Editorial

# Preeclampsia: Vascular Pathophysiological Mechanism and the Basis for Early Diagnosis and Treatment

## *Pré-eclâmpsia: mecanismo vascular na fisiopatologia e implicações para diagnóstico precoce e tratamento*

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Hypertensive disease of pregnancy, postpartum hemorrhage and infectious syndromes in pregnancy and puerperium are the leading causes of morbidity and mortality for pregnant women around the world.[1] Their frequency varies according to the country and accessibility to health care.[1] Hypertensive diseases, including preeclampsia, complicate 2–10% of all pregnancies.[1–3] In Latin America and the Caribbean, hypertensive disorders are responsible for at least 26% of maternal deaths.[3]

Preeclampsia is a multifactorial disease caused by environmental factors that act over a genetic base, permitting the occurrence of this disorder.[4–12] Based on this premise, the risk factors considered for the development of this disease are: overweightness; obesity; nulliparity and multiparity; being at the extremes of reproductive life; vascular diseases, such as chronic hypertension; metabolic diseases, such as diabetes mellitus; collagen diseases, such as systemic lupus erythematosus; multiple pregnancies; maternal and paternal family history[12–14] (paternal imprinting expressed in the mother); pregnancy by assisted reproductive techniques;[12,14] micropolycystic ovary syndrome with insulin resistance;[14,15] severe anemia;[16] antiphospholipid syndrome;[17] and low-calcium diets consumed by people living at high altitudes.[18,19]

The interaction of risk factors and multiple polymorphic genes induces the synthesis of several proteins with effects differing from their original function, leading to the impairment of placental perfusion and the consequent production of mediators that damage the endothelium. The main proteins and others factors involved are listed below.[7,8,20]

Group I – vasoactive and vascular remodeling proteins: nitric oxide synthase; renin; type I and II angiotensin receptors; angiotensin converting enzyme; polycarboxypeptidase; endothelin-1; alpha and beta estrogen receptors; endoglin; tyrosine-kinase fms-like receptor-1; placental growth factor; and vascular endothelial growth factor.[20]

Group II – thrombophilia and hypofibrinolysis: methyltetrahydrofolate reductase; Leiden Factor V; prothrombin; fetal thrombophilia; plasminogen activator inhibitor-1; B3 integrin; and glycoprotein IIIA.[20]

Group III – oxidative stress, lipid metabolism, endothelial injury: epoxide hydrolase; glutathione transferase; superoxide dismutase; cytochrome P450 1A1; lipoprotein lipase; apolipoprotein E; and long-chain 3-hydroxyacyl-CoA dehydrogenase.[20]

Group IV – immunogenetic: human leukocyte antigen; interleukins 1 and 10; and tumor necrosis factor.[20]

Physiologically, in order to promote vascular remodeling, the changes of the decidua also occur in the inner area of the myometrium.[21] An interaction of trophoblastic human leukocyte antigen (HLA) C, HLA-E, HLA-G with natural killer cells or dendritic cells or both is necessary for this event to occur. The presence of certain combinations of HLA-C and isoform types of immunoglobulin receptors bound to natural killer cells predispose to preeclampsia.[23–25]

The intervillous blood flow seems to begin by the 7th to 8th week of pregnancy, by connections between spiral arteries and lakes formed in the wall of the implanted blastocyst.[26] A tamponade is formed early by the trophoblast that protects

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the embryo from high oxygen concentrations. These blockades are then replaced by the intravascular migration of the trophoblast.[26,27] The onset of the circulation is normally a progressive periphery-center phenomenon, and high levels of oxidative stress in the periphery may induce the formation of the chorion laeve.[26,27] Thus, from the beginning of the implantation, this process will determine the absence or a decrease in the replacement of the muscle layer of the myometrial spiral arteries, causing a low flow and high resistance in these vessels instead of what is expected in a normal pregnancy. This determines placental hypoperfusion, hypoxia and the release of pro-inflammatory cytokines that favor the formation of free radicals.[7,8,28,29]

Superoxide ion, hydroxyls and hydrogen peroxide damage the lipid bilayer through peroxidation, destroying endothelial cells and exposing the subendothelium[28,29] to which platelets adhere and release thromboxane A2, causing vasoconstriction and platelet aggregation. Endothelial destruction and decreased prostacyclin production will then occur, with a vasodilating and antiaggregant effect.[28,29]

