Preeclampsia: an update

G. Lambert (*, **), J. F. Brichant (**), G. Hartstein (**), V. Bonhomme (*, **) and P. Y. Dewandre (*, **)

Abstract: Preeclampsia was formerly defined as a multisystemic disorder characterized by new onset of hypertension (i.e. systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg) and proteinuria (> 300 mg/24 h) arising after 20 weeks of gestation in a previously normotensive woman. Recently, the American College of Obstetricians and Gynecologists has stated that proteinuria is no longer required for the diagnosis of preeclampsia. This complication of pregnancy remains a leading cause of maternal morbidity and mortality.

Clinical signs appear in the second half of pregnancy, but initial pathogenic mechanisms arise much earlier. The cytrophoblast fails to remodel spiral arteries, leading to hypoperfusion and ischemia of the placenta. The fetal consequence is growth restriction. On the maternal side, the ischemic placenta releases factors that provoke a generalized maternal endothelial dysfunction. The endothelial dysfunction is in turn responsible for the symptoms and complications of preeclampsia. These include hypertension, proteinuria, renal impairment, thrombocytopenia, epigastric pain, liver dysfunction, hemolysis-elevated liver enzymes-low platelet count (HELLP) syndrome, visual disturbances, headache, and seizures. Despite a better understanding of preeclampsia pathophysiology and maternal hemodynamic alterations during preeclampsia, the only curative treatment remains placenta and fetus delivery.

At the time of diagnosis, the initial objective is the assessment of disease severity. Severe hypertension (SBP ≥ 160 mm Hg and/or DBP ≥ 110 mmHg), thrombocytopenia < 100,000/µL, liver transaminases above twice the normal values, HELLP syndrome, renal failure, persistent epigastric or right upper quadrant pain, visual or neurologic symptoms, and acute pulmonary edema are all severity criteria. Medical treatment depends on the severity of preeclampsia, and relies on antihypertensive medications and magnesium sulfate. Medical treatment does not alter the course of the disease, but aims at preventing the occurrence of intracranial hemorrhages and seizures. The decision of terminating pregnancy and perform delivery is based on gestational age, maternal and fetal conditions, and severity of preeclampsia. Delivery is proposed for patients with preeclampsia without severe features after 37 weeks of gestation and in case of severe preeclampsia after 34 weeks of gestation. Between 24 and 34 weeks of gestation, conservative management of severe preeclampsia may be considered in selected patients. Antenatal corticosteroids should be administered to less than 34 gestation week preeclamptic women to promote fetal lung maturity. Termination of pregnancy should be discussed if severe preeclampsia occurs before 24 weeks of gestation. Maternal end organ dysfunction and non-reassuring tests of fetal well-being are indications for delivery at any gestational age. Neuraxial analgesia and anesthesia are, in the absence of thrombocytopenia, strongly considered as first line anesthetic techniques in preeclamptic patients. Airway edema and tracheal intubation-induced elevation in blood pressure are important issues of general anesthesia in those patients. The major adverse outcomes associated with preeclampsia are related to maternal central nervous system hemorrhage, hepatic rupture, and renal failure. Preeclampsia is also a risk factor for developing cardiovascular disease later in life, and therefore mandates long-term follow-up.

Key words: Hemodynamic; hypertension; management; preeclampsia; pregnancy.

INTRODUCTION

Preeclampsia remains a leading cause of maternal and fetal morbidity and mortality (1, 2). Despite a better understanding of its pathophysiology and some improvements in the ability of monitoring
the hemodynamic alterations in this population, the only curative treatment remains fetus and placenta delivery. Medical treatment aims at avoiding maternal complications such as seizures, hemorrhagic stroke, renal failure, or pulmonary edema. Adequate timing of delivery is of paramount importance, as well as the optimization of obstetric analgesia or anesthesia during delivery. Preeclampsia is also a risk factor for developing cardiovascular diseases later in life, and an adequate long term follow up is therefore advised. This review will focus on recent developments in the definition of preeclampsia and severe preeclampsia, pathophysiology of the disease, recent advances in hemodynamic monitoring, and progresses in the medical, obstetrical, and anesthetic management of those parturient patients.

**NOSOLOGY**

**Hypertension** during pregnancy is defined as a systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg and is classified into four categories: preeclampsia, chronic hypertension, chronic hypertension with superimposed preeclampsia, and gestational hypertension. Hypertension is considered to be mild, moderate or severe when SBP is ≥ 140, 150 or 160 mmHg or DBP is ≥ 90,100 or 110 mmHg, respectively.

**Preeclampsia** was usually defined as new-onset hypertension (i.e. SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg) and proteinuria (> 0.3 g/day) arising after 20 weeks of gestation in a previously normotensive woman. Elevated BP should be recorded on two measurements at least four hours apart. Proteinuria is defined as the excretion of at least 300 mg of protein in a 24 hour urine collection. Alternatively, a urine protein (mg/dL)/creatinine ratio (mg/dL) ≥ 0.3 has good sensitivity (98.2%) and specificity (98.8%) as a diagnostic tool. Conversely, a positive qualitative dipstick test for proteinuria provides too variable results to be considered as a reliable diagnostic tool of proteinuria. It can be used if no other method is readily available. In that case only, a 1+ dipstick result is considered as the cut-off for the diagnosis of proteinuria.

