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**LITERATURE REVIEW ARTICLE ON PREECLAMPSIA****Tahar Ait Mouheb<sup>1</sup>, Nacira Benmouhoub<sup>2</sup>, Lynda Ait Mokhtar<sup>3</sup>, Sana Guedaoura<sup>4</sup>**<sup>1,2,3,4</sup>Faculty Of Medicine Of Algiers, India.DOI: <https://www.doi.org/10.58257/IJPREMS34338>

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**ABSTRACT**

Preeclampsia is a multi-system disorder of pregnancy characterized by varying degrees of impaired placental perfusion, with release of soluble factors into the circulation. These factors cause maternal vascular endothelial damage, which leads to hypertension and multiorgan damage. Placental disease can cause fetal growth restriction and result in stillbirth. Preeclampsia is a major cause of maternal and perinatal mortality and morbidity, particularly in low- and middle-income countries. Prophylactic low-dose aspirin may reduce the risk of early preeclampsia, but once preeclampsia is diagnosed, there is no cure except for childbirth, and no drugs have been shown to be effective on the progression of the disease. Timing of delivery is planned to optimize fetal and maternal outcomes. Clinical trials have reported diagnostic and prognostic strategies that may improve fetal and maternal outcomes and evaluated the optimal timing of delivery in women with early-onset preeclampsia. Ongoing studies are evaluating the effectiveness, dose, and timing of aspirin and calcium to prevent preeclampsia and evaluating other medications to control hypertension or improve disease progression.

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**1. INTRODUCTION**

Preeclampsia (PE) is a specific multi-system pathology that complicates 2 to 8% of pregnancies[1]. Her Incidence is very variable due to the ethnic, geographic and socio-economic differences of the populations studied, and especially the multiplicity of definitions and the frequency of diagnostic errors. It is 3 to 7% among nulliparous women and 1 to 3% among multiparous women in Anglo-Saxon countries.[2].

The gold standard of definition is high blood pressure associated with proteinuria[3]. PE significantly increases maternal morbidity and mortality[4], and perinatal[5]. In addition to the risk of severe complications such as retroplacental hematoma, thrombocytopenia, disseminated intravascular coagulation, pulmonary edema and bronchial inhalation[6], the impact on different organs liver, lung, kidneys and brain, coagulation abnormalities[7], as well as unfortunate consequences on newborns are increased[7], including growth retardation and prematurity[8]. The currently accepted pathophysiological mechanisms have allowed a broad definition of PE, associating pregnancy-related hypertension in the absence of proteinuria with one of the following circumstances: A platelet level PLQ < 100,000, liver enzymes (ALT and/or AST > 2x normal), Acute renal failure (creatinine > 11 mg/l) without any previous renal damage, acute lung edema and neurosensory disorders. Certain risk factors may play a major role in the etiology of preeclampsia. These risk factors include diabetes mellitus, obesity, overweight, maternal age, Nulliparity, high blood pressure, hypothyroidism, kidney disease and family history of preeclampsia[9]. The etiology of the pathogenesis of preeclampsia is not yet fully understood[10]. Some studies have proposed that the placenta releases soluble angiogenic factors, which play a crucial role in endothelial dysfunction and the development of preeclampsia-related symptoms before the clinical manifestation of preeclampsia. Soluble fms-like tyrosine kinase-1 (sFlt-1) is one such factor. It binds vascular endothelial growth factor (VEGF)A and placental growth factor (PlGF). These are the main angiogenic factors responsible for placental vascular development and maternal endothelial function.[11]

To date, there is no test that reliably predicts which women with gestational hypertension will later develop preeclampsia.. [12],

Preeclampsia is also associated with long-term cardiovascular disease. [13-14]

**What are the currently recognized definitions?**

Preeclampsia is a progressive disease of pregnancy involving multiple organs.

The clinical definition has evolved over time from simply hypertension and proteinuria to a broader classification that recognizes the multi-system involvement of multiple organs caused by the disease.

It is defined as the onset of hypertension during pregnancy (according to International

Society for the Study of Hypertension in Pregnancy (ISSHP) in 2014), which is characterized by persistently high systolic/diastolic blood pressure  $\geq 140/90$  mm Hg as well as proteinuria  $\geq 300$  mg/24 h after 20 weeks of gestation in women whose blood pressure was previously normal. According to new recommendations (2013) from the American Congress of Obstetricians and Gynecologists (ACOG), preeclampsia may or may not be accompanied by proteinuria.

International recommendations agree that preeclampsia can be defined as gestational hypertension (GAH) associated with one or more of the following conditions from 20 weeks of gestation:

**1. Proteinuria**( $\geq 300\text{mg}/24\text{h}$ ) [15-16]

**2. Other maternal organ dysfunction, including:** [15-17]

- Acute kidney injury (AKI) (creatinine  $\geq 90 \mu\text{mol/L}$ ; 1 mg/dL)
- Liver involvement (elevated transaminases, e.g. ALT or AST  $> 40 \text{ IU/L}$ ) with or without right upper quadrant or epigastric abdominal pain)
- Neurological complications (e.g., eclampsia, altered mental status, blindness, stroke, clonus, headache, and persistent visual scotomas)
- Hematological complications (thrombocytopenia – platelet counts below  $150,000/\mu\text{L}$ , DIC, hemolysis)

**3. Uteroplacental dysfunction**(such as fetal growth restriction, abnormal umbilical artery Doppler waveform analysis or stillbirth)

**What are the risk factors for the occurrence of preeclampsia?**

Clinical risk factors for preeclampsia are summarized in Table 1[18-19],the highest risk factors being a history of preeclampsia (an 8-fold risk), although the risk may be lower for people with preeclampsia in a first pregnancy but not in the next pregnancy) and hypertension chronic (risk multiplied by 5). A history of premature preeclampsia carries the greatest risk of developing preeclampsia, with approximately 25-30% of women experiencing recurrent disease. [20-21],Obstetric complications in a previous pregnancy, such as fetal growth restriction, stillbirth, and placental abruption, also pose an increased risk of preeclampsia, reflecting the potentially shared pathophysiology of clinical phenotypes related to placental dysfunction.

Some risk factors for developing preeclampsia may be more easily modifiable than others before pregnancy; interventions such as weight reduction, prevention of multi-fetal pregnancies through assisted reproductive technologies, increased societal awareness of adverse pregnancy outcomes associated with the age of Maternal and optimal treatment of chronic medical conditions (eg, systemic lupus erythematosus and chronic hypertension) could all be beneficial in reducing the risk of preeclampsia.

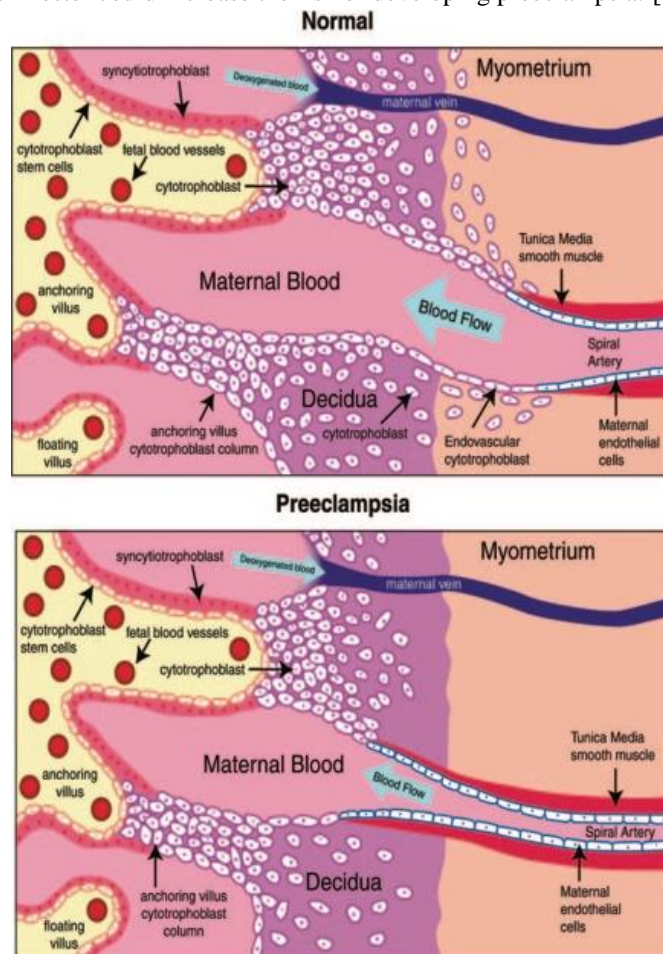
**Table 1:** Risk factors for preeclampsia with unadjusted relative risks from two systematic reviews (listed in descending order of risk)