Placental hypoxia generates the production of soluble fms-like tyrosine kinase receptor-1 (sFlt-1), which binds to the vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) that are responsible for the maintenance of endothelial integrity.[7,8] Therefore, the clinical expression of this process will involve elevated blood pressure powered by the decrease of nitric oxide and increased endothelin[7,8,28,29] and the presence of urinary protein.[30]

The pathophysiology of other signs and symptoms, such as headache, tinnitus, scotoma, vomiting, nausea, epigastric and right upper quadrant pain, oliguria, hyperreflexia, and convulsions[31,32] involves an imbalance between thromboxane and prostacyclin and the consequences of subsequent hypoxia and ischemia resulting from the obstruction of blood flow.[4,5,7,31,32] Blood concentration is further increased by volume changes due to loss of protein in the urine because of the presence of glomerular endotheliosis.[31,32]

It is important to note that in the brain there is a significant increase in the production of excitatory amino acids such as glutamate, which binds to the N-methyl D-aspartate (NMDA) receptor, allowing the opening of calcium channels in the cell membrane, with calcium entry into hypoxic cells triggering the typical tonic-clonic convulsions of eclampsia.[33]

The classification of hypertensive diseases has been changing, currently comprising preeclampsia-eclampsia, gestational hypertension, chronic hypertension and chronic hypertension plus superimposed preeclampsia, as well as the complication represented by the HELLP (H: hemolysis, EL: elevated liver enzymes, LP: low platelet count) syndrome.[2,34]

We use the term preeclampsia when systolic blood pressure and/or diastolic blood pressure are higher than 140/90 mmHg after 20 weeks of gestation and 300 mg or more of protein in a 24-hour urine collection, or when there is a + random protein strip or higher, or 24-hour protein levels higher than 300 mg/dL, and a protein/creatinine ratio greater than or equal to 0.3. The severity of the condition is based on the presence of arterial blood pressure higher than 160/110 mmHg, creatinine higher than 1.1 mg/dL, brain and visual disturbances, platelet count lower than 100.000/µL, and a 2-fold increase in liver enzymes. It should be remembered that the absence of urinary protein does not exclude the diagnosis because the diagnosis is made according to the severity of signs and symptoms even in the absence of proteinuria.[2,34]

Once the diagnosis is made and based on the proposed vascular pathophysiological mechanisms, the therapeutic approach can be focused on four objectives: to prevent and treat seizures;[35] to treat increased blood pressure; to determine the gestational age at which to end pregnancy; and to diagnose maternal and fetal complications.

Regarding the first objective, the drug of choice is magnesium sulfate,[33] which has been used since the early 1900's, although its effectiveness was demonstrated only one century later.[33] Its mechanism of action is central (blocking NMDA receptors) and peripheral, decreasing cytosolic calcium by blocking the calcium channels on the neuromotor plate and increasing intracellular magnesium and acetylcholine in the synaptic gap.

Despite the risk of cardiorespiratory arrest, we can avoid magnesium intoxication with optimal clinical control of respiratory rate, osteotendinous reflexes, and diuresis. A laboratory test is not necessary for the measurements of serum magnesium.[33,34,36] If cardiorespiratory arrest should occur, it may be corrected with intravenous calcium gluconate. Magnesium sulfate is administered up to 24 hours after delivery. Vasomotor symptoms should be checked before withdrawal of the drug, since their presence would be an indication to extend its administration.[34]

Unlike the first objective, the second one involves some concerns. Three drugs are available for the treatment of hypertensive crises: hydralazine, labetalol and nifedipine. The last two are superior, since hydralazine involves a higher risk of lowering the Apgar score at the first minute and inducing arterial hypotension and oliguria.[34,37] In contrast, nifedipine improves diuresis by inducing afferent arteriolar vasodilation. However, according to a Cochrane review,[38] medical experience is the determinant factor in choosing the ideal drug for each patient. The objective of the treatment is to maintain a diastolic pressure around 90 mmHg and a systolic pressure not exceeding 160 mmHg.[34,39] For this purpose, we could use fast or osmotic release nifedipine for maintenance or perform expectant management. Alpha-metyldopa is another option which is chosen by many clinicians with a broad experience with its use.[34,39,40]