Since recently, in recognition of the syndromic nature of preeclampsia, proteinuria is no longer considered as mandatory for the diagnosis of preeclampsia. Consequently, in the absence of proteinuria, preeclampsia can be diagnosed as new-onset hypertension associated with (Table 1):

- thrombocytopenia < 100,000/µL,
- elevated liver transaminases (> twice the normal values),
- impaired renal function (with serum creatinine > 1.1 mg/dL or doubling of serum creatinine level in the absence of any other renal disease),
- pulmonary edema,
- new-onset visual or cerebral disturbances.

**Severe preeclampsia** was usually defined as preeclampsia associated with any of the following:

- severe hypertension (i.e. SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg),
- thrombocytopenia < 100,000/µL,
- impaired liver function with liver transaminases higher than twice the normal values.

**Table 1**

<table>
<thead>
<tr>
<th>Diagnostic criteria for preeclampsia (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure</strong></td>
</tr>
<tr>
<td>• ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure.</td>
</tr>
<tr>
<td>• ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy.</td>
</tr>
<tr>
<td>and</td>
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<tr>
<td><strong>Proteinuria</strong></td>
</tr>
<tr>
<td>• ≥ 300 mg/24 h urine collection.</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>• Protein/creatinine ratio ≥ 0.3 (each measured as mg/dL).</td>
</tr>
<tr>
<td>• Dipstick reading of 1+ (if other methods not available).</td>
</tr>
<tr>
<td>Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
</tr>
<tr>
<td>• Platelet count &lt; 100,000/µL.</td>
</tr>
<tr>
<td><strong>Renal insufficiency</strong></td>
</tr>
<tr>
<td>• Serum creatinine level &gt; 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease.</td>
</tr>
<tr>
<td><strong>Impaired liver function</strong></td>
</tr>
<tr>
<td>• Elevated blood concentrations of liver transaminases to twice normal concentration.</td>
</tr>
<tr>
<td><strong>Pulmonary edema</strong></td>
</tr>
<tr>
<td><strong>Cerebral or visual symptoms</strong></td>
</tr>
</tbody>
</table>
**Table 2**
Severe features of preeclampsia (any of these findings)[4]

- SBP ≥ 160 mmHg or DBP ≥ 110 mmHg on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time).
- Thrombocytopenia (platelet count < 100 000/µL).
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnosis, or both.
- Progressive renal insufficiency (serum creatinine concentration > 1.1 mg/dL or doubling of the serum creatinine concentration in the absence of other renal disease).
- Pulmonary edema.
- New-onset cerebral or visual disturbances.

However, recent studies have demonstrated minimal to no influence of the severity of proteinuria on pregnancy outcome in preeclampsia; management of FGR is similar in pregnant women with or without preeclampsia (4, 6). Therefore, massive proteinuria (> 5 g/day), and FGR are no longer criteria of severe preeclampsia (Table 2). Diagnosing severe preeclampsia is of paramount importance, insofar as it has a major impact on medical treatment and timing of delivery as compared to preeclampsia without severe features. Recently, and according to the dynamic character of preeclampsia, the American College of Obstetricians and Gynaecologists (ACOG) has discouraged the diagnosis of “mild preeclampsia”, and proposed the diagnosis of “preeclampsia without severe features”.

**Gestational hypertension** is defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg after 20 gestation weeks in the absence of proteinuria, or any of the aforementioned systemic findings, and resolving before 12 postpartum weeks.

**Chronic hypertension** corresponds to hypertension existing before pregnancy, or appearing before 20 gestation weeks, and persisting more than 12 postpartum weeks.

**Superimposed preeclampsia** is new-onset proteinuria appearing after 20 gestation weeks in a previously hypertensive woman.

**Eclampsia** is defined as generalized tonico-clonic seizure that is not attributable to another cause, and occurring within the course of preeclampsia. Eclampsia generally spontaneously resolves within approximately 60 sec, or within less than 3 to 4 min. Eclampsia has a recurrence rate of about 10% without appropriate treatment.

**HELLP** is the acronym for Hemolysis, Elevated Liver enzymes, and Low Platelets count. It is a common complication of severe preeclampsia (10-20%). Even if HELLP should be suspected when confronted with clinical signs such as epigastric or RUQ pain, nausea, and vomiting, the diagnosis of HELLP syndrome relies on laboratory findings. These include microangiopathic hemolysis with schizocytes, increased lactate dehydrogenase (LDH) (twice the normal value), bilirubin > 1.2 mg/dL, low haptoglobin, liver transaminases > twice the normal values, and platelet count (PC) < 100,000/µL (Table 3).

