LUMEN ET VIRTUS

Current developments in the approach, diagnosis and treatment of preeclampsia

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Alejandra Giselle Estrada Jiménez[1], Zally Patricia Mandujano Trujillo[2], Tomasa de los Ángeles Jiménez Pirrón[3], Rosa Martha Velasco Martínez[4], Sonia Rosa Roblero Ochoa[5] and María Fernanda Martínez Medina[6]

ABSTRACT

Introduction: Preeclampsia is a clinical syndrome, characterized by predominantly cardiovascular symptoms, manifestations attributable to systemic inflammation, endothelial dysfunction and generalized vasoconstriction resulting in hypertension, hypoperfusion and multiorgan failure. It affects between 3 and 10% of pregnancies, and is the leading cause of maternal death in the world.
General objective: To know new strategies for approaching, diagnosing, and treating preeclampsia.
Materials and methods: Articles in English and Spanish published from 2019 to 2022 were selected, using available electronic databases.
Conclusions: New molecules have been discovered for the early diagnosis of preeclampsia, based on the angiogenic relationship, including high levels of sFlt-1, sEng, IL-16, Activin A, ICAM and VCAM, as well as low levels of PAPP-A, PlGF and placental protein 13. In addition, new drugs and treatments such as sildenafil, pravastatin, and stem cells are being researched for more effective management. However, due to discrepancies in outcomes for mother and fetus, its widespread recommendation is not yet possible.

Keywords: Preeclampsia, angiogenic relationship, maternal death.

[1] Bachelor of Medicine from the Faculty of Human Medicine, Dr. Manuel Velasco Suárez, Campus-II, UNACH
[2] Professor of the Bachelor's Degree in Medical Surgery at the Faculty of Human Medicine, Dr. Manuel Velasco Suárez, Campus-II, UNACH
[3] Professor of the Bachelor's Degree in Medical Surgery at the Faculty of Human Medicine, Dr. Manuel Velasco Suárez, Campus-II, UNACH
[4] Professor of the Bachelor's Degree in Medical Surgery at the Faculty of Human Medicine, Dr. Manuel Velasco Suárez, Campus-II, UNACH
[5] Professor of the Bachelor's Degree in Medical Surgery at the Faculty of Human Medicine, Dr. Manuel Velasco Suárez, Campus-II, UNACH
[6] Medical Intern in Social Service of the Bachelor's Degree in Medical Surgery of the Faculty of Human Medicine, Dr. Manuel Velasco Suárez, Campus-II, UNACH

INTRODUCTION

Preeclampsia is a clinical syndrome, characterized by predominantly cardiovascular symptoms, manifestations attributable to systemic inflammation, endothelial dysfunction, and generalized vasoconstriction resulting in hypertension, hypoperfusion, and multiorgan failure. (Melchiorre, 2022)

In 2014, the International Society for the Study of Hypertension in Pregnancy (ISSHP) issued an update stating that preeclampsia is defined as the de novo onset of blood pressure greater than or equal to 140/90 mmHg after the 20th week of gestation along with evidence of maternal organ damage. (Sasser, 2020)

The syndrome is thought to be triggered by abnormal levels of Fms-like Soluble Tyrosine Kinase-1 (sFlt-1) and Placental Growth Factor (PlGF), known as angiogenic imbalance. (Melchiorre, 2022)

Women with preeclampsia have lower PlGF and higher sFlt-1 concentrations compared to pregnant women without preeclampsia. PlGF-based tests are now recommended as a diagnostic adjunct in women with suspected pre-eclampsia for clinical use in the UK. (Wiles, 2020).

METHODOLOGY

The bibliographic review was based on the selection of articles in English and Spanish with a publication date from 2019 to 2022 in electronic media databases such as PubMed, UpToDate, Google Scholar, Elsevier, SciELO and Redalyc.

EPIDEMIOLOGY

Affecting between 8 and 10% of pregnant women, the incidence of Preeclampsia in Pregnancy (PE) is estimated to be approximately 1% of all pregnant women and 1.5% of primiparous women. It causes 16% of maternal deaths, being one of the main causes of maternal morbidity and mortality and premature birth in developing countries. (Poniedziałek- Czajkowska, 2021)

In Mexico, the prevalence of preeclampsia-eclampsia syndrome oscillates around 8%, corresponding to 3.75% to preeclampsia with severity criteria and 94.5% to preeclampsia without severity criteria and 1.75% to eclampsia, the latter being more frequent in primigestas, up to 85%, and in multigestas it appears in 14 to 20% of cases. Various reports indicate that maternal death occurs in one in 50 women with eclamptic symptoms. (López, 2022)