	Pooled unadjusted relative risk (95% CI)[18]	Unadjusted relative risk (95% CI)[19]
History of PE	8.4 (7.1-9.9)	7.19 (5.85-8.83)
Chronic hypertension	5.1 (4.0-6.5)	..
Pre-gestational diabetes	3.7 (3.1-4.3)	3.56 (2.54-4.99)
Maternal Age < 17ans	..	2.98 (0.39-22.76)
Multiple pregnancy	2.9 (2.6-3.1)	2.93 (2.04-4.21) g. twin 2.83 (1.25-.6.40) g. triplet
Family history of PE	..	2.9 (1.7-4.93)
SAPL	2.8 (1.8-4.3)	9.72 (4.43-21.75)
BMI > 30kg/m <sup>2</sup>	2.8 (2.6-3.1)	..
LED	2.5 (1.0-6.3)	..
History of stillbirth	2.4 (1.7-3.4)	..
Nulliparity	2.1 (1.2-2.4)	2.91(1.28-6.61)
Previous placental abortion	2.0 (1.4-2.7)	..
PMA	1.8 (1.6-2.1)	..
Chronic renal failure	1.8 (1.5-2.1)	..
Maternal Age > 40 ans	1.5(1.2-2.0)	1.68 (1.23-2.29) if primiparous 1.96 (1.34-2.87) if multiparous
Intrauterine growth retardation	1.4 (0.6-3.0)	..
Maternal Age > 35 ans	(1.2-2.4)	..

### What are the pathophysiological mechanisms of preeclampsia?

Early in a normal pregnancy, the placenta remodels the local uterine vasculature, creating optimal conditions for nutrient and oxygen exchange throughout the pregnancy. Extra villous placental trophoblast cells migrate through the inner third of the myometrium of the uterus and remove smooth muscle from maternal spiral arterioles [22], rendering the ends of the vessels unable to contract. Therefore, the terminal portion of the spiral arterioles remains wide open and the net result is a high capacitance, low resistance system at the maternal-fetal interface. The maternal-fetal interface promotes abundant blood flow to the implantation site, allowing for efficient exchange of nutrients between mother and fetus. Deficient remodeling of the spiral arteriole is observed in some women who develop preeclampsia, [23], especially with premature birth with fetal growth retardation. [24], The resulting decreased perfusion, high velocity, and turbulent blood flow (emanating from spiral arterioles) causes placental ischemia [25], and oxidative stress, [26-27], damages placental villi and leads to abnormal levels of angiogenic proteins in maternal blood [28]. This pathology of the maternal blood supply has been incorrectly renamed maternal vascular perfusion, [22-29] and is characterized histologically by reduced placental size, infarction, abnormal development of placental villi, and paucity of transformation of maternal deciduous spiral arterioles. [22] (Figure 1).

The histological severity of maternal vascular malperfusion disease correlates with the clinical severity of preeclampsia and inversely correlates with gestational age at delivery. [30-31]. The immune system plays an active role in the pathological interactions between extra villous trophoblast cells and the host decidua, and abnormal cellular interactions occurring early in the first trimester could increase the risk of developing preeclampsia. [32],



**Figure 1.** Abnormal placentation in preeclampsia.

In normal placental development, invasive cytotrophoblasts of fetal origin invade maternal spiral arteries, transforming them from small-caliber resistance vessels to high-caliber capacity vessels capable of providing adequate placental perfusion to support fetal growth.

During the process of vascular invasion, cytotrophoblasts differentiate from an epithelial phenotype to an endothelial phenotype, a process termed “pseudovasculogenesis” or “vascular mimicry” (top panel).

In preeclampsia, cytotrophoblasts fail to adopt an invasive endothelial phenotype. Instead, invasion of the spiral arteries is shallow and they remain small-caliber resistant vessels (lower panel).

### What is the role of biomarkers?

#### In the pathogenesis of PE?

As pregnancy continues into the second trimester, the diseased placenta gradually secretes high amounts of antiangiogenic factors that cause vascular inflammation, endothelial dysfunction, and maternal vascular damage.[33].The net result of this altered angiogenic profile is the clinical manifestation of maternal hypertension and multiple organ damage (Figure 1). Two-step process poor early placental development followed by multi-systemic endothelial dysfunction and severe maternal organ injury. There are many candidate factors secreted in excess by the preeclamptic placenta that could contribute to endothelial dysfunction: proinflammatory cytokines, exosomes 41 and extracellular vesicles;[34] and anti-angiogenic molecules such as soluble fms-like tyrosine kinase-1 (sFlt1)[35.36] and soluble endoglin.[37].These placenta-derived factors may act on maternal vascular endothelium to induce local endothelial release of other factors that worsen dysfunction, such as thromboxane, pro-inflammatory cytokines, and possibly sFlt-1 itself.[38]This event is associated with the suppression of the release of pro-angiogenic placental growth factor (PlGF).

sFlt-1 is an anti-angiogenic protein that binds to the functional receptor binding domain of vascular endothelial growth factor (VEGF), neutralizing the ability of VEGF to signal to endothelial cells that line arterioles, blood vessels to maintain vasorelaxation. Although sFlt-1 binding to VEGF is not the primary pathogenic event triggering preeclampsia, sFlt-1 has many features implicating it as a major factor in the disease. For example, elevated concentrations of sFlt-1 are observed weeks before the clinical onset of pre-eclampsia<sup>44</sup> and during pre-eclampsia;[36.39] given that sFlt-1 is anti-angiogenic, a pathogenic role is biologically plausible[33]

#### In predicting preeclampsia?

The use of biomarkers as diagnostic adjuncts in women with suspected preeclampsia may help clarify the likelihood of preeclampsia when the clinical picture is uncertain. In normal pregnancies, the concentration of PlGF (a pro-angiogenic protein secreted by the placenta) in the circulation increases as gestation advances before decreasing towards term and decreases in women with preeclampsia.[36.40] In contrast, circulating concentrations of sFlt-1, which increase toward term in normal pregnancies, are elevated in the circulation of women with preeclampsia. The discovery that low concentrations of PlGF and high concentrations of sFlt-1 predate the clinical diagnosis of preeclampsia by a few weeks[36] allows their potential use as diagnostic adjuncts. Prospective multicenter cohort studies evaluated the sFlt-1/PlGF<sup>58</sup> ratio and PlGF alone[41] in women with suspected preeclampsia, primarily to predict adverse pregnancy outcomes[42] or preeclampsia requiring delivery within 2 weeks.[41]

