12% (RR 5.2; 1.5 to 17.2).
3. Renal disease is a factor involved in development of PE. The prevalence of renal disease in women who develop PE is 5.3%.
4. Diabetes mellitus 1 and 2 are factors involved in development of PE. The probability of PE almost quadruples if diabetes is present before pregnancy (RR 3.56; 2.54 to 4.99).
5. Autoimmune diseases are important factors for developing PE. Women who develop PE are more likely to have an autoimmune disease (RR 6.9; 1.1 to 42.3). Antiphospholipid syndrome significantly increases the risk of developing PE (RR 9.72; 4.34 to 21.75).

Moderate risk factors of PE are as follows [13,14]:

1. A primigravid pregnancy is a moderate risk factor. Nulliparity almost triples the risk of PE (RR 2.91; 1.28 to 6.61).

2. Maternal age is a moderate risk factor, with the risk of PE increasing by 30% for every completed year after 34.9 years. The risk increases two-fold in nulliparous women aged  $\geq 40$  years (RR 1.68; 1.23 to 2.29).
3. An intergenetic interval  $>10$  years is a moderate risk factor of developing PE. The risk of PE in women with intergenetic interval greater than 10 years is approximately the same as that of nulliparous women (RR 1.12; 1.11 to 1.13).
4. Body mass index  $\geq 35$  kg/m<sup>2</sup> is a moderate risk factor, with the risk of PE increased up to 50% (RR 4.39; 3.52 to 5.49).
5. A family history of PE almost triples the risk of PE (RR 2.90; 1.70 to 4.93).
6. Multiple pregnancies are a moderate risk factor of developing PE. Twin pregnancies nearly triple the risk of PE (RR 2.93; 2.04 to 4.21), while a triplet pregnancy is nearly triple the risk of a twin pregnancy (RR 2.83; 1.25 to 6.40).

However, these factors predict only 30% of women who develop PE. Biomarkers in maternal blood have a modest predictive potential. Moreover, the combination of Doppler ultrasound at the end of the first quarter, combined with plasma levels of placental growth factor and pregnancy-associated plasma protein-A are proposed as predictors of early onset of PE in pregnancy [13].

Moreover, the combination of Doppler ultrasound at the end of the first quarter combined with plasma levels of placental growth factor and protein-A associated with pregnancy (PAPP-A) are proposed as predictors of early onset of PE in the pregnancy [13].

### Potential biomarkers of PE

As mentioned in previous lines, there is now a reliable biomarker to predict the onset of PE. However, many potential biomarkers are currently under investigation. Some of these novel biomarkers depend on molecular technology and deserve mention because they have been shown to be promising (Table 2).

The heterogeneity of the pathogenesis of PE makes it difficult to establish a single biomarker as a predictor of this disease. In the short term, a combination of markers may be appropriate. However, is not enough the information that currently exists. Moreover, if these biomarkers lack test can be used to detect the occurrence of PE in apparently healthy patients without risk.

## Treatment to prevent PE

### Calcium supplementation

A low calcium intake can cause high blood pressure, either by stimulating parathyroid hormone or renin release. This increases intracellular calcium in vascular smooth muscle and leads to vasoconstriction. Calcium supplements reduce the release of parathyroid hormone and intracellular calcium, and thus reduce smooth muscle contractility. Hofmeyr et al. conducted a systematic review in 2007 and found that women with a low calcium intake and a low risk of PE taking calcium have a relative risk of 0.48 (95% confidence interval 0.33 to 0.69) [27]. Additionally, this effect is greater in women at high risk (RR 0.22; 95% confidence interval 0.12 to 0.42).

### Acetylsalicylic acid

The rationale for administration of low-dose aspirin is based on its anti-platelet aggregating and anti-vasoconstrictor activity. This

