

Pre-eclampsia/Eclampsia

Pré-eclâmpsia/Eclâmpsia

José Carlos Peraçoli¹ Vera Therezinha Medeiros Borges¹ José Geraldo Lopes Ramos²
 Ricardo de Carvalho Cavalli³ Sérgio Hofmeister de Almeida Martins Costa²
 Leandro Gustavo de Oliveira¹ Francisco Lazaro Pereira de Souza⁴ Henri Augusto Korkes⁵
 Ione Rodrigues Brum⁶ Maria Laura Costa⁷ Mário Dias Corrêa Junior⁸ Nelson Sass⁹
 Angélica Lemos Debs Diniz¹⁰ Caio Antonio de Campos Prado³ Edson Viera da Cunha Filho¹¹

¹Department of Gynecology and Obstetrics, Botucatu Medical School, Universidade Estadual Paulista "Júlio de Mesquita Filho", Botucatu, SP, Brazil

²Department of Gynecology and Obstetrics, Faculty of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

³Department of Gynecology and Obstetrics, Faculty of Medicine, Universidade de São Paulo, Ribeirão Preto, SP, Brazil

⁴Department of Tocogynecology, Centro Universitário Lusíada, Santos, SP, Brazil

⁵Department of Obstetrics and Gynecology, Faculty of Medicine, Pontifícia Universidade Católica de São Paulo, São Paulo, SP, Brazil

⁶Department of Maternal and Child Health, Faculty of Medicine, Universidade Federal do Amazonas, Manaus, AM, Brazil

⁷Department of Gynecology and Obstetrics, Faculty of Medical Sciences, Universidade Estadual de Campinas, Campinas, SP, Brazil

⁸Department of Gynecology and Obstetrics, Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil

⁹Paulista School of Medicine, Universidade Federal de São Paulo, São Paulo, SP, Brazil

¹⁰Department of Obstetrics and Gynecology, Faculty of Medicine, Universidade Federal de Uberlândia, Uberlândia, MG, Brazil

¹¹Gynecology and Obstetrics Training Center, School of Medicine, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil

Rev Bras Ginecol Obstet 2019;41:318–332.

Abstract

Pre-eclampsia is a multifactorial and multisystemic disease specific to gestation. It is classically diagnosed by the presence of hypertension associated with proteinuria manifested in a previously normotensive pregnant woman after the 20th week of gestation. Pre-eclampsia is also considered in the absence of proteinuria if there is target organ damage. The present review takes a general approach focused on aspects of practical interest in the clinical and obstetric care of these women. Thus, it explores the still unknown etiology, current aspects of pathophysiology and of the diagnosis, the approach to disease prediction, its adverse outcomes and prevention. Management is based on general principles, on nonpharmacological and on pharmacological clinical treatment of severe or nonsevere situations with emphasis on the hypertensive crisis and eclampsia. Obstetric management is based on preeclampsia without or with signs of clinical and/or laboratory deterioration, stratification of gestational age

Keywords

- gestation
- hypertensive disorders
- pre-eclampsia
- eclampsia

Address for correspondence

José Carlos Peraçoli, PhD,
 Departamento de Ginecologia e Obstetrícia, Escola de Medicina de Botucatu, Universidade Estadual Paulista "Júlio de Mesquita Filho", Avenida Prof. Mário Rubens Guimarães Montenegro, sn. Distrito de Rubião Junior, Botucatu, SP 18618-687, Brazil
 (e-mail: jperacolifmb@gmail.com).

This document was prepared by the National Specialized Commission of Hypertension in Pregnancy of the Brazilian Federation of Gynecology and Obstetrics Associations - FEBRASGO.



in < 24 weeks, between 24 and less than 34 weeks, and ≥ 34 weeks of gestation, and guidance on route of delivery. An immediate puerperium approach and repercussions in the future life of pregnant women who develop preeclampsia is also presented.

Resumo

A pré-eclâmpsia é uma doença multifatorial e multissistêmica específica da gestação. É classicamente diagnosticada pela presença de hipertensão arterial associada à proteinúria em gestante previamente normotensa após a 20^a semana de gestação. A pré-eclâmpsia também é considerada na ausência de proteinúria se houver lesão de órgão-alvo. A presente revisão tem uma abordagem geral focada em aspectos de interesse prático na assistência clínica e obstétrica dessas mulheres. Assim, explora a etiologia ainda desconhecida, aspectos atuais da fisiopatologia e do diagnóstico e diagnóstico diferencial de convulsões, a abordagem da predição da doença, seus resultados adversos e prevenção. A conduta baseia-se em princípios gerais, tratamento clínico não farmacológico e farmacológico de situações graves ou não graves, com ênfase na crise hipertensiva e eclâmpsia. O controle obstétrico se fundamenta na pré-eclâmpsia sem ou com sinais de deterioração clínica e/ou laboratorial, estratificação da idade gestacional abaixo de 24 semanas, entre 24 e menos de 34 semanas e 34 ou mais semanas de gestação e orientação na via de parto. Uma abordagem imediata do puerpério e repercussões na vida futura de gestantes que desenvolvem pré-eclâmpsia também foram apresentadas.

Palavras-chave

- gestação
- distúrbios
- hipertensivos
- hipertensão arterial
- pré-eclâmpsia
- eclâmpsia

Introduction

Pre-eclampsia is a multifactorial and multisystemic disease specific to gestation that is classically diagnosed by the presence of hypertension associated with proteinuria manifested in a previously normotensive pregnant woman after the 20th week of gestation. Currently, pre-eclampsia is also considered when target organ damage occurs in the absence of proteinuria.¹ The multisystemic nature of pre-eclampsia implies the possibility of evolution to more severe situations such as eclampsia, hemorrhagic stroke, hemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome, renal failure, pulmonary edema, and death.² Eclampsia refers to the occurrence of generalized tonic-clonic seizures or coma in a pregnant woman with pre-eclampsia, and is one of the most serious complications of the disease.³

A systematic review of data made available between 2002 and 2010 showed an incidence of pre-eclampsia ranging from 1.2 to 4.2%, and of eclampsia ranging from 0.1 to 2.7%, with higher rates identified in regions of lesser socioeconomic development.⁴ It highlights the lack of information on these important outcomes, especially in places where the disease is more prevalent.

When evaluating the use of magnesium sulfate ($MgSO_4$), a medication of choice for the prevention or treatment of eclampsia, Sibai has demonstrated that eclampsia occurred in between 2 and 3% of pre-eclamptic women who developed signs of severity and did not receive prophylaxis for seizures. In addition, 0.6% of the patients with pre-eclampsia initially classified without signs of severity also evolved to eclampsia.⁵ In Brazil, Giordano et al⁶ evaluated 82,388 pregnant women attended at 27 reference maternity hospitals. The general prevalence reported was of 5.2 cases of eclampsia per

1,000 live births, ranging from 2.2:1000 in more developed areas to 8.3:1000 in less developed areas. In that study, eclampsia accounted for 20% of 910 cases classified as severe maternal outcomes.

According to the World Health Organization (WHO), hypertensive disorders of gestation are an important cause of severe morbidity, long-term disability, and both maternal and perinatal mortality. Although 10 to 15% of direct maternal deaths are associated with pre-eclampsia/eclampsia worldwide, 99% of these deaths occur in low- and middle-income countries.⁷ Severe morbidities associated with pre-eclampsia and eclampsia can lead to death, such as renal failure, stroke, heart failure, pulmonary edema, coagulopathy, and hepatic impairment.⁸ Fetal and neonatal complications result mainly from placental insufficiency and the frequent need for premature delivery that result in high rates of perinatal morbidity and mortality.⁹

Etiology

Identifying the exact cause of pre-eclampsia is likely to result in a significant reduction in maternal and perinatal morbidity and mortality. However, since its etiology remains unknown, acting effectively for preventing its development (primary prevention) is not possible. On the other hand, there is a constant concern with identifying risk factors for acting preventively against the manifestation of severe forms of the disease (secondary prevention).

Attempts to explain the etiology of pre-eclampsia have resulted in a myriad of hypotheses, although a single explanation for the disease is really unlikely.¹⁰⁻¹⁶ Currently, the most important pathogenesis involves deficient placentation, genetic predisposition, impaired immune tolerance,

systemic inflammatory response, angiogenic imbalance, and deficient nutritional status.^{17,18}

To improve the understanding of the pathophysiology of pre-eclampsia, the most important theories were integrated into two stages (preclinical and clinical) described by Redman et al.¹⁹ In the first stage, changes in the placental development and insufficient changes in uterine circulation are a result of hypoxia of the placental tissue, and mainly of the phenomenon of hypoxia and reoxygenation, and provide the development of oxidative stress and of excessive production of inflammatory and antiangiogenic factors.²⁰ In the second stage, placental dysfunction and the factors it releases damage the endothelium systemically by resulting in the appearance of hypertension and in the compromise of target organs. Glomerular changes (glomeruloendotheliosis) are the most characteristic, and are responsible for the appearance of proteinuria. Roberts et al proposed a more complex theory, in which they associate these stages with maternal constitutional factors in the belief that placental dysfunction per se is not enough to cause the disease.¹¹ Moreover, since most metabolic alterations of pre-eclampsia represent an exacerbation of changes observed in normal pregnancies, in pregnant women with predisposing factors (obesity, metabolic syndromes, diseases responsible for chronic basal inflammatory response), subtle placental changes, and even close to normal, may be sufficient to induce the second stage, that is, the clinical form of the disease.