In a multicenter randomized controlled trial, use of the PlGF test halved the time it took clinicians to diagnose preeclampsia compared with covert testing, from 4.1 to 1.9 days (time ratio 0.36; CI 95% 0.15–0.87) and significantly reduced a composite of serious maternal adverse events (adjusted odds ratio [aOR] 0.32; 95% CI 0.11–0.96), with no significant differences in the incidence of preterm birth, birth weight percentiles or neonatal unit admission rate.<sup>62</sup> In the United Kingdom, British guidelines recommend the use of the PlGF-based test for women suspected of preeclampsia before 35 weeks of amenorrhea[43] and its integration into the overall clinical assessment of the woman to guide monitoring strategies for future management[44]

#### What is the role of uterine and ophthalmic ultrasound in preeclampsia?

**Uterine Doppler:** Several studies, which combine different markers, have focused on the blood flow of the uterine artery in particular, its waveform. A pathological waveform identified by a high resistance index as well as an early diastolic notch (Figure 2). Evaluated during the second trimester, these abnormal Doppler results indicate a significantly increased risk of developing preeclampsia[45]

**Ophthalmic Doppler:** The ophthalmic artery, which is the first branch of the internal carotid artery and has embryologic, anatomical, and functional similarities to the intracranial vasculature, is an easily accessible vessel for Doppler evaluation that provides information about the intracranial circulation less accessible; Cross-sectional studies reported that compared with normal pregnancy, preeclampsia was accompanied by a decrease in flow impedance and an increase in velocities in the flow velocity waveforms of the ophthalmic arteries.[46.47] There is also evidence that the occurrence of preeclampsia is preceded by a decrease in flow impedance in the cerebral circulation.[48.49] Three small prospective studies, involving <450 patients each, examined the potential value of ophthalmic arterial Doppler in predicting preeclampsia during the first or second trimester of pregnancy; two of the studies reported that ophthalmic arterial Doppler was useful and one that it was not.[50.51]

At the bottom is the ophthalmic artery flow velocity waveform obtained by pulsed-wave Doppler illustrating first and second systolic velocity and end-diastolic velocity. Left Ophthalmic Artery Color Flow Demonstration

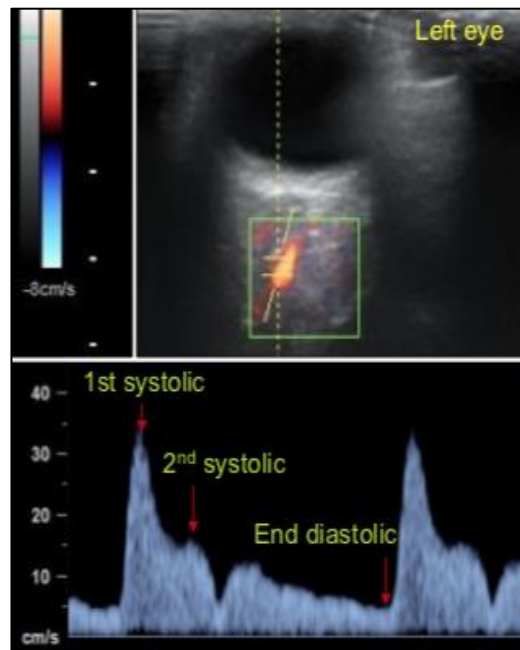


Figure 2

### Combination of biochemical markers on uterine artery Doppler

In recent years, none of the biomarkers evaluated to predict preeclampsia have yet been proven to have clinical value. Much effort has been made to evaluate their potential and their combination with other screening methods such as ultrasound. The most promising biochemical markers to date are PP 13 as well as sflt-1, PLGF and Seng. They allow the screening of PE and its complications, showing relatively high predictive values. Diagnostic performance is improved if these markers are combined with first trimester Doppler ultrasound. Further studies are important to justify their clinical use, always with the aim of reducing maternal and perinatal morbidity and relieving the “heavy burden” of pre-eclampsia.[52]

### How to Predict and Prevent Preeclampsia:

#### Screening at the start of pregnancy:

Current screening strategies rely on the combined use of clinical risk factors, maternal plasma or serum biomarkers, and imaging modalities such as uterine artery Doppler flow velocity waveform analysis. These methods are variably integrated into predictive algorithms used to stratify prenatal care monitoring and identify women most suitable for prophylactic aspirin treatment. A 2019 general review reported the identification of 90 predictors and 52 prediction models.

In one algorithm, researchers attempted to improve predictive ability by combining variables, maternal demographics, comorbidity and pregnancy-related, circulating levels of biomarkers (usually PIGF and pregnancy-associated plasma protein A), and uterine artery waveform on arterial Doppler (measured at approximately 13 weeks of gestation). Such an algorithm has been reported to have a higher detection rate for subsequent preeclampsia (detection rate 42.5%; 95% CI 38.0–46.9) than using clinical risk factors alone (30.4%; 95% CI 26.3–34.6).[53]

These multivariable prediction algorithms have higher test performance for preeclampsia requiring early delivery (usually before 34 weeks of gestation) than for late-onset preeclampsia, however, as the prevalence of early-onset disease is less than 1% of pregnancies, the positive predictive values are low although they can be considered high enough to initiate prophylactic treatment. The clinical implications and cost of implementing such a screening strategy require further investigation.[54]Although this first trimester screening and treatment approach is already approved in some international recommendations[55.56]but its cost-effectiveness compared to screening approaches based on clinical risk factors alone is unclear.

### Prevention of preeclampsia:

#### Aspirin:

Aspirin is the only preventive drug treatment for preeclampsia supported by solid evidence. A 2019 Cochrane review concluded that low-dose aspirin taken daily from the end of the first trimester through 36 weeks of gestation reduces the risk of preeclampsia by approximately 18% (relative risk 0.82; 95% CI 0.77–0.82).[57]How aspirin prevents preeclampsia is unclear. Theories include: that aspirin improves placental implantation, and protects the maternal

vasculature by decreasing platelet reactivity, thromboxane concentrations, and increasing prostacyclin production,[58]which would involve continuing aspirin treatment throughout pregnancy. Screening approaches to selecting individuals who are offered aspirin prophylaxis typically involve the use of clinical risk factors\*, such as treating people with two moderate risk factors or one high risk factor for preeclampsia.[59.60]Most recommendations use a dose of 75 to 100 mg of aspirin per day.[59.60]

\*Clinical risk factors used by different scientific societies: (ACOG = American College of Obstetricians and Gynecologists. NICE = National Institute for Health and Care Excellence. ISSHP = International Society for the Study of Hypertension during pregnancy FIGO = International Federation of Gynecology and Obstetrics) are as follows:

- Chronic hypertension,
- Type 1 or type 2 diabetes
- Kidney disease
- Autoimmune disease (SLE, APLS)
- History of preeclampsia
- Multi-fetal pregnancy
- History of other hypertensive disorder of pregnancy
- Use of PMA
- High BMI
- Nulliparity
- Family history of preeclampsia
- More than 10 years apart in pregnancy
- Maternal age (>35 years)
- Maternal size
- Obstetric history (low birth weight)
- Low socioeconomic

### **What are the therapeutic axes for the management of preeclampsia?**

#### **Pharmacological treatment of hypertension:**

Various antihypertensive agents have been used in the treatment of PE, without reaching consensus in the management of mild to moderate hypertension. Sodium restriction, bed rest, and restriction of physical activity are not recommended for the prevention or treatment of PE without serious features.[61]. At present, there is no recommendation for the use of one antihypertensive agent over another; the choice of treatment depends on the acuity and severity of hypertension. All antihypertensive medications have the potential to cross the placenta.

Methyl dopa has been widely used in the management of high blood pressure in pregnant women. It stimulates central alpha-adrenergic receptors through a false neurotransmitter ( $\alpha$ -methyl-norepinephrine), resulting in decreased sympathetic flow of norepinephrine to the heart, kidneys, and peripheral vasculature. Its long-term safety for the fetus has been demonstrated.

