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Pharmacological Opportunities for Prevention of Preeclampsia

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<http://dx.doi.org/10.5772/intechopen.70164>

Abstract

Preeclampsia (PE) is a disorder that occurs during pregnancy, it has an estimated world-wide prevalence of 5–8%, being one of the leading causes of maternal and perinatal morbidity and mortality. Currently, different diagnostic criteria exist, however, due to its complexity; the clinical presentation that makes up this syndrome could make its presence unclear. The pathophysiology of PE has been recently postulated and divided into three processes: inadequate uterine remodeling, placental dysfunction and maternal endothelial dysfunction. Despite the advances in the treatment of PE, the outcome of the medical interventions has failed to decrease the morbidity and mortality of this disease. The main reason might be the multifactorial origin of pathogenic processes that lead to the development of PE. That is why treatment is focused on the prevention of PE in patients that might present the risk before developing it late in pregnancy. The knowledge of the pathophysiological factors that trigger the processes that culminate in the presentation of PE, is key for prevention of this disease. However, the origin of these processes is poorly understood. It may be attributed to the ethical considerations that come with the study of these population of patients compared with the study of non-pregnant women.

Keywords: preeclampsia, eclampsia, pregnancy induced-hypertension, complications in pregnancy women

1. Introduction

Preeclampsia (PE) is defined as a dysfunction in pregnancy, with a prevalence of 5–8% associated with multiple complications and high rates of mortality around the globe. Around the world about 50,000–60,000 deaths contributing to PE occur annually, which describes its impact in maternal and fetal mortality globally. Hypertension is the main characteristic of this disease, with a blood pressure $\geq 140/90$ mmHg assessed two occasions with a 4-h time laps in between one another. The presence of proteinuria (≥ 0.3 g/24 h or positive dipstick proteinuria) after the 20th week of gestation or the appearance of thrombocytopenia in absence of proteinuria may also work as a diagnostic criterion [1, 2].

The risk of complications in the mother increases as a consequence of endothelial dysfunction. The risk of multiple cardiovascular diseases may increase in the fetus as well as in the mother later in life [2].

PE is a multisystem disease, a particular human syndrome that is specific to pregnancy. There are multiple factors present in the pathogenesis of preeclampsia, which go from genetic to environmental, but there is not a clear correlation between these factors and the development of PE. The scarce investigation in humans is due to legal and ethical limitations. Multiple animal models have been tested to explain the pathophysiology and characteristics of these diseases. Although there have been a great contribution, none have been able to completely reproduce all the events present in the human disease, such as the impaired trophoblast invasion and the disappearance of clinical findings once the placenta is removed. Still animal models have given us the biggest contributions to the understanding of the etiology of the disease and have allowed us to test the effectiveness of multiple pharmacological interventions.

The actual recommendations for protecting the life of the mother are the interruption of pregnancy. The appropriate time for interruption of pregnancy is subject of further investigation to facilitate decision making. Gestational age of the fetus should take into account while making decision without increasing the risk for the mother to develop severe complications that could lead to a maternal death. Despite all of these, the available medication for preventing or curing PE is not completely effective. For this reason, the objectives of this chapter are recommendations on the management of PE as well as new findings of the pathogenesis of the disease. Also, to establish rules and different genetic biomarkers to improve the identification of high risk patients and potential therapeutic targets that should be the focus of our attention in the coming years to prevent or manage adequate PE and avoid the consequences that involve one maternal death.

2. What is preeclampsia?

Preeclampsia is a disease defined as the presence of hypertension after the 20th week of gestation, accompanied by new onset proteinuria or by signs and symptoms regarding organ damage, these may include visual disturbances, headaches, epigastric pain and/or

rapid development edema. All of these manifestations are a result of the inadequate trophoblastic invasion that occurs during the second half of pregnancy and results in endothelial dysfunction [1, 2].

2.1. Diagnostic criteria PE

Many of the signs and symptoms that involve this syndrome might not become clearly evident, due to the complexity of PE, despite the systemic damage caused by endothelial dysfunction. The most notorious of these manifestations is the elevation of the blood pressure. The diagnostic criteria have evolved over time in order to achieve a specific and timely diagnosis.

Diagnosis includes the development of hypertension after 20 weeks of gestation in a woman with previous normal blood pressure. Hypertension is not the only criteria for diagnosing PE, in some cases other criteria such as proteinuria of new onset could be associated, or, in the case of absence of proteinuria, the diagnostic can be established with thrombocytopenia of new onset, pulmonary edema or visual or neurological disorders among others (**Table 1**) [1, 2].

2.2. Classification PE

PE is classified as:

- Mild: presence of hypertension with sustained SBP values: 140–159 mmHg or DBP 90–109 mmHg, proteinuria or one of the warning signs presented in **Table 1**.
- Severe: presence of SBP > 160 mmHg or DBP > 110 mmHg, proteinuria or one of the complications presented in **Table 1**.

There are several guides with different diagnostic criteria and all them coincide that the evidence of target organ damage can substitute the proteinuria accompanied to hypertension.

2.3. Current treatment of PE

The first consideration in the management of PE must be maintaining the safety of the mother and fetus. The second consideration has to be a delivery of a mature newborn that does not require prolonged intensive care (**Table 3**) [1, 2].