Despite the unknown etiology of pre-eclampsia, it is becoming evident that obese women or with high body mass index ($BMI > 30\text{kg}/\text{m}^2$) are at a particularly high risk for developing the disease.^{21,22} Other changes of risk are chronic hypertension, pregestational diabetes, and systemic lupus erythematosus.^{20,23} The association of pre-eclampsia with obesity may stem from the chronic state of systemic inflammation and, as the body mass index (BMI) increases, the activation of inflammatory pathways at the maternal-fetal interface is also exacerbated.^{21,24,25}

Diagnosis

The most widespread classification establishes four possible forms of hypertensive disorders during pregnancy: chronic hypertension, gestational hypertension, pre-eclampsia-eclampsia, and chronic hypertension with superimposed pre-eclampsia.¹ Recently, the International Society for the Study of Hypertension in Pregnancy (ISSHP) has admitted the possibility of "white-coat hypertension" occurring in the gestation, as seen in the medical clinic.²⁶ This condition is characterized by the presence of hypertension ($\geq 140 \times 90\text{ mmHg}$) during prenatal care, which is not presented in home evaluations. This form of hypertension should only be considered when present in the first half of gestation and should not be confused with pre-eclampsia, which is specific to the second half of gestation. However, the "white coat hypertension" is associated with worse maternal-fetal outcomes and is a risk factor for pre-eclampsia. For the current clinical practice, we consider the four forms described below:

Chronic hypertension: presence of hypertension before the pregnancy or identified before 20 weeks of gestation.

Pre-eclampsia: manifestation of hypertension after the 20th week of gestation associated with significant proteinuria. Although this association is classically considered, currently, the presence of proteinuria is not mandatory for the diagnosis of pre-eclampsia. If hypertension, after the 20th week, is associated with systemic impairment or target organ damage (thrombocytopenia, hepatic dysfunction, renal failure, pulmonary edema, imminent eclampsia, or eclampsia), the disease should be diagnosed even in the absence of proteinuria. The association of arterial hypertension with signs of placental impairment, such as fetal growth restriction and/or Doppler velocimetric changes should also call attention to the diagnosis of pre-eclampsia, even in the absence of proteinuria.²⁶

Chronic hypertension with superimposed pre-eclamp-sia: this diagnosis must be established in some specific situations, namely: 1) after 20 weeks of gestation, there is onset or worsening of proteinuria already detected in the first half of pregnancy (the increase must be greater than three times the initial value); 2) pregnant women with chronic hypertension who need an association of antihypertensive drugs or an increase in initial therapeutic doses; 3) in the occurrence of target organ damage.

Gestational hypertension: identification of arterial hypertension after the 20th week of gestation in a previously normotensive pregnant woman without proteinuria or manifestation of other signs/symptoms related to pre-eclampsia. This form of hypertension should disappear up to 12 weeks after childbirth. If blood pressure (BP) levels remain elevated, it should be reclassified as chronic arterial hypertension that was masked by physiological changes of the first half of pregnancy. Considering the current concepts about the diagnosis of pre-eclampsia, even in the absence of proteinuria, one must always be aware of the possibility of unfavorable evolution of cases initially diagnosed as gestational hypertension, since up to 25% of these patients will present pre-eclampsia signs and/or related symptoms, thus altering their diagnosis.

The classification of forms of arterial hypertension during pregnancy requires the definition of some concepts, as follows²⁷:

Hypertension: blood pressure value $\geq 140\text{ mmHg}$ and/or 90 mmHg measured after a rest period with the patient in a seated position, appropriate cuff, considering the 1st Korotkoff sound as the systolic pressure and the 5th Korotkoff sound as the diastolic pressure (disappearance of heart sound). In cases of persistence of sounds until the end of cuff deflation, the muffling of the sound should be considered as diastolic pressure. In the absence of a suitable cuff, the use of a BP correction table according to the arm circumference of the patient is advised. The measurement should be performed at the level of midpoint of the arm of the patient (►Annex A).

Significant proteinuria: presence of at least 300 mg in 24-hour urine with a trend in favor of replacing the 24-hour proteinuria test in clinical practice. The urinary protein/creatinine ratio has sufficient sensitivity to be used in the identification of significant proteinuria, and is an easier and lower cost examination. The ratio ≥ 0.3 is considered as altered (units of both proteinuria and creatinine should be in mg/dL). If it is not possible to determine proteinuria by the previous methods, the qualitative evaluation of protein by a

dipstick test can be considered. The presence of 1+ is considered as the cutoff for the diagnosis of proteinuria, an identification compatible with $\sim 30 \text{ mg/dL}$.¹

Pre-eclampsia with signs and/or symptoms of clinical deterioration: for a long time, patients with pre-eclampsia were classified as mild or severe based on the presence of clinical and/or laboratory manifestations demonstrating significant involvement of target organs. Recently, stratification in mild and severe pre-eclampsia has come to be criticized. Such a concept could be misleading, as all of the patients with pre-eclampsia may unexpectedly evolve with unfavorable outcomes. On the other hand, when a patient presents the diagnosis of severe pre-eclampsia, we can inadvertently induce anticipation of delivery, and sometimes in an iatrogenic way. Thus, we recommend that patients with pre-eclampsia should be evaluated for signs and/or symptoms of clinical and/or laboratory impairment and be promptly conducted accordingly, always considering the possibility of progressive clinical deterioration. In this context, the main clinical and laboratory parameters to be treated and monitored are:

- Hypertensive crisis: BP $\geq 160 \text{ mmHg}$ and/or 110 mmHg confirmed at 15-minute interval, preferably after a resting period with the patient seated.
- Signs of imminent eclampsia: in this case, patients present a clear nervous system compromise and report headache, photophobia, phosphenes, and scotomas. Peripherally, they present hyperreflexia. The presence of nausea and vomiting, epigastric pain and/or pain in the right hypochondrium is very important, since these symptoms are related to hepatic impairment.
- Eclampsia: development of tonic-clonic seizures in patients with a diagnostic of pre-eclampsia. Remember that, in a few cases, eclampsia presents as the initial condition, especially in patients whose pre-eclampsia diagnosis was not considered appropriately.
- Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome: HELLP derives from English and refers to the association of severe Hemolysis, Elevated Liver enzymes (liver impairment) and Low Platelets (platelets consumption) in patients with pre-eclampsia. The aforementioned changes are defined as follows: Hemolysis – presence of schizocytes and echinocytes in the peripheral blood and/or elevation of lactate dehydrogenase (LDH) levels $> 600 \text{ UI/L}$ and/or indirect bilirubin $> 1.2 \text{ mg/dL}$ and/or haptoglobin $\leq 0.3 \text{ g/L}$; hepatic impairment determined by elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values $>$ twice their normal value; platelet count defined as $< 100,000/\text{mm}^3$.
- Oliguria: diuresis $< 500 \text{ mL/24h}$. Oliguria may not be directly related to renal function impairment, but as a result of intense liquid extravasation into the third space, which is easily identified by the presence of generalized edema (anasarca).
- Acute renal failure: serum creatinine $\geq 1.2 \text{ mg/dL}$.
- Thoracic pain: in this case, the pain in the thoracic region (associated or not to respiration) indicates both endothe-

lial involvement of the lung and heart. This complaint is often devalued.

- Pulmonary edema: is related to intense involvement of the pulmonary endothelium associated or not with heart failure and/or severe hypertension. However, it is more frequent in these associations.

In 2013, the American College of Obstetricians and Gynecologists (ACOG) withdrew the levels of proteinuria ($> 5 \text{ g/24h}$) from the pre-eclampsia-related severity criteria.¹ In our opinion, the frequent use of proteinuria levels as a criterion for the anticipation of delivery made this evaluation controversial. Thus, we recommend that levels of proteinuria are not completely devalued, but interpreted in line with maternal clinical and fetal vitality tests, mainly when $> 10 \text{ g/24h}$. We reinforce that this parameter should not be used as a single criterion for the anticipation of labor.

Early or Late Pre-eclampsia

Considering the gestational age at the clinical manifestation of pre-eclampsia, the disease can be classified as early (< 34 weeks) or late (≥ 34 weeks). These two forms of manifestation of the disease have different etiologies.^{28,29} Early-onset pre-eclampsia is generally associated with increased impairment of the placental development and of the uteroplacental circulation, abnormal Doppler velocimetric evaluation of uterine arteries, fetuses growth restriction, and worse maternal and perinatal outcomes.^{30,31}

Late-onset pre-eclampsia is often associated with metabolic syndromes, inflammation, and chronic endothelial impairment. Thus, its association with obesity and chronic diseases is common. The evaluation of the uteroplacental compartment is often within the normal range or changes little. Maternal and perinatal outcomes are more favorable mainly because these manifestations are closer to the term, which does not mean that the disease should be followed-up with less care.³² Although the incidence of early pre-eclampsia is generally low, in Brazil it accounts for up to 40% of the cases of pre-eclampsia seen in tertiary centers.