Labetalol lowers blood pressure by blocking  $\beta$ - and  $\alpha$ -adrenergic receptors. It better preserves uteroplacental blood flow compared to other  $\beta$ -blockers. Its onset of action is rapid (2 hours) compared to methyldopa. Randomized clinical trials comparing Labetalol to methyldopa or nifedipine showed that labetalol was safe during pregnancy[62.63]On the other hand, studies have demonstrated that labetalol causes maternal hepatotoxicity. It is important to recognize this side effect because it can be confused with HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). Most cases of Labetalol-induced hepatotoxicity are reversible, but deaths have been reported.[64]

Nifedipine is a calcium channel blocker that has been used during pregnancy without major problems. Long-acting nifedipine is preferred over short-acting nifedipine because the short-acting version of the drug can cause a significant drop in blood pressure, possibly resulting in reduced uteroplacental perfusion. However, as discussed below, more recent evidence suggests that immediate-release oral nifedipine, under certain conditions, may be considered for safe BP reduction. Long-acting nifedipine may be administered as a sustained-release tablet in doses of 30 to 90 mg once daily. The dosage can be increased at intervals of 7 to 14 days, reaching a maximum dose of 120 mg per day[65]

Hydralazine is a direct vasodilator of arterioles. Its use is limited by its side effects, including lower extremity swelling and reflex tachycardia. Its hypotensive effect is less predictable than that of other parenteral agents. In case of PE with severe hypertension (sustained systolic blood pressure of at least 160 mm Hg or diastolic blood pressure of at least 110 mm Hg), the use of an antihypertensive[61]. Labetalol, nifedipine, or methyldopa are recommended as first-line treatment. Relatively recent studies suggest that the calcium channel blocker nifedipine, in its immediate oral release

form, may also be considered as a first-line treatment[66.67] In 2017, The American College of Gynecologists and Obstetricians recommended that the use of immediate-release oral nifedipine be considered first-line treatment, particularly when the intravenous route is not available. Blockers of the renin-angiotensin-aldosterone system, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralo-corticosteroid receptors should be avoided

Although magnesium sulfate is not recommended as an antihypertensive agent, it has been used over the years for the prevention of seizures in women with severe preeclampsia and for the management of recurrent seizures in eclampsia. ACOG limits its use for the prevention of eclampsia if BP is 160/110 or greater, or if blood pressure is less than 160/110, associated with other serious symptoms. Studies have shown that magnesium sulfate is more effective in preventing recurrent attacks of eclampsia than other traditional anticonvulsants, including phenytoin and diazepam, or lytic cocktails.[68.69].The mechanism of action of magnesium sulfate in preventing seizures is not completely understood, but is thought to be due to its effect on the central nervous system, perhaps due to its effect on N receptors -methyl D-aspartate (NMDA), calcium channels, and acetylcholine. Although data are limited, concerns that concurrent use of magnesium sulfate and nifedipine may result in serious side effects, including hypotension and neuromuscular inhibition, have not been supported by available evidence.[70]

#### **When is the delivery time?**

Childbirth is the only treatment for PE. The decision to deliver immediately versus expectantly depends on:

1. Rate and severity of disease progression
2. Gestational age
3. Maternal and fetal condition

NICE and ACOG recommendations recommend that women with preeclampsia give birth at 37 weeks gestation (SA).[71]. Before 34 (SA), management is expectant and planned delivery is not considered due to a worsening of unfavorable neonatal outcomes (respiratory distress syndrome, RR = 2.3-95 CI % (1.39-3.81) and necrotizing enterocolitis, RR = 5.54, 95% CI (1.04-29.56)[72].Between 34 and 37 (SA), the optimal time to give birth to prevent morbidity for mother and baby remains unknown.

#### **The indications are maternal and fetal:**

- **Kindergarten:**[73].
  - Severe uncontrolled blood pressure (persistent systolic blood pressure of 160 mm Hg or greater or diastolic blood pressure of 110 mm Hg or greater not responding to antihypertensive medications)
  - Persistent, refractory and treatment-resistant headaches
  - Epigastric pain not responding to repeated analgesics
  - Neurosensory disorders, motor or sensory deficit
  - Stroke
  - HELLP syndrome
  - Recent or worsening renal dysfunction (serum creatinine greater than 11 mg/dl)
  - Pulmonary edema
  - Eclampsia
  - Suspected acute placental abruption or vaginal bleeding in the absence of a placenta Praevia
- **Fetal:**[74].
  - Abnormal fetal FHR
  - Fetal death
  - Fetus with no expectation of survival at the time of maternal diagnosis (extreme prematurity)
  - Persistent reversed end-diastolic flow in the umbilical artery

#### **What are the recommendations to recommend in the postpartum period?**

Postpartum patient education prior to discharge should include information on the signs and symptoms of severe hypertension with instructions on when and where to seek care. Patients with severe hypertension should be evaluated within 7 to 14 days of discharge or sooner as clinically indicated. Follow-up verification should take place in the high-risk pregnancy clinic that provided the antenatal care. [75].

#### **What are the long-term complications of preeclampsia?**

Preeclampsia is responsible for both short and long term maternal morbidity and mortality. Endothelial dysfunction, a constant and early element of preeclampsia, promotes the development of atherosclerosis[76].PE is a risk factor for

cardiovascular and cerebrovascular events; twenty percent of women develop hypertension or microalbuminuria seven years later.[77]. In a meta-analysis, Bellamy showed after a pregnancy complicated by preeclampsia, that there was a high risk of chronic arterial hypertension, RR= 3.7-95% CI (2.70-5.05), coronary ischemia, RR= 2.16-95% CI (1.86-2.52), stroke, RR= 1.81(1.45-2.27) 95% CI, and thromboembolic accident RR= 1.19-95% CI (1.37-2.33). This risk is all the greater the earlier the preeclampsia occurs.[78]. In a systematic review and meta-analysis, Morven CB et al, reported that women with a history of PE or eclampsia were at high risk of cardiovascular events Odds Ratio, OR=2.28-95% CI (1.87-2.78) of cerebrovascular events, OR =1.76-95% CI (1.43-2.21) and chronic arterial hypertension with a relative risk, RR =3.13-CI at 95%, (2.51-3.89)[79].

## 2. MATERNAL MORBIDITY

Preeclampsia is responsible for a 5% increase in maternal morbidity, including seizures, pulmonary edema, renal failure, hepatic failure and stroke. They occur most often in preeclamptic women before 32 weeks and those with a predisposing pathology. [80,81,82] 80. Martin JN Jr, Thigpen BD, Moore RC, et al: Stroke and severe pre-eclampsia and eclampsia: A paradigm shift focusing on systolic blood pressure. *Obstet Gynecol* 105:246-254, 2005)

81. Kuklina EV, Ayala C, Callaghan WM: Hypertensive disorders and severe obstetric morbidity in the United States. *Obstet Gynecol* 113:1299-1306, 2009) 82. Sibai BM: Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. *Obstet Gynecol* 103:981-999, 2004)

### 1. Eclampsia

Eclampsia is a major neurological complication of PE, defined by the appearance of a generalized tonic-clonic seizure in the absence of any previous neurological pathology. It occurs following a pregnancy complicated by preeclampsia but it can be inaugural and precedes arterial hypertension and PE. It complicates severe preeclampsia in 0.5% of cases[83]. The prevalence of eclampsia has significantly decreased in industrialized countries, due to better monitoring of pregnant women and the implementation of prevention measures. However, it remains very common in developing countries; the lack of monitoring of pregnancies is the main factor in this increase. Its occurrence is concomitant with significant morbidity and maternal-fetal mortality. Maternal risk is represented by hypoxia and bronchial aspiration.