**PRES** is the acronym for Posterior Reversible Encephalopathy Syndrome, and is commonly seen in patients with eclampsia.

**Epidemiology, morbidity, and mortality associated with preeclampsia.**

Preeclampsia complicates 5 to 8% of all pregnancies. This represents 8.5 million cases a year worldwide. This pathology remains one of the three leading causes of maternal death. The majority of these maternal deaths are related to cerebral hemorrhage that is secondary to poorly controlled hypertension (SBP > 160 mmHg) (1, 2). Renal failure, pulmonary edema, liver failure or rupture, seizures (eclampsia), disseminated intravascular coagulation (DIC), retinal detachment, cortical blindness, abruptio placentae, and hemorrhage represent other complications of preeclampsia. All contribute to preeclampsia-associated maternal morbidity and mortality. Five percent of severe preeclamptic pa-

**Table 3**
Diagnosis criteria for HELLP syndrome

<table>
<thead>
<tr>
<th>Hemolysis</th>
<th>Serum lactate dehydrogenase &gt; 600 UI/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bilirubin level &gt; 1.2 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Schizocytes</td>
</tr>
<tr>
<td>Elevated liver transaminases</td>
<td>Twice normal value</td>
</tr>
<tr>
<td></td>
<td>ASAT &gt; 70 UI/L</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&lt; 100 000/µL</td>
</tr>
</tbody>
</table>

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tients are admitted to an ICU. Finally, preeclampsia is known to increase the risk of developing a cardiovascular disease later in life by a factor of 2.

Regarding the fetus and the neonate, preeclampsia is responsible for 5% of stillbirths in infants without congenital abnormalities, accounts for 8-10% of the overall preterm birth rate, and for 15-20% of the overall FGR and very low birth weight (VLBW) (7).

**PATHOPHYSIOLOGY OF PREECLAMPSIA**

a. Abnormal placental development

As opposed to normal pregnancy, preeclampsia is characterized by an immunologically-initiated impaired trophoblast invasion of the spiral arteries between 8 and 16 gestation weeks. This abnormal invasion of placenta nourishing arteries leads to a failure of their remodeling. Failed remodeling impairs the transformation of small high resistance muscular arteries into large capacitance vessels. Consequently, the utero-placental blood flow progressively fails to meet the needs. Placental ischemia ensues, with oxidative stress, inflammation, apoptosis, and structural damage (8).

b. Angiogenic imbalance

As a consequence of placental ischemia, secondary mediators are released. During normal pregnancy, placental growth factor (PIGF) and vascular endothelial growth factors (VEGF) are potent proangiogenic substances. They enhance the vasodilating properties of prostaglandins (PG) and nitrous oxide (NO), and promote endothelial health. In pre-eclampsia, several anti-angiogenic factors are produced. They are responsible for angiogenic imbalance, impaired vasodilation and an endothelial dysfunction. The soluble fms-like tyrosinekinase (sFlt-1) antagonises VEGF and PI. Soluble endoglin (sEng) antagonises TGF-β, and blocks NO. This imbalance between pro and anti-angiogenic factors produces generalized endothelial dysfunction, microangiopathy, and vasospasm. These rise to the various signs and symptoms of this multisystemic disease, which become clinically evident after 20 gestation weeks (8, 9).

c. Hemodynamic alterations in preeclampsia

The underlying mechanism of hypertension in preeclampsia remains somewhat controversial. Different hemodynamic states have been described in preeclamptic patients. These range from low cardiac output (CO) with increased systemic vascular resistance (SVR) to a hyperdynamic state with increased CO associated with an increased stroke volume and a moderate increase in SVR (10-15). These different hemodynamic situations might be related to the early or late onset of preeclampsia, as well as to its severity (16). Use of cardiac output, and not only blood pressure, as an endpoint when treating severe preeclampsia might improve the hemodynamic management of these patients (17, 18). The routine use of invasive hemodynamic monitoring (arterial line, pulmonary artery catheter, or devices estimating CO from the invasive arterial pressure waveform such as LiDCO® (LiDCO Group Plc., London, UK) PiCCO® (Pulsion Medical Systems, Munich, Germany), or Vigileo® (Edwards Lifesciences, Irvine, CA, USA)) is not common practice for preeclampsia management. Invasive techniques estimating CO do not have any proven benefits on maternal outcome, and may be associated with adverse events (19). Echocardiography may provide useful information but necessitates a trained operator, and does not allow continuous measurement (20). Recent non-invasive techniques based on pulse wave analysis for continuous assessment of CO and SVR might be associated with a better hemodynamic management and a better risk/benefit profile (17, 18, 21). Their impact on overall outcome needs to be evaluated on a larger scale.