DEFINITION

The American College of Obstetricians and Gynecologists (ACOG) defines PE as new-onset hypertension after the 20th week of gestation with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, measured twice at least 4 h apart and proteinuria ≥0.3 g per 24 h or ≥ 1+ proteinuria, detected by urine dipstick. PE may also be diagnosed in the absence of proteinuria when hypertension occurs with the onset of any of the following symptoms: thrombocytopenia (platelet count < 100,000/μL), renal failure (serum creatinine concentration > 1.1 mg/dL or a doubling in the absence of other kidney diseases), impaired liver function (elevated liver transaminase concentrations at twice the mean levels), pulmonary edema or brain or visual problems. (Poniedziałek- Czajkowska, 2021)

RISK FACTORS

The Centers for Disease Control and Prevention confirms that black women still have a maternal mortality rate 2.5 to 3 times higher. The higher prevalence of preeclampsia among them is thought to be related to the higher incidence of chronic hypertension in that population. (Johnson, 2022)

The protective effect of parity on the development of PE may be due to the persistence of maternal cardiac adaptation from previous pregnancies, which in cardiology is called "preconditioning". Capeless et al. (1991) performed an echocardiographic evaluation before pregnancy and found that ventricular volumes and cardiac output (CO) during pregnancy were significantly higher by 15% to 20% in multiparous women versus nulliparous women, and maternal cardiovascular indices (CG), peripheral vascular resistance, and uterine artery pulsatility in the first trimester of pregnancy improved with increasing parity.

The increased risk of PEs conceived through in vitro fertilization (IVF) has been consistently explained by advanced maternal age and multiple pregnancy, except in the case of egg donation. These risks confer a 2- to 3-fold increase in the likelihood of developing PE, the latter observation has been used to support the immunological origins of PE based on differences in human lymphocyte antigen compatibility between a hemialogenic fetoplacental graft at natural conception and a fully allogeneic conception with egg donation.

The main risk factors established for PE are obesity (body mass index >30), diabetes, chronic hypertension, chronic kidney disease, obstructive sleep apnea, systemic lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, maternal age over 35 years, multiple gestation, hydrops fetalis, hydatidiform mole and physical inactivity, so it is extremely important to take preventive measures and/or treat them even before the pregnancy. (Wiles et al, 2020)

PATHOPHYSIOLOGY

The clinical syndrome begins with an abnormal invasion of the trophoblast. During normal implantation, trophoblasts invade the decidualized endometrium, leading to remodeling of the spiral artery and obliteration of the tunica media of the spiral arteries of the myometrium, allowing for increased blood flow to the placenta. In preeclampsia, trophoblasts fail to adopt an endothelial phenotype, leading to impaired trophoblast invasion and incomplete remodeling of the spiral artery. The resulting placental ischemia leads to an increase in markers such as fms-like soluble tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng). sFlt-1 binds to and decreases levels of vascular endothelial growth factor (VEGF) and PlGF. Therefore, endothelial dysfunction develops in the maternal vasculature. sEng is a cell surface co-receptor that binds to and decreases levels of transforming growth factor (TGF)-β, which normally induces endothelial cell migration and proliferation. These factors mediate downstream effects that create endothelial dysfunction, a vasoconstrictor state, oxidative stress, and microemboli that contribute to the involvement of multiple organ systems. (Jena, 2020)

In preeclampsia, helper T cells shift toward the Th1 phenotype, which increases the release of proinflammatory cytokines such as interleukin (IL)-12 and IL-18, and decreases IL-10, leading to apoptosis and reducing trophoblast invasion. (Jena, 2020)

DIAGNOSTIC STRATEGIES

At a minimum, women should be screened for clinical risk markers for preeclampsia in prenatal care.

If tests are available, after appropriate counseling, women should be screened between 11 and 14 weeks for risk of premature preeclampsia, using a combination of risk factors, blood pressure, uterine artery pulsatility index, and PlGF. (Camacho-Mendez, 2018)

Moreno (2019) reports that angiogenic imbalance is assessed by reducing PlGF (< 5th percentile for gestational age) or increasing the sFlt/PlGF ratio (e.g., >38 according to the Roche trial).

With respect to the Doppler study of uterine artery resistance in cases of preeclampsia, according to Conde-Agudelo et al. (2004), it is determined that the ideal time during pregnancy to predict preeclampsia is between 20 and 24 SDGs, and they rate the usefulness of this study as "moderate".