The determination of the gestational age at which to end pregnancy depends on the presence of complications such as HELLP syndrome, eclampsia and uncontrolled arterial pressure. In any case, the patient should be first stabilized before ending the pregnancy.[41–44]

Between 24 and 34 weeks of gestation, two options are available for the management of severe preeclampsia:

1. interventionist management consisting of lung maturation with steroids and the termination of pregnancy;

2. expectant management consisting of lung maturation with steroids, determining whether platelet counts are above 100,000 µL, checking for the presence of vasomotor symptoms, determining if systolic blood pressure is below 160 mmHg and diastolic blood pressure is about 90 mmHg with or without drugs, and checking for adequate diuresis with or without fluids, in order to give the fetus more days in the uterus.[41–44]

An important factor to consider in the management of preeclampsia is fluid therapy. Although there is this false idea not supported by scientific evidence that enhancing the entry of fluids will improve the prognosis, intravascular volume expansion carries a serious risk of volume overload, which could lead to pulmonary or cerebral edemas. Physicians should be careful because of the risk of acute lung edema with the excessive use of fluids.[45,46]

Finally, in order to fulfill the objective of diagnosing maternal and fetal complications, we should determine perinatal comorbidities such as oligohydramnios, intrauterine growth restriction and abruption. For this purpose, we may use fetal biometry, umbilical artery, middle cerebral artery and venous duct flowmetry, and cardiotocography.[47]

Checking fetal movements daily, using a non-stressful test twice a week, determining fluid volume weekly and fetal growth every two weeks are helpful for the assessment of fetal wellbeing.[2,48]

In addition to the immediate risks and complications for both mother and fetus, gestations that include fetal exposure to preeclampsia appear to elevate the risk of cerebrovascular and neuroanatomical changes during development. Such changes during fetal life may explain the postnatal findings of elevated risks for stroke and specific deviations of cognitive functioning, including visual spatial processing and memory, as shown in an initial pilot study by a group of researchers at Queen's University, published in this issue.[49]

Although we have presented a review of the epidemiology, physiopathology, clinical features, diagnosis and treatment of hypertensive disease of pregnancy, we believe that the main goal should be to identify patients without a previous history of preeclampsia but with potential risk factors. In this situation, we should apply predictive tests to these patients in order to determine the risk and to administer low doses of calcium and aspirin if necessary.[2,43,44]

However, the available predictive tests are useless.[49] Furthermore, many biomarkers have been suggested,[47,50] but none has been demonstrated to be sufficiently predictive. The combination of three interventions, that is, risk factors questionnaire, uterine artery flowmetry and some biomarkers, such as serum pregnancy-associated plasma protein-Av (PAPP-A), sFlt-1 and PlGF,[48,51] performed during the first or second trimester may allow us to predict the possibility of the disease and to reduce the risk preeclampsia complications.[2,7,51,52]

Calcium administered at a daily dose of 1.5 to 2 g has proved to decrease the risk of preeclampsia in patients with low calcium intake[34] or with risk factors or positive predictive tests for the disease. At these doses, calcium reduces the release of the parathyroid hormone, thus reducing cytosolic calcium and vascular hyperresponsiveness.[41] Low aspirin doses of 80 to 150 mg have produced a modest drop of the disease in patients with risk factors.[53,54] The mechanism of the drug is mediated by the irreversible blocking of platelet cyclooxygenase 1 and 2, inhibiting the aggregation and the release of thromboxane.[43,44] Other drugs, such as low molecular weight heparins added to aspirin, have been suggested, but their efficacy still needs to be demonstrated.[55]

In view of the aforementioned considerations, we can see that progress is being made in the understanding of the pathophysiology of preeclampsia that allows us to explore new fields of scientific research, seeking therapeutic interventions to achieve success in the management of the disease.[49] Additionally, the advance of knowledge about the disease prediction should substantially contribute to the better understanding of the prevention of preeclampsia and consequently the reduction of maternal and perinatal morbidity and mortality.