d. Eclampsia

Eclampsia occurs in 0.5% of preeclamptic patients without severe features, and in 2-3% of severe preeclampsia. This corresponds up to 10/10000 deliveries in developed countries, and up to 157/10000 deliveries in developing countries (22). Eclamptic seizures contribute substantially to maternal morbidity and mortality. Several prodromal symptoms such as severe headache, altered mental status, blurred vision, and hyperreflexia with clonus may precede the onset of seizures. However, in 40% of eclampsia cases, no prodromal signs are present. Two different pathophysiologic mechanisms may underlie these neurologic symptoms. Vasospasm associated with hypertension and cerebrovascular overregulation might induce localized ischemia and cytotoxic edema. Alternatively, loss of cerebral autoregulation, hyperperfusion, and increased blood brain barrier (BBB) permeability may induce hypertensive encephalopathy, and vasogenic edema (23, 24). Reversibility of neurologic signs and
radiologic findings is in favor of the latter hypothesis. Radiologic findings have been described as the posterior reversible encephalopathy syndrome (PRES). A recent study has evidenced PRES in almost every eclamptic patient. Furthermore, PRES has been identified in multiple areas of the brain in a series of cases where severe hypertension was not a constant feature (25, 26).

**Risk factors, prediction and prevention of preeclampsia**

Several factors are associated with an increased risk of preeclampsia: antiphospholipid syndrome (risk ratio (RR): 9.72), past history of preeclampsia (RR: 7.19), gestational diabetes (RR: 3.56), multiple gestation (RR: 2.93), nulliparity (RR: 2.91), family history of preeclampsia (RR: 2.90), body mass index (BMI) > 30 before pregnancy (RR: 2.47), age ≥ 40 years (RR: 1.96), pre-existing hypertension (RR: 1.5), pre-existing renal disease, and pregnancy interval > 10 years (27, 28). Use of risk factors as predictive tools for preeclampsia has only modest success. Biomarkers of preeclampsia and its severity have also been proposed (8, 29). Placental expression and serum levels of sFlt-1 in preeclamptic women are increased during active disease, as compared with normal pregnancy. Serum levels of sFlt-1 are directly correlated with the severity of the disease. PlGF is low during pregnancy. Serum levels of sFlt-1 are directly correlated with the severity of the disease. In addition to bed rest during pregnancy have no effect on preeclampsia prevention (4). Statins, by stimulating heme oxygenase expression, inhibit sFlt-1 release and promote VEGF. Studies to explore a possible benefit of statins are currently being carried out (9).

**Management of preeclampsia**

The only etiologic treatment of preeclampsia is fetus and placenta delivery. Timing of delivery must take into account the gestational age, severity of preeclampsia, as well as maternal and fetal conditions. Current treatments aim at avoiding maternal complications such as cerebral hemorrhage, pulmonary edema, and eclampsia. Treatment is essentially based on antihypertensive therapy and magnesium sulfate (MgSO4).

During the last 6 years, guidelines aiming at improving outcome of women with preeclampsia have been published by several scientific societies. They provide a robust common basis with minor between-societies differences (4, 6, 7, 27, 32).

At the time of diagnosis, the initial objective is to assess the severity of the disease. In addition to blood pressure and proteinuria measurement and recording, clinical signs of severity must be searched for. Neurological symptoms such as headache, blurred vision, or altered mental status must be considered, as well as epigastric pain or RUQ pain, nausea and vomiting, oliguria, and dyspnea. Laboratory evaluation must assess platelet count, schistocytes count, serum creatinine, liver transaminases, bilirubin, LDH, haptoglobin, and coagulation tests.

Fetal assessment relies on fetal heart rate, fetal weight, amniotic fluid volume, biophysical profile, and umbilical artery Doppler velocimetry.

a. Management of preeclampsia without severe features

Recommendations for the management of preeclampsia without severe features before 37 weeks of gestation are mainly based on expert opinion. Fluorinated steroids should be administered in patients before 34 weeks of gestation, in order to favor fetal maturation. Antihypertensive treatment remains controversial in patients with mild to moderate hypertension (33). Prevention of eclampsia with MgSO4 is not recommended in preeclamptic pa-
tients with no severe features. Bed rest does not improve outcome. Preeclamptic patients with no severe features should be closely monitored. Monitoring includes several evaluations of maternal condition and fetal well-being. Maternal condition is assessed through inventory of clinical symptoms, at least twice weekly. Blood pressure should be measured frequently, and lab tests should be performed weekly, including platelet count and liver enzyme levels. Fetal well-being should be assessed daily by the mother herself (screening of fetal movements), fetal heart rate monitoring, at least twice a week, and ultrasound scanning to evaluate amniotic fluid volume, fetal growth, and umbilical artery velocimetry.

b. Management of severe preeclampsia

Women with severe preeclampsia must be admitted to a maternal high dependency unit, a labor and delivery ward, or a regular intensive care unit.

Severe preeclampsia is an indication for prompt delivery in women with gestational age above 34 weeks. Before 24 weeks, it is recommended to terminate the pregnancy immediately. In women with severe preeclampsia between 24 and 34 weeks, steroids are recommended to favor fetal maturation. In that case, delivery must be delayed for 48 hours, whenever possible.

