Preeclampsia: state of art and future perspectives. A special focus on possible preventions

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ABSTRACT

Preeclampsia (PE) is characterised by the new onset of hypertension after the 20th week of pregnancy, with or without proteinuria or hypertension that leads to end-organ dysfunction. Since the only definitive treatment is delivery, PE still represents one of the leading causes of preterm birth and perinatal mobility and mortality. Therefore, any strategies that aim to reduce adverse outcomes are based on early primary prevention, prenatal surveillance and prophylactic interventions. In the last decade, intense research has been focussed on the study of predictive models in order to identify women at higher risk accurately. To date, the most effective screening model is based on the combination of anamnestic, demographic, biophysical and maternal biochemical factors. In this review, we provide a detailed discussion about the current and future perspectives in the field of PE. We will examine pathogenesis, risk factors and clinical features. Moreover, recent developments in screening and prevention strategies, novel therapies and healthcare management strategies will be discussed.

KEYWORDS

Preeclampsia; hypertension; pregnancy; outcomes; diagnosis; management

Introduction

Preeclampsia (PE) is a multisystemic progressive disorder characterised by the new onset of hypertension (systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg) and proteinuria, or hypertension that leads to end-organ dysfunction (both presence or absence of proteinuria), after 20 weeks of gestation (Rye et al. 2016; Laganà, Giordano, et al. 2017; Laganà et al. 2018; ACOG 2019a). It represents one of the leading causes of maternal and perinatal morbidity and mortality, especially when the condition is of early-onset.

There is an international consensus nowadays to differentiate between early-onset PE (<34 weeks gestation) and late-onset PE (≥34 weeks gestation) (Tranquilli et al. 2013). This differentiation is crucial as late-onset PE represents the great majority of PE cases: 90% in the literature from developed countries and some 70% in low- and middle-income countries. In addition, early-onset PE is often associated with severe symptoms with a high maternal/foetal morbidity (Robillard, Dekker, Chaouat, et al. 2019).

A definitive screening test to predict the development, onset time and PE grade has not been yet confirmed. However, an elevated blood flow resistance in uterine arteries, performed with Doppler during the first trimester, represents an effective strategy to identify high-risk pregnancies and treat them with low-dose aspirin (Sotiriadis et al. 2019). Moreover, a combination of maternal factors and biomarkers could also be helpful to identify pregnancies that develop early and preterm PE (Tan et al. 2018).

However, the only definitive treatment for PE which develops antepartum, is childbirth, and the timing of delivery is critical to avoid premature births.

Complementary to current knowledge (Burton et al. 2019), the purpose of this review is to summarise current evidence regarding PE and its management in pregnancy and highlight areas that require further study. The authors wish to focus also on possible immediate accessible preventions.

Methodology

A non-systematic review was done through a search on the following databases: EMBASE, MEDLINE, Global Health, The Cochrane Library, Health Technology Assessment Database and Web of Science, research registers such as ClinicalTrials.gov; we used the medical subject heading (MeSH) term Pre-Eclampsia (MeSH Unique ID: D011225) in combination with: Diagnosis (MeSH Unique ID: D003933); Risk Factors (MeSH Unique ID: D012307); Therapy (MeSH Unique ID: D013812). We selected papers written in English, with no time restrictions about the year of publication. Titles

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independently by two review authors to select studies that potentially meet the aims of this non-systematic review. The full text of these potentially relevant articles was screened and independently assessed for eligibility by the other two authors. A discussion with an external collaborator clarified any disagreement over the eligibility of particular articles. Due to the nature of the findings, we opted for a narrative synthesis of the results from selected articles.

Definition

By definition, PE can be diagnosed as early as the 20th week of pregnancy, even though it frequently occurs near term. Epigastric pain and headache are symptoms of end-organ dysfunction. Proteinuria in PE is defined as the presence of more than 300 mg/dL protein in 24-hour urine or a serum protein/creatinine ratio greater than or equal to 0.30. If the aforementioned tests are not available, proteinuria can be determined with a simple dipstick test, but the rate of false negativity and false positivity is quite high (Phelan et al. 2004; Salman et al. 2018; Chen et al. 2019). In 2013, the American College of Obstetricians and Gynecologists (ACOG) defined the current diagnostic criteria (Hypertension in Pregnancy 2013) (Table 1).

Prevalence and risk factors

The prevalence of PE varies according to different factors such as race, ethnicity, age and genetic predisposition. Overall, PE affects 2–8% of all pregnancies (ACOG 2019a). The prevalence in White, Hispanic, African-American women

Table 1. Definition of preeclampsia according to ACOG guideline.

I. **Blood pressure (after 20 weeks of gestation)**
1. Systolic blood pressure: 140 mmHg or more on two occasions (min. four hours apart)
or
2. Diastolic blood pressure: 90 mmHg or more on two occasions (min. four hours apart)
or
3. Patients with a systolic blood pressure of 160 mmHg or more or diastolic blood pressure of 110 mmHg or more (within a short interval (minutes))
AND
II. Proteinuria
1. 24-hour urine: 300 mg or more protein
or
2. Protein/creatinine ratio: 0.3 g/dL or more
or
3. Dipstick: 2+ (used only when other quantitative methods are unavailable)
OR
III. New onset of any of the following
1. Thrombocytopenia: platelet count $<100{,}000 \times 10^9$/L.
2. Renal insufficiency: serum creatinine level more than 1.1 mg/dL or a doubling of the serum creatinine level when there is no other renal disease.
3. Impaired liver function: elevated liver transaminases to twice normal concentration.
4. Pulmonary oedema.
5. Headache unresponsive to medication (no any causal diagnosis) or visual symptoms.

women, multiple pregnancies, and those with a previous history of PE and the risk of PE in first pregnancies is 1.5–2-fold higher compared with multiparous women (Mayrink et al. 2019). Although it often affects young pregnant women (<18 years of age), also advanced maternal age (>40) is associated with an increased risk (Dugoff et al. 2004; Gui et al. 2020). Nonetheless, comorbidities such as diabetes, chronic hypertension, chronic kidney disease, obesity, antiphospholipid syndrome, systemic lupus erythematosus and hydatidiform mole are other risk factors (Mol et al. 2016; Budak et al. 2019; Gui et al. 2020). Preeclampsia is more prevalent among IVF pregnancies (Poon and Nicolaides 2014; Watanabe et al. 2014) and paternal factors could impact on the development, maybe due to genetic interactions with maternal genetic factors (Galaviz-Hernandez et al. 2018). Low socioeconomic status, maternal low birth weight and family history are other risk factors for PE (Mol et al. 2016).