Once PE is diagnosed, subsequent management will depend on: the results of maternal and fetal assessment, gestational age, presence of labor or premature rupture of the membranes, vaginal bleeding and the mother wishes to extend the pregnancy.

An expectant treatment, without pharmacological intervention is frequently carried on, in the medical practice, in woman with mild PE that have a blood pressure that does not exceed SBP <160 mmHg and DBP <110 mmHg, and without complications. Nevertheless, this practice has been declining because new data indicates a greater benefit with the use of drug therapy. However, antihypertensive treatment is limited to methyldopa, labetalol and nifedipine, these interventions reduce high hypertension, but do not diminish the progression of PE [2].

Blood pressure	<div>1. *SBP ≥ 140 or **DBP ≥ 90 mmHg on two occasions within 4 h after 20 WG in a woman with previous normal blood pressure.</div> <div>2. If SBP ≥ 160 or DBP ≥ 110 mmHg, hypertension can be confirmed in a short time interval (minutes) to facilitate the initiation of antihypertensive therapy.</div>
Plus	
Proteinuria	<div>• ≥ 300 mg in 24 h urine (can be extrapolated to the time of collection).</div> <div>• Ratio protein/creatinine ≥ 0.3 mg/dL.</div> <div>• Dipstick reading of (≥ 1+) used only if there are no other quantitative method.</div>
Or in the absence of proteinuria and or hypertension, with new onset of any of the following:	
Central nervous system	<div>1. Headache/visual disturbances.</div> <div>2. Eclampsia. <i>Reversible posterior leukoencephalopathy syndrome</i>. Cortical blindness or retinal detachment. Glasgow < 13. Stroke. <i>Transient ischemic attack</i>. Reversible ischemic neurological deficit.</div>
Cardiorespiratory system	<div>1. Chest pain. Sat O₂ < 97%.</div> <div>2. Severe uncontrolled hypertension over a period of 12 hours despite the use of 3 antihypertensive drugs. Oxygen saturation < 90%. Intubation, Pulmonary edema. The need of inotrope therapy.</div>
Hematology	<div>1. Leukocytosis. Elevation of ***INR or Prothrombin time. Thrombocytopenia.</div> <div>2. Platelet count less than 100,000/microliter. Blood transfusion requirement.</div>
Kidney	<div>1. Elevation of serum creatinine and/or serum uric acid.</div> <div>2. Acute kidney injury. Requirement for dialysis.</div>
Hepatic	<div>1. Nausea. Threw up. Epigastric pain right upper quadrant pain. Elevated liver enzymes, bilirubin or lactate <i>dehydrogenase</i>. Hypoalbuminemia.</div> <div>2. Liver failure. Bruising or hepatic rupture</div>
Feto-placental unit	<div>1. Abnormal Fetal Hearth Rate. Oligohydramnios.</div> <div>2. Abruption placentae with fetal and maternal morbidity. Fetal death.</div>

1. Warning signs; 2. Complications

*(SBP) systolic blood pressure

** (DBP) diastolic blood pressure.

*** (INR) International normalized ratio

Table 1. Diagnostic criteria for PE.

For women with severe PE presented before fetal viability, after interruption of pregnancy maternal stabilization is recommended. This must be done in an intensive care unit and combine the use of labetalol, hydralazine and even nitroglycerin or sodium nitroprusside in addition to the drugs mentioned in previous lines [2] (**Table 3**). The use of magnesium sulfate deserves a special mention as it is used primarily to prevent eclampsia and not to promote a hypotensive effect. However, when used in combination with antihypertensive therapy, it reduces morbidity in patients with critical elevation in blood pressure [3].

Monitoring is essential to prevent serious complications of PE and it should be continued even after the establishment of treatment. Complications are divided into maternal and fetal (**Table 2**) [2].

Maternal	Fetal
<ul style="list-style-type: none"> • Eclampsia • Reversible posterior leukoencephalopathy syndrome • Cortical blindness • Retinal detachment • Transient ischemic attack • Severe hypertension • Pulmonary edema • Myocardial infarction • Thrombocytopenia • Acute renal damage • Liver dysfunction • Abrupt placenta • Maternal death 	<ul style="list-style-type: none"> • Prematurity • Low birth weight • Intrauterine growth restriction • Delivery of a death product

Table 2. Complications of PE.

Despite efforts to treat PE, treatment is symptomatic and focused on controlling blood pressure, so the recommendation remains in the completion of the deed at the right time. As for the time of delivery, it is preferred to prolong gestational age as long as possible, however, in severe PE; antihypertensive treatment and termination of pregnancy are recommended, if it is greater than 34 weeks. If the pregnancy is less than 34 weeks and both mother and the product are stable it is recommended to continue the pregnancy and the administration of corticosteroids (**Table 3**) [1].

Currently, there are multiple criteria for better management of PE, but the only cure is the interruption of pregnancy, in which many times is a difficult decision for both the physician and the mother, due to the psychological burden, social, economic morbidity and mortality.

2.4. Clinical trials in 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 this disease. The main reason seems to be the multifactorial causes of the pathogenic processes

Mild PE	Severe PE
Antihypertensive treatment*	
24–<35 WG	
Corticosteroids 48 h before termination of complicated pregnancy	Corticosteroids 48 h and immediate termination of pregnancy after maternal stabilization
≥35 WG	
Should be immediate termination of pregnancy	Immediate termination of pregnancy

WG, weeks of gestation.
 *Methyldopa, labetalol, nifedipine, hydralazine.