Differential Diagnosis of Seizures

In pregnant women, the manifestation of seizures after the 20th week of gestation should always be diagnosed initially as eclampsia. Only after a careful approach, and often after treatment based on the diagnosis of eclampsia, it may be necessary to consider other differential causes for the seizures. The following special situations should be considered for differential diagnosis:

- Occurrence of pre-eclampsia/eclampsia before the 20th week of gestation is rare and one should consider the possibility of association with molar gestation.
- Persistent neurological changes and treatment-refractory cases suggest anatomical impairment regardless of the initial cause really being eclampsia. Whenever we face

seizures cases of difficult control, especially with MgSO₄, stroke should be investigated.

- Suddenly developing neurological signs and symptoms may include stroke, expansive brain injury, toxic and metabolic encephalopathies, reversible cerebral vasoconstriction syndrome, thrombotic thrombocytopenic purpura, and central nervous system (CNS) infection.³³
- Seizures without neurological deficits can be triggered by metabolic abnormalities (hypocalcemia, hyponatremia, and hypoglycemia), toxins (drug or alcohol withdrawal, drug intoxication), infection (meningitis, encephalitis, sepsis), or recent head trauma. However, the absence of neurological deficits does not exclude an anatomical brain abnormality.
- Gestation is a triggering factor for some disorders associated with seizures, such as thrombotic thrombocytopenic purpura and uremic hemolytic syndrome, which may be difficult to differentiate from eclampsia associated with HELLP syndrome. Another clinical disease that may initiate in pregnancy due to neurological manifestations is systemic lupus erythematosus.
- In summary, investigation with imaging tests is indicated whenever the patient presents neurological deficit, coma, seizures that are difficult to control, persistent visual changes, seizures before 20 weeks of gestational age without association with gestational trophoblastic disease and absence of prior diagnosis of epilepsy.

Pre-eclampsia Prediction

The identification of risks of developing a problem is what we mean by prediction. It is based on assumptions that phenomena will recur on a constant basis. Therefore, the prediction of pre-eclampsia involves several issues, such as gaps in its pathophysiology, the diversity of clinical forms, and the heterogeneity among populations. Therefore, we will focus on what is most effective and has consistent clinical applicability for the Brazilian reality.³⁴

In all contexts, the clinical history should not be underestimated, as it provides important data and remains the effective way to identify pregnant women at greater risk of developing pre-eclampsia. Regardless of the quantification of risk, the identification of these conditions should guide the expansion of prenatal surveillance by avoiding causing unnecessary anxiety in patients. ►Table 1 lists some of the most associated clinical conditions with the development of pre-eclampsia and demonstrates the relative risk posed by each one to contribute to this outcome.

The interpretation of the magnitude of relative risks (RRs) associated with each of these clinical conditions may be different according to the experience of each professional, and risks will be less or more valued. On the other hand, based on the exposed risks, all of the patients who present at least one of the characteristics in ►Table 1 should receive the forms of prevention presented in this chapter. According to the WHO and ISSHP guidelines, special attention should be given to the adoption of prevention methods in the presence of the following clinical conditions: antecedent of pre-eclampsia, chronic hypertension, obesity (BMI > 30), diabe-

Table 1 Risk factors related to the occurrence of preeclampsia

Clinical feature	Relative risk
Chronic hypertension (DBP between 80 and 89 mmHg in 1 st prenatal visit)	1.38 1.01–1.87
Age > 40 years and primiparous	1.69; 1.23–2.29
Age > 40 years and multiparous	1.96; 1.34 2.87
BMI > 30 in 1 st prenatal visit	2.12; 1.56–2.88
Family history of preeclampsia (mother, grandmother, sister)	2.90; 1.70–4.93
Nulliparity	2.91; 1.28–6.61
Multiple gestation	2.93; 2.04–4.21
Pre-existing diabetes mellitus	3.56; 2.54–4.99
Previous history of preeclampsia	7.19; 5.85–8.83
Antiphospholipid antibody syndrome	9.72; 4.34–21.75

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure.

Source: Duckitt et al.³⁴

tes, renal diseases, autoimmune diseases, antiphospholipid syndrome, and multiple pregnancies.

Considering the introduction of biomarkers in the context of predicting pre-eclampsia, there is no evidence that they should be routinely incorporated, due to of limitations in sensitivity and to the costs of their incorporation. This premise includes the Doppler of uterine arteries in the 1st and 2nd trimesters and the following blood markers: pregnancy-associated plasma protein A (PAPP-A), disintegrin and metalloprotease-12 (ADAM-12), placental protein-13 (PP-13), uric acid, leptin, homocysteine, soluble fms-like tyrosine kinase-1 (sFlt-1), and placental growth factor (PIGF), as well as urinary markers such as albuminuria and calciuria.

Considering the low occurrence of pre-eclampsia in the general population (2–5%), not all of the predictive tests offer reasonable sensitivity. Therefore, like the ACOG and the WHO, our recommendation is to base the prediction of pre-eclampsia on the clinical history of the patient.^{1,7}

Prediction of Adverse Outcomes in Pre-eclampsia

Expectant management in patients with pre-eclampsia is considered in the face of fetal prematurity or of the scarcity of resources for maternal and newborn support at the place of care. This decision allows the promotion of fetal lung maturity with the use of corticosteroids and removal of the pregnant woman to a more qualified center. However, the time for managing everything, including patient transportation, can delay actions and favor the worsening of clinical conditions, especially since decisions are based on subjectivity. The mathematical model called Pre-eclampsia Integrated and Estimated Risks (PIERS) was developed with the aim to reduce uncertainty in these decisions. It offers a predictive value to evaluate the odds of adverse outcomes within 48 hours of the admission of the patient.³⁵ The PIERS “risk

calculator" is available online at <https://pre-empt.bcchr.ca/> monitoring/fullpiers and in a mobile application.

The following adverse events are considered in the PIERS model: eclampsia, coma, central blindness, retinal detachment, stroke, early placental abruption, coagulopathy, severe hepatic dysfunction, hepatic hematoma, pulmonary edema, myocardial infarction, acute renal failure, and ascites. Considering that these are life-threatening events for pregnant women, the inclusion of a tool that can guide decision-making more objectively seems to be fundamental in terms of maternal and fetal protection. ►Fig. 1 illustrates the calculator and how to use it. The decision will be according to the care scenario, but the transportation of a 1.5% risk patient will be completely different if the calculated value is 26.5% (►Fig. 1).

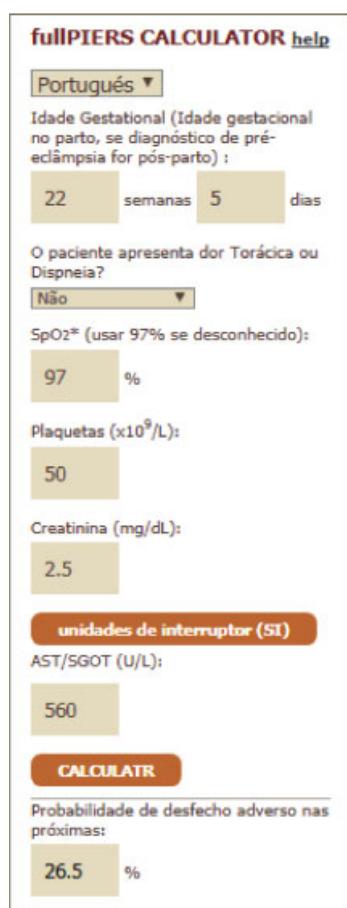
Prevention of Pre-eclampsia

Initially, we list the interventions that do not reduce the risk of pre-eclampsia; hence, they should not be applied in clinical practice. There is no reason to guide rest, salt restriction in the diet, use of antioxidants (vitamins C, E), vitamin D, omega-3 or enoxaparin for the prevention of pre-eclampsia.

The recommended interventions that may result in reduced risk of developing pre-eclampsia are the use of acetylsalicylic acid (ASA) and calcium supplementation.^{36,37}

The administration of a daily low dose of ASA (100 to 150 mg) is recommended for patients identified with a risk factor, according to the guidelines described above on the prediction of pre-eclampsia. Acetylsalicylic acid should be given as early as possible (before the 16th week), at night. It seems reasonable to start at around 12 weeks, even though there is no associated risk if it is started before that. It can be maintained until the end of the gestation, but suspension after the 36th week seems a rational conduct, because it allows the renewal of platelets with full functional capacity for the demands of childbirth.

Regarding calcium (Ca) supplementation, a systematic review concluded that, in general, it results in a 55% reduction in the risk of pre-eclampsia. This effect is even greater in women with low-Ca diet and results in a 74% reduction. In women with a risk factor for pre-eclampsia, this reduction may reach 78%. During pregnancy, all women should be instructed to eat a high-Ca diet, and for those at risk for pre-eclampsia and/or on a low-Ca diet, supplementation of 1.0 to 2.0 g/day is recommended (divided into 2 or 3 doses).