Aetiology

The placenta plays a critical role in the pathophysiology of PE. Preeclampsia can occur in pregnancies without a foetus but only having placental derived tissue, such as in molar pregnancies (Nugent et al. 1996; Moore-Maxwell and Robboy 2004). In addition, the remission of symptoms and the improvement of disease after removal of the placenta support this argument. Although the underlying cause of PE remains unknown, it is believed to be triggered by a defect in remodelling, and trophoblastic invasion in the spiral arteries (Salman et al. 2018; Ridder et al. 2019) and interestingly, these two pathological conditions are also involved in the pathophysiology of foetal growth restriction (Chiofalo et al. 2017). Women having an increased underlying endothelial cell inflammation such as diabetes, renal or cardiovascular diseases prior to pregnancy are also at risk for PE (Bilano et al. 2014; Bartsch et al. 2016; Villa et al. 2017; Fox et al. 2019; Vitale, Corrado, et al. 2021). According to several retrospective studies, PE presents a critical heritable component. Several polymorphisms of the vascular endothelial growth factor (VEGF) demonstrated an association with the PE onset (Procopciuc et al. 2014; Salimi et al. 2015; Silva et al. 2015). VEGF is a fundamental actor of the development of the placenta due to its involvement in angiogenesis and vessel growth, and the structure of the spiral arteries undergoes several changes during the early stages of pregnancy. As a result, the uteroplacental vessels become wider and less resistant, thereby increasing the blood flow to the foetus (Zhou et al. 1997; Raguema et al. 2020). The endovascular and interstitial trophoblasts are involved in this physiological change. The interstitial trophoblasts surround the spiral arteries, while endovascular trophoblasts provide vascular wall penetration and change by expressing CD56 through dNK (Zhang 2021). This process is completed at 20 weeks of pregnancy. However, there is an abnormality in the invasion of spiral arteries in PE. The trophoblasts demonstrated a superficial invasion so that the deep myometrial vessels, not

highly resistant and narrow. This condition causes hypoperfusion of the placenta. In the following periods, this may lead to preterm labour, intrauterine growth retardation, placental abruption and foetal death, and PE (Silasi et al. 2010; Vitale et al. 2014, 2015; Pratt et al. 2015; Correa et al. 2016).

The mechanism of defective trophoblast differentiation is based on changes in various cytokines, adhesion molecules, metalloproteinases, HLA-G and extracellular matrix elements involved in endothelial invasion (Cross et al. 1994; Silasi et al. 2010; Vetvicka et al. 2016; Laganà, Vitale, et al. 2017; Vitale et al. 2018; Torella et al. 2019). Semaphorin 3B may be responsible for the defective trophoblast differentiation and invasion by inhibiting the VEGF signalling (Zhou et al. 2013). In addition, highly differentiated gene transcriptions were detected in trophoblasts in severe preeclamptic pregnancy as well as the expression of novel messenger RNAs and non-coding RNAs was impaired (Gormley et al. 2017). In conclusion, abnormal trophoblastic invasion is associated with poor pregnancy outcomes leading to hypoperfusion, hypoxia, free radicals and oxidative stress, and hypertension. TNFα and IL-6 production are higher in pregnancies complicated by PE than in normal pregnancies, and the increase in these proinflammatory agents resulted in endothelial dysfunction (Hutabarat et al. 2017; Ali et al. 2019). TNFα leads to a reduction in nitric oxide synthase (NOS) gene transcription and an increase in endothelin-1, a potent vasoconstrictor. Inhibition of NOS interferes with the low pressure-vasodilation condition of normal pregnancy. Antiangiogenic factors are also increased as high blood levels of soluble fms-like tyrosine kinase-1 (sFlt-1) reduce VEGF. Additionally, soluble endoglin (sEng) reduces vasodilation by reducing transforming growth factor-beta (TGF-β) inhibition and nitric oxide release (Tannetta et al. 2013).

Pathophysiology

It is thought that changes in prostaglandin synthesis play a key role in microvascular dysfunction in PE. Thromboxane, which causes vasoconstriction and platelet aggregation, is increased while prostacyclin, which has the opposite effects, is reduced. The microvascular dysfunction is also due to an increased sensitivity to angiotensin II and the related augmented vasoconstriction. While normal pregnant women have insensitivity to vasopressor infusion, higher levels of angiotensin II have been shown in preeclamptic pregnant women (Lumbers et al. 2019). Various studies have shown that inhibition of angiotensin II type 1 receptor agonistic autoantibodies (AT_1-AAs) could be another cause of this condition resulting in reduced uterine perfusion pressure (Vaka et al. 2020). Also, vascular cell adhesion protein 1 (VCAM-1) and fibronectin levels are increased in preeclamptic women compared to physiological pregnancy levels (Madazli et al. 2000).

Pregnancy-associated plasma protein-A (PAPP-A) also impacts on the pathogenesis of PE. PAPP-A is a metalloproteinase involved in matrix mineralisation and angiogenesis. It improves the tissue availability of insulin-like growth factor-1 (IGF-1) by cleaving IGF-binding protein-4 (IGFBP-4). Low levels of PAPP-A have been associated with placental impairment and microvascular dysfunction (Iacobaeus et al. 2018).

Preeclampsia is mostly sporadic; however, genetic predisposition is also shown to increase the risk. Primigravid women with a history of PE in their mother or sister have twice the increased risk for PE (Carr et al. 2005; Skjaerven et al. 2005), and this risk is much higher in monozygotic twins. PAI-1 4G/5G polymorphism has also been strongly associated with PE (Giannakou et al. 2018). Although there are hundreds of genes detected in PE aetiology, they appear with different phenotypic expressions under the influence of environmental factors.

Regardless of which of these mechanisms is defective, there is generalised vasospasm and endothelial dysfunction and, accordingly, a hypertension onset. A reduced blood flow leads to ischaemia, necrosis and end-organ dysfunction with a parallel release of substances that increase sensitivity to coagulation and vasopressors.

Classification

Preeclampsia can be classified in two forms according to the severity of the disease: severe PE and, in the absence of severe findings, mild (or non-severe) PE. This classification is important since it guides clinical management. The criteria shown in Table 1 (I.3 and III) are used to diagnose the presence of severe PE. Of note, proteinuria was removed from the severe PE criteria since a value greater than 5 g/24 hours is not always associated with poor maternal or neonatal outcomes (Newman et al. 2003).

Moreover, according to the onset, PE could be divided into early-onset PE ($<$34 weeks gestation) and late-onset PE ($\geq$34 weeks gestation).

Ultrasonographic, serologic and urinary markers

Although encouraging studies are available, there is not yet a definitive screening test to predict the development, time of onset, and grade of PE (Roberge et al. 2018; Poon et al. 2019; Rolnik et al. 2020).