Table 3. Treatment of PE.

that lead to the development of PE. Its inception happens late in pregnancy that is why the approach to manage these patients must be prevention. Knowing the factors that trigger the pathophysiological mechanism that lead to PE, is essential for its prevention. However, the etiology is still unknown and research in these patients is complicated due to the ethical considerations that must be taken into account. The multifactorial origin and the difficulty of carrying out studies in the early stages of pregnancy can endanger for both mother and fetus [4].

There are currently 236,008 clinical trials registered in clinicalTrials.gov, of which only 3% are focused on pregnancy and of the latter 6.4% is about PE. Of all clinical trials dedicated to PE, 47.9% focus on strategies to improve treatment, 22.2% of the clinical trials aim to improve the diagnosis or its establishment in the early stages and 16.7% aims to establish the utility of new biomarkers, for both diagnostic and monitoring. Finally, only 10.7% of the clinical trials registered until February 1, 2017, are focused on the prevention of PE (Figure 1).

Another aspect that should be taken under consideration is that more than half of the clinical trials directed to PE are carried out in regions classified as first world, such as Europe and North America, whereas research in the rest of the world only constitutes 40%, despite the fact that developing countries are the ones that bear the greatest burden of morbidity and mortality caused by this disease (Figure 2).

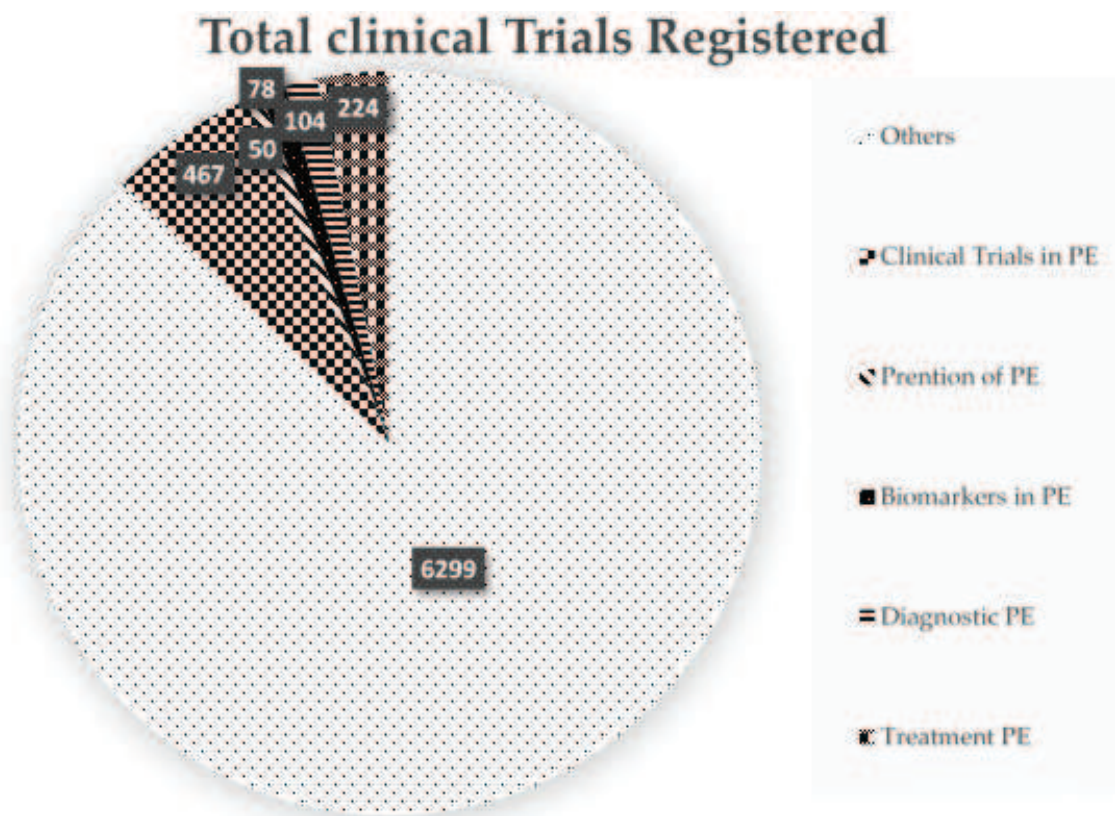


Figure 1. Clinical trials registered until February 1, 2017. Data from: clinicaltrials.gov.