Some rules must be followed for proper completion of the calculator.

The figure to the side shows an example of data insertion and the resulting risk. Some additional information:

- 1 – Gestational age in weeks and days. For full weeks, add "0". For example, fill in 22 weeks 0 days.
- 2 – If no oximeter is available, assume 97% saturation.
- 3 – For creatinine, use dot and not comma. Example 2.5 mg/dl and not 2,5 mg/dl.
- 4 – Attention to the units. There are two alternatives: Imperial Unit (IU) and International Standard (SI). For the Brazilian system use SI.

Fig. 1 Full Pre-eclampsia Integrated and Estimated Risks (PIERS) calculator with example of a clinical situation, laboratory data and the resulting calculation. Some rules must be followed for proper completion of the calculator. The figure to the side shows an example of data insertion and the resulting risk. Some additional information: 1–Gestational age in weeks and days. For full weeks, add "0." For example, fill in 22 weeks 0 days. 2–If no oximeter is available, assume 97% saturation. 3–For creatinine, use dot and not comma. Example 2.5 mg/dl and not 2,5 mg/dl. 4–Attention to the units. There are two alternatives: Imperial Unit (IU) and International Standard (SI). For the Brazilian system use SI.

The interventions discussed so far refer to the prenatal care scenario, and preventive actions are not limited to “preventing” the occurrence of pre-eclampsia, but also to reduce the risk of progression to more severe forms (tertiary prevention). Magnesium sulfate ($MgSO_4$) should be included in this issue, as it is admittedly the best alternative for the prevention and treatment of eclampsia. This medication should be available in all maternal-fetal care services, even in primary care settings. The use of $MgSO_4$ is always recommended in the case of imminent eclampsia, as well as in a liberal way in patients with pre-eclampsia with signs of severity, especially for those with difficult-to-control BP and HELLP syndrome. Finally, $MgSO_4$ should always be administered in the face of situations whose clinical perception does not rule out the possibility of evolution to more severe forms or eclampsia.

Management

General Principles

The search for the pre-eclampsia diagnosis is essential. In prenatal care, attention should be given to weight gain, especially when it happens quickly and is associated with hand and face edema, and with increased pressure levels and reports to signs or symptoms of target organ involvement.

In the case of the diagnosis of pre-eclampsia, the focus of clinical control is the prevention of maternal and perinatal morbidity and mortality through the following: guidelines on signs of disease involvement, referral and care in tertiary services with qualified neonatal care, good BP control, prevention of eclampsia or its recurrence, and early identification of laboratory abnormalities, especially those related to HELLP syndrome. The evaluation of fetal well-being is also recommended. The combination of these actions should enable the conduction of cases with the objective of performing the delivery, the only real way to avoid the immediate progression of the disease with balance between maternal-fetal repercussions and the impact of prematurity.

In the case of eclampsia, basic principles of conduct are considered, namely, avoid trauma from falls, maintain airway permeability and ensure oxygen support, and prevent aspiration in case of vomiting. Position the pregnant woman in left lateral or semi-sitting position in bed with lateral grids, use a Guedel cannula, provide nasal oxygen 5 L/min, and obtain venous access promptly.

Nonpharmacological Treatment

Diet

A normal diet is recommended without salt restriction, since there is no evidence supporting this recommendation for BP control or prevention of adverse outcomes. These patients must be reminded that they may need long periods of hospitalization, as well as of the importance of maintaining the minimum quality of their diet. The restriction in sodium intake contributes negatively to reduce intravascular volume.^{1,38}

Hospital or Home Rest

In spite of suggestions that reducing physical activity improves uteroplacental blood flow and prevents exacerbation of hypertension, particularly if BP is not well controlled, there is no evidence that it significantly improves the main maternal and perinatal outcomes. Thus, there is no reason to recommend absolute rest in patients with pre-eclampsia.³⁹

Laboratory Follow-up

The diagnosis of pre-eclampsia requires follow-up with laboratory tests for the early identification of target organ involvement and the diagnosis of HELLP syndrome in its early stages (only laboratory abnormalities without clinical signs and symptoms). The frequency of follow-up depends on the evolution and severity of each case, but the general recommendation is once a week. Values of hemoglobin, platelet counts, lactate dehydrogenase (LDH), total bilirubin or haptoglobin (gold standard for microangiopathic anemia), creatinine, and AST should be evaluated. Note that: 1) there is no need for repeated evaluations of proteinuria; 2) urea concentration should not be performed if there is no clear renal involvement or suspected uremic hemolytic syndrome; 3) for evaluation of hepatic impairment, the dosage of AST alone is enough; 4) Although uric acid concentration correlates with adverse outcomes, it is not a single marker for clinical decisions.

Hospital or Outpatient Follow-up

The degree of unpredictability of pre-eclampsia can justify the continuous hospital follow-up. Long periods of hospitalization are not easy for patients and their families, and overload hospital beds. Thus, hospitalization is recommended as soon as there is a strong suspicion or diagnostic confirmation of pre-eclampsia for the proper evaluation of maternal-fetal conditions, for the introduction/adjustment of an antihypertensive dose, and for the guidance of the patient and of her family members about the problem, the risks, and the types of complications. After an initial period that may vary for each patient, “permits” may be granted and the patient can intercalate periods of hospitalization (or hospital evaluation) and periods at home. Well-structured services with a specific outpatient clinic, especially those with day hospital programs, are perfect for such cases. The decision for hospital or outpatient follow-up will depend heavily on the sociocultural conditions of the patient, and when identifying any problems that may compromise the proper surveillance of cases, hospitalization becomes essential.

Pharmacological Treatment

Antihypertensives

The decision to introduce antihypertensives should consider the risks and benefits for the mother and the fetus, and take as main factors the value of the BP and the presence or absence of signs and/or of symptoms. Chronic hypertensive patients often tolerate elevated BP levels without presenting any clinical manifestations. In contrast, young patients

with previous low BP levels may progress to severe conditions and eclampsia even with slightly high levels of BP. When considering the need for drug treatment, the initial recommendation for classification of BP during pregnancy is the following:

Mild hypertension: systolic BP ≥ 140 mmHg and < 150 mmHg and/or diastolic BP ≥ 90 mmHg and < 100 mmHg

Moderate hypertension: systolic BP between ≥ 150 mmHg and < 160 mmHg and/or diastolic BP ≥ 100 mmHg and < 110 mmHg

Severe hypertension: systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 110 mmHg

There is a consensus that cases of severe hypertension, also referred to as hypertensive crisis, should be treated promptly, and patients should be admitted to and/or referred to referral centers to investigate target organ involvement and fetal conditions.

Regarding the use of antihypertensives for the treatment of mild to moderate hypertension levels, the major concern is the excessive and/or abrupt reduction of BP. This concern originates from the fact that, although the reduction of BP improves circulatory systemic conditions, little effect is obtained with respect to uteroplacental circulation. The difficulties to maintain perfusion of this compartment in the face of an aggressive reduction of systemic BP could contribute negatively to fetal nutrition and/or oxygenation. In meta-analyses of randomized trials that considered the antihypertensive treatment of pregnant women with mild to moderate hypertension and the recent Control of Hypertension in Pregnancy Study (CHIPS) trial, increased growth restrictions or other adverse perinatal outcomes were not found.^{40–42} These data contrast with an earlier meta-analysis that evaluated the effect of antihypertensive therapy on fetal weight and concluded that the reduction of 10 mmHg in the mean BP was associated with a reduction of 176 g in birth weight.⁴³ We believe this controversial point was better studied in the CHIPS trial, in which a more rigorous treatment of BP for maintaining diastolic BP levels around 85 mm Hg prevented the occurrence of severe hypertension and exerted maternal protective factor without promoting fetal risks.⁴²

All of the antihypertensive drugs cross the placental barrier, but the agents listed below (**Tables 2** and **3**) present an acceptable safety profile during pregnancy. The choice of each one will depend on the familiarity of each obstetrician with them and the possible form of administration in each situation, that is, oral or intravenous.

Since hypertensive crisis treatment is imperative, antihypertensives should be introduced whenever the BP reaches ≥ 150 mmHg and/or 100 mmHg levels, ≥ 140 mmHg and/or 90 mm Hg persistent levels, or if the patient is symptomatic. In line with these recommendations, the ISSHP agrees and recommends the treatment goal is maintaining diastolic BP levels ~ 85 mm Hg.²⁶

Mild to moderate hypertension

►Table 2 presents the antihypertensives recommended for use in mild to moderate hypertension in pregnant women.