Biomarker	Characteristics	Studies
sFlt-1/PIGF [15]	It has been included sFlt-1/PIGF ratio German PE guidelines for care. A ratio of sFlt-1/PIGF: 38 at any time during pregnancy is considered suspected PE, while PE is considered diagnostic of figures 85 and 110 before and after 34 weeks of gestation, respectively.	Stepan in 2015, shows that circulating levels of sFlt-1 are increased significantly more than a month before the appearance of the first clinical symptoms detectable. In the case of PIGF, significantly lower concentrations observed in women who subsequently presents placental dysfunction since the end of the first quarter. They concluded that s and need further studies to demonstrate the benefits of using the ratio of sFlt-1/PIGF in terms of reduction of maternal and fetal risks and resource optimization.
Soluble endoglin (Seng) [16]	A truncated form of the receptor for transforming growth factor-β1 (TGF) TGF-β2 and that interferes with binding of TGF-β1 to its receptor, and thereby affect the production of nitric oxide, vasodilation, and capillary formation by the endothelial cells in vitro.	Levine et al. Showed in 2006, in a nested case study that circulating levels of soluble endoglin increased from two to three months before the clinical onset of PE controls. After the onset of the disease, the average level of serum in women with PE remains high until the end of pregnancy (31.0 ng per milliliter, as compared to 13.3 ng per milliliter in controls (p<0.001 ) A higher level of soluble endoglin is usually accompanied by an increase in the proportion of sFlt1:PIGF.
PAPP-α [17, 18]	Highly glycosylated protein that is produced by the development of trophoblast cells has proven to be a factor, insulin-like growth, therefore, as expected, low serum levels of PAPP-A are associated with a higher incidence of PE.	The studies are contradictory, while some show association with low levels of PAPP-A, others observed elevations in serum. Both observations were made by Bersinger et al. In two separate case-control study in 2003 and 2004 respectively.
Activin-A [19]	This glycoprotein is released largely by the unit of placental fetus during pregnancy. Activin-A is involved in various biological activities.	A case-control study conducted in 2004 by Ong et al. They found that levels of activin-A, glycoprotein and member of the TGF-β family, is higher in the late-onset PE in the early start (1.92 MoM). It has been observed that increasing Activin-A occurs before 14 weeks gestation in pregnancies with PE.
PP-13 [20]	The severity of the signs of PE is proportional to the increase PP13 the first to the third trimester of pregnancy.	Gonen et al, in 2008 they conducted a study of cases and controls to determine the values of PP-13, a member of a family of binding proteins b-galactoside-specific in the syncytiotrophoblast, during pregnancy carbohydrates called lectins. At the beginning of pregnancy, between weeks 5-7, serum levels are significantly lower than in normal pregnancies. With increasing STBM release, the concentration of PP-13 in maternal blood as the PE advances.
cystatin C [21]	A marker set for kidney function, which increases as the glomerular filtration rate falls controls.	Thilaganathan et al., in 2009, conducted a nested case study to determine levels of cystatin C. Finding that in the PE, placental expression of cystatin C is significantly increased in the first trimester of pregnancy compared to those with normal pregnancy (0.65 mg / L, p=0.0001).
Fetal hemoglobin [22]	Oxidative damage induced placental production and leakage in the fetal-maternal fetal hemoglobin barrier.	Recent studies have identified as a predictor in the first and second quarters.
ADMA and Homocysteine [23]	Serial measurements of their concentrations may be useful to identify women at risk.	López-Alarcón et al, in a cohort study in 2015 found that ADMA and homocysteine (Hcy) increases gradually throughout pregnancy with PE, but remain constant in women without complications. ADMA and homocysteine increase 1 month prior to the onset of PE. Increases of up to 80 nmol of ADMA and Hcy 1000 nmol to 1 month prior to the onset of PE have demonstrated the best potential for prediction.
AngiomiRNAs [24-26]	The AngiomiRNAs expressed in the EP are: miR-210. His expression is stimulated by hypoxia. Inhibits migration of cytotrophoblast cells. miR-16 represses miR-VEGF production in mesenchymal stem cells derived from the decidua (MSCs), and induces cell cycle arrest in the transition G0 / G1. miR-155, Its overexpression reduces NOS expression.	There are many more angiomiRNAs that have been found and depending on its expression level, participate in the processes taking place in the PE, but despite the knowledge and the great advances of the role of angiomiRNAs, research to validate them as biomarkers predictive is still scarce.

**Table 2:** Potential biomarkers of PE.

activity inhibits TXA<sub>2</sub> formation without inhibiting the production of prostaglandins. However, less restricted conditions of studies in gestational age of onset of the intervention, the administered dose and schedule have led to controversial results about the positive role of the administration of aspirin at the onset of PE and severity thereof.