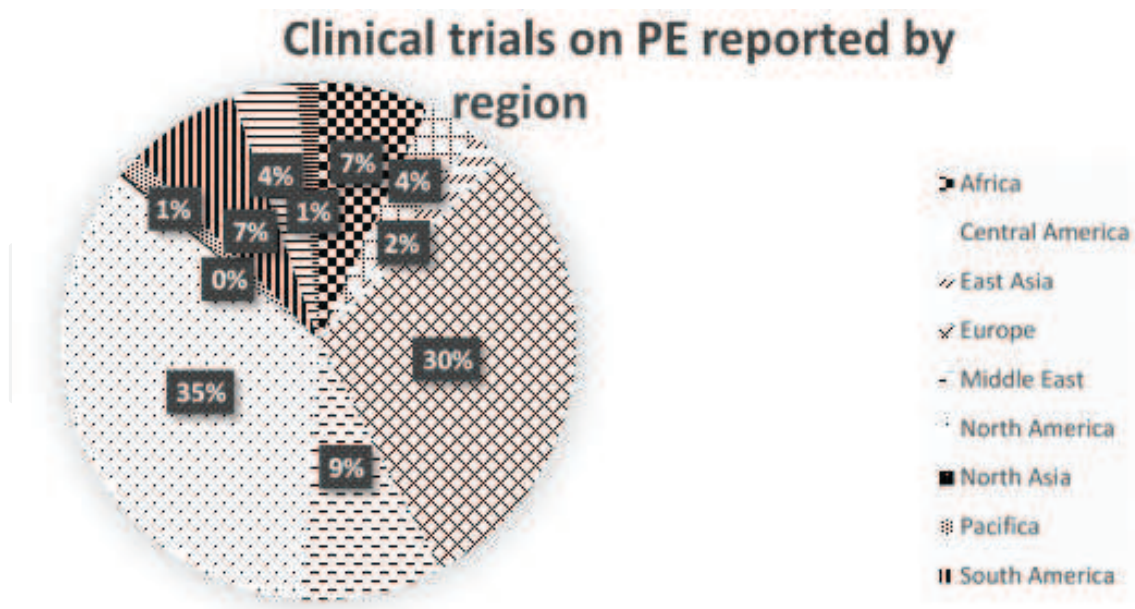


Figure 2. Clinical trials on PE reported by region. Reference: Clinicaltrials.gov.

2.5. Strategies in the prevention of PE

The understanding of the development of the placenta in patients with high risk pregnancy is essential to comprehend the pathophysiology for developing strategies of prevention.

Traditionally, the pathophysiological process has been divided into three stages.

2.5.1. Inadequate uterine remodeling

The invasion by the villi of the cytotrophoblasts in the decidual arteries and the myometrium arteries decreases to 56% and 76–18%, respectively. Neither endothelial cells nor smooth muscle cells are replaced by trophoblasts, therefore they are not affected. Thus, the uterine arteries, which have a smaller diameter, retain their vasoconstrictor potential which is the source of placental hypoxia, maladaptation of blood flow, as well as the phenomenon of ischemia–reperfusion of the uterus and placenta [4, 5].

Inadequate trophoblastic invasion produces an imbalance between angiogenic factors, such as the vascular endothelial growth factor (VEGF), placental growth factor (PlGF) and anti-angiogenic factors as soluble fms-like tyrosine kinase 1 (sFlt-1 or sVEGFR1), a splice variant of the VEGF-receptor. During the first 10 weeks of gestation, sFlt-1 is elevated, even more in pregnant women with PE than in those healthy, with a second peak between 26 and 29 weeks.

In preeclamptic pregnancies, sFlt-1 is produced excessively by the placenta much earlier than in healthy pregnancies and secreted into the maternal blood stream, where it is thought to bind and neutralize VEGF, and the VEGF subfamily member; PlGF with high affinity. This causes a decrease of VEGF and PlGF in maternal blood, and VEGF-signaling in the endothelial cells is disrupted as less VEGF receptors are bound. However, it is still unclear

what causes the excessive sFlt-1 production and release. It could be shown that hypoxias, as well as the placental mass are triggers, but there may be others. The consequence of blocking VEGF and PlGF is a poor formation of the vascular bed of the placenta [6].

Another event that occurs early in the onset of symptoms, is the elevation of certain inflammatory cytokines such as alpha tumor necrosis factor (TNF- α) and interleukins IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 and IL-8; these may initially lessen compared to healthy pregnant women. As the disease progresses over time, such cytokines showed an elevation in plasma levels. The activation of macrophages and natural killer cells leads to lysis of the trophoblast decidua cells [6].

Women that have a predisposition to develop PE, prior to the trophoblast invasion a generalized breakdown of the spiral arteries occurs, causing changes in preexisting vascular bed [4].

2.5.2. Placental dysfunction

At the beginning of the pregnancy, a state of hypoxia is presented, however, at the 10th week an increase of oxygen by the spiral arteries to overcome this state. In PE, placental dysfunction results from an inadequate placental trophoblast invasion which results in a release of placental products into maternal circulation. Placental dysfunction causes a prolonged state of hypoxia throughout the whole pregnancy resulting in high levels of hypoxia-induced factor-1 (HIF-1 α) during gestation. The prolonged state of hypoxia causes an oxidative damage to the placental barrier which increases fetal hemoglobin gene expression and free fetal hemoglobin accumulation in placenta. The accumulation of fetal hemoglobin and its metabolites due to is toxicity results in damage through three pathways [4, 7].

- 1st pathway: ferrous hemoglobin (Fe²⁺) binds to nitric oxide (NO), a potent vasodilator, and reduces the availability inducing vasoconstriction.
- 2nd pathway: Fe²⁺ hemoglobin is oxidized and reactive oxygen species (ROS) are released, provoking endothelial damage.
- 3rd pathway: the heme group of the hemoglobin molecule triggers an inflammatory response by activating neutrophils and cytokines production [4, 7].