The use of angiogenic markers can reduce adverse maternal outcomes (4-5%), the time to diagnosis of preeclampsia (by an average of 2 days), identifies women at higher risk of severe maternal peripartum morbidity (including postnatal hypertension), and saves costs that may be

particularly useful in the face of pre-existing proteinuria, chronic hypertension, or Chronic Kidney Disease (CKD).

The concentration of Pregnancy-Associated Plasma Protein A (PAPP-A) increases continuously until the time of delivery. However, research has shown that in patients who later develop preeclampsia, a decrease in PAPP-A levels is observed.

Placental growth factor (PlGF) in normal pregnancies generates an uninterrupted increase during the first two trimesters of pregnancy of PIGF, with a maximum peak at 29-32 weeks of gestation. (Moreno, 2019)

Activin A is thought to play an essential role in the early stages of embryo implantation, invasion of the extravillous trophoblast, and the production of placental hormones. It is significantly elevated in the blood of pregnant women prior to the presentation of clinical symptoms, and has been investigated as a potential biomarker for the early identification of women who will develop preeclampsia. The combination of maternal factors, biophysical markers (mean arterial pressure and uterine artery pulsatility index) and multiple biomarkers (PAPP-A, PlGF, activin A and soluble endoglin) gave a detection rate of 91% with a false-positive result of 5% in singleton pregnancies. (Barber, 2023)

IL-16 is a cytokine with potent action on the vascular endothelium that induces structural and functional alteration in these susceptible patients, as well as oxidative damage, leading to alterations in vascular integrity and tone. (Camacho-Méndez, 2018)

In a study carried out at the Hospital de Especialidades of Centro Médico Nacional Siglo XXI, ICAM and VCAM found that only VCAM-1 concentrations were different with the control group, resulting higher in PE, correlating with systolic blood pressure. (Camacho-Méndez, 2018)

SEng is elevated in the sera of preeclamptic women and has been correlated with disease severity at weeks 17-20. (Camacho-Méndez, 2018)

Placental protein 13 is involved in placental implantation, vascular remodeling, trophoblastic migration, regulation of blood pressure of the spiral arteries, and placental tissue oxygenation. Low concentrations were found at 11-13 weeks of pregnancy in women who developed intravascular coagulation and PE, compared to controls. The first trimester of gestation is considered the optimal time for the determination of placental protein 13, because it has been given the greatest predictive capacity in this period. (Camacho-Méndez, 2018)

The first evidence linking micro-RNA (miRNA) and PE was found in Pineles' study. miRNAs play an important role in angiogenesis, crucial for the remodeling of the spiral arteries of the placenta during pregnancy. Several upregulated miRNAs in the human placenta, such as miR-210 and miR-20b, block angiogenesis and/or trophoblast proliferation, invasion, and migration. miR-16, miR-26b, miR-29b, miR-181a, miR-195, miR-222, and miR-335 have been determined to

be overexpressed in preeclamptic placentas. Because these miRNAs alter the expression of angiogenic factors, including VEGF, they can cause downregulation of those target genes. (Hornakova, 2020)

In the case of PE, the most studied miRNAs are miR-155 and miR-210. miR-155 can affect trophoblast migration and differentiation and is upregulated in preeclamptic placentas, elevated levels of circulating miRNAs, including miR-155, miR-210, and also miR-215, miR-650, and miR-21, were detected in women with PE. (Hornakova, 2020)

MacDonald (2021) mentions GATA2 and nitric oxide. GATA2 is a transcription factor expressed in the endothelium, it regulates vascular homeostasis by controlling the transcription of genes and miRNA, including miR-126. Both GATA2 and miR-126 in whole blood were reduced in the circulation of patients with early-onset preeclampsia (<34 weeks) and before diagnosis of preeclampsia at term.

Nitric Oxide (NO) is an important signaling messenger in the cardiovascular system, maintaining endothelial integrity by regulating vasodilation, leukocyte adhesion and platelet aggregation. It is synthesized by Nitric Oxide Synthase (NOS), using L-arginine as a precursor. Several groups have evaluated the biomarker potential of Asymmetric Dimethyl Arginine (ADMA) for preeclampsia. It is a methylated product of L-arginine that endogenously inhibits NOS to reduce NO production. Two meta-analyses have recently evaluated ADMA and show that it is altered in those people destined to develop early-onset preeclampsia if samples are taken after 20 weeks, albeit with modest predictive efficacy. Endothelin-1 (ET-1) is a potent vasoconstrictor peptide, secreted predominantly by vascular smooth muscle and endothelial cells. Early studies and more recent work have shown 2- to 3-fold increases in circulating ET-1 in preeclamptics. A combination of stable circulating precursor protein, terminal proendothelin-1 C (CT-pro-ET1), sFlt-1, and systolic blood pressure produced a sensitivity of 80% with a specificity of 90% for the development of severe preeclampsia within one week in women with subclinical preeclampsia, gestational hypertension, essential hypertension, or moderate preeclampsia. (Mcdonal, 2020, p 7)