In selected women who are cared for in specialized units, expectant management of preeclampsia can be considered. Expectant management includes antihypertensive treatment in patients with severe hypertension, and MgSO4 to prevent eclamptic seizures.

However, it must be kept in mind that, while expectant management of severe preeclampsia improves neonatal outcome, it is not associated with any benefit to the future mother.

Delaying delivery in women with severe preeclampsia can be associated with several complications such as ICU admission (27.6%), HELLP syndrome (11%), recurrent severe hypertension (8.5%), pulmonary edema (2.9%), eclampsia (1.1%), and sub-capsular hematoma of the liver (0.5%). Regarding fetal and neonatal complications, delaying delivery can lead to non-reassuring fetal heart rate (50%), fetal growth retardation (37%), prenatal death (7.3%) and/or abruptio placentae (5.1%) (34).

Contra-indications to expectant management beyond 48 hours include fetal growth retardation (< 5th percentile), severe oligohydramnios, reverse end-diastolic flow in the umbilical artery as assessed by Doppler ultrasound, new-onset or increasing renal dysfunction, liver disease, coagulation disorders, preterm rupture of membranes (PROM), and preterm labor.

In case of uncontrollable severe hypertension, eclampsia, pulmonary edema, disseminated intravascular coagulation, abruptio placentae, non-reassuring fetal status, or fetal demise, it is recommended to proceed to delivery as soon as possible after maternal stabilization.

Expectant management of severe preeclampsia can be considered in pregnancy between 24 and 34 gestation weeks, with controlled hypertension, moderately and transiently abnormal lab tests and fetal weight above the 5th percentile.

c. Antihypertensive treatment in preeclampsia

Antihypertensive therapy of non-severe hypertension: a controversy

The purpose of treating severe hypertension is to prevent complications such as intracranial hemorrhage, hypertensive encephalopathy, and pulmonary edema. There is no worldwide consensus regarding the management of non-severe hypertension, insofar as the evidence of an improvement of maternal and neonatal outcome by treatment is lacking (33). Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guidelines consider that antihypertensive treatment can be initiated when blood pressure ranges from 140/160 mmHg SBP and/or 90/100 mmHg DBP (27). National Institute for Health and Clinical Excellence (NICE) guidelines recommend treating hypertension when SBP > 150 mmHg and DBP > 100 mmHg (7), and the last ACOG task force report on hypertension in pregnancy recommend treating women with SBP ≥ 160 mm Hg or DBP ≥ 110 mm Hg (4). In 2010, a Cochrane review concluded that the benefit of treating mild to moderate hypertension was unclear (33). Oral labetalol, nifedipine or nicardipine, methyldopa, and clonidine can be used for the treatment of non-severe hypertension (Table 4). Angiotensin-converting-enzyme (ACE)-inhibitors and angiotensin receptor (AR)-blockers are contraindicated.

Antihypertensive therapy of severe hypertension

Treatment is recommended for SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg with a target between 130 and 150 mmHg for SBP, and between 80 and 100 mmHg for DBP (7). General agreement exists on the need to avoid precipitous decreases in blood pressure, which could affect utero-placental blood flow. A decrease of 10 to
20 mmHg every 10 to 20 min has been suggested by some authors (35). The most frequently recommended medications for the treatment of severe hypertension during pregnancy are hydralazine, labetalol, calcium channel blockers and clonidine (Table 5).

Among antihypertensive medications that are considered to be safe in this context, no evidence supports one drug over another. Consequently, choice should be based on the clinician’s experience and available resources. However, nitroprusside, diazoxide, ketanserin, chlorpromazine should be avoided. MgSO₄ is not considered as an effective treatment for very high blood pressure (although this is indicated for prevention and treatment of eclampsia) (36).

d. Management of HELLP syndrome

Corticosteroid administration to favor fetal maturation reverses HELLP-associated laboratory abnormalities in subgroup of patients, and might prolong pregnancy for 3-14 days. However, there is no evidence for a maternal or perinatal corticosteroid-related improved outcome. Expectant management of HELLP syndrome beyond 48 hours remains an experimental approach, and is not recommended (37). Medical treatment of HELLP syndrome relies on antihypertensive treatment and MgSO₄. Platelet transfusion should be considered if PC falls below 20,000/µL, in case of bleeding, and to achieve a PC of 40-50,000/µL in case of caesarean section (6). Randomized controlled trials have provided evidence of improvement in platelet count with corticosteroids, but no improved overall maternal outcome. In clinical settings where an improvement of platelet count is considered useful, corticosteroids could be used (38). Worsening of hemolysis, thrombocytopenia, and liver dysfunction is common during the first 24-48 postpartum hours. A rise in PC > 100,000/µL usually occurs at day 3 post nadir, or day 6 postpartum.

e. Prevention and management of eclampsia

Treatment of eclamptic seizures consists in the administration of MgSO₄ (Table 6), and in the treatment of hypertension (Table 5). The Collaborative Eclampsia Trial showed a 67% reduction of recurrent seizures in eclamptic women treated with MgSO₄, as compared with those treated by phenytoin. There was a 52% reduction in recurrence as compared to diazepam. For women with eclampsia, MgSO₄ should be continued for at least 24 hours after the last seizure (39).