Ultrasonographic anomalies

Normally, uterine artery resistance should decline with increasing gestational age. On the contrary, in early-onset preeclamptic pregnancies, especially in the second trimester, there could be an increase of resistance in uterine artery Doppler (UAD) measurement (Cnossen et al. 2008). However, the UAD ultrasound screening is not recommended in low-risk patients because of its low sensitivity and high false positivity rates (Myatt et al. 2012; Cignini, Laganà, et al. 2016).

The measurement of resistance to flow in uterine arteries, performed with Doppler in the first trimester, represents an effective strategy to identify high-risk pregnancies and treat them with low-dose aspirin (Poon et al. 2019; Sotiriadis et al. 2019).

As mentioned before, sFlt-1 and sEng levels are increased in preeclamptic pregnancies. The use of a sEng cut-off has a positive predictive rate of 91%, whereas the ratio of sFlt-1 to placental growth factor (PlGF) value can predict PE four weeks ahead with a high negative predictive value (94.3%) and high sensitivity and specificity (66.2% and 83.1%, respectively) (Wang et al. 2016; Wright and Nicolaides 2019; Zeisler et al. 2019). Low PAPP-A and high free β-hCG values, which were also analysed during the first-trimester maternal serum screening test, were associated with poor pregnancy outcomes, including hypertensive diseases and PE (Cignini, Savasta, et al. 2016; Felicia Sunjaya and Paulo Sunjaya 2019). The placental protein-13 (PP-13) biomarker, which increases 2–3 times in the serum in normal pregnancies, has been found in lower concentrations in patients with PE, and it has been suggested that it can predict the disease 5–7 weeks in advance (Gonen et al. 2008). In addition, alpha-fetoprotein (AFP), VEGF, serum-free PlGF, ADAM-12 and body mass index (BMI) are among the investigated tests.

However, the Nicolaides–Poon's algorithm suggests a screening by a combination of maternal risk factors, UAD, mean arterial pressure, PAPP-A and PlGF to identify about 95% of cases of early-onset PE (Poon and Nicolaides 2014).

In conclusion, the UAD examination and the serologic markers are not routinely used to screen for PE for their low cost-effectiveness ratio. Today, a detailed physical examination and medical history are the most important criteria for determining pregnant women at risk.

Urinary markers

As no longer proteinuria is considered as a diagnostic criteria for PE, the quantity of proteins filtered in the kidneys, represents a critical aspect related to the severity of PE (Guo et al. 2019). Moreover, proteinuria represents a cheap procedure to assess the conditions of glomerular filtration and the metabolic status of the body.

A recent systematic review with meta-analysis found out that inositol phosphoglycans P-type (IPG-P) could identify in advance, up to four weeks before the onset of the disease, early and late-onset PE (Scioscia, Noventa, et al. 2019). Therefore, given the above, it could represent a reliable and low cost urinary screening test (Scioscia, Dekker, et al. 2019).

Management

The only definitive treatment for PE is childbirth. The disease usually regresses within 24–48 hours after delivery. However, timing is important to avoid premature births in planning the delivery. The criteria for determining delivery timing include the severity of PE, gestational week, maternal and foetal conditions. In the initial evaluation, the complete blood count with platelet count, serum creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) values and proteinuria should be tested. Next, ultrasound should be used for assessment of foetal weight, amniotic fluid volume, UAD measurements and

Preeclampsia with severe features

Pregnant women with severe PE are more likely to have maternal and foetal complications. These include pulmonary oedema, renal failure, coagulopathy, myocardial infarction, cerebral haemorrhage, placental abruption, foetal growth restriction and foetal demise (Chappell et al. 2019; Li et al. 2019). Due to the high complication rate, the diagnosis of severe PE is an indication for delivery in $\geq 34 + 0$ weeks pregnancies. In this scenario, delivery should not be postponed to administer steroids for lung maturation (ACOG 2019a). Similarly, delivery in patients with nonviable pregnancies who present severe PE should not be delayed. Expectant management can only be chosen under certain conditions in pregnancies that exceed the viability limit but are less than 34 weeks of gestation. First, the maternal and foetal conditions should be stable. Delivery may be postponed for antenatal corticosteroid administration only in asymptomatic pregnant women with high blood pressure or severe PE laboratory criteria. Maternal hospitalisation should be considered, and laboratory evaluation repeated every six hours. In case of liver function impairment or platelet values continuously decreasing, an emergency delivery should be planned (Sibai et al. 1994; Schiattarella, Riemma, et al. 2021). Expectant management of PE can improve neonatal outcomes even if it does not benefit the mother. Conversely, it is safe and beneficial for the foetus if women are under efficacious antihypertensive drugs and who meet only this criterion (Odendaal et al. 1990). In addition, a Cochrane review of preeclamptic pregnancies managed with expectant approach found that neonatal morbidities such as admission to the intensive care unit were significantly less common (Churchill et al. 2018).

Patients eligible for the expectant approach should be admitted to the hospital and monitored until delivery, and they should receive antenatal corticosteroids. In addition, arterial blood pressure monitoring should be performed at four-hour intervals, and preeclamptic symptoms such as headache, epigastric pain and vision changes should be monitored and promptly recognised. Delivery should be planned in the presence of any of the symptoms mentioned above. Laboratory tests should be repeated at least twice a week. In case of deterioration of the test values, second tests should be performed after 6–12 hours, and delivery is recommended if the creatinine value rises above 1.1 mg/dL or reaches twice the basal value if the thrombocyte count drops to $<$100,000 platelets μL or the liver function tests double the upper limits. Renal function is evaluated by monitoring urine output. Regarding seizure prophylaxis, magnesium sulphate is a valid option. The foetal well-being surveillance considers cardiotocography, biophysical profile, amniotic fluid volume measurement with ultrasound, and foetal growth assessment. In the case of intrauterine growth restriction, the umbilical artery and ductus venosus should be evaluated

Preeclampsia without severe features

Delivery is recommended in pregnant women diagnosed with PE over 37 weeks of gestation, even if there are no signs of severe disease (ACOG 2019a). In the HYPITAT-I randomised controlled, multicentre study, pregnant women with 36–41 weeks of gestation and mild hypertension were examined, and it was found that induction of labour and delivery was associated with a decrease in poor maternal outcomes compared with the expectant approach. No difference in neonatal complications was observed during this period (Vijgen et al. 2010). Following HYPITAT-I study results, long-term follow-up of mildly hypertensive patients who were managed with induction of labour at near term or term showed that obstetric outcomes significantly improve without any harm to mother (Sonnaville et al. 2020). Preterm pregnancies before 34 weeks should be managed with expectant management without severe findings (Mol et al. 2016; ACOG 2019a). According to those above, the morbidities due to preterm delivery are avoided. However, a full consensus cannot be achieved in pregnancies between 34 and 36 weeks. In the case of spontaneous labour, rupture of membranes or placental abruption at $\geq$34 weeks of gestation, delivery should be performed immediately. If these conditions are not present and there are no severe findings, it is a common opinion that expectant management can be carried out until the 37 weeks of gestation with a thorough counselling and a close follow-up. The PHOENIX study, a multicentre randomised controlled trial on late preterm PE (from 34 to less than 37 weeks of gestation), compared planned early delivery ($n = 450$) and expectant management ($n = 451$) and found that poor maternal outcomes reduced but neonatal morbidity increases in those who were subjected to preterm labour (Chappell et al. 2019). However, severe adverse outcomes were similar in both groups.