In an American study[84] out of a total of 4024 maternal deaths, 790 (19.6%) were due to pre-eclampsia, and 49% of which were directly attributable to eclampsia. The risk factors reported in this study were age over 30 years and failure to monitor the pregnancy.

PE being an organ failure, other morbidities can be associated such as retroplacental hematoma, disseminated vascular coagulopathy, pulmonary edema, inhalation of gastric fluid and in utero fetal death due to hypoxia. Adult respiratory distress syndrome and cerebral hemorrhage are complications rarely observed in studies from industrialized countries. The radiological lesions found in eclampsia are similar to those found in hypertensive encephalopathy: cerebral edema, infarction and hemorrhage.[85]

Posterior reversible encephalopathy syndrome (PRES) is often found after an eclamptic attack. (PRES) is a reversible neurological disorder manifested by headache, visual disturbances, altered consciousness, confusion, and seizures.[86] .The pathophysiological mechanism is represented by vasogenic edema localized in the posterior parietal and occipital regions.[87]

Seizure alone is not an indication for systematic neuroradiological examination. Indeed, brain computed tomography (CT) and magnetic resonance imaging (MRI) are not routine examinations. Imaging is indicated in the presence of prolonged coma and signs of focus looking for intracranial hemorrhage or venous thrombosis requiring specific therapy. Imaging is of great help in the diagnosis of atypical forms of eclampsia, especially those occurring before 20 weeks of amenorrhea and those occurring after 48 hours postpartum and those refractory despite adequate treatment with magnesium sulfate.[88.89];

Electroencephalography (EEG) recording shows diffuse abnormalities in 70% of cases and localized slowing in 30% of cases[90]

The standard treatment remains magnesium sulfate at a dose of 4 grams as a slow infusion over twenty minutes followed by a continuous infusion for maintenance.[91]If the attack recurs, an additional dose of two grams is administered. Given that the margin between the therapeutic and toxic dose is narrow, it is necessary to monitor the Magnesemia which must be between 2 and 4 mmol/l. The alteration of renal function, common in this context of preeclampsia, makes it possible to maintain the loading dose and to reduce the maintenance dose as much as possible or even to stop it. At the same time, blood pressure control is imperative.[93]



### 3. HELLP SYNDROME

HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets) is a particular form of preeclampsia. According to ACOG, the diagnosis of HELLP is based on the following biological elements: elevated lactate dehydrogenase (LDH) greater than 600 IU/L, aspartate aminotransferase (ASAT) or alanine aminotransferase (ALT) elevated more than twice the upper limit of normal, and platelet count less than 100,000 109/l.[94]

It is serious when the platelet count  $\leq 50,000/\text{mm}^3$ , complicates 5-20% of serious pre-eclampsia and occurs more often in older women (compared to the average of pre-eclamptic women), multiparous and white. In 70% of cases, HELLP occurs prepartum and in 30% of cases after delivery, most often within 48 hours (range from a few hours to six days postpartum)..[95]

The existence of a HELLP syndrome increases the risk of occurrence of convulsions by a factor of 3 compared to women with severe preeclampsia without HELLP.[96.97]

HELLP syndrome manifests itself clinically by variable and non-specific signs, predominantly digestive. Epigastric bar pain and/or pain in the right hypochondrium are the most frequently found clinical sign (65 to 86% of cases). This pain is the result of obstruction of blood flow in the sinusoids and hepatocyte necrosis. Any epigastric pain occurring in the second or third trimester of pregnancy should raise suspicion of HELLP syndrome. Other symptoms may be encountered, nausea and vomiting in 36-84% of cases, malaise in 90% of cases and jaundice in 5% of cases. The fever should suggest a hepatic infarction. Ascites is sometimes observed during cesarean section, it is an excellent predictive factor for the occurrence of cardiac and respiratory complications in the postpartum period..[95.98]

Maternal morbidity is all the more severe the later the diagnosis is made.

The complications found by Sibai in the absence of conservative treatment include 21% of DIC, 16% of retroplacental hematoma (RPH), 8% of acute renal failure (ARI), 6% of acute lung edema (OAP), 2% laparotomies for hemorrhage, 1% subcapsular hematoma of the liver and retinal detachment. HELLP also places patients at increased risk of postpartum hemorrhage. This risk is essentially due to DIC and not to thrombocytopenia even if it is severe. Transfusion of platelet pellets does not prevent its occurrence.[95.98]

HELLP syndrome is evidence of multiorgan failure, its discovery is always synonymous with seriousness, requiring hospitalization of parturients in a structure including both maternal and neonatal intensive care. Its one and only treatment remains the termination of the pregnancy. However, it is the delay of this interruption which remains a subject of great divergence between practitioners. In all cases, two possibilities present themselves to us: the first, when the term of the pregnancy is  $> 34$  weeks in which case the termination of the pregnancy is necessary as soon as possible. The second, when the term is  $< 34$  weeks, the risk of fetal complications linked to prematurity is significant.

In this case, most authors propose a therapeutic approach involving several stages essentially combining the usual treatment of preeclampsia and corticosteroid therapy under the cover of intensive maternal and fetal monitoring.

- Control of any severe blood pressure (SBP $\geq 160$  mm Hg and/or DBP $\geq 110$  mm Hg) with vasodilators, mainly calcium channel blockers (Nicardipine) and/or labetalol can prevent maternal complications including heart failure, congestive disease, hypertensive encephalopathy, stroke, and PHR.
- Transfusion of packed red blood cells in cases of severe or poorly tolerated anemia.
- Similarly, coagulation disorders should be corrected with fresh frozen plasma.
- Platelet transfusion is only indicated in cases of significant hemorrhagic syndrome and severe thrombocytopenia ( $< 50,000$  per cubic millimeter).
- Any repeated transfusion is illusory due to the process of platelet consumption, or even dangerous due to the thrombotic risk. Platelet concentrates are administered at the time of delivery, generally in the event of a cesarean section under general anesthesia, in order to reduce the risk of operative bleeding.

Special case of hepatic hematomas:

The management of subcapsular hematoma of the liver (HSCF) seems to be more consensual. In cases of unruptured HSCF, it is important to correct hemostasis disorders by transfusions of fresh frozen plasma and ultrasound monitoring. If this is broken, correct hemodynamics must be maintained, hemostasis disorders corrected and hepatic surgical hemostasis performed.

We must never lose sight of the fact that in order to gain fetal maturity, waiting exposes in addition to the usual complications of severe PE (PAO, eclampsia, HRP) the risk of liver rupture. These hematomas are rare (1/45,000 pregnancies), predominantly in the right lobe. The clinical picture is that of violent abdominal pain with hypovolemic shock.

The fetomaternal mortality of this hepatic rupture (80 and 50% respectively) has prompted more aggressive management. Embolization, ligation of the hepatic artery, and packing have been successively proposed without the small number of series making it possible to conclude the superiority of one or the other technique.

Liver transplantation was performed in patients with HELLP syndrome refractory to treatment, with uncontrollable hemorrhage from hepatic necrosis.[99,100,101]

Regardless of the type of treatment considered, no author recommends a systematic cesarean section. The low route is authorized because there is no correlation between the platelet counts of the fetus and those of the mother, even if the thrombocytopenia is less than 50,000/mm<sup>3</sup>. Regional anesthesia is always preferred to general anesthesia in preeclamptic patients. During childbirth, transfusions of platelet concentrates should not be systematic because the destruction of platelets is rapid. When cesarean section is indicated, it is essential to have 6 to 10 units of platelet pellets, just before intubation. During the cesarean section, the surgeon does not attempt to check the liver and manipulation of the liver mass is not recommended. Thus, cesarean section does not exempt from liver ultrasound, which if not performed before the cesarean section, must be done after it in order to rule out HSCF.[102]

Postpartum, monitoring in an intensive care unit for at least 48 hours is essential. Resolution is usually spontaneous within 36 to 72 hours.

