Preeclampsia*

*Pré-eclâmpsia**

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Abstract

The authors review hypertensive disease during pregnancy with an academic and practical view, and using the best evidence available. This disease, which is the most important clinical disease in Brazilian pregnant women, may have its incidence reduced with prevention through the use of calcium and aspirin in pregnant women at risk. Previously, it was a disease that presented with *hypertension with proteinuria,* but it has now been classified with new clinical parameters besides proteinuria. Morbidity and mortality should be reduced in a continental country such as Brazil using protocols for the early treatment of complications by calculating severe outcomes in preeclampsia. The early treatment of acute hypertension, use of magnesium sulfate and early hospitalization in cases of preeclampsia are concepts to pursue the reduction of our pregnant women's mortality.

Keywords
- pregnancy arterial hypertension
- preeclampsia
- HELLP syndrome
- high risk pregnancy
- pregnancy complications

Resumo

Os autores revisam a doença hipertensiva na gestação com uma visão acadêmica e prática, utilizando as melhores evidências disponíveis. A doença clínica mais importante na gestante brasileira pode ter sua incidência diminuída com a prevenção por meio do uso de cálcio e aspirina em gestantes de risco. Antes uma doença que apresentava hipertensão *arterial com proteinúria,* agora vem sendo classificada com novos parâmetros clínicos além da proteinúria. A morbidade e mortalidade devem ser diminuídas, em um país continental como o Brasil, utilizando-se protocolos para o tratamento precoce de suas complicações mediante o cálculo de desfechos graves em pré-eclâmpsia. O tratamento precoce da hipertensão arterial, o uso do sulfato de magnésio e a internação precoce em casos de pré-eclâmpsia são conceitos para perseguirmos a diminuição da mortalidade de nossas gestantes.

Palavras-chave
- hipertensão arterial na gestação
- pré-eclâmpsia
- síndrome HELLP
- gestação de alto risco
- complicações na gravidez

Highlights

- New concepts of diagnosis and risk for preeclampsia;
- Guidelines for preeclampsia prevention treatment;
- Prediction model of severe maternal outcomes in preeclampsia (fullPIERS) 12.

Introduction

The hypertensive syndromes that occur during pregnancy, especially preeclampsia (PE), result in real risk and significant impact on indicators related to maternal and child health. These syndromes are causal factors related to maternal and perinatal death, and they cause definitive limitations to maternal health and serious problems resulting from associated elective prematurity. In Brazil, PE is the main cause of elective prematurity.

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There is no accurate information on the incidence of preeclampsia worldwide, but it is estimated to occur in 3–5% of pregnancies. Specifically in Brazil, a systematic review identified an incidence of 1.5% for PE and of 0.6% for eclampsia.[1] Certainly, information concerning Brazil is still underestimated, and definitely varies according to the country's regions. A Brazilian study[2] reports that the estimated prevalence of eclampsia is of 0.2% in the most developed areas, with a maternal death rate of 0.8%, whereas in less favored regions this prevalence rises to 8.1%, with a maternal mortality rate corresponding to 22.0%.

The aim of this text is to sensitize health providers about the magnitude of the problem, recognize local specificities, and adopt interventions based on the best scientific evidence available to develop strategies for prevention, early detection of the disease, and reduction of maternal and perinatal harm.

Pathophysiological Foundations

Some evidence supports the hypothesis of maternal immune system involvement in the disease. In case there are problems of immunological adaptation to the trophoblast, there will be problems in trophoblast perfusion, with consequent hypoxia. These primary alterations would trigger a series of local hypoxia phenomena, and reoxygenation could amplify the local effects, such as the formation of oxygen-reactive species, activation of the maternal inflammatory system, and acceleration of cellular apoptosis processes that would limit the establishment of normal placentation and imbalance between pro-angiogenic factors, such as the vascular endothelial growth factor (VEGF) and the placental growth factor (PlGF), and soluble anti-angiogenic factors such as the soluble fms-like tyrosine kinase-1 (sFLT-1), with predominance of the latter, resulting in generalized activation of the maternal inflammatory system, universal endothelial dysfunction, and limited placental vascularization.[3,4]

Universal arteriolar spasm due to endothelial activation results in an insidious and progressive process, culminating in multiple organ insufficiency. Preeclampsia should be interpreted as a chronic disease with potential for progressive multiple organ failure. This evolutionary character must be taken into account, as well as its unpredictability and clinical instability in decisions. Endothelial activation basically determines: vasoconstriction and consequent increase in peripheral resistance; changes in capillary permeability, which are responsible for edema; and activation of the coagulation system.

The kidneys suffer from anatomopathological patterns (glomerular endotheliosis and focal sclerosis), with consequent proteinuria and impairment of the glomerular filtration. In the liver, ischemia occurs with varying intensity, leading to dysfunction with elevated levels of transaminases. Focal or confluent edema and/or hemorrhage distend the capsule, and may result in hepatic rupture with massive bleeding.

Vasospasm hinders the uteroplacental blood flow with varying intensity, depending on the moment of the process and on the existence of a chronic pre-existing injury. Regarding coagulation, there is activation and consumption of platelets with progressive consumption and disseminated coagulation. The brain can be affected by ischemia aggravated by diffuse edema, resulting in seizure (eclampsia) or stroke. Patients presenting severe conditions, particularly eclampsia, should receive differentiated care, given the progressive functional limitation of multiple organs.

Definitions of Hypertensive States during Pregnancy

The expansion of pathophysiological knowledge has resulted in the expansion of clinical possibilities to define PE. However, the recommendations adopted by the International Society for the Study of Hypertension in Pregnancy (ISSHP)[5] remain. According to such recommendations, arterial hypertension is characterized when the systolic blood pressure (SBP) is $\geq$ 140 mm Hg and/or the diastolic blood pressure (DBP) is $\geq$ 90 mm Hg, considering the fifth Korotkoff sound (silence). For the measurement, the patient should sit and place one of the forearms at the height of the atrium (half of the external bone); the measurement should be repeated in one or two five-minute intervals. The usually available cuffs are used for readings in arms with perimeter around 30 cm. Obese patients need appropriate cuffs or correction tables according to their brachial perimeter.

Protein loss of 300 mg or more in 24-hour urine specimen collection should be considered for the definition of proteinuria. For more agility in the diagnosis, evaluations in an isolated sample of urine with proteinuria/creatininuria (P/C) ratio (both in mg/dL) $\geq$ 0.3 are considered adequate. In the absence of such diagnostic possibilities, proteinuria with at least 1+ reagent tape may be considered as long as the quality of the method is assured. Differently from previous recommendations, the intensity of the proteinuria should no longer be associated with the maternal prognosis, nor be the only aspect to guide decisions.

Preeclampsia is defined as arterial hypertension identified for the first time after the 20th week associated with proteinuria, and it may overlap with another hypertensive state. Taking into account the current concept of PE syndrome, rigid concepts have been abandoned.[6] Thus, in the absence of proteinuria, the diagnosis of PE may be based on the presence of headache, visual turbidity, abdominal pain or altered laboratory tests, such as thrombocytopenia (less than 100,000/mm^3), hepatic enzyme elevation (double the basal), renal impairment ($>$ 1.1 mg/dL or double the baseline), or pulmonary edema and visual or brain disorders such as headache, scotomas, or convulsions.

These criteria should be adopted for patients with preexisting hypertension (arterial hypertension preceding pregnancy or identified before 20 weeks), with worsening of baseline blood pressure (BP), and the onset of proteinuria, suggesting PE overlap. Hence, concerning the diagnosis,

Table 1 Severe complications of preeclampsia

Affected organic system	Adverse conditions	Severe complications indicating termination of pregnancy
Central nervous system	Headache; visual symptoms	Eclampsia; PRES; cortical blindness; Retinal detachment; Glasgow scale < 13; TIA; stroke; RND.
Cardiorespiratory	Chest pain; dyspnea; saturation O_2 < 97%	Severe uncontrolled hypertension (for a 12-hour period despite maximum doses of hypotensive agents); SO_2 < 90%, need for O_2 > 50% for > 1 hour, intubation, support with vasoactive drugs; pulmonary edema; myocardial ischemia or infarction.
Hematological	Leukocytosis; thrombocytopenia; high INR PTT	Platelets < 50.000/dL;* need for transfusion of any blood product.
Renal	Elevated creatinine and uric acid	ARF (creatinine > 1.5 mg/dL without previous renal disease); need for dialysis (without previous CRF).
Hepatic	Nausea; vomiting epigastralgia; URQ pain; SGOT; SGTP; LDH; elevated bilirubin; low plasma albumin	Hepatic impairment (INR > 2 in absence of DIC or use of warfarin); hepatic hematoma with or without rupture.
Fetoplacental	Non-reactive CTG; Oligohydramnios; IUGR; Doppler of umbilical artery with absent or reversed diastolic flow	PA; reversed a-wave in ductus venous; fetal death.