Careful follow-up is crucial in pregnant women candidates to expectant management. Outpatient follow-up can be performed after informing the patients who do not have severe symptoms. Whether outpatient or inpatient, every patient should have a laboratory assessment at least twice a week and blood pressure measurement should be performed. Likewise, foetal evaluation should be done twice a week. Antenatal steroids should be given if the gestational week is below 34, but delivery should not be postponed for the second dose if severe signs develop. During this period, preterm delivery should be performed if an abnormality in the antepartum assessments is found, in case of preterm prelabour rupture of membranes, vaginal bleeding and severe features.

Intrapartum management

The two most crucial issues in intrapartum management are seizure prophylaxis and control of hypertension.

The most effective and commonly used agent in seizure prophylaxis is magnesium sulphate. Magnesium halves the risk of eclampsia and significantly reduces placental abruption and maternal mortality. However, no difference was found in maternal morbidity and neonatal mortality rates with magnesium sulphate (Magpie Trial Follow-Up Study Collaborative Group 2007). Although prophylaxis is recommended, especially in preeclamptic women with severe symptoms, there is no definite approach in patients without severe features. The risk of eclampsia in severe PE is four times higher when compared to non-severe disease (Magpie Trial Follow-Up Study Collaborative Group 2007). However, magnesium prophylaxis can be given in patients with PE without severe features, depending on the doctor's decision and the patient's clinical condition. Apart from magnesium, drugs such as phenytoin, diazepam or nimodipine can be used in prophylaxis, but none have superiority to magnesium (Duley, Gülmezoglu, et al. 2003). However, they may be offered in diseases such as severe renal failure, myasthenia gravis, cardiac ischaemia where magnesium cannot be used or is contraindicated. Magnesium is contraindicated in myasthenia gravis disease which may trigger a myasthenic crisis. In renal insufficiency, the loading dose of the magnesium can be given, while the maintenance should be reduced. Other side effects may include mild discomforts such as nausea, vomiting, visual disturbances and flushing (Altman et al. 2002). The effective magnesium dose is 4.8–8.4 mg/dL (Sibai 2004). Although its tocolytic effect is controversial, these doses are not thought to cause an interruption of the labour. The toxicity of magnesium appears at increasing doses. First, deep tendon reflexes disappear at values above 9 mg/dL, and a person with positive deep tendon reflexes is unlikely to have reached the toxic dose. Therefore, deep tendon reflex should be monitored in patients with oliguria. If side effects were reported, such as respiratory depression, calcium gluconate or calcium chloride should be given as the antidote to magnesium. In this case, 10 mL of calcium gluconate in a 10% solution is given intravenously in three minutes.

Control of hypertension

Patients with SBP $\geq$160 mmHg and/or DBP $\geq$110 mmHg should receive antihypertensive therapy. The aim is primarily to prevent maternal complications such as stroke. Antihypertensive therapy may be started at lower blood pressure values in people with end organ damage. Target values are 140–150 mmHg for systolic pressure and 90 mmHg for diastolic pressure. Drugs used in emergency blood pressure control are labetalol, hydralazine and nifedipine. Although, any of them can be used, they have no advantage over each other (Cox et al. 2019). Methyldopa, which has been used for many years, has been proven to be highly safe for the foetus, but it is effective only in treating mild hypertension and the onset of its effect is relatively late (within 3–6 hours) (El-Qarmalawi et al. 1995). Labetalol, a combined α blocker and β blocker, may preserve uteroplacental blood flow to a greater extent than β blockers, and its onset of action is

Labetalol	10–20 mg IV, followed by 20–80 mg every 10–20 minutes	Combined α blocker and β blocker	1–2 minutes	Bradycardia	Orally/IV
Hydralazine	5–10 mg IV, followed by 5–10 mg every 20 minutes	Vasodilator	10–20 minutes	Maternal hypotension, reflex tachycardia, fluid retention	IV/IM
Nifedipine (immediate-release)	10–20 mg orally, repeat in every 30 minutes	Calcium channel antagonist	5–10 minutes	Tachycardia, headache	Orally

faster than methyldopa (within two hours) (Molvi et al. 2012; Peacock et al. 2012). Hydralazine is the most commonly used drug in gestational hypertension since it significantly reduces cerebral haemorrhage. Starting with an initial dose of 5–10 mg (IV or IM), it can be repeated every 20 minutes, and the maximum dose is 30 mg. In case of no effect, treatment should be switched to another drug. Of note, it has more maternal side effects such as reflex tachycardia and fluid retention than labetalol and nifedipine (Magee et al. 2003). Nifedipine (immediate release) is used by repeating every 30 minutes after starting 10–20 mg orally, and it should not be used sublingually. ACOG Committee recommends its use as a first-line treatment in acute, severe hypertension in pregnancy or postpartum (ACOG 2019b). Its onset and duration of action are very short, with tachycardia and headache as common side effects. Commonly used antihypertensive drugs are summarised in Table 2.

In a recent randomised controlled trial on the use of nifedipine retard ($n = 298$) vs. labetalol ($n = 295$) vs. methyldopa ($n = 391$) in pregnant women with severe hypertension, blood pressure control within six hours without adverse events was more common in nifedipine group, namely 84%, 76% and 77%, in nifedipine retard, labetalol and methyldopa groups, respectively (Easterling et al. 2019).

Prevention

Nutritional recommendations

An inadequate dietary calcium intake and hypocalcaemia have been associated with an eightfold increase in the risk of PE (Rizzo et al. 2019; Abbasalizadeh et al. 2020). During pregnancy is recommended to take approximately 1000 mg of calcium daily. The WHO recommends 1500–2000 mg of calcium intake per day for malnourished pregnant women, especially those at high risk of PE (World Health Organization 2013). Apart from these, there is no proven agent in PE prophylaxis yet. Anti-hypertensive drugs reduce the severity of hypertension but do not have preventive effects on pregnancy outcomes. They are ineffective in preventing the development of placental abruption, growth restriction, preterm birth and PE (Abalos et al. 2001; Fedullo et al. 2021). There is no clear evidence regarding the use of anticoagulants. However, prophylactic anticoagulants can be used, especially in people with thrombophilic mutations such as factor V Leiden and a history of poor pregnancy outcomes in a previous pregnancy (Karadağ et al. 2020). Vitamin C, vitamin D and vitamin E supplements were also investigated, but no effect on PE has been demonstrated (Basaran et al. 2010; Schiattarella, Lombardo, et al. 2021). Nutritional supplements such as nitric oxide donors, folic acid and fish oil are not helpful. Salt restriction is ineffective, and a salt-free diet is not recommended (Duley et al. 2005). Bed rest and movement restriction are also not recommended; on the contrary, they should be avoided, increasing the risk of thromboembolism (Kasawara et al. 2012).