Delivery is the only curative treatment. So far, any other treatment is palliative. Expectant management of eclampsia to prolong gestation for fetal benefit is associated with a substantial increase in maternal and perinatal morbidity and mortality. Delaying delivery for 24-48 hours in order to allow the administration of corticosteroids prior to 34 gestation weeks has been reported in one retrospective study, but the safety of such an approach has not been proved. Induction of labor is sometimes possible after maternal stabilization, and in case of an expected delivery within 24 hours. Cesarean section can be considered before 32 gestation weeks, or in case of unfavorable cervix. MgSO₄ is the cornerstone of the prevention and treatment of eclampsia. Its use is associated with a 50% reduction of eclampsia episodes in severe preeclampsia. It also reduces the risk of maternal death. The number needed to treat (NNT) to observe 1 beneficial effect is 50 for severe preeclampsia patients, whereas it rises to 100 for patients with preeclampsia without severe features (40). In case of severe preeclampsia arising in the postpartum period, the administration of MgSO₄ is also recommended for at least 24 hours. The effect of MgSO₄ is likely multifactorial, includ-
ing both vascular and neurological mechanisms. Magnesium is a calcium antagonist and induces vasodilation. In addition, MgSO₄ may decrease blood brain barrier (BBB) permeability and limit vasogenic edema (41). In addition, MgSO₄ has anticonvulsant properties, which may be related to its N-methyl-D-aspartate (NMDA) glutamate receptor antagonist activity. The adverse effects of MgSO₄ consist in flushing, palpitations, nausea, vomiting, sedation, respiratory depression, and cardiac arrest (42). These side effects follow a dose-response relationship and occur more frequently in patients with impaired renal function. Close monitoring of the patellar reflex, oxygen saturation, respiration rate, urine output, blood pressure, heart rate and level of consciousness is recommended to detect toxicity. Routine serum magnesium measurement is not necessary. In case of toxicity, calcium gluconate administration is recommended (1g over 10 minutes). MgSO₄ must be continued during labor or C-section, and during the first 24 postpartum hours. Despite theoretical concerns about potential synergistic cardiac depression, the simultaneous administration of MgSO₄ with calcium channel blockers is not contraindicated (43).

f. Fluid management

Pulmonary edema is a potential complication of preeclampsia. Decreased colloid osmotic pressure, increased capillary permeability, increased hydrostatic pressure, and cardiac diastolic dysfunction may all contribute to this complication (11, 44, 45). Preeclampsia is also regarded as a hemodynamic state of depleted intravascular volume, submitting the patient to a higher risk of renal failure. The intravenous administration of fluids to increase plasma volume or to improve renal perfusion is not recommended in women with normal renal function. In case of oliguria, variable invasive monitoring has been proposed to guide fluid therapy. This invasive monitoring may be associated with several complications. Echocardiography and pulmonary ultrasound, allowing interstitial fluid imaging (B lines), may provide useful information to guide fluid therapy in this situation, where the risk of renal failure must be balanced against the risk of pulmonary edema.

Table 5
Antihypertensive agents used for severe hypertension treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Action</th>
<th>Contra-indications</th>
<th>Secondary effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>IV 20 mg/10 min + 5-20 mg/h</td>
<td>β-blocker with vascular α-receptor blocking ability</td>
<td>Asthma</td>
<td>Bradycardia, bronchospasm, headache, nausea</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>IV 5 mg/20 min + 0.5-10 mg/h</td>
<td>Vasodilator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>PO 10 mg/30 min</td>
<td>Calcium channel antagonist</td>
<td>Aortic stenosis</td>
<td>Headache, flushing, tachycardia</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>IV 0.5 mg + 1-5 mg/h</td>
<td>Calcium channel antagonist</td>
<td>Aortic stenosis</td>
<td>Headache, flushing, tachycardia</td>
</tr>
<tr>
<td>Clonidine</td>
<td>IV 15-40 µg/h</td>
<td>α₂-agonist</td>
<td></td>
<td>Dry mouth, sedation</td>
</tr>
</tbody>
</table>

Table 6
Rules for the administration of magnesium sulfate

- Loading dose: 4-6 g over 30 minutes
- Infusion: 1-2 g/hour for 24 hours
- If recurrent seizure, 2-4 g over 5 minutes

The intravenous administration of fluids to increase plasma volume or to improve renal perfusion is not recommended in women with normal renal function. In case of oliguria, variable invasive monitoring has been proposed to guide fluid therapy. This invasive monitoring may be associated with several complications. Echocardiography and pulmonary ultrasound, allowing interstitial fluid imaging (B lines), may provide useful information to guide fluid therapy in this situation, where the risk of renal failure must be balanced against the risk of pulmonary edema.

g. Timing of delivery

For women with chronic hypertension and no additional maternal or fetal complications, delivery before 38 0/7 gestation weeks is not recommended.