Abbreviations: ARF, acute renal failure; CRF, chronic renal failure; CTG, cardiotocography; DIC, disseminated intravascular coagulation; INR; IUGR, intrauterine growth restriction; LDH, lactate dehydrogenase; PA, placental abruption; PPT, prothrombin time; PRES, posterior reversible encephalopathy syndrome; RND, reversible neurological deficit; SGOT, serum glutamic oxaloacetic transaminase; SGTP, serum glutamic pyruvic transaminase; TIA, transient ischemic attack; URQ, upper right quadrant of the abdomen.
Note: *Platelets < 100.000 are considered as indication of interruption of pregnancy.
Adapted from: Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P; Canadian Hypertensive Disorders of Pregnancy (HDP) Working Group (2014).[8]

preeclampsia is considered hypertension after the twentieth week and one of the following criteria:

1. Significant proteinuria (P/C ratio > 0.3; > 1.0 g/L on reagent tape);
2. Maternal organic dysfunctions;
   - Loss of renal function (creatinine > 1.02 mg/dL);
   - Hepatic dysfunction (increase of transaminases by > 2 times the normal upper limit; epigastralgia);
   - Neurologic complications (altered mental state; blindness; hyperreflexia with clonus, scotomas, visual blurring, diplopia, Doppler of maternal ophthalmic artery with peak ratio > 0.78);
   - Hematologic complications (thrombocytopenia, disseminated intravascular coagulation [DIC] < hemolysis);
   - Antiangiogenesis status (PlGF < 36 pg/mL or sFlt-1/PlGF ratio > 85).
3. Uteroplacental dysfunction (asymmetric intrauterine growth restriction [IUGR]; altered umbilical Doppler, especially if the Doppler is altered in both maternal uterine arteries).

When PE occurs in pregnant women with chronic hypertension, it is considered overlapping preeclampsia. Severe preeclampsia is defined as PE associated with severe enough maternal-fetal complications to pose imminent risk of maternal-fetal impairment. Persistent SBP ≥ 160 mm Hg or DBP ≥ 110 mm Hg or presence of any of the criteria listed in ►**Table 1** characterize a pregnant woman as having severe PE. In general, pregnant women with signs or symptoms of severe PE have a decompensated disease that may rapidly progress to maternal and perinatal morbidity and mortality. Proteinuria levels should not be considered criteria of severity in PE.[7,8] The presence of PE, regardless of its severity, entails increased fetal and maternal risk. Eclampsia is the occurrence of generalized motor seizures (grand mal seizures) in pregnant women with PE that are not caused by coincident neurological disease and may occur in the prepartum period (50%), during delivery (20%), and in the postpartum period (between 11 and 44%).

Classification

There are several classifications described for hypertensive disorders in pregnancy. In 2014, the ISSHP reviewed the classification of hypertensive disorders during pregnancy (►**Table 2**).[5]

Significant Proteinuria

It is the excretion of 300 mg or more of proteins in a 24-hour urine collection. The 24-hour collection is subject to many collection and storage errors, and should not be used for clinical purposes unless 24-hour creatinine clearance is also

Table 2 Classification of hypertensive disorders of pregnancy

Classification
1. Chronic hypertension
2. Gestational hypertension
3. Preeclampsia with or without overlapping chronic hypertension
4. White coat hypertension

Adapted from: Tranquilli et al (2014).[5]

measured to assess the adequacy of the collection.[5] The measurement of the P/C ratio in the urine sample has been of clinical utility, and values ≥ 0.3 demonstrate a good correlation with significant proteinuria. A P/C ratio in an isolated sample of urine ≥ 0.3 corresponds to significant proteinuria 92% of times, and a ratio ≥ 0.5 corresponds to significant proteinuria 100% of times.[9] The presence of 1.0 g/l or more of proteins on the reagent tape strongly suggests significant proteinuria.

Chronic Arterial Hypertension

Chronic arterial hypertension in pregnancy is the occurrence of systemic arterial hypertension (SAH) preceding pregnancy. As there often are no records of BP measurements before gestation, SAH is considered chronic when observed in the first trimester of gestation or, at most, up to the 20th week. In most cases, chronic hypertension refers to essential hypertension, usually associated with family history of hypertension, and often accompanied by overweightness or obesity. More rarely, secondary hypertension may occur. Given the age range of the pregnant women, the presence of secondary hypertension is usually due to underlying parenchymal renal diseases, such as glomerulonephritis and reflux nephropathy.

Gestational Hypertension

Gestational hypertension is defined as arterial hypertension arising for the first time after the 20th week of gestation without being accompanied by any signs, symptoms or laboratory abnormalities that characterize preeclampsia.

White Coat Hypertension (Syndrome)

About 25% of people with increased BP measurements in medical consultations have white coat hypertension. The diagnosis can be confirmed by serial measurements (preferably taken by nurses) or ambulatory BP monitoring (ABPM). There are few studies on the repercussion of this type of disorder in pregnancy, some suggesting that up to 50% of these cases evolve to gestational hypertension or PE.[5]

Preeclampsia diagnosis should be presumed in pregnant women with arterial hypertension and significant proteinuria occurring after the 20th week of gestation (except in cases of hydatidiform mole, when PE can occur before the 20th week). If the increase in BP and proteinuria occurs after the 20th week in a primigravida with family history (mainly sister or mother) of PE or eclampsia, the probability of correct PE diagnosis will be greater than 90%.

Even in the absence of significant proteinuria, the occurrence of hypertension after the 20th week should translate into a PE diagnosis if there are signs of maternal or placental dysfunction (sFLT-1/PlGF ratio > 85, PlGF < 36 pg/mL, creatinine > 1.02 mg/dL; increased transaminase levels by > 2 times the upper limit of normal; epigastralgia; altered mental status; blindness; hyperreflexia with clonus, scotomas, visual disturbance, diplopia, maternal ophthalmic artery Doppler with peak ratio > 0.78; thrombocytopenia $< 150{,}000$/dL, DIC, hemolysis; asymmetric IUGR, umbilical Doppler with decrease or absence of diastolic flow, reverse diastolic flow in umbilical, especially if it is a Doppler with a protodiastolic notch in both maternal uterine arteries).

Serum uric acid increases early in PE, and has a positive correlation with placental bed atheromatosis injuries, lower birth weight infants,[10] degree of hemoconcentration[11] and severity of glomerular endotheliosis.[12] Uric acid levels > 4.5 mg/dL are abnormal in gestation.[13]

The decreased activity of antithrombin III (AT III, $< 70\%$) correlates with renal glomerular endotheliosis, and its measurement may be important in the differential diagnosis with chronic hypertension.[14] Calciuria is decreased in PE, and may also be useful in the differential diagnosis with chronic hypertension. A 24-hour calciuria below 100 mg suggests PE.[15]

In patients at high risk for PE (►**Table 1**), it is prudent to perform baseline tests at the beginning of pregnancy for further comparison. This evaluation should be restricted to the measurement of platelets, creatinine, uric acid, and a search for basal proteinuria (that is, a P/C ratio in the urine sample). In these patients, a precise dating of the gestational age (GA) through ultrasonographic examination in the first trimester is fundamental. A Doppler evaluation of the uterine arteries after the 23rd week of GA is useful to evaluate the presence of an adequate placental implantation or not. Uterine arteries with normal resistance indices indicate low probability of occurrence of PE during pregnancy (high negative predictive value).[16,17] However, pulsatility indices above the 95th percentile for GA and presence of bilateral protodiastolic notch beyond 27 weeks are signs of deficient trophoblastic invasion and consequent increased risk of PE and/or IUGR.