Table 2 Antihypertensives recommended for use in pregnancy

Agent class	Agent	Posology
Central-acting sympatholytics, α_2 -agonists	Methyldopa 250 mg and 500 mg tablets	750 to 2,000 mg/day 2 to 4x/day
	Clonidine 0.1 mg and 0.2 mg tablets	0.2 to 0.6 mg/day 2 to 3x/day
Calcium channel blockers	Nifedipine retard 10 mg and 20 mg	20 to 120 mg/day 1 to 3x/day
	Amlodipine 2.5 mg, 5 mg, and 10 mg tablets	5 to 20 mg/day 1 to 2x/day
Peripheral vasodilator*	Hydralazine 25 mg and 50mg dragees	50–150 mg/day
β -blockers*	Metoprolol 25 mg, 50 mg, and 100mg tablets	100 to 200 mg/day 1 to 2x/day
	Carvedilol 6.25 mg and 12.5mg tablets	12.5 to 50 mg/day 1 to 2x/day Recommendation is to start with 12.5 mg/day for 2 days and then increase the dose

*We recommend these medications as the third drug for the association of medications for blood pressure control or if drugs of first choice are unavailable. β -blockers with the highest clinical experience are labetalol and pindolol, but the former is not produced in Brazil and the latter has recently been withdrawn from the market.

Table 3 Agents recommended for the treatment of hypertensive crisis in pregnant women

Agent	Initial dose	Repeat if necessary	Maximum dose
Hydralazine 20 mg/mL ampoule	5 mg intravenous	5 mg every 20 minutes	45 mg
Ampoule of hydralazine contains 1 mL at a concentration of 20mg/mL. Dilute one ampoule (1mL) in 19mL of distilled water, thus obtaining a concentration of 1mg/mL.			
Nifedipine 10 mg tablet	10 mg oral administration	10 mg every 20–30 minutes oral administration	30 mg
Sodium nitroprusside 50 mg/2mL ampoule	0.5 to 10 mcg/kg/min continuous intravenous infusion	#	
The sodium nitroprusside ampoule contains 2mL at the concentration of 50 mg/2mL. Dilute one ampoule (2mL) in 248 mL of 5% glycosated serum, thus obtaining a concentration of 200 mcg/mL.			

Choices should be based on the degree of experience/familiarity presented by the professional prescribing the medication.

Angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB II) and direct renin inhibitors (Aliskiren) are contraindicated in pregnancy, because they

are associated with abnormalities in the development of fetal kidneys when used from the 2nd trimester of gestation on. Patients should be instructed to discontinue and/or replace this type of medication in the 1st trimester as soon as they confirm the pregnancy. However, it is important to reassure these patients about the use of medications in the beginning of pregnancy, since these drugs are not teratogenic but fetotoxic, and offer no risks of malformation with the use in the 1st trimester.⁴⁴ Still, the ideal planning for such cases is preconceptional guidance.

Aspects related to the use of diuretics indicate controversies in the role of thiazide diuretics, although some guidelines suggest these agents may be maintained in women with chronic hypertension who used them before pregnancy.^{26,45} These guidelines are based on the fact that the reduction in circulatory volume, which occurs in the first weeks, by the use of these drugs, would probably not occur in this situation (assuming that drug dose and sodium intake will be constant throughout the pregnancy). The use of diuretics in chronic hypertensive pregnant women should be interrupted if there is a reduction in the volume of amniotic fluid (oligoamnion) or superimposed pre-eclampsia, since this condition in itself determines contraction of circulatory volume. Exceptions are made for cases of acute pulmonary edema or of renal impairment, in which cases the diuretic of choice is furosemide.³⁹

Severe Hypertension

The aim of treatment is to reduce the BP by 15 to 25% and to reach systolic BP values between 140 mmHg and 150 mmHg, and diastolic BP values between 90 mmHg and 100 mmHg. Regardless of the antihypertensive used, abrupt drops in BP should be avoided due to maternal risks (stroke, infarction) and risks of reducing the uteroplacental perfusion too much, thus increasing the negative effects on the fetal well-being.² Once the desired reductions in systolic and diastolic pressures are obtained, the use of oral maintenance antihypertensives is initiated or optimized rapidly (**Tables 3 and 4**).

Hydralazine

Hydralazine is a peripheral vasodilator widely used in the pre-eclampsia situation for the acute treatment of severe hypertension.⁴⁶ Its maximum action occurs in 20 minutes, and BP monitoring should be rigorous, since there are risks of

hypotension that should be promptly corrected with elevation of the lower limbs and removal of medications or factors that may be acting potentiators. If the return of the BP is not achieved, careful hydration is recommended.

Nifedipine

Immediate-release oral Nifedipine, a calcium channel blocker, can also be used as first-line therapy, especially when intravenous access is not available.⁴⁷ Its maximum action is between 30 and 40 minutes, tablets should not be chewed, and formulations should not be used sublingually.

Sodium Nitroprusside

Sodium nitroprusside is a potent arterial and venous vasodilator. Limited clinical experience and fears about the potential for fetal cyanide poisoning have long restricted the use of nitroprusside in pregnancy. However, there is no evidence to support fetal risk, especially in cases of short-term use (6 to 12 hours). Nitroprusside is especially recommended for pregnant women with pulmonary edema associated with cardiac functional impairment, since it exerts important benefits in both post- and preload.⁴⁸⁻⁵⁰

Magnesium Sulfate

Since the publication of results of The Collaborative Eclampsia Trial – Magpie Trial, MgSO₄ is considered the drug of choice for the treatment of imminent eclampsia and of eclampsia.⁵¹ Systematic reviews indicate that magnesium sulfate is safer and more effective than phenytoin, diazepam, or lithic cocktail (chlorpromazine, prometazine and pethidine) for preventing recurrent seizures in eclampsia, in addition to being low-cost, easy to administer and not causing sedation.⁵²⁻⁵⁴ Recently, fetal exposure to magnesium sulfate therapy has been shown to be a useful weapon in reducing cases of cerebral palsy and severe motor dysfunction in preterm infants (< 32 weeks of gestation).³ Therefore, the use of magnesium sulfate is highly recommended for cases of imminent eclampsia, eclampsia, HELLP syndrome (15% of these patients develop eclampsia), and pre-eclampsia with clinical and/or laboratory deterioration, including difficult-to-control hypertension (**Table 5**).

The Pritchard and the Zuspan schemes are the main ones for the use of magnesium sulfate. They must be adopted

Table 4 Recommended infusion regimen for sodium nitroprusside

Desired dose (mcg/Kg/min)		0.5	1.0	2.0	3.0	4.0	5.0	Infusion rate (mL/h)
Patient weight	50 kg	7.5	15.0	30.0	60.0	90.0	120.0	
	60 kg	9.0	18.0	36.0	72.0	108.0	144.0	
	70 kg	10.0	21.0	42.0	84.0	126.0	168.0	
	80 kg	12.0	24.0	48.0	96.0	144.0	192.0	
	90 kg	14.0	27.0	54.0	108.0	162.0	216.0	
	100 kg	15.0	30.0	60.0	120.0	180.0	240.0	

From the practical point of view, recommendation is to start with the minimum dose and increase 1 mL/h every 10 minutes. # When necessary, the maximum dose should not be used for > 10 minutes, then, reduced by half. The nitroprusside stops acting 3 minutes after the interruption of the infusion.

Table 5 Magnesium sulfate scheme for prevention and treatment of eclampsia

Magnesium sulfate scheme	Initial dose	Maintenance dose
Pritchard scheme Intravenous and intramuscular	4 g intravenously (bolus) administered slowly ^a + 10 g intramuscularly (5 g on each buttock) ^b	5 g deep intramuscularly every 4 hours ^b
Zuspan scheme Exclusively intravenous	4 g intravenously (bolus) administered slowly ^a	1 g intravenously per hour in continuous infusion pump (CIP) ^c

^aPreparation of intravenous loading dose: MgSO₄ 50% - 1 ampoule contains 10mL with 5 g of MgSO₄.

Dilute 8 mL of MgSO₄ 50% (4 g) in 12 mL of distilled water or saline solution. The final concentration will be 4 g/20mL. Infuse the solution intravenously slowly (15–20 minutes).

Another possibility: dilute 8 mL in 100 mL of saline solution 0.9%. Infuse in continuous infusion pump at 300 mL/h. The total volume will be infused in ~20 minutes.

^bPreparation of maintenance dose – Pritchard scheme: Use 10 mL of the 50% MgSO₄ ampoule. Other presentations should not be used for this regimen due to their excessive volume.

^cPreparation of maintenance dose – Zuspan scheme: Dilute 10mL of 50% MgSO₄ (1 ampoule) in 490 mL of 0.9% saline solution. The final concentration will be 1 g/100mL. Infuse the solution intravenously at the rate of 100 mL per hour.

according to the experience of each service, since they are equally effective.