Prevention of early-onset PE

To date, many studies focussed on preventing PE in those under risk. The most studied treatment option for preventing PE is low-dose (75–150 mg/day) aspirin.

The ASPRE trial identified that a daily dose of 150 mg, commenced before 16 weeks of gestational age, and given at night to a high-risk population, identified by a combined first-trimester screening test, reduces the incidence of early-onset PE up to 60% of cases (Rolnik et al. 2017). Aspirin, a cyclooxygenase inhibitor, inhibits thromboxane synthesis, enhances uteroplacental blood flow, reduces apoptosis. In addition, it has positive effects on endothelial dysfunction and placentation. It also has a positive effect on poor pregnancy outcomes such as preterm labour, intrauterine growth restriction (Bujold et al. 2014).

According to maternal characteristics, several screening models for PE were developed in the past years. Advanced maternal age, increased weight, Afro-Caribbean and South Asian race, history of chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome, family history and personal history of PE, and conception by *in vitro* fertilisation, are critical factors for the assessment of a priori risk for PE (Wright et al. 2015).

Moreover, a combination of maternal characteristics with serum levels of PAPP-A and PlGF, represents an effective first-trimester screening for early-onset PE (O'Gorman et al. 2016).

Given the above, screening by a combination of maternal risk factors, UAD, mean arterial pressure, PAPP-A and PlGF can identify about 95% of cases of early-onset PE (Poon and Nicolaides 2014).

Although there is no consensus on the definition of risk in pregnancy, the criteria specified by ACOG help determine high-risk pregnancies (ACOG 2018).

U.S. Preventive Services Task Force (USPSTF) recommends a low dosage of aspirin (81 mg/d) as preventive medication after 12 weeks of PE high-risk gestation (LeFevre 2014). High risk is defined by one or more of the following factors (LeFevre 2014):

- Multifoetal gestation.
- Chronic hypertension.
- Type 1 or 2 diabetes mellitus.
- Chronic kidney disease.
- Autoimmune disease with potential vascular complications (antiphospholipid syndrome, systemic lupus erythematosus).

Suppose a patient has more than of the moderate risk factors (namely nulliparity, obesity, family history of PE, African American race, low socioeconomic status, age more than 35 years, personal history of low birth weight or small for gestational age, previous adverse pregnancy outcome, or more than 10-year pregnancy interval), in that case, the use of low-dose aspirin may be considered (ACOG 2018).

The indications, dosage and timing for low dosage aspirin differ among national guidelines, and a comparison is shown in Table 3.

The optimal aspirin dose is controversial. A protective effect of aspirin was shown when it was started at 16 week of pregnancy or before (RR, 0.57; 95% CI 0.43–0.75, $p < .001$); conversely, aspirin initiated after 16 weeks of pregnancy was linked with a reduction on protective effect (RR, 0.81, 95% CI 0.66–0.99, $p = .04$) (Roberge et al. 2017).

The World Health Organization (WHO) recommends using 75 mg aspirin per day before the 20 weeks of gestation in high-risk pregnant women (World Health Organization 2011). ACOG recommends 81 mg/d aspirin prophylaxis in high-risk pregnant women from 12 to 28 weeks to delivery (ACOG 2019a).

A comprehensive meta-analysis revealed that the response to aspirin was dose-dependent and at higher doses, aspirin prevented PE at a higher rate (Roberge et al. 2017). From the same team, the 'Aspirin for evidence-based PE Prevention' propose now a daily dose of 150 mg, taken at night beginning at the 16th week of gestation (Rolnik et al. 2020).

Aspirin prophylaxis is not recommended to prevent growth restriction, preterm labour or early pregnancy loss in the absence of PE risk factors (ACOG 2018, 2019a). Randomised controlled studies on the maternal risks of aspirin use during pregnancy demonstrated that low-dose aspirin does not increase haemorrhagic complications, such as placental abruption, postpartum haemorrhage and average blood loss (Duley, Henderson-Smart, et al. 2003; Askie et al. 2007). In addition, low-dose aspirin does not increase foetal congenital anomalies (Ahrens et al. 2016); however, it has been suggested that the risk of gastroschisis may increase with the use of aspirin in the first trimester (OR, not associated with early closure of the ductus arteriosus (Wyatt-Ashmead 2011). Although there is no consensus on when to stop aspirin, the general approach is to use it until delivery (ACOG 2019a). Some centres may prefer stopping aspirin at week 37 or one week before birth to avoid increased bleeding during delivery.

Prevention of late onset preeclampsia

Late-onset PE represents the most prevalent phenotype of this condition and accounts for 90% of cases (Lisonkova et al. 2014); several evidence underlines that late-onset PE is associated with rising maternal pre-pregnancy BMI (Robillard, Dekker, Scioscia, et al. 2019). That late-onset PE (and much less early-onset PE) is largely and specifically linearly associated with rising maternal BMI, which has been recently confirmed in a study from the USA (Bicocca et al. 2020). Further research is urgently required in order to properly understand the main drivers and pathways on how the cardiometabolic syndrome leads to late-onset PE (Scioscia et al. 2015).

Given the above, it is considered a frequent condition in the high-income countries as 90% of PE cases are late-onset, while in medium-low countries, this incidence is lower (60–70%) (Robillard et al. 2016).

Nevertheless, there are no markers that could be considered for the prevention (Erez et al. 2017). In the first trimester, some authors identified, an increase of matrix metalloproteinase 7 (MMP-7) and reduced PlGF levels, as useful predictors for the development of late-onset PE (Erez et al. 2017). Therefore, a prevention could be monitoring the gestational weight gain since the beginning of pregnancy (Robillard et al. 2020a).

A targeted and strictly monitored intervention on achieving an optimal gestational weight could represent an effective method to reduce the rate of late-onset PE (Robillard et al. 2020b). However, it is crucial to determinate the specific linear-curve of optimal gestational weight for each ethnic area (Robillard et al. 2020b).

Prognosis

Preeclampsia improves following childbirth, and diuresis is the best indicator of recovery. Foetal prognosis varies according to the gestational week at birth and is entirely related to prematurity. The risk of PE also increased in the subsequent pregnancy of a woman with PE; this risk is also related to the onset time and severity of PE. The earlier the gestational week of onset and accompanied by severe findings, the higher the risk of recurrence. In addition, women who have a

Table 3. Indication for aspirin for prevention of preeclampsia according to RANZCOG, NICE, USPSTF and ACOG.