Differential Diagnosis between Preeclampsia and Chronic Systemic Arterial Hypertension

The first onset of hypertension and proteinuria in a primigravida after the 20th week of gestation easily leads to the diagnosis of PE. Likewise, pregnant women with high BP levels before the 20th week or even before the beginning of pregnancy should be diagnosed as having chronic hypertension. However, the differential diagnosis can become difficult when the pregnant woman is seen for the first time after the 20th week with arterial hypertension and cannot inform her previous blood pressure levels accurately. If the pregnant woman is not a primigravida, her serum uric acid level is < 4.5 mg/dL, and the 24-hour calciuria > 100 mg, the diagnosis of chronic hypertension is more likely.

Prediction of Preeclampsia

Advances in the knowledge of the pathophysiology of PE have resulted in the adoption of prediction methods. Through epidemiological data, it is possible to recognize women more likely to develop the disease[18] (►**Table 1**), and develop a differentiated prenatal follow-up strategy. In addition to the clinical features, the literature is rich in publications suggesting prediction methods. Among the several alternatives, the use of Doppler of the uterine arteries and detection of plasmatic substances, such as proteins of placental origin or resulting from angiogenic imbalance, stand out.

The uterine artery Doppler performed in the first or second trimesters has limited accuracy, presents difficulties in assuring the standardization and qualifications in its measurement, and the equipment is costly. The various alternatives of plasma markers also lack the accuracy that justifies their adoption in the clinical practice. The use of plasma markers related to angiogenesis/antiangiogenesis imbalance has been described in the literature as a promising tool for the early detection of PE. However, additional studies are needed to define uniform methods of quantification and evaluate their accuracy before recommending the use in the clinical practice. Despite the large number of 'predictive factors,' there is no consistent evidence identifying the impact of these methods on maternal and perinatal prognosis. Thus, there is no consistent evidence to adopt universal screening in the clinical practice besides the identification of clinical risk.

Due to the high incidence and severity of PE, several attempts have been made to identify the patients at greatest risk of developing it. Preeclampsia in a previous pregnancy poses an average risk of around 15% for PE recurrence, and of 22% for gestational hypertension. Recurrence is more likely if the previous PE had early onset, was severe, or complicated by eclampsia or HELLP syndrome. A high BMI during the previous PE increases the risk of recurrence.[8] Among the several tests proposed to predict the occurrence of PE, the most used currently is the Doppler flowmetry of the uterine arteries.

The Doppler study of the uterine arteries in patients at risk for PE showing persistent protodiastolic incisions beyond the 23rd week of gestation identifies high-resistance placental circulation that usually results from this deficiency of vascular invasion by the trophoblast and consequent increased risk of PE and/or IUGR in the current pregnancy. In a systematic review including 74 studies with 79,547 patients, it was concluded that the 24-week uterine artery Doppler study is the best predictor of PE. The Doppler should be considered positive in the presence of an altered pulsatility index (above the 95th percentile for GA) in combination or not with the persistence of a bilateral protodiastolic notch in the uterine arteries.[19] The presence of these alterations in the velocimetry test is not a diagnosis of PE, but in patients with clinical risk, it shows a greater chance of having pregnancy-specific hypertensive disease and/or IUGR in the current gestation. The greatest usefulness of this Doppler evaluation is its high negative predictive value. Thus, if a patient at high clinical risk for PE (that is, mother and sister with positive history of PE) has a Doppler flowmetry test indicating good diastolic flow in the uterine arteries after the 25th week, her risk of developing PE decreases. In pregnant women at low clinical risk for PE and IUGR, there is no use for a Doppler evaluation of the uterine arteries, since this test cannot identify an increased risk in this population of pregnant women.

Prevention

Only the use of calcium and low-dose aspirin are recommended and considered effective in the clinical practice. Calcium supplementation (calcium carbonate, 1,000–2,000 mg/day) and the use of small daily doses (50–170 mg) of aspirin for at-risk groups are the only alternatives that have shown some degree of effectiveness in randomized clinical trials (Grade A of recommendation).

Antiplatelet Agents

Since 1985, several studies have been published analyzing the effects of using low doses of aspirin for PE prevention. A systematic review published in the Cochrane Library[20] included 37,560 pregnant women at moderate and high risk for preeclampsia. The authors concluded that low-dose aspirin (50–150 mg/day) reduces by 17% the risk of developing PE (risk ratio [RR]: 0.83) with a number needed to treat (NNT) of 72 pregnant women.

Roberge et al[21] reviewed 42 randomized clinical trials (27,222 women) comparing groups using acetylsalicylic acid (ASA, 50–150 mg once a day) with controls. When compared with controls, the groups using ASA initiated before 16 weeks compared with initiation after the 16th week was associated with: a large reduction in perinatal mortality (RR: 0.41, 95% confidence interval [95%CI]: 0.9–0.92 versus RR: 0.93, 95%CI: 0.73–1.19); PE (RR: 0.47, 95%CI: 0.36–0.62 versus RR = 0.78, 95%CI: 0.61–0.99); severe PE (RR: 0.18, 95%CI: 0.08–0.41 versus RR: 0.65, 95%CI: 0.40–1.07); IUGR (RR: 0.46, 95%CI: 0.33–0.64 versus RR: 0.98, 95%CI: 0.88–1.08); and preterm birth (RR: 0.35, 95%CI: 0.22–0.57 versus RR = 0.90, 95%CI: 0.83–0.97).

A critical analysis of the various studies enables the conclusion that although there is no benefit in prescribing aspirin for patients at low risk for PE, its use in the high-risk population can bring benefits. For pregnant women at risk (of PE, eclampsia or hemolysis, elevated liver enzymes and low platelet count [HELLP] syndrome in the previous gestation, recurrent fetal loss or antiphospholipid antibody syndrome), aspirin should be administered prophylactically at low doses (75–170 mg) once a day in the evening (before going to sleep), and initiated before the 16th week. Although it can be maintained until delivery, suspension after the 36th week is rational, as it would avoid potential risks of increased bleeding during delivery.

Based on the current evidence, the use of low molecular weight heparin (enoxaparin 40 mg/day) or sodium heparin (10,000 15,000 IU/day) is not indicated for PE prevention in any patient group.

Supplementation with Calcium

The use of calcium is based on the relationship between a diet with little calcium and increased incidence of eclampsia. Furthermore, in low-income populations with calcium-rich diets, there is lower incidence of PE and eclampsia. There are several studies correlating calcium supplementation and the ingested amounts of calcium in the diet with BP levels and PE.

According to a Cochrane Library review,[22] in 12 studies involving 15,206 pregnant women, calcium supplementation reduced the risk of PE (RR: 0.7) and hypertension (RR: 0.48). This effect is higher among pregnant women at high risk for PE and among those on a low-calcium diet. There was no increase in maternal or fetal adverse events in the population studied. The largest study on calcium supplementation performed with low-risk pregnant women did not show decreased PE frequency,[23] while the majority of randomized controlled trials with pregnant women at high risk for PE have shown a significant decrease of the disorder.[24] The use of calcium (1 g/day) is recommended from the 12th week of gestation, and only for pregnant women at high risk for PE development, especially those on a low-calcium diet.

Screening

The main risk factors for the development of PE are first pregnancy, previous or family history of PE, chronic hypertension, diabetes, collagenosis, black ethnicity, obesity and thrombophilia (►**Table 3**).[25,26] Special attention must be paid during the prenatal care of these patients to perform the diagnosis of preeclampsia as early as possible.