Magnesium sulfate heptahydrated (MgSO₄.7H₂O) should be used with attention to the available concentration of magnesium:

- MgSO₄ 50% - 10 mL ampoule contains 5 g of magnesium
- MgSO₄ 20% - 10 mL ampoule contains 2 g of magnesium
- MgSO₄ 10% - 10 mL ampoule contains 1 g of magnesium

Aspects Related to the Use of Magnesium Sulfate

The obstetrician should not be afraid about the use of MgSO₄, since chances of complications related to this medication are rare, and failing to administer it will be much more reckless than any risk from it. A few precautions need to be followed:

- If it is necessary to refer the pregnant woman to another service, the preferential scheme is the intramuscular (Pritchard), since it is safer for the transportation.
- The therapeutic concentration of the magnesium ion varies from 4 to 7 mEq/L (4.8 to 8.4 mg/dL), the patellar reflex is abolished with 8 to 10 mEq/L, and there is risk of respiratory arrest from 12 mEq/L. A properly administered initial dose does not pose a risk of intoxication. Subsequently, the following parameters should be monitored to maintain the intravenous dose or apply a new intramuscular dose: patellar reflex present, respiratory rate \geq 16 irpm and diuresis \geq 25 mL/h. If any changes occur in these parameters, reduction or interruption of intravenous infusion and non-performance of intramuscular dose are recommended. Then, the concentration of MgSO₄ and renal function are determined. If values are within the limits of normality, the treatment should be restarted. Calcium gluconate (1 g intravenously – 10 mL 10% – slowly administered) should be used in cases of signs of magnesium poisoning.
- In cases of recurrent seizures, 2 g of MgSO₄ is administered intravenously (bolus) and the dose of 2 g/h is used as maintenance. If two of these bolus do not control seizures, the drug of choice will be phenylhydantoin in its classic regimen for treatment of seizures. In these cases, it is also

recommended to investigate brain complications, mainly intracranial hemorrhages.

- In patients with renal impairment (creatinine \geq 1.2 mg/dL), the maintenance dose should be half the recommended dose. Infusion of magnesium sulfate should be discontinued only if diuresis is < 25 mL/h.
- The maintenance of MgSO₄ is recommended for 24 hours after the resolution of gestation or after the last seizure.

Obstetric Management

Pre-eclampsia without Signs of Clinical and Laboratory Deterioration

According to the best evidence, we recommend the expectant management only up to 37 weeks of gestation. From this moment on and whenever pre-eclampsia is diagnosed at term, the resolution of gestation is indicated, thereby reducing maternal risks without altering perinatal outcomes.^{55–57} Obviously, it is necessary to:

- Maintain control of BP;
- Monitor signs and symptoms of imminent eclampsia;
- Periodically monitor laboratory changes (hemogram, renal and hepatic function). Weekly reassessment or in the face of clinical changes and/or of uncontrolled BP is recommended;
- Maintain monitoring of fetal well-being and growth. The combination of biophysical (mainly cardiotocography) and hemodynamic (Doppler velocimetry) evaluations is recommended. However, different centers may follow specific protocols based on the availability of evaluation methods.

Pre-eclampsia with Signs or Symptoms of Clinical and/or Laboratory Deterioration

It is important to keep in mind that signs and symptoms of severity of pre-eclampsia are often transient. Arterial hypertension itself is an example, since after being controlled, it can remain stable for a variable time. Thus, it is always prudent to institute the pertinent treatment for each case and reassess the patient clinically and laboratorially before proceeding with the indication of delivery.

Within this context, the clinical deterioration situations that indicate the resolution of gestation are:

- HELLP syndrome;
- Eclampsia;
- Placental abruption;
- Hypertension refractory to treatment with three antihypertensive drugs;
- Pulmonary edema/cardiac involvement;
- Progressive laboratory abnormalities (thrombocytopenia, elevation of liver enzymes);
- Renal insufficiency assessed mainly by progressive elevation of urea and creatinine levels, oliguria, and anasarca;
- Changes in fetal well-being.

Gestational Age Less than 24 Weeks

At this gestational age, expectant management is associated with high perinatal mortality (>80%) and maternal morbidity and mortality (27–71%).^{58,59} Therefore, in the case of clinical deterioration, the interruption of the gestation is recommended, since neonatal viability is low and associated with several complications and sequelae. Of course, such a decision should be shared with the patient and her family. Even with the interruption of gestation, maternal care must be maintained. Recommendations are the following:

- To maintain adequate BP control;
- To use MgSO₄;
- Watch for signs and symptoms of imminent eclampsia;
- To maintain laboratory monitoring according to each case (platelet count, renal and hepatic function).

Gestational age equal to or above 24 weeks and less than 34 weeks

As the burden of prematurity is very high at this stage, the resolution of gestation should only occur if the patient fits the aforementioned changes. Guidelines for these cases are:

- To maintain adequate BP control;
- To use MgSO₄. If there is no absolute indication for delivery, medication can be given for 24 hours or according to the clinical evaluation;
- Watch for signs and symptoms of imminent eclampsia;
- Maintain laboratory monitoring according to each case (platelet count, renal and hepatic function);
- Monitoring of the well-being and growth of the fetus;

The combination of biophysical (mainly cardiotocography) and hemodynamic (Doppler velocimetry) evaluations is recommended. Different centers may follow specific protocols based on the availability of the methods used:

- Corticosteroid therapy for fetal lung maturation

Betamethasone (12 mg/intramuscularly every 24 hours/for 48 hours) or

Dexamethasone (6 mg/ intramuscularly every 12 hours/for 48 hours).

The drug of choice is betamethasone, and dexamethasone should be used only in the absence of betamethasone. In these cases, the use of MgSO₄ also acts on fetal neuro-

protection and should be used for this purpose at gestational ages between 24 and < 32 weeks. Even in cases of absolute indication for the resolution of the gestation, maternal clinical stabilization is mandatory, especially with the introduction of MgSO₄.

Gestational Age between 34 and 37 Weeks

The conduct of these cases is the same as that described for gestational ages between 24 and 34 weeks. Although prematurity-related complications are shorter after 34 weeks, they still exist, so in the face of clinical and laboratorial improvement of the mother, and preserved fetal vitality, it is recommended to postpone delivery to the nearest term.⁵⁶

Delivery Route

The delivery route is based on the obstetric indication. Transpelvic delivery is always desired, both in prematurity and at term, and it is possible to perform the procedures of the preparation of the cervix in the presence of preserved fetal vitality. However, in cases of pre-eclampsia with clinical and/or laboratorial deterioration and unfavorable cervix, we often find ourselves in situations of poor safety to await the evolution of delivery labor; therefore, cesarean section is justified. The procedure is also justified by changes in fetal vitality.

In cases of pre-eclampsia without signs of deterioration, evidently at term with unfavorable cervix, the preparation of the cervix with misoprostol or with a Foley catheter is indicated in order to obtain greater success with vaginal delivery. Special attention is advised in cases of oxytocin use, as this medication promotes water retention and hyponatremia; therefore, concentrated solutions and 0.9% saline solution should be used. This way, the water supply and sodium concentrations are maintained. An alternative is to use 10 UI of oxytocin in 500 mL of saline, starting infusion with 12 mL/h. The flowchart below is an attempt to guide the management of cases by associating of maternal clinic and the assessment of fetal vitality (**►Fig. 2**).

In HELLP syndrome, when cesarean delivery is indicated and the platelet count is < 50,000/mm³, the following precautions are recommended:

- evaluate coagulogram;
- perform general anesthesia;
- replace platelets in the surgical procedure. Usually, five units are enough;
- perform hemostasis carefully.

Puerperal Care

In the immediate puerperium, it is necessary to:

- Monitor the BP every 4 hours, or more frequently according to specific cases. It is prudent to suppress the nocturnal BP evaluation if the patient is controlled to allow her to rest, given the complex initial activity of the maternity that has just started.