PREVENTION

The American College of Obstetricians and Gynecologists, the U.S. Preventive Services Task Force, and the International Society for the Study of Hypertension in Pregnancy recommend daily aspirin for high-risk women 12-16 weeks gestation (SDG) to reduce the risk of preeclampsia. After multivariable screening, aspirin should be administered at a dose of 150 mg/night. (Magee, 2022)

Aspirin also reduces the risk of preeclampsia by inhibiting cyclooxygenase-1 and cyclooxygenase 2, which contribute to prostaglandin biosynthesis and subsequent endothelial dysfunction. (Wiles et al, 2020)

Administration of acetylsalicylic acid results in downregulation of transcription of the proinflammatory cytokines TNFα, IFN-γ, IL1, IL6, and IL8, whose genes are regulated by NFkB; All of these cytokines are strongly related to the mechanical pathway of preeclampsia. It is possible that oral administration of acetylsalicylic acid before 16 SDGs effectively inhibits the secretion of these factors by maternal immune cells, allowing a shift from a profile of pro-inflammatory cytokines, associated with Th1 and Th17 cells, to an anti-inflammatory profile, associated with Th2 lymphocytes, this change is desirable for the normal evolution of pregnancy. The anti-inflammatory activity of salicylates is related to the regulation of NFkB activity; in fact, aspirin prevents the nuclear translocation of NFkB and its consequent binding to the DNA motive element. Aspirin was also found to act as a competitive inhibitor of ATP, binding to the IKKβ protein, one of the activators of NFkβ in the canonical pathway. After inactivation, IKKβ cannot activate NFkβ, thus inhibiting its nuclear translocation. (Sakowicz, 2022)

It is recommended to follow the protocol of a previous study of 50 min of exercise at least 3 days per week, which was associated with a reduction in weight gain and the incidence of PE. (Poniedziałek-Czajkowska, 2021)

Women with a dietary calcium intake <900 mg/day, oral calcium supplementation of at least 500 mg/day is suggested. One proposed mechanism is that hypocalcemia may stimulate the release of parathyroid hormone or renin, which may increase intracellular calcium in vascular smooth muscle, leading to vasoconstriction and higher blood pressure. Calcium supplementation can reduce the release of parathormona, thereby reducing intracellular calcium and smooth muscle contractility. Similarly, calcium administration can reduce uterine smooth muscle contractility and improve placental uterine blood flow, preventing labor and preterm birth. (Poniedziałek-Czajkowska, 2021)

The relationship between vitamin D and PE development may explain its impact on implantation, angiogenesis and endothelial status, regulation of immune response, effect on the renin-angiotensin-aldosterone system (RAAS), and calcium metabolism. A beneficial effect of vitamin D on pregnancy development could only be observed if supplementation is initiated during placental implantation. Vitamin D indirectly by intensifying the synthesis of progesterone and human chorionic gonadotropin (hCG) can improve trophoblast implantation.

The process of implantation of the trophoblast requires the destruction of the extracellular matrix, for which metalloproteins (MMPs) are responsible. Reduced levels of vascular MMP-2 and MMP-9 have been shown to be responsible for vasoconstriction and, as a result, lead to PE

development; vitamin D by enhancing the expression of MMP-2 and MMP-9 promotes human trophoblastic migration and invasion in the first trimester of pregnancy.

It is essential to evaluate the concentration of vitamin D in the periconceptional period and/or the beginning of the first trimester and to define levels that reduce the risk of developing PE. Women with risk factors for vitamin D deficiency, such as obesity, kidney, liver, thyroid gland diseases, chronic intestinal diseases, autoimmune diseases, asthma, diabetes, hypertension and chronic treatment with glucocorticoids, antiepileptics and antiretrovirals, would benefit the most. Patients with risk factors for the development of PE and vitamin D deficiency may require higher doses than those commonly recommended for pregnant women (Poniedziałek-Czajkowska, 2021)

Women should not receive low molecular weight heparin, vitamins C or E, or folic acid for the prevention of preeclampsia. This recommendation relates to the use of heparin for the prevention of preeclampsia and not for other indications, such as thromboprophylaxis in antiphospholipid antibody syndrome.