The evaluation of biomarkers for PE has been the subject of numerous studies, and may be useful in the early diagnosis of PE. Ideally, the biomarker evaluation should be easy to perform, low-cost, and enable the detection of pregnancy-specific hypertensive disease as early as possible, preferably in the first trimester of pregnancy, before the onset of hypertension. Recent reviews show that, to date, none of the available clinical trials has achieved an ideal sensitivity level ($>$ 90%) for the prediction of PE. Only the Doppler

Table 3 Risk factors for PE

Risk factors	Risks
Strong evidence	
Prestimoniário	2.4 (2.1–2.7, 95%CI)
Diabetes mellitus	RR: 2–3 and higher if decompensated DM
Twin pregnancy	RR: 3 (2–4.2, 95%CI)
Sister with PE	RR: 3.3 (1.5–7.5, 95%CI)
Sister, mother or grandmother with eclampsia	Respectively 37%, 26% and 16% of PE
Chronic SAH	25% of developing PE overlap
PE in previous pregnancy	25% of PE recurrence
Fetal hydrops (non-immune)	RR: 10
Molar pregnancy	RR: 10
New paternity	Similar risk to first pregnancy
APS	Increases risk
Medium or weak evidence	
BMI $\geq$ 25.8	RR: 2.3–2.7
Maternal age $>$ 40 years	RR: 3–4
Use of contraceptive barrier method	Increased risk
Longer duration of sexual activity	Decreased risk
Prior abortion $<$ 10 weeks with the same father	Decreased risk
Excessive weight gain	Increased risk
Artificial insemination	Increased risk
'Risk man' (previous partner had PE)	RR: 1.8 (1.2–2.6)
Pregnant woman born with low birth weight	Increases the risk
Bleeding in 1st trimester	Increases the risk

Abbreviations: APS, antiphospholipid syndrome; BMI, body mass index; PE, preeclampsia; RR, relative risk; PA, placental abruption; SAH, systemic arterial hypertension.
Notes: Medium or weak evidence, some studies have demonstrated the association; strong evidence, several studies have shown risk.
Adapted from: Magee et al & Canadian Hypertensive Disorders of Pregnancy (HDP) Working Group (2014)[8] , Corrêa Júnior et al (2009)[25] and Sibai et al (2005).[26]

performed between 20–24 weeks showed sensitivity > 60% for PE detection, particularly if performed in pregnant women at increased risk in the 2nd trimester, and to predict severe PE of early onset.[19,27–30]

Using a mathematical model and taking into account the relative risk regarding the maternal age, nuchal translucency procedure, beta-human chorionic gonadotrophin (β-HCG) and pregnancy-associated plasma protein A (PAPP-A) dosing, Nicolaides classifies pregnant women as being at high risk (> 1/50), intermediate risk (1/51–1,000) and low risk (<1/1000) of having preeclampsia. Therefore, low-risk pregnant women are advised to undergo only three prenatal consultations, while high-risk pregnant women are advised to undergo more visits. This structure of prenatal care has been criticized because when classified as low-risk, many pregnant women could have a delayed PE diagnosis, especially those with later onset of PE. This prenatal care model to predict preeclampsia must be effectively tested.[31]

Model to Predict Severe Maternal Outcomes

Von Dadelszen et al[32] have developed an interesting and practical model to predict severe maternal outcomes (►**Fig. 1**). This model was developed in four countries (Canada, New Zealand, Australia and the United Kingdom) and externally validated.[33] It can assist clinicians to assess the patients' percentage of risk of having a fatal outcome or a severe complication within the following seven days. For its use, simply access the fullPIERS calculator website (available in four languages) and find a risk calculator (►**Fig. 1**), insert the data on GA, presence or absence of dyspnea or chest pain, O_2 saturation, dosage of creatinine, platelets, serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT), and obtain the percentage of occurrence of severe complications.

Complications

Systemic arterial hypertension during pregnancy can generate several complications (►**Table 4**) that will invariably require careful evaluation and management by the medical staff.

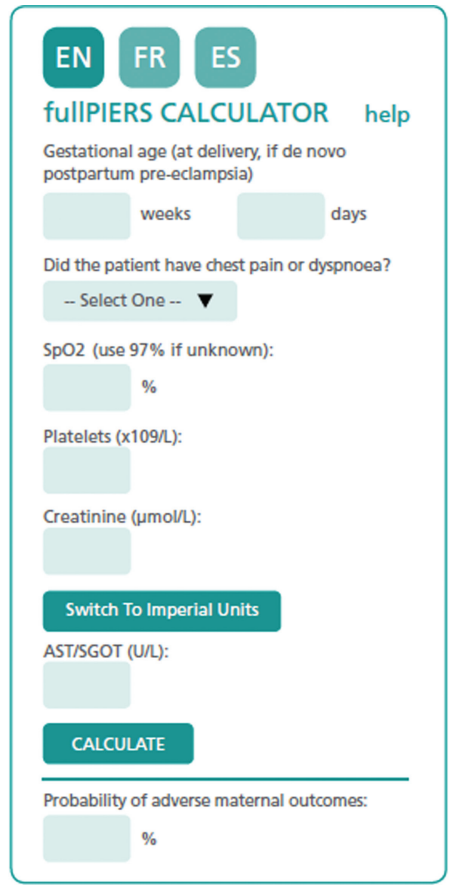

Fig. 1 Risk calculator. **Source:** von Dadelszen, Payne (2011).[32]

Renal Insufficiency

Renal capillary glomerular endotheliosis was considered the characteristic injury of PE for many years. Some authors only considered the PE diagnosis to be accurate in the presence of this renal injury. Damage to the glomerular membrane causes renal dysfunction, and the glomerular filtration rate and renal plasma flow are decreased in relation to healthy pregnant women. There is hyperuricemia in PE, but the elevation of uric acid plasma is transient (dependent on the contraction of plasma volume), and the levels return to

Table 4 Complications of SAH in pregnancy

Affected system	Disorder
Cardiovascular	Severe SAH, pulmonary edema, pulmonary embolism, vascular accidents
Renal	Oliguria, ARF
Hematological	Hemolysis, thrombocytopenia, DIC
Neurological	Eclampsia, cerebral edema, stroke, PRES
Ophthalmologic	Amaurosis, retinal hemorrhages, exudates, papilledema
Hepatic	Dysfunction, ischemia, hematoma, capsular rupture
Placental	Ischemia, thrombosis, PA, fetal hypoperfusion

Abbreviations: ARF, acute renal failure; DIC, disseminated intravascular coagulation; PRES, posterior reversible encephalopathy syndrome; PA, placental abruption; SAH, systemic arterial hypertension.

normal figures after childbirth. Acute renal failure (ARF) is an uncommon event in PE. In general, bilateral cortical necrosis is associated with bleeding and excessive hypotension.[34]

Oliguria in PE has a pre-renal cause most of the times. Therefore, when the urine output drops < 25 mL/h, 1,000 mL of saline solution should be administered within 30 minutes. If the urinary output does not normalize, central hemodynamic monitoring is indicated. Normal or increased pulmonary capillary pressure (PCP) and increased urinary concentration mean that oliguria is caused by intrinsic renal arteriolar spasm caused by angiospasm. At other times, oliguria may be a consequence of decreased ventricular function. In general, these patients have very high PCP and incipient pulmonary edema.

Pulmonary Edema

Most pulmonary edema cases in pregnant women are associated with difficult-to-control hypertension. In PE, pulmonary edema occurs more frequently after delivery, associated with excessive fluid infusion.

The etiology of pulmonary edema in PE appears to be multifactorial. The reduction in colloid osmotic pressure (COP), increase in capillary permeability, and elevation in vascular hydrostatic pressure produce extravasation of fluids in the interstitium and alveolar space. In non-pregnant patients, the decrease in COP/PCP gradient has been correlated with pulmonary edema development. Gestation induces decreased COP, and this decrease is accentuated in PE.

The diagnosis and treatment of pulmonary edema in PE is similar to those of non-pregnant patients: oxygen therapy, water restriction, intravenous (IV) furosemide (80 mg initially) and central hemodynamic monitoring. Reduction in afterload is obtained with the use of vasodilators (hydralazine, nifedipine).

Coagulopathy

Patients with PE frequently have abnormalities in the coagulation system. Reduction in AT III activity (< 70%), increase in factor VIII consumption, and elevation of platelet factor IV can be detected before the clinical manifestations.[13] Although there are changes in the coagulation system since the onset of the disease, in patients with PE, most blood coagulability changes occur due to HELLP syndrome (thrombocytopenia and hepatic dysfunction) and not to DIC.

Management of Preeclampsia

Regardless of the severity of the clinical picture, every patient diagnosed with PE should be hospitalized for follow-up in a high-risk gestational unit. Any patient with PE apparently with a benign condition may suddenly develop complications severe enough to result in maternal and/or fetal death.