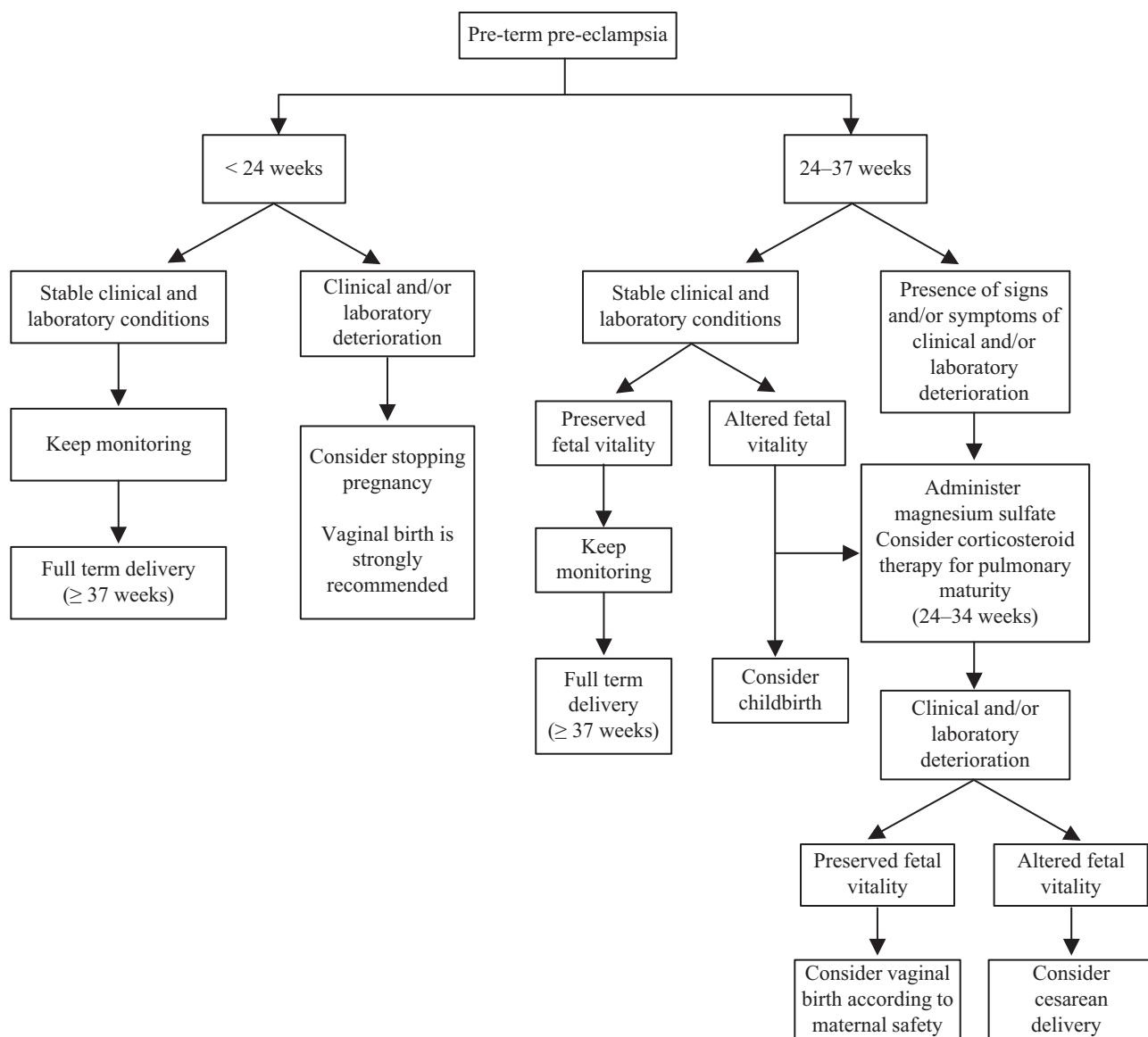


Fig. 2 Flowchart for conducting preeclampsia cases. Altered fetal vitality is defined by the presence of Doppler velocimetry of umbilical arteries with zero or reverse diastole and/or ductus venosus pulsatility index – PI > P95 according to gestational age and/or cardiotocography considered abnormal.

- Avoid using nonsteroidal anti-inflammatory drugs to control pain, especially in patients with impaired renal function and/or with significant blood loss that may have caused renal impairment.
- Avoid using medications intended to suppress lactation, such as bromoergocriptine and cabergoline, since they are associated with increased risk of cerebrovascular events.
- In cases of use of magnesium sulfate, maintain the medication for 24h. If the patient has difficult-to-control BP and/or signs and symptoms of imminent eclampsia, magnesium sulfate should also be used in the puerperium due to the persistent risk of seizures, especially in the first five days.
- The maintenance or introduction of antihypertensive drugs in the immediate puerperium is recommended especially in severe cases, unless the BP is < 110 × 70 mmHg. In addition to the antihypertensives recommended during pregnancy, medication prohibited for use in pregnancy is now allowed.
- In severe hypertension, follow the recommendations already given during gestation.
- Attention to clinical and/or laboratory deterioration. Laboratory reassessment is recommended within 24 hours postpartum, and new tests will be requested according to each case.
- Patients with pre-existing hypertension, who used antihypertensive medication and used to have good BP control, should restart it immediately after delivery if there is no contraindication to breastfeeding. If the patient reports poor BP control with the previous medication, it should be replaced. However, do not introduce diuretics in the puerperal period given the risk of reduction of vascular volume and compromise of breastfeeding.
- Patients with chronic kidney disease need to be guided according to recommendations of the nephrologist.
- Hospital monitoring is recommended until at least the 3rd day postpartum, remembering that the circulatory

- dynamics and water reabsorption into the intravascular volume usually reestablish between the 3rd and 5th days. Thus, early discharges do not allow adequate monitoring of these events.
- Even after hospital discharge, patients need to be advised of the possibility of complications and undergo reassessment in ~ 7 days.
 - All of the patients who had pre-eclampsia should be advised of the risk of developing cardiovascular and renal diseases. The potential negative impact throughout the life of the woman demands a better multidisciplinary follow-up, including control of the BP, of the renal function, and of the lipid and glycemic profiles,⁶⁰ as well as lifestyle change (physical activity, balanced diet).

Conflicts of Interests

The present manuscript was prepared by members of the National Specialized Commission on Hypertension in the Gestation of the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO, in the Portuguese acronym). The authors did not participate in the evaluation process, thereby respecting the evaluative ethical precepts of publication of scientific articles.

References

- 1 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(05):1122–1131. Doi: 10.1097/01.AOG.0000437382.03963.88
- 2 Amaral LM, Wallace K, Owens M, LaMarca B. Pathophysiology and current clinical management of preeclampsia. *Curr Hypertens Rep* 2017;19(08):61. Doi: 10.1007/s11906-017-0757-7
- 3 Norwitz ER. Eclampsia. December 2017 <https://www.uptodate.com/contents/eclampsia>. Accessed December 27, 2017.
- 4 Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2013;170(01):1–7. Doi: 10.1016/j.ejogrb.2013.05.005
- 5 Sibai BM. Magnesium sulfate prophylaxis in preeclampsia: Lessons learned from recent trials. *Am J Obstet Gynecol* 2004;190(06):1520–1526. Doi: 10.1016/j.ajog.2003.12.057
- 6 Giordano JC, Parpinelli MA, Cecatti JG, et al. The burden of eclampsia: results from a multicenter study on surveillance of severe maternal morbidity in Brazil. *PLoS One* 2014;9(05):e97401. Doi: 10.1371/journal.pone.0097401
- 7 World Health Organization. WHO Recommendations for Prevention and Treatment of Pre-Eclampsia and Eclampsia. Geneva: World Health Organization; 2011
- 8 Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009;33(03):130–137. Doi: 10.1053/j.semperi.2009.02.010
- 9 Ananth CV, Vintzileos AM. Medically indicated preterm birth: recognizing the importance of the problem. *Clin Perinatol* 2008;35(01):53–67, viii. Doi: 10.1016/j.clp.2007.11.001
- 10 Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest* 2003;111(05):649–658. Doi: 10.1172/JCI17189
- 11 Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. *Placenta* 2009;30(Suppl A):S32–S37. Doi: 10.1016/j.placenta.2008.11.009
- 12 Quinn MJ. Pre-eclampsia - The “uterine reinnervation” view. *Med Hypotheses* 2014;83(05):575–579. Doi: 10.1016/j.mehy.2014.08.020
- 13 Abou El Hassan M, Diamandis EP, Karumanchi SA, Shennan AH, Taylor RN. Preeclampsia: an old disease with new tools for better diagnosis and risk management. *Clin Chem* 2015;61(05):694–698. Doi: 10.1373/clinchem.2014.230565
- 14 Tanrikulu L, Naraghi R, Ernst V, et al. Neurovascular compression of medulla oblongata - association for gestation-induced hypertension. *Med Hypotheses* 2015;84:605–610. Doi: 10.1016/j.mehy.2015.03.024
- 15 Gathiram P, Moodley J. Pre-eclampsia: its pathogenesis and pathophysiology. *Cardiovasc J Afr* 2016;27(02):71–78. Doi: 10.5830/CVJA-2016-009
- 16 Brew O, Sullivan MH, Woodman A. Comparison of normal and pre-eclamptic placental gene expression: a systematic review with meta-analysis. *PLoS One* 2016;11(08):e0161504. Doi: 10.1371/journal.pone.0161504
- 17 Cunningham GF, Leveno KJ, Bloom SL, et al. *Williams Obstetrics*. 24th ed. New York, NY: McGraw-Hill Education; 2014
- 18 Ngene NC, Moodley J. Role of angiogenic factors in the pathogenesis and management of pre-eclampsia. *Int J Gynaecol Obstet* 2018;141(01):5–13. Doi: 10.1002/ijgo.12424
- 19 Redman CW, Sargent IL. Latest advances in understanding pre-eclampsia. *Science* 2005;308(5728):1592–1594. Doi: 10.1126/science.1111726
- 20 Jauniaux E, Burton GJ. [The role of oxidative stress in placental-related diseases of pregnancy]. *J Gynecol Obstet Biol Reprod (Paris)* 2016;45(08):775–785. Doi: 10.1016/j.jgyn.2016.02.012
- 21 Walsh SW. Obesity: a risk factor for preeclampsia. *Trends Endocrinol Metab* 2007;18(10):365–370. Doi: 10.1016/j.tem.2007.09.003
- 22 Spradley FT, Palei AC, Granger JP. Increased risk for the development of preeclampsia in obese pregnancies: weighing in on the mechanisms. *Am J Physiol Regul Integr Comp Physiol* 2015;309(11):R1326–R1343. Doi: 10.1152/ajpregu.00178.2015
- 23 Villa PM, Marttinen P, Gillberg J, et al. Cluster analysis to estimate the risk of preeclampsia in the high-risk Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) study. *PLoS One* 2017;12(03):e0174399. Doi: 10.1371/journal.pone.0174399
- 24 Womack J, Tien PC, Feldman J, et al. Obesity and immune cell counts in women. *Metabolism* 2007;56(07):998–1004. Doi: 10.1016/j.metabol.2007.03.008
- 25 Aye IL, Lager S, Ramirez VI, et al. Increasing maternal body mass index is associated with systemic inflammation in the mother and the activation of distinct placental inflammatory pathways. *Biol Reprod* 2014;90(06):129. Doi: 10.1095/biolreprod.113.116186
- 26 Brown MA, Magee LA, Kenny LC, et al; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. *Hypertension* 2018;72(01):24–43. Doi: 10.1161/HYPERTENSIONAHA.117.10803
- 27 Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000;183(01):S1–S22. Doi: 10.1067/mob.2000.107928
- 28 von Dadelszen P, Magee LA, Roberts JM. Subclassification of preeclampsia. *Hypertens Pregnancy* 2003;22(02):143–148. Doi: 10.1081/PRG-120021060
- 29 Huppertz B. Placental origins of preeclampsia: challenging the current hypothesis. *Hypertension* 2008;51(04):970–975. Doi: 10.1161/HYPERTENSIONAHA.107.107607
- 30 Murphy DJ, Stirrat GM. Mortality and morbidity associated with early-onset preeclampsia. *Hypertens Pregnancy* 2000;19(02):221–231. Doi: 10.1081/PRG-100100138
- 31 Ness RB, Sibai BM. Shared and disparate components of the pathophysiology of fetal growth restriction and preeclampsia. *Am J Obstet Gynecol* 2006;195(01):40–49. Doi: 10.1016/j.ajog.2005.07.049
- 32 Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet* 2005;365(9461):785–799. Doi: 10.1016/S0140-6736(05)17987-2