The phenomenon of reoxygenation hypoxia generates oxidative stress, which induces placental dysfunction. Many cellular stress situations, such as an alteration in the redox state alters the maturation of proteins, leading to the accumulation of misfolded proteins in the lumen of the endoplasmic reticulum (ER), thereby producing a condition called “endoplasmic reticulum stress”, which triggers an adaptive response, called “unfolded protein response”, which aims to reduce the decrease proteins. In PE, the phenotype of placenta and intrauterine growth restriction are correlated with ER stress. In urine, misfolded proteins can be found, making it a viable biomarker for the Congo red test [7, 8].

The mother mounts an immune response against fetal trophoblast, which is detected as an alloantigen. PE could be consequential to a secondary inflammatory response derived from microparticles of microvilli of the syncytiotrophoblast (STMBs). The uterus-fetal perfusion

begins close to the end of the first trimester, and during the second and third trimester high levels of STMBs are detected in maternal circulation. The release of STMBs is affected by oxidative stress, which increases its release to maternal circulation creating an inflammatory response [4, 6].

Reactive oxygen species (ROS), like nitric oxide (NO), superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH) and peroxynitrite (ONOO $^-$) are present all the time. Oxidative stress from unbalanced free radical formation is produced within the trophoblast cell, the sources may vary from O $_2$, eNOS uncoupling, NADPH oxidase and mitochondria. Peroxynitrite formation, lipid peroxidation, protein modification, matrix metalloproteinase (MMP) activation and DNA damage contribute to endothelial dysfunction and are a result of the combination of these events [7, 9].

The main catalysts of O_2^- are the antioxidant enzyme, superoxide dismutase (SOD) that converts it to H_2O_2 and water. H_2O_2 is immediately neutralized by the enzyme, catalase (CAT). PE is one of several conditions that after the ischemia-reperfusion, produces O_2^- and by converting xanthine dehydrogenase (XD) to xanthine oxidase (XO) causes oxidative damage. Additionally, ATP metabolism in ischemic tissues forms hypoxanthine (HX) as a breakdown product. Xanthine and HX are converted into uric acid by XO, which also does the conversion of oxygen to O_2^- and H_2O_2 . In PE, superoxide generation by XO has been shown in placental reperfusion injury. Since PE is characterized by hyperuricemia, XO is presumably the source of uncontrolled ROS production when the concentration of its oxidase form is increased [7, 9].

Another source of O_2^- formation is NADPH oxidases. NADPH oxidase is a membrane-bound enzyme complex that catalyzes a one-electron reduction of oxygen and its transference to form O_2^- . It has been demonstrated that NADPH oxidase isoform, NOX1, is overexpressed in syncytiotrophoblast of preeclamptic placentas [7, 9].

3-nitrotyrosine residues have been observed in normal and complicated pregnancies, predominantly, in endothelium, surrounding smooth muscle and villous stroma. One of the key targets of ONOO $^-$ in PE is p38 mitogen-activated protein kinase (p38 MAPK), that has appeared significantly nitrated in placentas from preeclamptic women compared to normotensive controls. Activation of the p38 MAPK pathway plays an important role in the release of pro-inflammatory cytokines and the induction of enzymes such as COX-2 which controls connective tissue remodeling in pathological conditions. Inducible nitric oxide synthase (iNOS) expression, induction of VCAM-1 and, other adherent proteins along with other inflammatory-related molecules, and the effect of nitration of p38 MAPK in PE is currently under investigation for their use as molecular targets [7, 9].

But, not all free radicals cause disturbances in the organism and NO is an example. NO is a potent vasodilator, which acts on GTP to produce cGMP that causes relaxation of smooth muscle. It mediates endothelial function by regulating vascular tone, platelet aggregation, leukocyte adhesion and smooth muscle cells development. It is synthesized by the NOS family of enzymes, which consist in three isoforms: nNOS or neuronal isoform, iNOS the inducible and eNOS the endothelial NOS, formed from the reduction of L-arginine to L-citrulline,

which is capable of dilating blood vessels. In placenta, eNOS expression is associated with cytotrophoblast to syncytiotrophoblast differentiation [7, 9].

2.5.3. Maternal endothelial dysfunction

A reduction of vasodilating agents, such as NO and platelet PG2, a proliferation of vasopressor agents and platelet aggregating agents, such as thromboxane A2 (TXA2) and endothelin-1, alter the endothelial function. As a consequence of this imbalance, higher sensitivity combined with angiotensin II results in a state of vasoconstriction with an increased peripheral vascular resistance that creates an increase in blood pressure. Endothelial permeability is increased as well [10].

Regulation of the fetoplacental vascular reactivity, trophoblast invasion and apoptosis, and adhesion and aggregation of platelets in the intervillous space are all affected by NO, the main vasodilator in placenta. L-Arginine is the precursor of NO, which is formed in the presence of oxygen and tetrahydrobiopterin, a cofactor, resulting in the production of L-citrulline. When arginine residues in proteins are methylated by methyltransferases type I and II, they form asymmetric dimethylarginine (ADMA), a competitive inhibitor of L-arginine for the NOS isoform [11].