The fetuses of mothers with PE who remain hospitalized have half the risk of death compared with fetuses of mothers who are not hospitalized. In addition, hospital-based patients with PE have newborns with more advanced GA at delivery and greater birthweight.[35]

Antihypertensive Therapy in Preeclampsia

Severe systolic hypertension is an independent factor for stroke in pregnancy.[36] The goal of the antihypertensive treatment is to protect the pregnant women from stroke (stroke, rupture of hepatic hematoma). In 2011, the World Health Organization (WHO) strongly recommended the antihypertensive treatment for severe preeclampsia with the aim of reducing maternal morbidity and mortality.[37] Moderate hypertensive pregnant women with long-term SAH and those with secondary SAH and/or repercussion in target organs should be treated with antihypertensive medication to remain normotensive. The CHIPS study demonstrated that strict control of arterial hypertension with initiation of antihypertensive treatment from pressure levels of 140/90 mm Hg improves fetal weight, decreases prematurity rates, the diagnosis of severe SAH, and cases of thrombocytopenia and transfusion. This study advises the initiation of the hypertension treatment earlier than we had previously indicated.[38]

Acute Hypertension

Nifedipine administered orally is the first drug of choice for the treatment of a hypertensive crisis (►**Table 5**). Alternatively, hydralazine can be used intravenously or intramuscularly with similar success as nifedipine.[39] However, the meta-analysis of Magee et al[40] showed that the use of hydralazine for hypertensive crisis control presented disadvantages compared with nifedipine and labetalol, demonstrating increased risk of maternal hypotension (RR: 3.29), placental abruption (PA; RR: 4.17), fetal adverse events and fetal bradycardia (RR: 2.04). Labetalol is an effective alternative for the treatment of acute hypertension during pregnancy, even though it is not commercially available in Brazil. Sodium nitroprusside should be reserved for cases of hypertensive encephalopathy or hypertensive crisis not responsive to other treatments, and the dose should always be > 4 µg/kg/min per infusion pump.[16,39,41,42] Angiotensin-converting-enzyme inhibitors, angiotensin inhibitors or blockers, diazoxide and propranolol should not be used in PE because they pose too much risk to the health of the fetuses.[40,43]

Anticonvulsive Preventive Therapy

Magnesium sulfate ($MgSO_4$) is the drug of choice for preventing eclampsia, and the only drug with proven preventive effects against eclamptic seizures. Randomized clinical trials demonstrate that $MgSO_4$ is superior to hydantoin, diazepam, and placebo for the prevention of eclampsia and its recurrent seizures. The treatment with $MgSO_4$ should be used during labor, prior to cesarean section, or whenever there are signs/symptoms consistent with imminent eclampsia. Magnesium sulfate reduces the risk of eclampsia by 57%, and decreases the risk (RR: 0.55) of maternal death without deleterious effects on the fetus.[44]

Magnesium sulfate should be used for up to 24 hours postpartum in cases of eclampsia and severe PE. Magnesium sulfate is not a risk-free drug, and its administration should be monitored. When administered intravenously, an infusion pump with strict nursing control to avoid the risks of

Table 5 Treatment of acute hypertension (BP > 160/110 mm Hg)

1. Position the patient in left lateral decubitus.
2. Infuse 5% glucose serum into the peripheral vein.
3. Administer nifedipine 10 mg orally and repeat 10 mg every 30 minutes if necessary.
If there is no adequate response, administer IV hydralazine 5 mg.* If BP is not controlled, repeat 5–10 mg every 20 minutes.
4. Check maternal BP every 5 minutes for 20 minutes after medication administration.
5. Evaluate fetal cardiac frequency (cardiotocography) for at least 20 minutes after medication administration.
6. Repeat medication if necessary (BP > 155/105 mm Hg), up to the maximum dose of 30 mg for each drug.
7. Maintain BP < 160/110 mm Hg and > 135/85 mm Hg.
8. Other options:
A. Labetalol 20 mg IV bolus and, if necessary, repeat 40 mg in 10 minutes, and up to two doses of 80 mg every 10 minutes up to a maximum dose of 220 mg. Do not use in asthmatics patients or in those with heart failure.
B. Sodium nitrate 0.25 µg (kg/min) up to maximum of 4 µg (kg/min) and do not use for more than 4 hours.

Abbreviations: BP, blood pressure; IV, intravenous.
Note: *Dilute 1 ampoule (20 mg 2 mL) in 3 mL of distilled water: each milliliter will have 5 mg of hydralazine.
Adapted from: Report of the National High Blood Pressure Education Program (2000).[15]

depression and respiratory arrest due to overdosage should be used.

Although $MgSO_4$ therapy has been more effective than placebo for the prevention of eclampsia, even in mild PE cases, and its use has not been associated with unfavorable maternal fetal outcomes,[44,45] the use in patients with mild PE is controversial, given the low incidence (0.6%) of eclampsia in these patients. In patients with mild PE, the NNT for the prevention of 1 case is 129, while in patients with severe PE it is 36. The rational use of $MgSO_4$, avoiding routine use in the group known to have mild PE, has a lower cost.

The use of a low-dose $MgSO_4$ infusion (0.6 g/h) after a standard 4 g IV attack dose was as effective as the traditional 4 g intramuscular (IM) regimen of 4/4 hours, with 3.3% recurrence in patients with IM $MgSO_4$, and 2% in patients with IV infusion of 0.6 g/h.[46] Therefore, continuous IV infusion at a low dose (0.6 g/h) may be an alternative, especially in patients with higher incidence of side effects or even impaired renal function. The preferred treatment is IV therapy in infusion pump at a concentration of 1 g/h. Schemes for the use of $MgSO_4$ are shown in ►**Tables 6** and **7**.

The degree of maternal and fetal impairment should be assessed simultaneously with the treatment of severe hypertension and prevention of eclampsia. If there is intense and persistent epigastralgia, mainly associated with very high BP levels, there may be distension of the hepatic capsule by subcapsular hemorrhage. In this situation, it is important to evaluate the liver with an ultrasound or tomography. The confirmation of a hematoma implies the necessity of strict BP control and the indication of cesarean section, because there

Table 6 Prevention of convulsions with magnesium sulfate heptahydrate ($MgSO_4$ $7H_2O$)

I. Attack dose: 4 g of $MgSO_4$ (8 mL of 50% $MgSO_4$ 7H2O diluted in 12 mL of distilled water) IV in 5–10 minutes.
II. Maintenance dose IV: 0.6–2 g/h IV (dilute 10 mL of 50% $MgSO_4$ 7H2O in 240 mL of saline solution and infuse at a rate of 50 mL/hour (1 g/hour) or 100 mL/hour (2 g/hour) continuously. Every 120 minutes, check if diuresis is preserved (> 25 mL/hour) and if tendon reflexes are present.
III. Maintenance dose IM:* 10 mL at 50% in the upper outer quadrant of the buttock every 4 hours (alternating buttocks). Evaluate diuresis (> 25 mL/hour) and patellar reflexes before each application.

Abbreviations: IM, intramuscular; IV, intravenous.
Note:* Especially useful for transporting patients in ambulance and in ambulatories, situations in which IV infusion control is precarious.

Table 7 Magnesium sulfate therapy: special situations

I. If there is a lapse ≥ 6 hours between maintenance doses and diuresis is ≥ 25 mL/hour, restart treatment with the attack dose.
II. If renal function is impaired (serum creatinine ≥ 1.3 mg/dL): Apply half the maintenance dose. Measure the serum magnesium level before each new dose 4–7 mEq/L: therapeutic levels 8–10 mEq/L: inhibition of tendon reflexes > 10 mEq/L: risk of cardiorespiratory arrest.
III. Respiratory function impairment: Respiratory depression: 1 g intravenous calcium gluconate and oxygen therapy. Respiratory arrest: *besides calcium gluconate*, endotracheal intubation and assisted ventilation.

Table 8 Laboratory evaluation in PE

Suspected diagnosis	Initial evaluation	Follow-up
Proteinuria/creatininuria ratio or proteinuria in reagent tape	Pulse oximetry Hemogram Creatinine Platelets Serum glutamic oxaloacetic transaminase or lactate dehydrogenase	Platelets Serum glutamic oxaloacetic transaminase or lactate dehydrogenase

may be hepatic rupture during the expulsive period. In addition, laboratory tests should be requested to evaluate renal and hepatic functions and possible hematological changes (►**Table 8**).

Management in Pregnancy at Gestational Age > 36 Weeks or with Proven Fetal Lung Maturity

The cure of PE occurs only after the removal of the placenta; thus, the clinical management depends basically on a balance between the severity of the disease and the GA. Aimed at reducing maternal and fetal complications, patients should be referred to tertiary services where pre-established protocols are followed. These measures lead to a reduction from 5.1% to 0.7% in the occurrence of combined maternal adverse events.[47] In addition, delivery before 37 weeks is an independent factor that protects against the recurrence of PE in the next gestation.[48] Koopmans et al[49] randomized 756 patients with mild PE or gestational hypertension for expectant management (watchful waiting) or induction of labor from the 36th week. In the induction group, fewer maternal complications occurred, with no difference in the rates of cesarean or perinatal complications. The planned induction in PE with mature fetuses significantly reduces the morbidity of PE with a significant decrease in care costs.