For women with mild gestational hypertension or preeclampsia without severe features, and no other indication for delivery, expectant management with maternal and fetal monitoring is suggested until the 37 0/7 gestation week. At or beyond 37 0/7 WG, delivery rather than continued observation is suggested. Delivery should be planned within 24-48 hours.

In case of severe preeclampsia at or beyond 34 0/7 gestation weeks, and in case of unstable maternal or fetal conditions, irrespective of gestational age, delivery is recommended soon after maternal stabilization. In case of severe preeclampsia before fetal viability (24 gestation weeks), delivery after maternal stabilization should be performed. In that case, expectant management should not even be considered. When gestation is less than 34 0/7, with stable maternal and fetal conditions, expectant management can only be undertaken at facilities with adequate maternal and neonatal intensive care resources. In any case, for women with preeclampsia, a decision of delivery should not be based on the amount or change in the amount of proteinuria.
HELLP syndrome before fetal viability is an indication of delivery, shortly after maternal stabilization. When those patients are at or beyond 34 gestation weeks, it is recommended to proceed to delivery soon after initial maternal stabilization. In between gestational age of fetal viability and 33 6/7 gestation weeks, it is suggested to delay delivery for 24-48 hours, but only if maternal and fetal conditions remain stable and allow completing a course of corticosteroids for fetal benefits.

h. Mode of delivery

For women with preeclampsia, the mode of delivery should be determined by the fetal gestational age, fetal presentation, cervical status, and maternal and fetal condition. Caesarean delivery is therefore not mandatory. Cervix ripening with induction of labor should be considered when possible. After 32 gestation weeks, a 60% vaginal birth rate is achievable (46).

ANESTHESIA AND ANALGESIA FOR THE PREECLAMPTIC PARTURIENT

a. Coagulopathy and regional techniques

The risk of spinal hematoma associated with a coagulopathy has always been a concern in preeclamptic women. Preeclampsia is associated with an increased incidence of thrombocytopenia, and potentially other coagulation abnormalities. On the other hand, spinal hematoma is less frequent in parturient women as compared to the general population. The very few cases reported in obstetrics are associated with HELLP syndrome (47). Several studies have addressed the incidence of thrombocytopenia and coagulopathy in preeclampsia, and demonstrate a maximal 10% incidence of thrombocytopenia (< 100,000/µL) in preeclamptic patients. Increase in prothrombin time (PT), partial thromboplastin time (PTT), or decreased fibrinogen have only been described in severe preeclampsia associated with a thrombocytopenia below 100,000/µL. These data lead to the conclusion that, in preeclampsia, the sole monitoring of platelet count, and reserving PT, PTT and fibrinogen monitoring for patients with thrombocytopenia, is a safe policy (48, 49). Guidelines suggest that monitoring platelet count in preeclamptic patients (as opposed to normal pregnancy) reduces maternal anesthesia complications (50). A stable platelet count > 75,000/µL in the absence of other coagulation abnormalities is usually considered safe for neuraxial techniques. Some authors consider a platelet count of 50,000/µL as acceptable for spinal anesthesia (32).

b. Neuraxial analgesia for labor

Unless contraindicated, preeclampsia is considered to be a medical indication for epidural or combined spinal epidural analgesia (CSE) during labor. These techniques not only provide optimal analgesia, but also give better maternal hemodynamic control. In addition, an in situ epidural catheter during labor may avoid the risks associated with general anesthesia, should an emergency cesarean section become necessary during labor.

c. Neuraxial anesthesia for cesarean delivery

Unless contraindicated, neuraxial anesthesia is the technique of choice for cesarean delivery. Neuraxial anesthesia provides satisfactory hemodynamic stability, and avoids the risks associated with general anesthesia in preeclamptic patients. These risks include the potential presence of a difficult airway, and severe hypertension associated with tracheal intubation. For many years, the fear of profound hypotension caused by the sympathetic blockade in patients with increased vascular resistance and depleted intravascular volume precluded the use of spinal anesthesia, and favored the use of epidural anesthesia. However, numerous studies have demonstrated that spinal anesthesia in preeclamptic women is associated with less hypotension, less vasopressor requirement, and minimal changes in CO (51-53). It has also been demonstrated that regional anesthesia for cesarean section in preeclamptic women is associated with a two times higher stroke-free survival rate, as compared to general anesthesia (54). Therefore, spinal anesthesia can be safely used in this population (55). Combined spinal-epidural anesthesia is also an appropriate technique for these patients (56). Epidural anesthesia is the technique of choice when a cesarean section is required during labor under epidural analgesia.

d. General anesthesia for cesarean section

In case of contraindications to neuraxial anesthesia (i.e. pulmonary edema, coagulopathy, altered consciousness following eclamptic seizures), general anesthesia may be required for cesarean delivery. General anesthesia may lead to several difficulties. Intubation can be complicated by airway edema, while a severe hypertensive response may
result from laryngoscopy and tracheal intubation. Opioids (remifentanil, fentanyl, sufentanil) must be used in combination with antihypertensive drugs (labetalol, esmolol, MgSO₄) in order to blunt the blood pressure response to this noxious stimulation (27). For women treated with MgSO₄, monitoring neuromuscular blockade is necessary, insofar as MgSO₄ potentiates and prolongs the effects of non-depolarizing muscle relaxants.

e. Uterotonic agents in preeclampsia.