	RANZCOG	NICE 2010	USPSTF 2014	ACOG 2018
Indication for aspirin	2 moderate or 1 high risk factor	2 moderate or 1 high risk factor	1 high risk factor	1 high risk factor
Dosage	Unclear	75 mg/d from 12 weeks	81 mg/d optimally before 16 weeks	81 mg/d optimally before 16 weeks
Timing	Until 37 weeks or until delivery	Continue daily until delivery	Continue daily until delivery	Continue daily until delivery

RANZCOG: Royal Australian and New Zealand College of Obstetricians and Gynaecologists; NICE: National Institute for Health and Care Excellence; USPSTF US: Preventive Services Task Force; ACOG: American Congress of Obstetricians and Gynecologists.

ischaemic heart disease, stroke, venous thromboembolism, chronic hypertension and type II diabetes mellitus, renal failure during the rest of their lives (Hernández-Díaz et al. 2009; Magnussen et al. 2009; Mosca et al. 2011; Butticè et al. 2017; Sturlese et al. 2017; Vitale, Fiore, et al. 2022).

Post-partum preeclampsia

Postpartum PE, also known as late postpartum PE, represents a rare condition that develops within 48 hours of childbirth. Sometimes the onset can be delayed up to six weeks or later after childbirth. If left untreated, it could evolve in eclampsia, pulmonary oedema, stroke, thromboembolism or HELLP syndrome. The ACOG guidelines recommend clinic surveillance for at least 72 hours postpartum to identify early signs and symptoms of PE. A follow-up blood pressure check 7–10 days later should be performed (Hypertension in Pregnancy 2013). Emergency treatment is warranted when criteria for severe PE are met. Similarly to antepartum PE, the treatment is based on immediate-release oral nifedipine, mainly when intravenous access is not disposable (ACOG 2019b) and if it is not available, labetalol and hydralazine represent valid choices (ACOG 2019b). Magnesium sulphate is helpful for seizure prophylaxis for high-risk women but is not recommended as an antihypertensive agent (ACOG 2019b).

What about the future?

In 2017, the ACC-AHA Task Force on clinical practice changed the criteria for the diagnosis of first stage hypertension, moving the blood pressure cut-off from 140/90 mmHg to 130/80 mmHg (Hypertension in Pregnancy 2013). Moreover, there is evidence from retrospective studies regarding the possibility using 130/80 mmHg cut off for pregnant women against the actual one (Hauspurg et al. 2019; Hu et al. 2019; Sisti 2019; Sisti et al. 2021). This option could impact the diagnosis and the treatment of PE, but new studies are required (Sisti and Colombi 2019; Sisti and Williams 2019).

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Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. 2001. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews 10: CD002252.

Abbasalizadeh S, Abam F, Mirghafourvand M, Abbasalizadeh F, Taghavi S, Hajizadeh K. 2020. Comparing levels of vitamin D, calcium and phosphorus in normotensive pregnant women and pregnant women with preeclampsia. Journal of Obstetrics and Gynaecology 40: 1069–1073.

ACOG. 2019a. ACOG Practice Bulletin No. 202: gestational hypertension and preeclampsia. Obstetrics & Gynecology 133:e1–e25.

[ACOG]. 2018. ACOG Committee Opinion No. 743: low-dose aspirin use during pregnancy. Obstetrics & Gynecology. 132:e44–e52.

[ACOG]. 2019b. ACOG Committee Opinion No. 767: emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. Obstetrics & Gynecology 133:e174–e180.

Ahrens KA, Silver RM, Mumford SL, Sjaarda LA, Perkins NJ, Wactawski-Wende J, et al. 2016. Complications and safety of preconception low-dose aspirin among women with prior pregnancy losses. Obstetrics and Gynecology 127:689–698.

Ali D-S, Shah M, Ali A, Malik MO, Rehman F, Badshah H, et al. 2019. Treatment with metformin and combination of metformin plus pioglitazone on serum levels of IL-6 and IL-8 in polycystic ovary syndrome: a randomized clinical trial. Hormone and Metabolic Research 51: 714–722.

Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, et al. 2002. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 359:1877–1890.

Arce-Sánchez L, Vitale SG, Flores-Robles CM, Godines-Enriquez MS, Noventa M, Urquia-Figueroa CM, et al. 2021. Effect of the cut-off level for thyroid-stimulating hormone on the prevalence of subclinical hypothyroidism among infertile Mexican women. Diagnostics 11:417.

Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. 2007. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet 369:1791–1798.

Bartsch E, Medcalf KE, Park AL, Ray JG. 2016. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. British Medical Journal (Clinical Research ed.) 353:i1753.

Basaran A, Basaran M, Topatan B. 2010. Combined vitamin C and E supplementation for the prevention of preeclampsia: a systematic review and meta-analysis. Obstetrical & Gynecological Survey 65:653–667.

Bicocca MJ, Mendez-Figueroa H, Chauhan SP, Sibai BM. 2020. Maternal obesity and the risk of early-onset and late-onset hypertensive disorders of pregnancy. Obstetrics and Gynecology 136:118–127.

Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP. 2014. Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: a WHO secondary analysis. PLOS One 9: e91198.

Budak MS, Kahramanoglu I, Vitale SG, Akgol S, Dilek ME, Kartal S, et al. 2019. Maternal abdominal subcutaneous fat thickness as a simple predictor for gestational diabetes mellitus. Journal of Perinatal Medicine 47:605–610.

Bujold E, Roberge S, Nicolaides KH. 2014. Low-dose aspirin for prevention of adverse outcomes related to abnormal placentation. Prenatal Diagnosis 34:642–648.

Burton GJ, Redman CW, Roberts JM, Moffett A. 2019. Pre-eclampsia: pathophysiology and clinical implications. British Medical Journal (Clinical Research ed.) 366:l2381.

Butticè S, Laganà AS, Vitale SG, Netsch C, Tanidir Y, Cantiello F, et al. 2017. Ureteroscopy in pregnant women with complicated colic pain: is there any risk of premature labor? Archivio Italiano di Urologia, Andrologia 89:287–292.

Carr DB, Epplein M, Johnson CO, Easterling TR, Critchlow CW. 2005. A sister's risk: family history as a predictor of preeclampsia. American Journal of Obstetrics and Gynecology 193:965–972.

Chappell LC, Brocklehurst P, Green ME, Hunter R, Hardy P, Juszczak E, et al. 2019. Planned early delivery or expectant management for late

Chen H, Jiang F, Drzymalski D, Chen W, Feng Y, Miao J, et al. 2019. A novel parameter derived from photoplethysmographic pulse wave to distinguish preeclampsia from non-preeclampsia. Pregnancy Hypertension 15:166–170.