The existence of a mature fetus is sufficient reason for the definitive treatment of the disease (birth). Therefore, the management of pregnant women with fetuses close to term (GA $\geq$ 36 weeks) and PE (even mild PE) should be based on the following parameters:

a. Patient hospitalization in an obstetric center.
b. Treatment of acute arterial hypertension episodes (►**Table 5**).
c. Prevention of severe forms of convulsions with $MgSO_4$ (►**Tables 6** and **7**).
d. Evaluation of the degree of maternal and fetal impairment.
e. Interruption of the gestation, preferably by inducing labor.

Management in Pregnancy at Gestational Age > 33 Weeks and < 36 Weeks

Pregnant women with PE and a preterm fetus should be admitted to a hospital obstetrical center with neonatal and maternal intensive care unit (ICU) facilities for evaluation and treatment. The goal of the management is to reach a GA closer to term without this posing too much risk for the pregnant woman and the concept.

Initially, antihypertensive and anticonvulsant therapies should be used as described before (►**Tables 5**, **6** and **7**). The $MgSO_4$ treatment will be discontinued if the conservative management is adopted. The use of hypotensive drugs (methyldopa) is reserved for cases in which the BP exceeds safe levels (SBP > 160 mm Hg or DBP > 110 mm Hg) and in the presence of other risk components indicating immediate cessation of pregnancy.

The assessment of the maternal involvement by physical examination (BP, diuresis, state of consciousness, O_2 saturation), laboratory evaluation (►**Table 8**), and fetal impairment screening are indicated.

After the first 24 hours of observation and evaluation, it is necessary to decide for conservative conduct or interruption of gestation. The definition of the best moment to interrupt the pregnancy depends on several individual factors, neonatal ICU conditions, and the degree of maternal and/or fetal impairment. As a general rule: 1) if the PE is classified as mild, that is, without imminent risk to maternal and fetal health, the interruption should be postponed, if possible, up to the 36th week; and 2) if the PE is classified as severe (►**Table 9**), the pregnancy should be interrupted.

By adopting the conservative approach, pregnant women should remain hospitalized with restricted physical activity (avoid resting restricted to the bed because it does not contribute to the stabilization of the clinical picture and increases the risk of thrombosis). The diet can be unrestricted and normosodic. The pregnant woman's weight should be recorded every two days, and the vital signs should be evaluated only during the waking period, avoiding waking the patient up during sleep. Weekly or in a shorter term, in case of clinical necessity, a laboratory evaluation should be performed (►**Table 8**). The fetus should be auscultated every day, with observation of the daily rate of fetal movement. In patients with mild PE, it is advisable to evaluate the fetal well-being once a week, and whenever any changes in the maternal state occur. Ultrasonography to check fetal development and assessment of fetal-maternal hemodynamics (Doppler flowmetry) should be performed at the time of PE diagnosis.

To monitor fetal development, an ultrasound should be repeated at least in ten-day intervals due to the high incidence of IUGR. The evaluation of placental circulation by the Doppler study of the umbilical arteries is the only fetal evaluation test with level 1 of evidence that has proven to decrease perinatal mortality in pregnant women with SAH and IUGR.[16] Therefore, ideally, patients with PE in conservative management should undergo at least one weekly

Table 9 Maternal and fetal indications of termination of pregnancy in severe preeclampsia < 34 weeks[39]

Maternal	Fetal
HELLP syndrome	Fetal growth below percentile 5
Eclampsia	Repeated late fetal decelerations on cardiotocography
Pulmonary edema or O_2 saturation < 94%	Vein Doppler with pathological a-wave
BP without control despite medications	Fetal death
Serum creatinine > 1.5 mg/dL or oliguria (< 500 mL/ mL/24 hours)	Suspected PA, ROM or onset of labor
Suspected PA, ROM or onset of labor	

Abbreviations: BP, blood pressure; HELLP, hemolysis, elevated liver enzymes and low platelet count; PA, placental abruption; ROM, rupture of membranes.
Adapted from: Sibai, Barton (2009).[53]

Doppler evaluation. Antepartum cardiotocography and fetal biophysical profile may be used complementarily when the Doppler examination is altered in preterm gestations, and when there is need or possibility of prolonging gestation. During labor, cardiotocography with continuous or intermittent monitoring of the fetal heart rate is the test of choice for fetal surveillance.

The induction of fetal lung maturity with corticosteroids can be performed in pregnancies < 34 weeks in which the birth is predicted for the next the 24 or 48 hours.[16] If an elective cesarean is indicated (without labor) for a pregnant woman at < 39 weeks, the use of corticosteroids for pulmonary maturation brings benefits by reducing the need for hospitalization in the neonatal ICU for the newborn's mechanical ventilation.[50,51] When pregnancy interruption is indicated and the fetus is < 36 weeks of GA, the patient has to be hospitalized or transferred to a tertiary-level healthcare hospital.

Management in Pregnancy at Gestational Age < 33 Weeks

In pregnant women at GA < 33 weeks and stable fetal maternal condition, we can opt for conservative management with assiduous management of all parameters of maternal and fetal well-being. By choosing the expectant management, one should be alert to any signs of clinical decompensation. Particular attention should be paid to the degree of maternal thrombocytopenia, which is an important indicator of morbidity and mortality. Patients with PE and platelets between 150,000 and 100,000 cells/mm^3 already have an increase in fetal and maternal morbidity and mortality, which will be greater the lower the platelet count.

Conservative Management of Severe Preeclampsia

The prevalence of severe PE is of ~ 1% of pregnancies, and is associated with progressive deterioration of the fetal-maternal picture.[52,53] All pregnant women with severe PE should be hospitalized, and the initial management should include administration of $MgSO_4$ and antihypertensive drugs (SBP ≥ 160 mm Hg or DBP ≤ 110 mm Hg).[52] In the presence of eclampsia, pulmonary edema, coagulopathy and non-reactive fetal evaluation, labor should be performed even before the completion of the corticosteroid therapy for fetal maturity. ►**Table 4** shows the main parameters for the interruption of gestation.

Several studies[52,53] describe the complications in the conservative management of severe PE < 34 weeks, namely: PA (16–39%); perinatal death (up to 17%); small fetuses for GA (up to 70%); presence of nonreactive fetal tests (26–74%); pulmonary edema (up to 8%); eclampsia (up to 5.6%); HELLP syndrome (4–27%); and renal failure (up to 17%). The main reason for gestational discontinuation in this group of pregnant women is the worsening of the fetal status; therefore, fetal and maternal evaluation should be performed daily, using the various methods available. If the pregnancy is ≤ 32 weeks, but there is risk of maternal and/or fetal death, PA, HELLP syndrome, DIC, eclampsia, severe uncontrollable hypertension (≥ 160/110 mm Hg) or hepatic hematoma, the choice should be interruption of pregnancy.

The prospective fullPIERS study[32] assessed the occurrence of severe maternal outcomes (maternal death and life-threatening complications) in 2,023 pregnant women with PE admitted to tertiary-level hospitals for follow-up in four countries (Canada, New Zealand, Australia and the United Kingdom) in. There were severe complications in 261 women (5%). The predictors for these complications were: GA < 34 weeks, chest pain, dyspnea, low O_2 saturation, thrombocytopenia, increased serum creatinine and altered hepatic transaminases (SGOT). The authors also showed that requiring lactate dehydrogenase (LDH) measurement when the liver enzymes are normal is redundant and should be avoided. It is only necessary to titrate one of the liver enzymes (SGOT or SGPT), and it is not necessary to request coagulation tests.