At the early stages of pregnancy, a hemodynamic adaptation as a response of an extra need for perfusion is induced by an increase in NO and a reduction in ADMA. As well, this adaptation permits uterine relaxation, which is necessary for intrauterine growth. Towards the end of pregnancy, the muscle fibers of the uterus suffer change, due to an increase in physiological ADMA, to undergo greater contractile activity and antagonize the effect of NO. In pregnancy with high risk of PE, ADMA levels increase to higher than normal, reason why many studies have suggested the possibility of using it as a biomarker of endothelial dysfunction [11, 12].

TXA2 works as a vasoconstrictor and in patients with high risk of PE, its levels increase all together with the circulating levels of TXB2, one of its metabolites. TXA2 is produced in platelets and endothelial cells and is one the many molecules derived from arachidonic acid through prostaglandin H synthase (PGHS). The TXA2 receptor (TP) mediates the constrictor effects of TXA2 in vascular smooth muscle.

The vasoconstrictive effects of TxA2 in PE are amplified because of their ability to potentiate the vasoconstrictor effects of angiotensin II and endothelin-1. NO and I2 (PGI2) inhibit prostaglandin TxA2 actions through TP receptor desensitization; however, in pregnancies with PE, NO production and PGI2 are affected. Research profiles of DNA methylation of omental arteries reveal that the gene, thromboxane synthase (TBXAS1), is hypomethylated, even more significantly in the vessels of women with PE and this was associated with the increased expression of thromboxane synthase in the omental arteries women with PE. Taken together, these data suggest that, in PE, there is an imbalance in the production of vasoconstrictors (TxA2) and vasodilator prostanoids (PGI2), modulated by epigenetic modifications [13].

It is also reported in the literature the presence of autoantibodies against angiotensin receptor 1 (AT-1). These autoantibodies have a pharmacological effect similar to that of angiotensin II agonist. Stimulation of the AT-1 receptor by these circulating autoantibodies could also be responsible for hypertensive symptoms in PE, as the concentration of circulating autoantibodies increases after 20 weeks of gestation [6, 14].

3. Identification of high risk patients

PEs pathogenic process begins during the first quarter, long before clinical signs are evident. Therefore, it is difficult to identify early biomarkers. Although there is no perfect way to predict the development of PE, it is possible to distinguish between women who have a high risk of developing PE of those whom have a low risk (**Table 4**).

However, these factors predict only 30% of women who develop PE. Biomarkers in maternal blood have a modest predictive potential. Prediction of early onset of PE at the end of the first quarter of pregnancy can be done using Doppler ultrasound combined with plasma levels of placental growth factor and protein-A associated with pregnancy (PAPP-A) [15].

High risk factors	Moderate risk factors
PE in previous pregnancies. Women who have PE in the first pregnancy have 7 times more risk of developing PE in a second pregnancy (RR 7.19; 5.85–8.83).	Primigravid. Nulliparity almost triples the risk of PE (RR 2.91; 1.28–6.61).
Hypertension in pregnancy. The prevalence of chronic hypertension in women who develop PE is 12% (RR 5.2; 1.5–17.2).	Maternal age. The risk increases 30% for every completed year after 34.9. The risk increases twice in nulliparous ≥ 40 years (RR 1.68; 1.23–2.29).
Renal disease. The prevalence of renal disease in women who develop PE is 5.3%.	Interval intergenesic >10 years. The risk of PE is about the same as that of nulliparous (RR 1.12; 1.11–1.13).
Diabetes mellitus 1 and 2. The probability of PE almost quadruples if diabetes is present before pregnancy (RR 3.56; 2.54–4.99).	Body mass index (BMI) ≥ 35 kg/m ² . The risk of PE is increased up to 50% (RR 4.39; 3.52–5.49).
Autoimmune diseases. Women who develop PE are more likely to have an autoimmune disease (RR 6.9; 1.1–42.3).	Family history of PE. This almost triples the risk of PE (RR 2.90; 1.70–4.93).
Antiphospholipid syndrome significantly increases the risk of developing PE (RR 9.72; 4.34–21.75).	Multiple pregnancy. Twin pregnancy nearly triples the risk of PE (RR 2.93; 2.04–4.21), while a triplet pregnancy nearly triples the risk of twin pregnancy (RR 2.83; 1.25–6.40).

Table 4. The most important for the development of PE factors [15, 16].

4. The use of biomarkers for PE

An effective biomarker to predict of the onset of PE has not been established, some the most promising biomarkers are listed in **Table 2**. The heterogeneity of the pathogenesis of PE makes it difficult to establish a single biomarker as a predictor of the disease; the best approach might be a combination of markers. However, much research and development of criteria