Chiofalo B, Laganà AS, Vaiarelli A, La Rosa VL, Rossetti D, Palmara V, et al. 2017. Do miRNAs play a role in fetal growth restriction? A fresh look to a busy corner. BioMed Research International 2017:6073167.

Churchill D, Duley L, Thornton JG, Moussa M, Ali HS, Walker KF. 2018. Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation. The Cochrane Database of Systematic Reviews 10:CD003106.

Cignini P, Laganà AS, Retto A, Vitale SG. 2016. Knotting on heaven's door: 3D color Doppler ultrasound imaging of a true cord knot. Archives of Gynecology and Obstetrics 293:1357–1358.

Cignini P, Savasta LM, Gulino FA, Vitale SG, Mangiafico L, Mesoraca A, Giorlandino C. 2016. Predictive value of pregnancy-associated plasma protein-A (PAPP-A) and free beta-hCG on fetal growth restriction: results of a prospective study. Archives of Gynecology and Obstetrics 293:1227–1233.

Cnossen JS, Morris RK, ter Riet G, Mol BWJ, van der Post JAM, Coomarasamy A, et al. 2008. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. Canadian Medical Association Journal = Journal de L'Association Medicale Canadienne 178:701–711.

Correa PJ, Palmeiro Y, Soto MJ, Ugarte C, Illanes SE. 2016. Etiopathogenesis, prediction, and prevention of preeclampsia. Hypertension in Pregnancy 35:280–294.

Cox AG, Marshall SA, Palmer KR, Wallace EM. 2019. Current and emerging pharmacotherapy for emergency management of preeclampsia. Expert Opinion on Pharmacotherapy 20:701–712.

Cross J, Werb Z, Fisher S. 1994. Implantation and the placenta: key pieces of the development puzzle. Science 266:1508–1518.

Dugoff L, Hobbins JC, Malone FD, Porter TF, Luthy D, Comstock CH, et al. 2004. First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (The FASTER Trial). American Journal of Obstetrics and Gynecology 191:1446–1451.

Duley L, Gülmezoglu AM, Henderson-Smart DJ. 2003. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. Cochrane Database of Systematic Reviews 2:CD000025.

Duley L, Henderson-Smart D, Knight M, King J. 2003. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 1:CD004659.

Duley L, Henderson-Smart DJ, Meher S. 2005. Altered dietary salt for preventing pre-eclampsia, and its complications. Cochrane Database of Systematic Reviews 2005:CD005548.

Easterling T, Mundle S, Bracken H, Parvekar S, Mool S, Magee LA, et al. 2019. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. Lancet 394:1011–1021.

El-Qarmalawi AM, Morsy AH, Al-Fadly A, Obeid A, Hashem M. 1995. Labetalol vs. methyldopa in the treatment of pregnancy-induced hypertension. International Journal of Gynecology & Obstetrics 49: 125–130.

Erez O, Romero R, Maymon E, Chaemsaithong P, Done B, Pacora P, et al. 2017. The prediction of late-onset preeclampsia: results from a longitudinal proteomics study. PLOS One 12: e0181468.

Fedullo AL, Schiattarella A, Morlando M, Raguzzini A, Toti E, De Franciscis P, Peluso I. 2021. Mediterranean diet for the prevention of gestational diabetes in the Covid-19 era: implications of IL-6 in diabesity. International Journal of Molecular Sciences 22:1213.

Felicia Sunjaya A, Paulo Sunjaya A. 2019. Evaluation of serum biomarkers and other diagnostic modalities for early diagnosis of preeclampsia. Journal of Family & Reproductive Health 13:56–69.

Perinatology 31:163–166.

Fox R, Kitt J, Leeson P, Aye CYL, Lewandowski AJ. 2019. Preeclampsia: risk factors, diagnosis, management, and the cardiovascular impact on the offspring. Journal of Clinical Medicine 8:1625.

Galaviz-Hernandez C, Sosa-Macias M, Teran E, Garcia-Ortiz JE, Lazalde-Ramos BP. 2018. Paternal determinants in preeclampsia. Frontiers in Physiology 9:1870.

Giannakou K, Evangelou E, Papatheodorou SI. 2018. Genetic and non-genetic risk factors for pre-eclampsia: umbrella review of systematic reviews and meta-analyses of observational studies. Ultrasound in Obstetrics & Gynecology 51:720–730.

Gonen R, Shahar R, Grimpel YI, Chefetz I, Sammar M, Meiri H, Gibor Y. 2008. Placental protein 13 as an early marker for pre-eclampsia: a prospective longitudinal study. British Journal of Gynecology 115: 1465–1472.

Gormley M, Ona K, Kapidzic M, Garrido-Gomez T, Zdravkovic T, Fisher SJ. 2017. Preeclampsia: novel insights from global RNA profiling of trophoblast subpopulations. American Journal of Obstetrics and Gynecology 217:200.e1–200.e17.

Gui J, Ling Z, Hou X, Fan Y, Xie K, Shen R. 2020. In vitro fertilization is associated with the onset and progression of preeclampsia. Placenta 89:50–57.

Guo H, Zhu Y, Wu C, Zhong M, Hu S. 2019. Potential urine biomarkers for gestational hypertension and preeclampsia. Molecular Medicine Reports 19:2463–2470.

Hauspurg A, Parry S, Mercer BM, Grobman W, Hatfield T, Silver RM, et al. 2019. Blood pressure trajectory and category and risk of hypertensive disorders of pregnancy in nulliparous women. American Journal of Obstetrics and Gynecology 221:277.e1–277–e8.

Hernández-Díaz S, Toh S, Cnattingius S. 2009. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. British Medical Journal (Clinical Research ed.) 338:b2255.

Hu J, Li Y, Zhang B, Zheng T, Li J, Peng Y, et al. 2019. Impact of the 2017 ACC/AHA guideline for high blood pressure on evaluating gestational hypertension-associated risks for newborns and mothers. Circulation Research 125:184–194.

Hutabarat M, Wibowo N, Huppertz B. 2017. The trophoblast survival capacity in preeclampsia. PLOS One 12: e0186909.

Hypertension in Pregnancy. 2013. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstetrics and Gynecology 122:1122–1131.

Iacobaeus C, Kahan T, Jörneskog G, Bremme K, Andolf E, Thorsell M. 2018. Pregnancy-associated plasma protein-A is positively correlated with first-trimester skin microvascular reactivity. Ultrasound in Obstetrics and Gynecology 51:361–367.

Karadağ C, Akar B, Gönenç G, Aslancan R, Yılmaz N, Çalışkan E. 2020. Aspirin, low molecular weight heparin, or both in preventing pregnancy complications in women with recurrent pregnancy loss and factor V Leiden mutation. The Journal of Maternal-Fetal & Neonatal Medicine 33:1934–1939.