The recurrence of HELLP syndrome is low for some (4%), a little more frequent (20%) for others, but it increases to 60% when HELLP appears before 32 weeks. These figures highlight the importance of disease prevention and monitoring of patients with a history of HELLP syndrome.[95]

#### 4. ACUTE RENAL FAILURE

AKI is a rare complication of severe PE. In this context, it reflects multiorgan damage, and is often associated with HELLP syndrome, retroplacental hematoma (RPH), and coagulopathy in 50% of cases.[103]

The occurrence of AKI always worsens the maternal prognosis. There is a relative reduction in renal plasma flow and glomerular filtration responsible for an increase in plasma creatinine and urea as well as serum uric acid, correlated with the increase in renal vascular resistance and/or the volume. Proteinuria indicates glomerular damage. It is usually moderate, of the order of 1–2 g/24 h, but can be more abundant (> 5 g/d), leading to nephrotic syndrome which is an indicator of poor prognosis.[104]

Renal failure during PE is defined by concentrations of creatinine exceeding 90 mmol/l and urea exceeding 7 mmol/l. The renal histological abnormalities correspond to acute tubular necrosis associated with glomerular endotheliosis lesions suggestive of renal damage in severe PE. Recovery of renal function is usually complete.[105]

#### Maternal mortality linked to preeclampsia

Although the maternal mortality rate has declined in recent years, there are still cases of deaths considered preventable. The majority of the 600,000 cases of maternal deaths/year occur in low-resource countries, explained by the high number of severe forms of preeclampsia observed[106, 107, 108, 109].The danger of elevated SBP, especially if it is associated with thrombocytopenia, is the occurrence of a cerebral hemorrhage.[110].

Endothelial dysfunction, thrombocytopenia and sudden changes in blood pressure lead to a high risk of cerebral complications in preeclampsia.[110,111].

#### 5. CONCLUSION

Preeclampsia is a multi-system disorder of pregnancy characterized by varying degrees of impaired placental perfusion, with release of soluble factors into the circulation. It is a major cause of maternal and perinatal mortality and morbidity, particularly in low- and middle-income countries. Timing of delivery is planned to optimize fetal and maternal outcomes

#### 6. BIBLIOGRAPHY

- [1] Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980–2010: age-period-cohort analysis. *BMJ* 2013;347:f6564.
- [2] Zhang J, Zeisler J, Hatch Mc, Berkowitz G. Epidemiology of Pregnancy-Induced Hypertension. *Epidemiol Rev* 1997; 19:218–232.
- [3] Gifford RW Jr, August PA, Cunningham G, Green LA, Lindheimer MD, McNellis D, et al. Report of the national high blood pressure education program working group on high blood pressure in pregnancy. *American Journal of Obstetrics and Gynecology* 2000;183(Suppl):1-22.
- [4] Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Global Health* 2014;2(6): e323-e333.

- [5] Ananth CV, Savitz DA, Bowes WA. Hypertensive disorders of pregnancy and stillbirth in North Carolina, 1988-1991. *Acta Obstetrica et Gynecologica Scandinavica* 1995;74:788-93.
- [6] Labib Ghulmiyyah, and Baha Sibai. Maternal Mortality from Preeclampsia/Eclampsia. *Semin Perinatol* 2012. 36:56-59
- [7] Mol BW, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet* 2016;387(10022):999-1011.
- [8] Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 2008;371(9608):261-9.
- [9] Poorolajal J, Jenabi E. The association between body mass index and preeclampsia: a meta-analysis. *J Matern Fetal Neonatal Med* 2016; 29:3670–3676.
- [10] Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. *Traffic* 2011; 123:2856–2869.
- [11] Tarasevičienė V, Grybauskienė R, Mačiulevičienė R. sFlt-1, PIGF, sFlt-1/PIGF ratio and uterine artery Doppler for preeclampsia diagnoses. *Medicina (Kaunas)* 2016; 52:349–353.
- [12] Davis GK, Mackenzie C, Brown MA, Homer CS, Holt J, McHugh L, Mangos G. Predicting transformation from gestational hypertension to preeclampsia in clinical practice: a possible role for 24-hour ambulatory blood pressure monitoring. *Hypertensive Pregnancy*. 2007; 26:77–87. doi:10.1080/10641950601147952.Crossref.PubMed.
- [13] Theilen LH, Fraser A, Hollingshaus MS, Schliep KC, Varner MW, Smith KR, Esplin MS. All-cause and cause-specific mortality after hypertensive disease of pregnancy. *Obstet Gynecol*. 2016;128:238–244. doi: 10.1097/AOG.0000000000001534.Crossref.PubMed.
- [14] Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension*. 2009;53:944–951.HYPERTENSION AHA.109.130765.Crossref.PubMed.
- [15] ACOG. Gestational hypertension and preeclampsia: ACOG practice bulletin, number 222. *Obstet Gynecol* 2020; 135:e237–60.
- [16] Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. *J Obstet Gynaecol Can* 2014; 36:575–76.
- [17] Levytska K, Higgins M, Keating S, et al. Placental pathology in relation to uterine artery Doppler findings in pregnancies with severe intrauterine growth restriction and abnormal umbilical artery Doppler changes. *Am J Perinatol* 2017; 34:451–57.
- [18] Bartsch E, Medcalf KE, Park AL, Ray JG. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ* 2016; 353: i1753.
- [19] Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ* 2005; 330:565.
- [20] Dildy GA 3rd, Belfort MA, Smulian JC. Preeclampsia recurrence and prevention. *Semin Perinatol* 2007; 31:135–41.
- [21] Hofmeyr GJ, Betrán AP, Singata-Madliki M, et al. Prepregnancy and early pregnancy calcium supplementation among women at high risk of pre-eclampsia: a multicenter, double-blind, randomized, placebo-controlled trial. *Lancet* 2019; 393:330–39.
- [22] Ernst LM. Maternal vascular malperfusion of the placental bed. *APMIS* 2018; 126:551–60.
- [23] Wright E, Audette MC, Ye XY, et al. Maternal vascular malperfusion and adverse perinatal outcomes in low-risk nulliparous women. *Obstet Gynecol* 2017; 130:1112–20.
- [24] Levytska K, Higgins M, Keating S, et al. Placental pathology in relation to uterine artery Doppler findings in pregnancies with severe intrauterine growth restriction and abnormal umbilical artery Doppler changes. *Am J Perinatol* 2017; 34:451–57
- [25] Burton GJ, Woods AW, Jauniaux E, Kingdom JC. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. *Placenta* 2009; 30:473–82.
- [26] Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: pathophysiology, challenges, and perspectives. *Circ Res* 2019; 124:1094–112.