## References


1 Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol 2009;33(3):130–137
2 American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122(5):1122–1131
3 Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PFA. WHO analysis of causes of maternal death: a systematic review. Lancet 2006;367(9516):1066–1074
4 Brosens I, Robertson WB, Dixon HG. The role of spiral arteries in the pathogenesis of preeclampsia. In: Obstetrics and Gynecology Annual, ed Wynn RM. New York: Appleton-Century-Crofts; 1972:177–91
5 Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. Placenta 2006; 27(9–10):939–958
6 Founds SA, Dorman JS, Conley YP. Microarray technology applied to the complex disorder of preeclampsia. J Obstet Gynecol Neonatal Nurs 2008;37(2):146–157
7 Baumann MU, Bersinger NA, Surbek DV. Serum markers for predicting pre-eclampsia. Mol Aspects Med 2007;28(2): 227–244
8 Sibai BM. Hypertensive disorders of pregnancy: the United States perspective. Curr Opin Obstet Gynecol 2008;20(2):102–106
9 Chappell S, Morgan L. Searching for genetic clues to the causes of pre-eclampsia. Clin Sci (Lond) 2006;110(4):443–458
10 Nejatizadeh A, Stobdan T, Malhotra N, Pasha MA. The genetic aspects of pre-eclampsia: achievements and limitations. Biochem Genet 2008;46(7–8):451–479
11 Wright D, Akolekar R, Syngelaki A, Poon LC, Nicolaides KH. A competing risks model in early screening for preeclampsia. Fetal Diagn Ther 2012;32(3):171–178
12 Paré E, Parry S, McElrath TF, Pucci D, Newton A, Lim KH. Clinical risk factors for preeclampsia in the 21st century. Obstet Gynecol 2014;124(4):763–770
13 Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 2005; 330(7491):565
14 Lie RT, Rasmussen S, Brunborg H, Gjessing HK, Lie-Nielsen E, Irgens LM. Fetal and maternal contributions to risk of preeclampsia: population based study. BMJ 1998;316(7141): 1343–1347
15 Martinez Abundis E, Gonzalez Ortiz M, Quiñones Galvan A, Ferrannini E. Hyperinsulinemia in glucose-tolerant women with preeclampsia. A controlled study. Am J Hypertens 1996;9(6):610–614