Some authors recommend trying the conservative management in women with severe PE who received betamethasone only up to the 32nd week on the grounds that the risk of serious maternal complications is not compensated by the additional gain in fetal maturity.[54]

HELLP Syndrome

The acronym HELLP stands for hemolysis, elevated liver enzymes and low platelet count (►**Table 10**). The

Table 10 Diagnosis of HELLP syndrome

	Exam	Parameter
Hemolysis Peripheral blood smear (schistocytosis, anisocytosis, echinocytosis, poikilocytosis)	Bilirubin	> 1.2 mg/dL
	Lactate dehydrogenase	> 600 U/L
Hepatic impairment	Serum glutamic oxaloacetic transaminase	> 70 U/L
Thrombocytopenia	Platelets	< 100,000/mm^3

Abbreviation: HELLP, hemolysis, elevated liver enzymes and low platelet count.
Source: Sibai et al (1986).[55]

pathophysiology of this disease is unclear, but the hepatic hematologic involvement of PE can be considered. Hemolysis, elevated liver enzymes and low platelet count syndrome develops in 0.1 to 0.8 of all pregnancies, and in 10–20% of pregnant women with severe PE/eclampsia. About a third of HELLP syndrome diagnoses are performed in the postpartum period. In patients with antepartum diagnosis, 10% of diagnoses were performed before the 27th week, 20% after the 37th week, and 70% between the 27th and 37th weeks.[55,56]

Hemolysis, elevated liver enzymes and low platelet count syndrome is related to microangiopathic hemolytic anemia and vasospasm in the maternal liver. The symptomatology is usually poor, and may include malaise, epigastralgia, nausea and headache. The degree of clinical suspicion of HELLP syndrome cases is very important. In the presence of thrombocytopenia in a patient with PE, HELLP syndrome should be strongly considered. Many cases go through days with a vague symptom of malaise and the patient reporting nonspecific symptoms, similar to a cold, with generalized pain, nausea and epigastric pain. Some studies point to a varying prevalence of the main symptoms, such as malaise (50 to 90%), pain in the right hypochondrium or epigastralgia (30 to 90%), and nausea and vomiting (20 to 50%); proteinuria may be absent.[57,58]

The diagnostic confirmation of HELLP syndrome is by laboratory tests (►**Table 10**), using the laboratory parameters described by Sibai.[55] Thrombocytopenia is the main and earliest laboratorial modification found. The appearance of coagulation abnormalities, such as change in prothrombin time, partial thromboplastin time, and fibrinogen, is uncommon. When thrombocytopenia is severe (< 50,000/mm^3), products of fibrin degradation and activation of AT III appear, indicating the initiation of an intravascular coagulation process. Eventually, patients with HELLP syndrome have hemorrhagic diastasis with bleeding at multiple sites (hematuria, hematemesis, surgical wound bleeding). Red cell fragmentation is present in HELLP syndrome, and although the amount of fragmentation is not associated with the severity of multiple organ dysfunction, it represents the involvement of the endothelial system in the microcirculation. Fragmentation is a result of the passage of red blood cells through small damaged vessels. Hepatic dysfunction can be measured by various parameters, such as increased LDH and transaminases (SGOT and SGPT). Renal dysfunction will depend on the severity of the condition, and it can be diagnosed in up to 46% of HELLP syndrome cases.[59] After hepatic and renal dysfunction, the patient may present pulmonary damage with DIC, characterizing a multiple organ dysfunction. In less than 2% of HELLP syndrome cases, a hepatic hematoma is formed. The diagnosis can be made by ultrasonography, and the treatment varies from conservative therapy to surgical management in cases of hepatic rupture.[60] If there is hepatic hematoma without rupture, a cesarean section is indicated, and surgical exploration should not be performed given the risk of rupture at that time.

Differential Diagnosis

Differential diagnosis between HELLP syndrome and other pathologies (especially hemorrhagic and hepatic pathologies) that may occur in the puerperal cycle is fundamental. Among the main pathologies, the following stand out: acute hepatitis, cholecystitis, pancreatitis, lupus, fatty liver of pregnancy, thrombocytopenic purpura, hemolytic-uremic syndrome, and septic or hemorrhagic shock, among others. Severe complications of HELLP syndrome occur with hemorrhage (central nervous system, liver, operative wound, PA).

Thrombocytopenia < 50,000/mm^3 is associated with the occurrence of DIC and a strong indicator of hemorrhagic complications. The presence of headache, visual changes and epigastralgia significantly increases the risk of eclampsia. In a Brazilian study[61] performed with 105 patients with HELLP syndrome, the main complications found were bleeding (34%), oliguria (47%), acute renal failure (20%), acute pulmonary edema (7%), need for blood transfusion (33%), and maternal death (4%). These data confirm the severity of this syndrome and the importance of the management at a tertiary center with experienced teams. The most important factor for the reduction of maternal morbidity and mortality is the early diagnosis, which should be made in the asymptomatic phase through laboratory investigation of thrombocytopenia, hemolysis and hepatic alterations in all patients with PE. Although the main cause of jaundice in pregnancy is hepatitis, if it occurs, the presence of HELLP syndrome with advanced hemolysis should always be ruled out.

Management in HELLP Syndrome

As it happens with eclampsia, HELLP syndrome should be regarded as an obstetric emergency requiring immediate care. The treatment is based on the prevention of hemorrhagic complications and eclampsia, control of SAH and the onset of labor.

The timing of interruption can be programmed depending on the severity of each case and the GA. In pregnancies > 34 weeks, labor induction should start immediately, with simultaneous control of the hypertensive crisis by using $MgSO_4$ and blood products when indicated. In pregnant women at GA< 34 weeks, in the absence of serious complications, such as hepatic hematoma, severe thrombocytopenia and eclampsia, corticosteroid therapy should be performed for pulmonary maturation before the interruption of pregnancy. O'Brien et al[62] propose fundamental steps for the care of HELLP syndrome, as follows:

1. Have high diagnostic suspicion in pregnant women with PE;
2. Perform laboratory tests and differential diagnosis;
3. Evaluate maternal and fetal conditions;
4. Control blood pressure;
5. Stabilize the clinical picture: venous access; administration of $MgSO_4$ and antihypertensive drugs;
6. Consider the use of corticosteroids for fetal maturity;
7. Hemotherapy if necessary;
8. Check if there is need for hepatic imaging (epigastralgia);
9. If cesarean section is indicated, evaluate with the anesthesiologist the technique to be adopted;
10. Actively manage labor or plan the cesarean section with the proper technique;
11. Plan for care in maternal and neonatal ICUs if necessary;
12. Perform laboratory evaluation every 6–24 hours, depending on the severity of the condition, until stabilization;
13. Maintain the use of antihypertensive and $MgSO_4$ in the puerperal period; and
14. Counseling for future pregnancies.

As the management of patients with HELLP syndrome should be performed in tertiary centers with maternal and neonatal ICUs, suspected cases should be transferred immediately in an adequate ambulance in the presence of a life-saving physician after contact with the reference maternity. The patient should be on IV $MgSO_4$, and if an infusion pump is not available, the attack dose should be administered intravenously, avoiding IM administration if thrombocytopenia $< 100{,}000/mm^3$ due to the risk of gluteal hematoma. Magnesium sulfate should be started immediately, and maintained for up to 24 hours postpartum, with control of diuresis, tendon reflexes, and respiratory rate (►**Table 10**).

Fetal conditions, GA and uterine cervix (Bishop score) are fundamental in deciding the route of birth. If < 30 weeks, in absence of labor, and Bishop score < 5, elective caesarean section is recommended after initiating $MgSO_4$.[6] In pregnant women with < 32 weeks and fetuses with restricted growth, and alteration of the umbilical artery Doppler, it is preferable to perform a cesarean section, except in cases already in labor.[61] The other patients may be submitted to labor induction. Anesthesia of the pudendal nerve should be avoided due to the risk of hematoma. Caesarean sections should be performed by experienced professionals using the best surgical technique and with attention to intraoperative hemostasis. In the presence of thrombocytopenia ($< 100{,}000/mm^3$), infraumbilical median laparotomy is recommended to reduce the risk of hematomas in the aponeurotic detachment. If thrombocytopenia is $< 75{,}000/mm^3$, epidural or subdural anesthesia should be avoided, and general anesthesia should be performed. The use of an aspiration drain is recommended in the most severe patients, especially in those with DIC, facilitating postoperative control. The Portovac (Howmedica, Toronto, Ontario, Canada) drain (polyethylene with closed drainage system) or the Blake (Ethicon, Somerville, NJ, US) drain (silicone, soft, continuous drainage) can be used. The latter has the advantage of continuous drainage, and since it does not have a closed drainage system, it causes less obstruction problems due to small clots. These should be removed 24 to 48 hours after the cesarean section, depending on the evolution of the patient's surgical clinical status and the amount of drainage. Care should be taken with puerperal blood loss and the risk of uterine hypotonia. Thus, the prophylactic use of IV oxytocin and misoprostol (rectal or intrauterine) is extremely valuable.