- 33 Wright WL. Neurologic complications in critically ill pregnant patients. *Handb Clin Neurol* 2017;141:657–674. Doi: 10.1016/B978-0-444-63599-0.00035-1
- 34 Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ* 2005; 330(7491):565. Doi: 10.1136/bmj.38380.674340.E0
- 35 von Dadelszen P, Payne B, Li J, et al; PIERS Study Group. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. *Lancet* 2011;377 (9761):219–227. Doi: 10.1016/S0140-6736(10)61351-7
- 36 Henderson JT, Whitlock EP, O'Connor E, Senger CA, Thompson JH, Rowland MG. Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2014;160 (10):695–703. Doi: 10.7326/M13-2844
- 37 Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev* 2014;(06):CD001059. Doi: 10.1002/14651858.CD001059.pub4
- 38 Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al; European Society of Gynecology (ESG); Association for European Paediatric Cardiology (AEPC); German Society for Gender Medicine (DGesGM); ESC Committee for Practice Guidelines. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32(24):3147–3197. Doi: 10.1093/eurheartj/ehr218
- 39 Meher S, Abalos E, Carroli G. Bed rest with or without hospitalisation for hypertension during pregnancy. *Cochrane Database Syst Rev* 2005;(04):CD003514. Doi: 10.1002/14651858.CD003514.pub2
- 40 Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2014;(02):CD002252. Doi: 10.1002/14651858.CD002252.pub3
- 41 Webster LM, Conti-Ramsden F, Seed PT, Webb AJ, Nelson-Piercy C, Chappell LC. Impact of antihypertensive treatment on maternal and perinatal outcomes in pregnancy complicated by chronic hypertension: a systematic review and meta-analysis. *J Am Heart Assoc* 2017;6(05):e005526. Doi: 10.1161/JAHA.117.005526
- 42 Magee LA, von Dadelszen P, Singer J, et al; CHIPS Study Group*. The CHIPS randomized controlled trial (Control of Hypertension in Pregnancy Study): is severe hypertension just an elevated blood pressure? *Hypertension* 2016;68(05):1153–1159. Doi: 10.1161/HYPERTENSIONAHA.116.07862
- 43 von Dadelszen P, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: an updated metaregression analysis. *J Obstet Gynaecol Can* 2002;24(12):941–945. Doi: 10.1016/S1701-2163(16)30592-8
- 44 Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006;354(23):2443–2451. Doi: 10.1056/NEJMoa055202
- 45 Collins R, Yusuf S, Peto R. Overview of randomised trials of diuretics in pregnancy. *Br Med J (Clin Res Ed)* 1985;290 (6461):17–23. Doi: 10.1136/bmj.290.6461.17
- 46 American College of Obstetricians and Gynecologists. ACOG committee opinion no. 560: Medically indicated late-preterm and early-term deliveries. *Obstet Gynecol* 2013;121(04):908–910. Doi: 10.1097/01.AOG.0000428648.75548.00
- 47 Too GT, Hill JB. Hypertensive crisis during pregnancy and postpartum period. *Semin Perinatol* 2013;37(04):280–287. Doi: 10.1053/j.semperi.2013.04.007
- 48 Sass N, Itamoto CH, Silva MP, Torloni MR, Atallah AN. Does sodium nitroprusside kill babies? A systematic review. *Sao Paulo Med J* 2007;125(02):108–111. Doi: 10.1590/S1516-31802007000200008
- 49 Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P; Canadian Hypertensive Disorders of Pregnancy Working Group. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. *J Obstet Gynaecol Can* 2014;36 (05):416–441. Doi: 10.1016/S1701-2163(15)30588-0
- 50 Committee on Obstetric Practice. Committee Opinion No. 692: emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. *Obstet Gynecol* 2017;129 (04):e90–e95. Doi: 10.1097/AOG.0000000000002019
- 51 Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995;345(8963):1455–1463. Doi: 10.5555/uri:pii:S0140673695910344
- 52 Duley L, Gulmezoglu AM. Magnesium sulphate versus lytic cocktail for eclampsia. *Cochrane Database Syst Rev* 2001;(01): CD002960. Doi: 10.1002/14651858.CD002960
- 53 Duley L, Henderson-Smart D. Magnesium sulphate versus diazepam for eclampsia. *Cochrane Database Syst Rev* 2003;(04): CD000127. Doi: 10.1002/14651858.CD000127
- 54 Duley L, Henderson-Smart D. Magnesium sulphate versus phenytoin for eclampsia. *Cochrane Database Syst Rev* 2003;(04): CD000128. Doi: 10.1002/14651858.CD000128
- 55 van der Tuuk K, Holswilder-Olle Scholtenhuis MA, Koopmans CM, et al; HYPITAT study group. Prediction of neonatal outcome in women with gestational hypertension or mild preeclampsia after 36 weeks of gestation. *J Matern Fetal Neonatal Med* 2015;28(07): 783–789. Doi: 10.3109/14767058.2014.935323
- 56 Broekhuizen K, van Baaren GJ, van Pampus MG, et al; HYPITAT-II study group. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial. *Lancet* 2015; 385(9986):2492–2501. Doi: 10.1016/S0140-6736(14)61998-X
- 57 Guida JPS, Surita FG, Parpinelli MA, Costa ML. Preterm preeclampsia and timing of delivery: a systematic literature review. *Rev Bras Ginecol Obstet* 2017;39(11):622–631. Doi: 10.1055/s-0037-1604103
- 58 Magee LA, Hall D, van der Merwe JL, Qureshi R, Rey E, Escobar Vidarte MF. Fluids, drugs and transfusion. In: Magee LA, von Dadelszen P, Stones W, Mathai M, eds. *The FIGO Textbook of Pregnancy Hypertension: an Evidence-Based Guide to Monitoring, Prevention and Management*. London: The Global Library of Women's Medicine; 2016:133–166
- 59 Ganzevoort W, Sibai BM. Temporising versus interventionist management (preterm and at term). *Best Pract Res Clin Obstet Gynaecol* 2011;25(04):463–476. Doi: 10.1016/j.bpb.2011.01.004
- 60 Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *Circulation* 2011;123(11):1243–1262. Doi: 10.1161/CIR.0b013e31820faaf8
- 61 Maxwell MH, Waks AU, Schroth PC, Karam M, Dornfeld LP. Error in blood-pressure measurement due to incorrect cuff size in obese patients. *Lancet* 1982;2(8288):33–36. Doi: 10.1016/S0140-6736(82)91163-1
- 62 Secretaria da Saúde do Estado de São Paulo. Coordenadoria de Planejamento em Saúde. Assessoria Técnica em Saúde da Mulher. *Atenção à Gestante e à Puerpera no SUS-SP: Manual Técnico do Pré-Natal e Puerpério*. São Paulo, SP: SES/SP; 2010

Annex A Correction of blood pressure according to the circumference of the arm of the patient

Arm circumference: cm	Systolic BP: mmHg	Diastolic BP: mmHg
20	+ 11	+7
22	+ 9	+6
24	+ 7	+4
26	+ 5	+3
28	+ 3	+2
30	0	0
32	-2	-1
34	-4	-3
36	-6	-4
38	-8	-6
40	-10	-7
42	-12	-9
44	-14	-10
46	-16	-11
48	-18	-13
50	-21	-14

Source: Maxwell et al⁶¹ and Secretaria de Estado da Saúde de São Paulo.⁶²

Erratum: The names and affiliations have been corrected as per Erratum published on February 11, 2020.
DOI of the Erratum is 10.1055/s-0040-1702167.