For patients with preeclampsia, slow administration of 3 IU of oxytocin is recommended as the first line uterotonic measure. It must be followed by an infusion at the lowest effective rate, in order to avoid acute vasodilation, tachycardia, increased cardiac output, and fluid retention (antidiuretic hormone (ADH) effect) (57-59). Carbetocin is associated with the same side effects as oxytocin (60). Given its vasoconstrictive effects, ergometrine is usually considered to be contra-indicated in preeclampsia (61).

**Management during the postpartum period**

a. Management of postpartum hypertension

In women with preeclampsia, blood pressure usually decreases within 48 hours after, but may rise again after 3-6 postpartum days. Preeclampsia may also appear up to 4 weeks after delivery. It is therefore recommended to closely follow blood pressure after delivery (62). Antihypertensive treatment is suggested if SBP remains above 150 mmHg and/or DBP persists above 100 mmHg, on at least two occasions at least 4-6 hours apart. Persistent SBP of 160 mmHg or DBP of 110 mmHg or higher should be treated within 1 hour. As opposed to during pregnancy, some ACE-inhibitors (captopril and enalapril) are considered to be safe during breast-feeding. Conversely, clonidine is best avoided in the nursing mother. The use of methyldopa is controversial during that period (Table 7). The choice of the antihypertensive agent should be based on the clinician’s familiarity with the drug. The use of furosemide may decrease the need for other antihypertensive therapy, but more data are necessary before recommending this treatment (63). When blood pressure is adequately controlled for at least 48 h, medication can be reduced progressively. Resolution may take several weeks. During the postpartum period, non-steroidal anti-inflammatory drugs should be avoided.

b. Thromboprophylaxis

Preeclampsia is a risk factor for thrombosis, particularly if additional risk factors are present (BMI > 30, age > 35, multiparity). Unless contraindicated, postpartum thromboprophylaxis with low molecular weight heparins should be given, particularly in case of antenatal bed rest for more than four days, or after caesarean section (6, 27).

c. Medical follow-up

Women with a history of preeclampsia or eclampsia are at higher risk (approximately two-fold) of early cardiac, cerebrovascular, peripheral arterial disease, and cardiovascular mortality (64). For women with a history of preeclampsia, yearly assessment of blood pressure, lipids, fasting blood glucose, and body mass index is suggested (4).

**Conclusion**

Preeclampsia remains a leading cause of maternal and fetal morbidity and mortality. Despite a better understanding of the pathophysiologic mechanisms underlying the disease, the only curative treatment is delivery. Medical treatment does not

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Action</th>
<th>Contra-indications</th>
<th>Secondary effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>20-120 mg/d</td>
<td>Calcium channel antagonist</td>
<td>Aortic stenosis</td>
<td>Headache, flushing, tachycardia</td>
</tr>
<tr>
<td>Oral labetalol</td>
<td>200-1200 mg/d in two or three divided doses</td>
<td>β-blocker with vascular α-receptor blocking ability</td>
<td>Asthma</td>
<td>Bradycardia, bronchospasm, headache, nausea</td>
</tr>
<tr>
<td>Propranolol</td>
<td>120-240 mg/d in three divided doses</td>
<td>β-blocker</td>
<td>Asthma</td>
<td>Bradycardia, bronchospasm, nausea</td>
</tr>
<tr>
<td>Captopril</td>
<td>50 mg/d in two divided doses</td>
<td>ACE inhibitor</td>
<td>Pregnancy, renal artery stenosis</td>
<td>Hyperkaliemia, angioneurotic edema, reduced lactation</td>
</tr>
</tbody>
</table>

Table 7

Example of treatment of postpartum hypertension
alter the course of the disease, but is important to prevent maternal complications such as eclampsia, cerebral hemorrhage, and pulmonary edema. Adequate knowledge of the guidelines for the management of preeclampsia in terms of antihypertensive treatment, timing of delivery, and anesthetic management for delivery is of paramount importance to limit the morbidity and mortality associated with this pathology. Women with a history of preeclampsia have approximately a twofold increased risk of long term cardiovascular complications, and therefore need a medical follow-up. Future research should focus on the discovery of an etiologic treatment, the prevention of the disease, and the optimal hemodynamic management, taking account of not only the blood pressure, but also cardiac output.

References


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