Use of Corticosteroids for Thrombocytopenia Rescue

Corticosteroids have been used for the treatment of women with HELLP syndrome, especially those with platelets $< 50{,}000/mm^3$. The mechanism of action includes reduction of platelet adhesion, reduction in platelet removal by the spleen, and increase in platelet activation. Currently, a Brazilian study (COHELLP) is underway to verify the efficacy of dexamethasone in patients with HELLP and thrombocytopenia < 50,000.

Some centers use dexamethasone 10 mg intravenously every 12 hours before delivery and after birth until laboratory recovery. Some studies have demonstrated an improvement in thrombocytopenia and other laboratory tests with this practice, as well as a decrease in the need for transfusions, hypertension and the use of antihypertensive drugs, presenting a postpartum recovery with lower morbidity.[63] However, this finding has not been reported in other studies.[64] We still lack more consistent evidence on the benefit of corticosteroid therapy in maternal morbidity and mortality. In a recent systematic review of the Cochrane Library, the conclusion is that there is insufficient evidence for the routine use of steroids in HELLP syndrome, and that their use may be justified in special situations in which platelet increase is important.[65] Intravenous dexamethasone may be used if platelets are < 50,000/dL. This recommendation may open a window of opportunity, rescuing thrombocytopenia even temporarily, enabling, for example, the use of blockade anesthesia in a caesarean section.

Blood and Platelet Transfusion

In the presence of abnormal bleeding and HELLP syndrome, or in the presence of severe thrombocytopenia ($<$ 20,000 platelets), even without bleeding, transfusion of platelet concentrate is always indicated. If the patient underwent a cesarean section, the transfusion of platelets is recommended when the count is $<$ 50,000/mm^3. Each platelet concentrate unit elevates the platelets by $\sim$ 5,000 mm^3 to 10,000 mm^3 in an adult weighing 70 kg.[62]

Postpartum Management

The postpartum period remains extremely critical. In general, in the first 24 hours of the puerperal period, there is a transient worsening of the clinical picture due to consumption of platelets and coagulation factors. This worsening is more pronounced when the birth occurs by caesarean section. Therefore, we should not base on the postoperative process of preeclampsia. Many maternal deaths have occurred in the postpartum period because of hemorrhagic complications and some degree of little importance given to care in that period. Even if the patient does not have clinical parameters for an ICU admission yet, she must be admitted to this type of unit for immediate control of any kind of postpartum change. Laboratory control will be performed using the same parameters of diagnosis (platelets, LDH, SGOT, bilirubin). Diuresis should be controlled and maintained above 25 mL/hour. Hypertension should be maintained below 160/100 mm Hg. If there is spontaneous diuresis above 25 mL/hour, normal creatinine, LDH decrease, improvement in platelet levels and hepatic transaminases, we can consider the disease entered remission.

Preeclampsia Delivery Route

The preferred route of delivery in PE is vaginal, with no contraindication for cervical maturation procedures (Foley catheter, prostaglandin analogues), and cesarean section is reserved for usual obstetric indications. There should be constant monitoring of the fetal heart rate (FHR) during the first or second periods of childbirth. The presence of uterine hyperactivity, increased uterine tone, vaginal bleeding or pathological decelerations of the fetal heart rate should be seen as signs of possible PA.

For the cesarean section, epidural or subdural anesthesia may be used. In this situation, the patient should be hydrated with an infusion of 1,000 mL lactated ringer or saline before sympathetic block to avoid severe hypotension with decreased tissue perfusion of vital organs (kidneys and placenta).

In addition, while the patient remains supine during cesarean section, a cushion should be placed under the pregnant woman's right flank, thereby reducing the compression of the uterus on the large vessels of the abdomen. If severe hypotension still occurs, liquid infusion will be necessary to fill the dilated vascular space, avoiding the use of vasopressor substances. In emergency situations or when there is a complicated pregnancy-specific hypertensive disease (eclampsia, HELLP syndrome, DIC), general anesthesia is the preferred option. In this eventuality, it is important to alert the anesthesiologist about the use of $MgSO_4$, because its sedative action may be dangerous in conjunction with succinylcholine.

In general, the hypertensive picture disappears or improves substantially in the first 24 hours of the puerperal period, although the symptoms may remain up to six weeks after childbirth. If BP is $<$ 150/100 mm Hg, the patient may be discharged without antihypertensive therapy and undergo a weekly evaluation in an outpatient setting until PE signs disappear.

Management in Gestational Age $<$ 24 Weeks

The presence of severe PE in the second trimester, and especially $<$ 25 weeks, is associated with high rates of perinatal mortality (up to 83%) and maternal complications (27 to 71%), including maternal death.[52,66] Immediate delivery is associated with a lower chance of fetal survival, while prolongation of the pregnancy may somewhat increase the chance of fetal survival, but it adds an important risk of maternal morbidity and mortality. In these cases, the ideal management is not established yet, and is the reason for numerous studies and discussions in the literature. Some authors[52–54] recommend the interruption of pregnancy in these cases after discussing with the couple and obtaining signed informed consent. When the option is for expectant management, fetal and maternal evaluations should be performed daily, controlled in centers with obstetricians, neonatologists and intensivists experienced in high-risk obstetrics.

Persistent Postpartum Hypertension

Chronic hypertensive patients may develop hypertensive encephalopathy, pulmonary edema and cardiac insufficiency in the puerperal period. These events are more frequent in patients with overlapping PE, previous cardiac or renal disease, PA, or with difficult to control BP. In patients who remain hypertensive, drugs for its control should be administered orally. In the other patients, BP can be controlled weekly for a month, then at intervals of three to six months for one year.

When prescribing antihypertensive medication, it is necessary to bear in mind that the vast majority is excreted in human milk and can be absorbed by the newborn. Although there is a lack of good studies on the use of antihypertensive drugs in lactation, the recommendation to avoid diuretics seems reasonable, given their potential to suppress lactation. Neonatal exposure to methyldopa, labetalol, captopril and nifedipine is considered safe, and, therefore, a good option in the breastfeeding period.

Atenolol and metoprolol should be avoided because of their higher concentration in the breast milk, with potential effects on the newborn.[67] In patients with severe PE, but not

in those with mild or overlapping PE, the use of furosemide 20 mg/day after delivery improves BP control and decreases the need for antihypertensive drugs.[68]

Postpartum Counseling and Prognosis

Patients should be followed up in the puerperal period and, if they remain hypertensive, for at least 12 weeks. Persistent hypertension after this period should be considered as chronic hypertension. Patients with PE before the 30th week of pregnancy have a 10% chance of recurrence in the next gestation. The rate may be greater in black women. The recurrence rate of the HELLP syndrome is $\sim$ 5% of times. The recurrence of PE is also higher among multiparous women than among those who had the disease in the first pregnancy, especially if there is a change of partner in the next pregnancy.

Apparently, human pregnancy is an excellent cardiovascular stress test, and the occurrence of PE, especially if early onset PE ($<$ 32 weeks), means a failure in the cardiovascular capacity of the pregnant woman. The literature has an increasing number of studies with long-term follow-up in which the data point to a positive relationship between PE/eclampsia and hypertension, cardiovascular disease, ischemic stroke and early mortality in the future.[47]

A population study[69] demonstrated an association between the occurrence of chronic renal failure (CRF) and previous history of PE. The occurrence of PE in the first pregnancy was associated with a 4.7-fold higher risk (3.6–6.1, 95%CI) of developing CRF, and this risk was even greater (15.5 times) in women who had developed PE in 2 or 3 pregnancies. The study concluded that PE is a marker of risk for future development of CRF. In another population-based study in Norway, Irgens et al[68] confirmed that patients with preeclampsia have a 20% higher risk of death from cardiovascular disease (RR = 1.2 [1.02–1.37, 95%CI]) than the population without PE and, when it occurs at younger GAs associated with prematurity, the risk is almost 8 times higher (RR = 8.12 [4.31–15.33, 95%CI]). Patients with a history of PE for more than ten years had DBP and body mass index (BMI) higher than the controls.[71]

For these reasons, after the hospital discharge of patients who had PE, especially if diagnosed before the 32nd week, the women should always be advised to maintain healthy lifestyles from the cardiovascular and metabolic points of view. In these patients, more than in all others, guidelines on avoiding smoking, obesity, hyperglycemia and hypercholesterolemia, as well as the prescription of physical exercises and diet, are a medical obligation.

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