In 2015, Campos published a systematic review of the results obtained in studies with aspirin as an intervention for preventing PE based on papers published in the last 30 years. For analysis, this author divided the studies into two groups: one with early administration of aspirin, defined as administration in the first quarter and before 16 weeks of gestation; and a second group with late administration, defined as subsequent administration to the 16 weeks of gestation. Campos concluded that because there are no pharmacological alternatives, physicians should administer low doses of aspirin from 60 to 150 mg per day starting in the first quarter through to week 16 (Figure 1). This should be performed overnight because it helps in reducing the risk of PE [28].

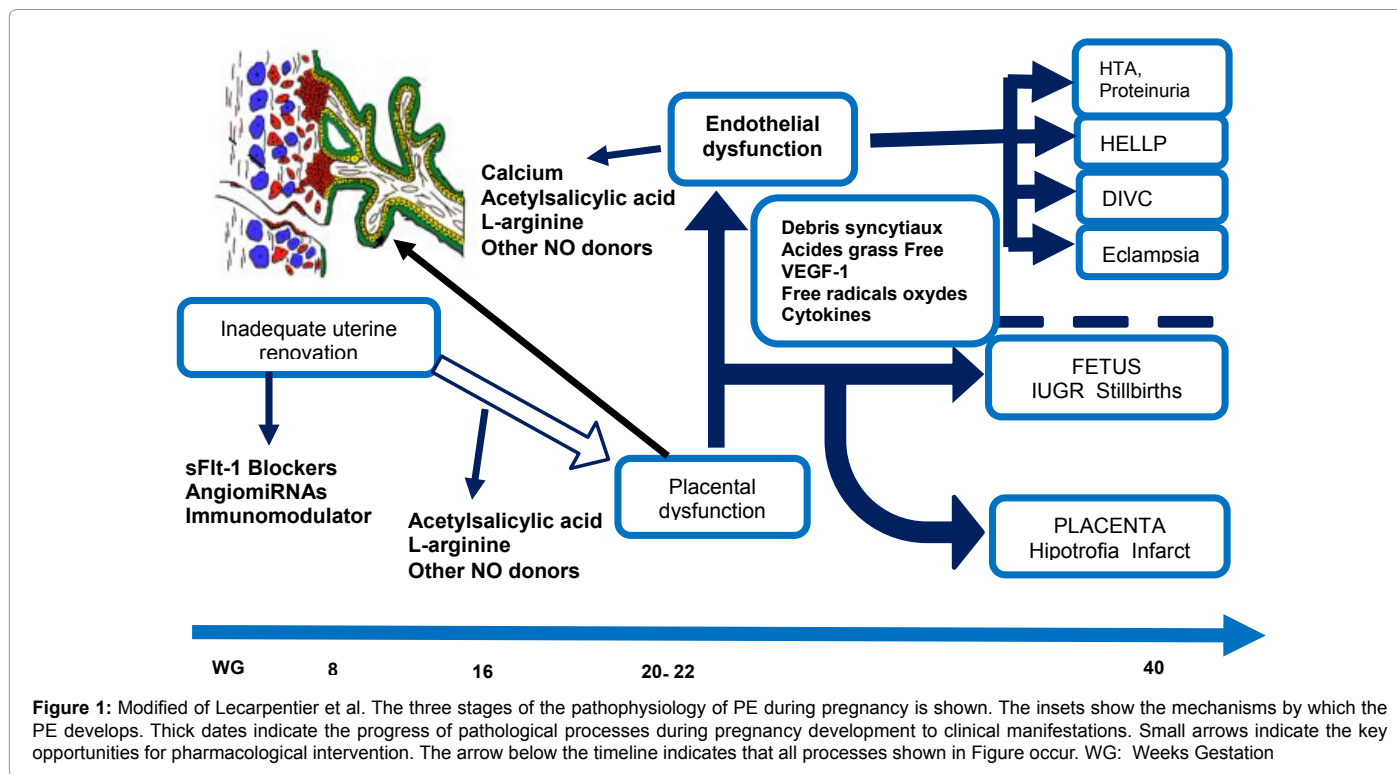
## NO pathway

Endothelial dysfunction and impaired bioavailability of NO are maternal manifestations of PE. Therefore, supplementation with

exogenous NO donors could be a solution of treatment (Figure 1). L-arginine acts as a precursor of NO, and becomes NO and L-citrulline by NO synthase. L-arginine has been the subject of studies designed to investigate its preventive role in women with a high risk of developing PE.