Biomarker	Characteristics	Studies
sFlt-1/PlGF	It has been included sFlt-1/PlGF ratio into German PE guidelines for care. A ratio of sFlt-1/PlGF: 38 at any time during pregnancy is considered as 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 a month before the appearance of the first clinical symptoms detectable. In the case of PlGF, significantly lower concentrations are observed in women who subsequently present placental dysfunction since the end of the first quarter. They concluded that further studies are needed to demonstrate the benefits of using the ratio of sFlt-1/PlGF in terms of reduction of maternal and fetal risks and resource optimization [17].
Soluble endoglin (Seng)	A truncated form of the receptor for β 1-transforming growth factor (TGF- β 1) and TGF- β 2 that interferes with the binding of TGF- β 1 to its receptor, and thereby affects 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 2 to 3 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/ml, as compared to 13.3 ng/ml in controls ($p < 0.001$)). A higher level of soluble endoglin is usually accompanied by an increase in the proportion of sFlt1: PlGF [18].
PAPP- α	A highly glycosylated protein that is produced by trophoblast cells in development has proven to be an insulin-like growth factor. Therefore, as expected, low serum levels of PAPP- α are associated with a higher incidence of PE.	The studies are contradictory, while some show association with low levels of PAPP- α , others observed elevations in serum. Both observations were made by Bersinger et al. In two separate case-control study in 2003 and 2004, respectively [19, 20].
Activin-A	This is a glycoprotein member of the TGF- β family that is released by the placental-fetus unit during pregnancy. Activin-A is involved in various biological activities [21].	A case-control study conducted in 2004 by Ong et al. found that levels of activin-A are higher PE than in normal pregnancies. It has been observed that an increase in activin-A occurs before 14 weeks of gestation in pregnancies with PE.
PP-13	A 32-kd dimer protein is one of 56 known placental proteins, produced exclusively by placenta and it facilitates trophoblast invasion and maternal artery remodeling [22]. A higher magnitude of increase of PP13 from the first to the third trimester was observed in PE [23].	Gonen et al., in 2008 conducted a study of cases and controls in pregnancy between 5 and 7 weeks and determined the relation of lower values of PP-13 in PE than in normal pregnancies. The increase of PP-13 in maternal blood seems to coincide with STBM release as the PE advances.
Cystatin C	A protease inhibitor is widely used by clinicians as a sensitive marker for renal function and for estimating glomerular filtration rate. Increased levels of cystatin-C may be attributed to an increased placental production.	Thilaganathan et al. in 2009 conducted a nested case study to determine levels of cystatin C, a marker set for kidney function, which increases progressively as the glomerular filtration rate falls. In PE, placental expression of cystatin C is significantly increased in the first trimester of pregnancy compared to those with normal pregnancy [24].
Fetal hemoglobin	Oxidative damage induces placental production and leakage in the fetal-maternal hemoglobin barrier.	Recent studies have identified it as a predictor in the first and second quarters [25].

Biomarker	Characteristics	Studies
ADMA and homocysteine	Serial measurements of their concentrations may be useful to identify women at risk [26].	López-Alarcón et al., in a cohort study in 2015 found that ADMA and homocysteine (Hcy) increases gradually throughout pregnancy with PE, but remains 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, a month prior to the onset of PE. This has demonstrated the best potential for prediction
miRNA	miR-16 is stimulated by hypoxia and inhibits migration of cytotrophoblast cells [27], it represses production of VEGF receptors in mesenchymal stem cells derived from the decidua (MSCs), and induces cell cycle arrest in the transition G0/G1 [28]. miRNA-155 overexpression reduces the expression of NOS [29]. C19MC miRNAs are downregulated exclusively associated with preeclampsia [30].	There are more angiomiRNAs that have been found and vary on their level of expression. However, there is still a lack of investigations to understand their role as biomarkers.

Table 5. Potential biomarkers in preeclampsia.

are needed. There is a need for biomarkers that could also apply to patients that apparently do not have any risk factors for developing PE, and research should expand its investigation regarding these patients (**Table 5**).

sFlt-1, soluble fms-like tyrosine kinase 1; PlGF, placental growth factor; ADMA, asymmetric dimethylarginine; PAPP α , pregnancy-associated plasma protein-A; PP-13, placental protein 13; miRNA, microRNA; STMB, syncytiotrophoblast microvesicles.

5. Pharmacological approach for prevention

5.1. Calcium administration

According to an study conducted by Hofmeyr et al., supplementation of calcium in women that have a low calcium intake and mild risk of PE have a relative risk of 0.48 (95% CL 0.33–0.69). However, patients that have a low calcium intake and a high risk of PE displayed a major benefit (RR .22; 95% CL 0.12–0.42). Low levels of calcium increase vasoconstriction resulting in high blood pressure, by liberating parathyroid hormone or releasing renin, and consequently increasing intracellular calcium in vascular smooth muscle. Parathyroid hormone release and intracellular calcium levels are reduced with calcium administration [31].

5.2. Acetylsalicylic acid administration

The inhibition of thromboxane A2 formation without affecting the production of prostacyclins, gives acetylsalicylic acid in low doses an anti-platelet aggregating an anti-vasoconstrictor effect. This justifies its use in PE; however, the results have been controversial about the positive role of its administration at the onset of the pregnancy and the severity of its use.

Campos concluded, from a systemic review, that since 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. Administration should be performed overnight because it helps in reducing the risk of PE [32].

5.3. NO pathway

Since endothelial dysfunction and impaired bioavailability of NO are taxpayers of maternal manifestations of PE, supplementation with exogenous NO donors would be an apparent solution.

Trapani et al. conducted a study in which nitroglycerin transdermal patches were applied into the mother’s abdomen to improve the uteroplacental circulation. They reported an increase of the blood flow in the uterine and umbilical arteries. However, further investigation is needed for their effect reducing the incidence of PE [33].

Groten et al. found that pentaerythritol tetranitrate, an organic nitrate of prolonged action, improves uteroplacental perfusion in women at risk of PE, as well as reducing its frequency, growth restriction and premature births it may cause in these women [34].