16 Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP. Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: a WHO secondary analysis. PLoS ONE 2014;9(3):e91198
17 Bartsch E, Medcalf KE, Park AL, Ray JG; High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ 2016;353:i1753
18 Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev 2010;8(8):CD001059
19 Herrera-Suárez CC, Vásquez-Garibay EM, Romero-Velarde E, Romo-Huerta HP, García De Alba García JE, Troyo-Sanromán R. [Food habits and culture factors in pregnant adolescents]. Arch Latinoam Nutr 2008;58(1):19–26
20 Mütze S, Rudnik-Schöneborn S, Zerres K, Rath W. Genes and the preeclampsia syndrome. J Perinat Med 2008;36(1):38–58
21 Ng EH, Chan CC, Tang OS, Yeung WS, Ho PC. The role of endometrial and subendometrial vascularity measured by three-dimensional power Doppler ultrasound in the prediction of pregnancy during frozen-thawed embryo transfer cycles. Hum Reprod 2006; 21(6):1612–1617
22 Hanna J, Goldman-Wohl D, Hamani Y, et al. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat Med 2006;12(9):1065–1074
23 Goldman-Wohl DS, Ariel I, Greenfield C, et al. Lack of human leukocyte antigen-G expression in extravillous trophoblasts is associated with pre-eclampsia. Mol Hum Reprod 2000;6(1):88–95
24 Le Bouteiller P, Pizzato N, Barakonyi A, Solier C. HLA-G, pre-eclampsia, immunity and vascular events. J Reprod Immunol 2003;59(2):219–234
25 Moffett A, Hiby SE. How Does the maternal immune system contribute to the development of pre-eclampsia? Placenta 2007;28(Suppl A ):S51–S56
26 Burton GJ, Jauniaux E, Watson AL. Maternal arterial connections to the placental intervillous space during the first trimester of human pregnancy: the Boyd collection revisited. Am J Obstet Gynecol 1999;181(3):718–724
27 Burton GJ, Jauniaux E. Placental oxidative stress: from miscarriage to preeclampsia. J Soc Gynecol Investig 2004;11(6):342–352
28 Pijnenborg R, Brosens I. Deep trophoblast invasion and spiral artery remodelling. In: Pijnenborg R, Brosens I, Romero R, eds. Placental bed disorders: basic science and its translation to obstetrics. Cambridge: Cambridge University Press; 2010: 97–107
29 Plasencia W, Maiz N, Bonino S, Kaihura C, Nicolaides KH. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks in the prediction of pre-eclampsia. Ultrasound Obstet Gynecol 2007;30(5):742–749
30 Craici IM, Wagner SJ, Bailey KR, et al. Podocyturia predates proteinuria and clinical features of preeclampsia: longitudinal prospective study. Hypertension 2013;61(6):1289–1296
31 Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol 2004;103(5 Pt 1):981–991
32 Cavkaytar S, Ugurlu EN, Karaer A, Tapisiz OL, Danisman N. Are clinical symptoms more predictive than laboratory parameters for adverse maternal outcome in HELLP syndrome? Acta Obstet Gynecol Scand 2007;86(6):648–651
33 Altman D, Carroli G, Duley L, et al; Magpie Trial Collaboration Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 2002;359(9321):1877–1890
34 Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000;183(1):S1–S22
35 Witlin AG, Sibai BM. Randomized trials for prevention and treatment of eclamptic convulsions. In: Sibai BM, ed. Hypertensive disorders in women. Philadelphia: Saunders; 2001:221–27
36 Sibai BM. Magnesium sulfate prophylaxis in preeclampsia: Lessons learned from recent trials. Am J Obstet Gynecol 2004;190(6): 1520–1526
37 Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. BMJ 2003;327(7421):955–960
38 Duley L, Henderson-Smart DJ, Meher S. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev 2006;3(3):CD001449
39 Brown MA, Hague WM, Higgins J, et al; Australasian Society for the Study of Hypertension in Pregnancy. The detection, investigation and management of hypertension in pregnancy: executive summary. Aust N Z J Obstet Gynaecol 2000;40(2):133–138
40 Rey E, LeLorier J, Burgess E, Lange IR, Leduc L. Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy. CMAJ 1997;157(9):1245–1254
41 Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol 2003;102(1):181–192
42 Vigil-De Gracia P, Montufar-Rueda C, Ruiz J. Expectant management of severe preeclampsia and preeclampsia superimposed on chronic hypertension between 24 and 34 weeks' gestation. Eur J Obstet Gynecol Reprod Biol 2003;107(1):24–27
43 Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 2005; 365(9461):785–799
44 Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet 2010;376(9741):631–644
45 Heilmann L, Gerhold S, von Tempelhoff GF, Pollow K. The role of intravenous volume expansion in moderate pre-eclampsia. Clin Hemorheol Microcirc 2001;25(3–4):83–89
46 Duley L, Williams J, Henderson-Smart DJ. Plasma volume expansion for treatment of women with pre-eclampsia. Cochrane Database Syst Rev 2000;4(2):CD001805
47 Leveno KJ, Cunningham FG. Management. In: Lindheimer MD, Roberts JM, Cunningham FG, eds. Chesley's hypertensive disorders in pregnancy. Amsterdam: Academic Press, Elsevier; 2009:389–414
48 Chaiworapongsa T, Chaemsaithong P, Korzeniewski SJ, Yeo L, Romero R. Pre-eclampsia part 2: prediction, prevention and management. Nat Rev Nephrol 2014;10(9):531–540 10.1038/nrneph.2014.103
49 Dang F, Croy BA, Stroman PW, Figueiró-Filho EA. Impacts of Preeclampsia on the Brain of the Offspring. Rev Bras Ginecol Obstet 2016
50 Poon LC, Nicolaides KH. Early prediction of preeclampsia. Obstet Gynecol Int 2014;2014:297397
51 Papageorghiou AT, Campbell S. First trimester screening for preeclampsia. Curr Opin Obstet Gynecol 2006;18(6):594–600
52 O'Gorman N, Wright D, Syngelaki A, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. Am J Obstet Gynecol 2016;214(1):103.e1–103.e12
53 Roberge S, Giguère Y, Villa P, et al. Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: a systematic review and meta-analysis. Am J Perinatol 2012;29(7):551–556
54 Roberge S, Villa P, Nicolaides K, et al. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis. Fetal Diagn Ther 2012;31(3):141–146
55 Roberge S, Demers S, Nicolaides KH, Bureau M, Côté S, Bujold E. Prevention of pre-eclampsia by low-molecular-weight heparin in addition to aspirin: a meta-analysis. Ultrasound Obstet Gynecol 2016;47(5):548–553