- [27] Burton GJ, Yung HW, Cindrova-Davies T, Charnock-Jones DS. Placental endoplasmic reticulum stress and oxidative stress in the pathophysiology of unexplained intrauterine growth restriction and early onset preeclampsia. *Placenta* 2009; 30 (suppl A): 43–48.
- [28] Zur RL, Kingdom JC, Parks WT, Hobson SR. The placental basis of fetal growth restriction. *Obstet Gynecol Clin North Am* 2020; 47:81–98.
- [29] Khong TY, Mooney EE, Ariel I, et al. Sampling and definitions of placental lesions: Amsterdam Placental Workshop Group consensus statement. *Arch Pathol Lab Med* 2016; 140:698–713.
- [30] Stevens DU, Al-Nasiry S, Bulten J, Spaanderman ME. Decidual vasculopathy in preeclampsia: lesion characteristics relate to disease severity and perinatal outcome. *Placenta* 2013; 34:805–09.
- [31] Weiner E, Feldstein O, Tamayev L, et al. Placental histopathological lesions in correlation with neonatal outcome in preeclampsia with and without severe features. *Pregnancy Hypertension* 2018; 12:6–10.
- [32] Faas MM, De Vos P. Innate immune cells in the placental bed in healthy pregnancy and preeclampsia. *Placenta* 2018; 69:125–33
- [33] Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: pathophysiology, challenges, and perspectives. *Circ Res* 2019; 124:1094–112.
- [34] Han C, Han L, Huang P, Chen Y, Wang Y, Xue F. Syncytiotrophoblast-derived extracellular vesicles in pathophysiology of preeclampsia. *Front Physiol* 2019; 10:1236.
- [35] 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; 111:649–58.
- [36] Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med* 2004; 350:672–83.
- [37] Levine RJ, Lam C, Qian C, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med* 2006; 355:992–1005.
- [38] Granger JP, Spradley FT, Bakrania BA. The endothelin system: a critical player in the pathophysiology of preeclampsia. *Curr Hypertens Rep* 2018; 20:32.
- [39] Zeisler H, Llorba E, Chantraine F, et al. Predictive value of the sFlt-1: PIGF ratio in women with suspected preeclampsia. *N Engl J Med* 2016; 374:13–22.
- [40] Saffer C, Olson G, Boggess KA, Beyerlein R, Eubank C, Sibai BM. Determination of placental growth factor (PlGF) levels in healthy pregnant women without signs or symptoms of preeclampsia. *Pregnancy Hypertension* 2013; 3:124–32.
- [41] Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. *Traffic* 2013; 128:2121–31.
- [42] Rana S, Powe CE, Salahuddin S, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. *Traffic* 2012; 125:911–19.
- [43] National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management. June 25, 2019. <https://www.nice.org.uk/guidance/NG133> (accessed April 1, 2020).
- [44] Duhig KE, Myers J, Seed PT, et al. Placental growth factor testing to assess women with suspected preeclampsia: a multicenter, pragmatic, stepped-wedge cluster-randomized controlled trial. *Lancet* 2019; 393:1807–18.
- [45] Venkatesha, S. Toporsian, M. Lam, C. and Al. 2006. Soluble Endoglin Contributes To The Pathogenesis Of Preeclampsia. *Nat. Med.* 12, 642–649.
- [46] Hata T, Senoh D, Hata K, Kitao M. Ophthalmic artery velocimetry in pregnant women. *Lancet* 1992; 340:182–183.
- [47] Kane SC, Brennecke SP, da Silva Costa F. Ophthalmic artery Doppler analysis: a window into the cerebrovasculature of women with pre-eclampsia. *Ultrasound Obstet Gynecol* 2017; 49:15-21.
- [48] Riskin-Mashiah S, Belfort MA, Saade GR, Herd JA. Transcranial doppler measurement of cerebral velocity indices as a predictor of preeclampsia. *Am J Obstet Gynecol* 2002; 187:1667–1672.
- [49] Belfort M, Van Veen T, White GL, Kofford S, Allred J, Postma I, Varner M. Low maternal middle cerebral artery Doppler resistance indices can predict future development of pre-eclampsia. *Ultrasound Obstet Gynecol* 2012; 40:406–411.

- [50] Gurgel Alves JA, Praciano de Sousa PC, Bezerra Maia e Holanda Moura S, Kane SC, da Silva Costa F. First trimester maternal ophthalmic artery doppler analysis for prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2014; 44:411–418.
- [51] Praciano de Souza PC, Gurgel Alves JA, Bezerra Maia EHMS, Araujo Junior E, Martins WP, Da Silva Costa F. Second trimester screening of preeclampsia using maternal characteristics and uterine and ophthalmic artery doppler. *Ultraschall Med* 2018; 39:190-197.
- [52] Chien, PF Arnott, N. Gordon, A. Et Al. 2000. How Useful Is Uterine Artery Doppler Flow Velocimetry In The Prediction Of Pre-Eclampsia, Intrauterine Growth Retardation And Perinatal Death? An Overview. *Bjog* 107, 196–208.
- [53] Tan MY, Wright D, Syngelaki A, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. *Ultrasound Obstet Gynecol* 2018; 51:743–50.
- [54] Henderson JT, Thompson JH, Burda BU, Cantor A. Preeclampsia screening: evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2017; 317:1668–83.
- [55] Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. *Hypertension* 2018; 13:291–310.
- [56] Poon LC, Shennan A, Hyett JA, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. *Int J Gynaecol Obstet* 2019; 145 (suppl 1): 1–33.
- [57] Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev* 2019; 2019: CD004659.
- [58] ACOG. ACOG committee opinion no. 743 summary: low-dose aspirin use during pregnancy. *Obstet Gynecol* 2018; 132:254–56
- [59] ACOG. Gestational hypertension and preeclampsia: ACOG practice bulletin, number 222. *Obstet Gynecol* 2020; 135:e237–60.
- [60] Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. *Hypertension* 2018;13:291–310.
- [61] American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* (2013) 122(5):1122–31. doi:10.1097/01.AOG.0000437382.03963.88
- [62] Peacock WF, Hilleman DE, Levy PD, Rhoney DH, Varon J. A systematic review of nifedipine vs labetalol for the management of hypertensive crises. *Am J Emerg Med* (2012) 30(6):981–93. doi: 10.1016/j.ajem.2011.06.040
- [63] Molvi SN, Mir S, Rana VS, Jabeen F, Malik AR. Role of antihypertensive therapy in mild to moderate pregnancy-induced hypertension: a prospective randomized study comparing labetalol with alpha methyl dopa. *Arch Gynecol Obstet* (2012) 285(6):1553–62. doi:10.1007/s00404-011-2205-2
- [64] Clark JA, Zimmerman HJ, Tanner LA, Hepatotoxicity L. *Ann Intern Med* (1990) 113(3):210–3.
- [65] Smith P, Anthony J, Johanson R. Nifedipine in pregnancy. *BJOG* (2000) 107(3):299–307. doi:10.1111/j.1471-0528.2000.tb13222.x
- [66] Vermillion ST, Scardo JA, Newman RB, Chauhan SP. A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. *Am J Obstet Gynecol* (1999) 181(4):858–61. doi: 10.1016/S0002-9378(99)70314-5
- [67] Rezaei Z, Sharbaf FR, Pourmojib M, Youefzadeh-Fard Y, Motevalian M, Khazaeipour Z, et al. Comparison of the efficacy of nifedipine and hydralazine in hypertensive crisis in pregnancy. *Acta Med Iran* (2011) 49(11):701–6.
- [68] Duley L, Henderson-Smart D. Magnesium sulfate versus phenytoin for eclampsia. *Cochrane Database Syst Rev* (2003).
- [69] Duley L, Gulmezoglu AM. Magnesium sulfate versus lytic cocktail for eclampsia. *Cochrane Database Syst Rev* (2001) (1):CD002960. doi:10.1002/14651858.CD002960
- [70] Magee LA, Miremadi S, Li J, Cheng C, Ensom MH, Carleton B, et al. Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia. *Am J Obstet Gynecol* (2005) 193(1):153–63. doi: 10.1016/j.ajog.2004.11.059