In a clinical trial, Lees et al. found that low doses of a nitroglycerin transdermal patch, as prophylaxis, starting late in the second quarter did not reduce the incidence of PE, premature delivery, or restriction of fetal growth [29]. However, survival analysis of adverse events showed a significantly reduced risk of an adverse event, equivalent to a 73% reduction in risk [29]. Another clinical trial conducted by Groten et al. found that pentaerythritol tetranitrate, an organic nitrate with prolonged action, improved uteroplacental perfusion in women at risk of PE [30]. This compound also reduced the frequency of PE, growth restriction, and premature birth in high-risk women [30].

Camarena et al. performed a clinical trial, which included 100 pregnant women at high risk for PE to estimate the effectiveness and safety of L-arginine in preventing PE in this population [31]. They included two study groups; one group was administered 3 g of L-arginine per day in 600 mg capsules, and the second group was provided placebo capsules. They found a significantly lower incidence



of PE in the L-arginine group compared with the placebo group (6% vs 23%,  $p=0.016$ ). They also reported a higher incidence of severe PE in the placebo group compared with the L-arginine group (14% vs 2%,  $p=0.02$ ). Additionally, SBP, DBP, and mean arterial pressure were significantly lower in the L-arginine group compared with the placebo group ( $p=0.022$ ,  $p=0.035$ , and  $p=0.023$ , respectively). The most common adverse event was dyspepsia, which was higher in the L-arginine group than in the placebo group (26% vs 6%,  $p=0.008$ ). The authors concluded that administration of L-arginine is effective and safe for preventing PE [31].

## Conclusions

Currently, there is no effective treatment for decreasing the morbidity and mortality of women with PE. Antihypertensives are used to reduce hypertension, which is the main symptom of PE and produces the most serious consequences. However, antihypertensives only prolong pregnancy until the fetus reaches sufficient maturity to live outside the uterine environment. Therefore, administration of corticosteroids after 34 weeks becomes necessary for lung maturation. However, antihypertensives do not always reduce the effects of PE, and often the outcome for the mother and fetus is not favorable. Therefore, in recent years, efforts have focused on finding a way to prevent the occurrence of PE.

More studies are required to identify the intrinsic factors involved in development of the early stages of changes that occur during placentation because information of current studies is limited. Information is also needed regarding the possible differences between healthy women and those presenting with PE, even before trophoblast invasion occurs. However, studies of this nature are not acceptable because the risk of subjecting pregnant women to invasive procedures is not justified without a clear benefit.

Identification of women at high and low risk for PE through

the clinic is currently the best tool to determine the use of available resources in the management of these patients. However, these factors predict only 30% of women who will develop PE and biomarkers in human blood have a modest predictive potential. Heterogeneity of the pathogenesis of PE makes establishing a single biomarker as a predictor of this disease difficult. The best chance in the short term for prediction may be using a combination of several markers. Moreover, the combination of Doppler ultrasound at the end of the first quarter combined with plasma levels of placental growth factor and PAPP- $\alpha$ , are proposed as predictors of early onset of PE in pregnancy. However, further research and development of criteria that can be used are required.

Once patients who develop PE are identified, interventions that eliminate the risk or delay their appearance during the course of pregnancy are required. However, there is also a gap in knowledge in this area because there are few interventions that are useful. Oral calcium supplementation is recommended as a preventive measure for PE in pregnant women with risk factors for PE and low calcium intake. However, calcium does not have any observable effect on women with adequate calcium intake. Ingesting low doses of aspirin discretely decreases the incidence of PE. However, the effectiveness of aspirin is controversial, despite being a recommendation in every guideline for management of PE. The use of NO donors, such as nitroglycerin or pentaerythritol tetranitrate, shows no benefit in reducing the incidence of PE. Moreover, L-arginine has been the subject of many recent studies as a precursor of NO synthesis, and has been shown to reduce the incidence of PE. However, studies have differed as to the time of administration, dose, and the characteristics of the study population, as is the case of aspirin. Therefore, well-designed, randomized, controlled studies are required to establish the effectiveness of treatments. Considering that L-arginine is a food supplement that is widely available, conclusive evidence about its beneficial effects could provide a viable means to prevent PE.

Finally, innovative therapies focused on elimination or antagonism of anti-angiogenic factors, such as sFlt1, are also being investigated. Additionally, there has been a failure to prove whether the derivative knowledge of angiomiRNA studies can be applied to preventive treatment of PE as a method to increase or silence gene expression of factors involved in the early development of PE.

Current research suggests that there is hope that the presentation of PE will no longer have unpredictable and devastating consequences.

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