Moreover L-arginine acts as a precursor of NO and becomes NO and L-citrulline by NOS, as described in the pathophysiology of PE. It has been the subject of studies designed to investigate its preventive role in women with high risk of developing PE.

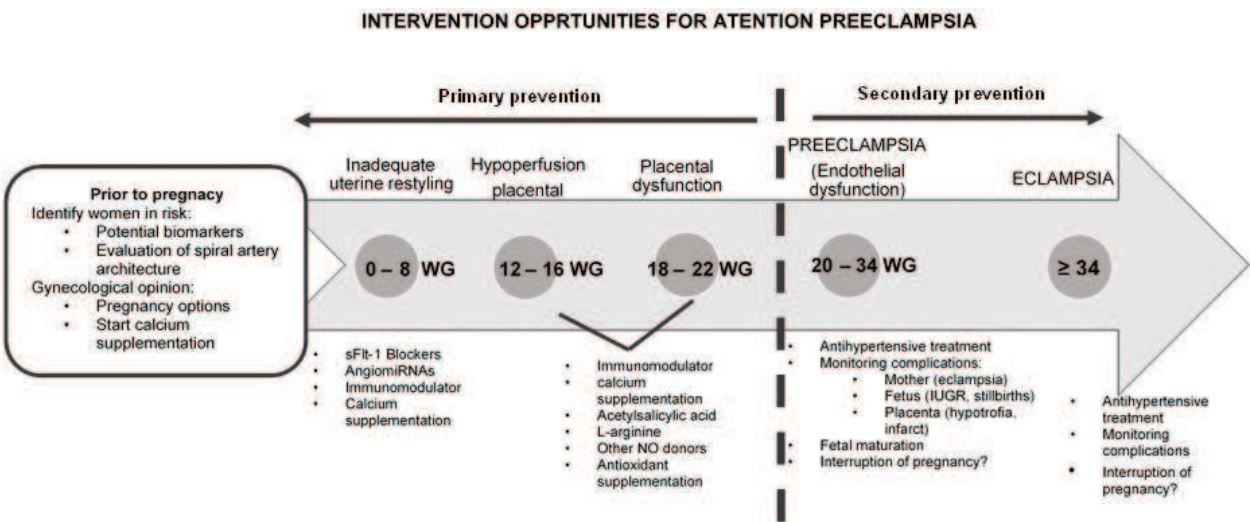


Figure 3. The pathological processes and the clinical manifestations are listed chronologically, with the key moments for pharmacological intervention pointed out at every stage of the pregnancy.

Camarena et al. published in 2016 a clinical trial which included 100 pregnant women at high risk for PE to estimate the effectiveness and safety of L-arginine for preventing PE. They formed two study groups, one was given 3 g of L-arginine per day in 600 mg capsules, and a second group was given placebo capsules approved with L-arginine. They found a lower incidence of PE in the group receiving L-arginine to the placebo (6 and 23%, respectively; $p = 0.016$) group, which was statistically significant, and also reported an increased incidence of severe PE in the placebo compared to the intervention group (14 and 2%, respectively, $p = 0.02$) group. SBP, DBP and MAP decreased significantly in the group treated with L-arginine compared with the placebo ($p = 0.022$, $p = 0.035$ and $p = 0.023$, respectively). The most common adverse event was dyspepsia, which was higher in the intervention group than in the placebo (26 and 6%, respectively; $p = 0.008$) group. The authors concluded that administration of L-arginine is effective and safe to prevent PE [35].

As seen in **Figure 3**, we can establish several moments as opportunities for prevention or management of PE, the best opportunity for treating PE is prior to pregnancy by identifying women with high risk and creating strategies to prevent the development of the disease. During pregnancy, several potential targets could modify its course; we listed in a timeline the molecules that have an implication in the pathogenesis of PE.

6. Conclusions

PE is a serious complication of pregnancy, which has a high rate of morbidity and mortality worldwide. Due to the complexity of PE, and despite the systemic damage caused by endothelial dysfunction, many of the signs and symptoms that make up this syndrome may not be clearly evident, being the most notorious sign an elevation of the blood pressure. The diagnostic criteria have evolved over time in order to achieve a timely and specific diagnosis, but this has only caused a more complex evaluation, so it requires new tools to achieve an early and accurate diagnosis of the PE.

Antihypertensives are an alternative for the treatment of PE, however, they stretch the pregnancy until the product is viable to live outside the uterine environment, shortening gestation. The outcome using hypertensives is not always favorable for the mother and the fetus and their effect on PE is variable.

During the early stages of placentation, various changes may occur due to intrinsic factors, so this should be the focus of investigation. However, invasive procedures to pregnant women are not acceptable because of the risk they might represent without any notable benefit.

The combination of several biomarkers could contribute to identify women with mild and high risk of developing the disease, which is the best strategy for prevention and management of PE.

In past years, a lack of therapeutic options regarding PE was notorious. However, new opportunities have surged in present years such as, immunomodulators, antioxidants, angiomiRNAs and nitric oxide donors, which are still under investigation but have shown promising results. Nevertheless, prevention persists as the principal strategy to reduce morbi-mortality

of PE. The obstetrician is responsible for evaluating the individual options each patients has, even before conception and research should focus on developing new and better strategies.

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