- [71] ACOG Committee Opinion No. 764. Medically indicated late-preterm and early-term deliveries. *Obstet Gynecol* 2019;133:e151-e155.
- [72] Churchill D, Duley L, Thornton JG, et al.: Interventionist versus expectant care for severe pre-eclampsia between 24- and 34-weeks' gestation. *Cochrane Database Syst Rev.* 2013; (7): CD003106.
- [73] ACOG Practice Bulletin No. 202. Gestational hypertension and preeclampsia. *Obstet Gynecol* 2019;133:e1-e25.
- [74] Balogun OA, Sibai BM. Advice, management and results in women with severe preeclampsia between 23 and 28 weeks of gestation. *Clin Obstet Gynecol* 2017;60:183–9.
- [75] Sutton EF, Hauspurg A, Caritis SN, Powers RW, Catov JM. Maternal outcomes associated with lower range State 1 hypertension. *Obstet Gynecol* 2018; 132:843-849.
- [76] Pre-eclampsia: major vascular disease, pathophysiology, recent developments. Marilucy Lopez-Sublet, Bernard Levy. *Blood Thrombosis Vessels* 2018; 30, No. 4: 161-9)
- [77] Labib Ghulmiyyah, MD, \* and Baha Sibai, MD. Maternal Mortality from Preeclampsia/Eclampsia. *Semin Perinatol* 2012; 36:56-59 ©
- [78] Bellamy L, Casas JP, Hingorani AD, et al: Pre-eclampsia and risk of cardiovascular disease and cancer in later life: Systematic review and meta-analysis. *BMJ* 335:974, 2007
- [79] Morven Caroline Brown<sup>1</sup>, Kate Elizabeth Best, Mark Stephen Pearce, Jason Waugh, Stephen Courtenay Robson, Ruth Bell. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. *Eur J Epidemiol.* 2013 Jan;28(1):1-19. doi: 10.1007/s10654-013-9762-6. Epub 2013 Feb 9.
- [80] Martin JN Jr, Thigpen BD, Moore RC, et al: Stroke and severe pre-eclampsia and eclampsia: A paradigm shift focusing on systolic blood pressure. *Obstet Gynecol* 105:246-254, 2005
- [81] Kuklina EV, Ayala C, Callaghan WM: Hypertensive disorders and severe obstetric morbidity in the United States. *Obstet Gynecol* 113:1299-1306, 2009
- [82] Sibai BM: Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. *Obstet Gynecol* 103:981-999, 2004
- [83] Labib Ghulmiyyah, and Baha Sibai. Maternal Mortality from Preeclampsia/Eclampsia. *Semin Perinatol* 2012. 36:56-59
- [84] MacKay AP, Berg CJ, Atrash HK: Pregnancy-related mortality from preeclampsia and eclampsia. *Obstet Gynecol* 97:533-538, 2001
- [85] Di X, Mai H, Zheng Z, Guo K, Morse AN, Liu H. Neuroimaging findings in women who develop neurologic symptoms in severe pre-eclampsia with or without eclampsia. *Hypertens Res* 2018;41:598–604.
- [86] Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. *J Neurol* 2017;264:1608–16.
- [87] Shankar J, Banfield J. Posterior reversible encephalopathy syndrome: a review. *Can Assoc Radiol J* 2017;68:147–53.
- [88] Sibai BM, Stella CL. Diagnosis and management of atypical preeclampsia-eclampsia. *Am J Obstet Gynecol* 2009; 200:481. e1–7
- [89] Zeeman GG. Neurological complications of pre-eclampsia. *Semin Perinatol* 2009;33:166–72
- [90] Osmanagaoglu MA, Dinc G, Osmanagaoglu S, Dinc H, Bozkaya H. Comparison of cerebral magnetic resonance and electroencephalogram findings in pre-eclamptic and eclamptic women. *Aust NZJ Obstet Gynaecol* 2005; 45:384–90.
- [91] Duley L, Henderson-Smart DJ, Walker GJ, Chou D. Magnesium sulfate versus diazepam for eclampsia. *Cochrane Database Syst Rev.* 2010 Dec 8;2010(12):CD000127.)
- [92] Multidisciplinary management of severe forms of preeclampsia. RFE 2009. *Ann Fr Anest Réanim* 2009; 28:275
- [93] RFE 2020. Management of the patient with severe pre-eclampsia. SFAR-CNGOF
- [94] ACOG Practice Bulletin No. 202: gestational hypertension and preeclampsia. *Obstet Gynecol.* 2019;133:e1–e25.
- [95] Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 422 pregnancies with hemolysis, elevated liver enzymes and low platelets. *Am J Obstet Gynecol* 1993; 169:1000-6.)
- [96] Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes and low platelets): Much ado about nothing? *Am J Obstet Gynecol* 1990; 162:311-6.

- [97] Martin JN, Rinehart Bk, May WL, Magann EF, Terrone DA, Blake PG. The spectrum of severe preeclampsia: comparative analysis by HELLP (hemolysis, elevated liver enzymes, and low platelets count) syndrome classification. *Am J Obstet Gynecol* 1999; 180:1373–1384.
- [98] Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes and low platelets. *Obstet Gynecol* 2004; 103:981–91.)
- [99] G. Seren, J. Morel, R. Jospe, P. Mahul, A. Dumont, M. Cuileron, O. Tiffet, C. Auboyer. HELLP syndrome and subcapsular hematoma of the ruptured liver. Therapeutic strategy based on a clinical case. *AFR* 2006; 25:1067-9.)
- [100] Sheikh RA, Yasmeeen S, Pauly MP, Riegler JL. Spontaneous intrahepatic hemorrhage and hepatic rupture in the Hellp syndrome. Four cases and a review. *J Clin Gastroenterol* 1999; 28:323-8.)
- [101] Shames BD, Fernandez LA, Sollinger HW and al. Liver transplantation for Hellp syndrome. *Liver Trans.* 2005 Feb; 11 (2): 224-8.)
- [102] Vigil-De-Gracia P, Silva S, Montufar C, Carrol I, De Los Rioss. Anesthesia in pregnancy with HELLP syndrome. *Int J Gynecol Obstet* 2001; 74:23–7.
- [103] Baha Sibai, Gus Dekker, Michael Kupferminc Maternal and fetal complications in severe preeclampsia. *Lancet* 2005; 365:785–99
- [104] Thangaratnam S., Ismail K., Sharp S, Coomarasamy A., O'Mahony F., Khan KS, et al. Prioritization of tests for the prediction of preeclampsia complications: a Delphi survey. *Hypertensive Pregnancy* 2007; 26:131–8.
- [105] B. Moulin, A. Hertig, E. Rondeau. Kidney and preeclampsia. In: *Multidisciplinary management of preeclampsia* 2009; Page: 171-186.
- [106] Schutte J, Schuitemaker N, van Roosmalen J, et al: Substandard care in maternal mortality due to hypertensive disease in pregnancy in the Netherlands. *Br J Obstet Gynaecol* 115:732-736, 2008.
- [107] Karolinski A, Mazzoni A, Belizan JM, et al: Lost opportunities for effective management of obstetric conditions to reduce maternal mortality and severe maternal morbidity in Argentina and Uruguay. *Int J Gynecol Obstet* 110:175-180, 2010.
- [108] Clark SL, Belfort MA, Dildy GA, et al: Maternal death in the 21st century: Causes, prevention, and relationship to cesarean delivery. *Am J Obstet Gynecol* 199:36. e1-36. e5, 2008.
- [109] Allen VM, Campbell M, Carson G, et al; for the Canadian Maternal Morbidity Working Group: Maternal mortality and severe maternal morbidity surveillance in Canada. *J Obstet Gynaecol Can* 32:1140-1146, 2010
- [110] Martin JN Jr, Thigpen BD, Moore RC, et al: Stroke and severe pre-eclampsia and eclampsia: A paradigm shift focusing on systolic blood pressure. *Obstet Gynecol* 105:246-254, 2005
- [111] Moodley J: Maternal deaths associated with hypertensive disorders of pregnancy: A population-based study. *Hypertens Pregnancy* 23:247-256, 2004