Pravastatin has been proposed as an adjunctive therapy to reduce the risk of preeclampsia. Statin treatment led to a reduction in LDL levels, resulting in a depletion of its oxidative forms, which are strong stimulators of Toll-like receptors (TLRs). TLR signaling is one of the most important mechanisms that elevate IL6 and TNFα levels following increased transcriptional activity of NFκ β. In addition, statins inhibit the activation mechanism of NFκ β by blocking phosphatidylinositol 3-kinase (PI3k)/protein kinase β (Akt) signaling. This pathway is activated in endothelial cells in response to TNFα stimulation. It has also been involved in the generation of reactive oxygen species. (Sakowicz, 2023)

The American Food and Drug Administration (FDA) does not yet recommend the use of these medications for all pregnant women. Statins lower cholesterol levels, reducing their accessibility to the developing fetus and thus increasing the risk of miscarriages or fetal birth defects. (Sakowicz, 2023)

MANAGEMENT

ANTIHYPERTENSIVE THERAPY

Severe hypertension during pregnancy, i.e., Systolic Blood Pressure (SBP) ≥160 mmHg or Diastolic Blood Pressure (DBP) ≥ 110 mmHg, requires urgent antihypertensive treatment, in a monitored setting. The target for treatment should be a DBP of 85 mmHg, regardless of SBP. Non-severe hypertension should be treated with the first-line agents: oral methyldopa, oral labetalol, or oral nifedipine. Severe hypertension should be treated with first-line agents or intravenous (IV) labetalol or IV hydralazine.

Women with eclampsia should be given magnesium sulfate to prevent recurrent seizures, and women with preeclampsia with severity data should be given for the prevention of eclampsia. (Magee, 2022)

SCHEDULED BIRTH

Indications for planned birth at any gestational age include: Abnormal neurological features (such as eclampsia, severe intractable headache, or repeated visual scotomas), repeated episodes of severe hypertension despite maintenance.

CORTICOSTEROIDES PRENATALES

Do not administer corticosteroids to accelerate resolution of Hemolysis Syndrome, Elevated Hepatic Enzymes and Low Platelets (HELLP). (Magee, 2022)

PHARMACOLOGICAL TREATMENT

Drugs such as sulfasalazine (an anti-inflammatory and antioxidant) that reduces sFlt-1 and sEng levels and increases PlGF secretion, and relaxin plays an important role in maintaining blood pressure in normal pregnancy, are under investigation and could be used as therapeutic agents.

Fasudil is a first-generation Rho/Rho-associated protein kinase (ROCK) inhibitor that is frequently used for the treatment of hypertension and other cardiovascular diseases. RhoA proteins (Ras homologous gene family, member A) are expressed at higher levels in PE, suggesting a role in the pathogenesis of PE.

Antioxidants such as vitamin C and vitamin E inhibit the p38 signaling pathway and thus block the secretion of sFlt-1.

Studies have also revealed that exogenous antitrypsin α-1 can alleviate hypoxia/reoxygenation injury by reducing oxidative stress by inactivating Rac1/p38 signaling. Eduardo et al. (2018) reviewed the use of VEGF and PlGF as therapies to curb PE and suggested that modified stabilized members of the VEGF family could be used as therapeutic agents for treatment, but recent studies reveal that VEGF and PlGF could be triggers for increased sFlt-1 production.

A study of metformin showed that it was able to prevent PE by reducing the production of sFlt-1 and sEng and improving endothelial dysfunction through effects on mitochondria.

MSCs are adult stem cells that have an anti-inflammatory, immune regulator and repairing effect. The regenerative potential of MSCs isolated from the placenta and umbilical cord could be harnessed for the treatment of hypertension in PE, ameliorate the damage caused by Intrauterine Growth Restriction (IUGR), kidney damage, and impaired spiral artery remodeling. (Jena, 2020)

Sildenafil citrate enhances the action of NO by inhibiting the enzyme phosphodiesterase-5, which is responsible for the degradation of cyclic GMP, a key second messenger for NO signaling. Consequently, several preclinical studies have evaluated the efficacy of sildenafil as a treatment in established phenotypes similar to preeclampsia, consistently lowers maternal blood pressure, and in most studies also reduces proteinuria and maternal kidney damage.

CONCLUSIONS

New molecules have been found for early diagnosis based on the angiogenic relationship present in preeclampsia, such as high levels of sFlt-1, sEng, IL-16, Activin A, ICAM and VCAM, as well as low levels of PAPP-A, PlGF and placental protein 13, as well as new drugs and interventions for effective treatment such as sildenafil, pravastatin, stem cells, however, Due to discrepancies in outcomes for both mother and fetus, they cannot yet be widely recommended.

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