Kasawara KT, Nascimento SLD, Costa ML, Surita FG, Silva JLPE. 2012. Exercise and physical activity in the prevention of pre-eclampsia: systematic review. Acta Obstetricia et Gynecologica Scandinavica 91: 1147–1157.

Kozer E, Nikfar S, Costei A, Boskovic R, Nulman I, Koren G. 2002. Aspirin consumption during the first trimester of pregnancy and congenital anomalies: a meta-analysis. American Journal of Obstetrics and Gynecology 187:1623–1630.

Laganà AS, Giordano D, Loddo S, Zoccali G, Vitale SG, Santamaria A, et al. 2017. Decreased endothelial progenitor cells (EPCs) and increased natural killer (NK) cells in peripheral blood as possible early markers of preeclampsia: a case-control analysis. Archives of Gynecology and Obstetrics 295:867–872.

Laganà AS, Vitale SG, Salmeri FM, Triolo O, Ban Frangež H, Vrtačnik-Bokal E, et al. 2017. Unus pro omnibus, omnes pro uno: a novel, evidence-based, unifying theory for the pathogenesis of endometriosis. Medical Hypotheses 103:10–20.

hype? The Journal of Maternal-Fetal & Neonatal Medicine 31:817–821.
LeFevre ML. 2014. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force Recommendation Statement. Annals of Internal Medicine 161: 819–826.
Li J-Y, Wang P-H, Vitale SG, Chen S-N, Marranzano M, Cianci A, et al. 2019. Pregnancy-induced hypertension is an independent risk factor for meconium aspiration syndrome: a retrospective population based cohort study. Taiwanese Journal of Obstetrics and Gynecology 58: 396–400.
Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. 2014. Maternal morbidity associated with early-onset and late-onset preeclampsia. Obstetrics and Gynecology 124:771–781.
Lumbers ER, Delforce SJ, Arthurs AL, Pringle KG. 2019. Causes and consequences of the dysregulated maternal renin–angiotensin system in preeclampsia. Frontiers in Endocrinology 10:563.
Madazli R, Budak E, Calay Z, Aksu MF. 2000. Correlation between placental bed biopsy findings, vascular cell adhesion molecule and fibronectin levels in pre-eclampsia. British Journal of Gynecology 107:514–518.
Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. 2003. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. British Medical Journal (Clinical Research ed.) 327:955–960.
Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. 2009. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. Obstetrics and Gynecology 114:961–970.
Magpie Trial Follow-Up Study Collaborative Group. 2007. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia. Outcome for women at 2 years. British Journal of Gynecology 114:300–309.
Mayrink J, Souza RT, Feitosa FE, Rocha Filho EA, Leite DF, Vettorazzi J, et al. 2019. Incidence and risk factors for preeclampsia in a cohort of healthy nulliparous pregnant women: a nested case-control study. Scientific Reports 9:9517.
Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. 2016. Pre-eclampsia. Lancet 387:999–1011.
Molvi SN, Mir S, Rana VS, Jabeen F, Malik AR. 2012. Role of antihypertensive therapy in mild to moderate pregnancy-induced hypertension: a prospective randomized study comparing labetalol with alpha methyldopa. Archives of Gynecology and Obstetrics 285:1553–1562.
Moore-Maxwell CA, Robboy SJ. 2004. Placental site trophoblastic tumor arising from antecedent molar pregnancy. Gynecologic Oncology 92: 708–712.
Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. 2011. Effectiveness-based guidelines for the prevention of cardiovascular disease in women-2011 update: a guideline from the American Heart Association. Journal of the American College of Cardiology 57:1404–1423.
Myatt L, Clifton RG, Roberts JM, Spong CY, Hauth JC, Varner MW, et al. 2012. The utility of uterine artery Doppler velocimetry in prediction of preeclampsia in a low-risk population. Obstetrics and Gynecology 120(4):815–822.
Newman MG, Robichaux AG, Stedman CM, Jaekle RK, Fontenot MT, Dotson T, Lewis DF. 2003. Perinatal outcomes in preeclampsia that is complicated by massive proteinuria. American Journal of Obstetrics and Gynecology 188:264–268.
Nugent CE, Punch MR, Barr M Jr, LeBlanc L, Johnson MP, Evans MI. 1996. Persistence of partial molar placenta and severe preeclampsia after selective termination in a twin pregnancy. Obstetrics & Gynecology 87:829–831.
O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH. 2016. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11–13 weeks gestation. American Journal of Obstetrics and Gynecology 214: 103.e1–103.e12.
Odendaal HJ, Pattinson RC, Bam R, Grove D, Kotze TJ. 1990. Aggressive or expectant management for patients with severe preeclampsia between 28–34 weeks' gestation: a randomized controlled trial. Obstetrics and Gynecology 76:1070–1075.
tensive crises. The American Journal of Emergency Medicine 30: 981–993.
Phelan LK, Brown MA, Davis GK, Mangos G. 2004. A prospective study of the impact of automated dipstick urinalysis on the diagnosis of preeclampsia. Hypertension in Pregnancy 23:135–142.
Poon LC, Nicolaides KH. 2014. Early prediction of preeclampsia. Obstetrics and Gynecology International 2014:297397.
Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, et al. 2019. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. International Journal of Gynecology & Obstetrics 145:1–33.
Pratt A, Da Silva Costa F, Borg AJ, Kalionis B, Keogh R, Murthi P. 2015. Placenta-derived angiogenic proteins and their contribution to the pathogenesis of preeclampsia. Angiogenesis 18:115–123.
Procopciuc LM, Caracostea G, Zaharie G, Stamatian F. 2014. Maternal/newborn VEGF-C936T interaction and its influence on the risk, severity and prognosis of preeclampsia, as well as on the maternal angiogenic profile. The Journal of Maternal-Fetal & Neonatal Medicine 27: 1754–1760.
Raguema N, Moustadraf S, Bertagnolli M. 2020. Immune and apoptosis mechanisms regulating placental development and vascularization in preeclampsia. Frontiers in Physiology 11:98.
Ridder A, Giorgione V, Khalil A, Thilaganathan B. 2019. Preeclampsia: the relationship between uterine artery blood flow and trophoblast function. International Journal of Molecular Sciences 20:3263.
Rizzo G, Garzon S, Fichera M, Panella MM, Catena U, Schiattarella A, et al. 2019. Vitamin D and gestational diabetes mellitus: is there a link? Antioxidants 8:511.
Roberge S, Bujold E, Nicolaides KH. 2018. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. American Journal of Obstetrics and Gynecology 218:287–293.e1.
Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. 2017. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. American Journal of Obstetrics and Gynecology 216:110–120.e6.
Robillard P-Y, Dekker G, Boukerrou M, Boumahni B, Hulsey T, Scioscia M. 2020a. Gestational weight gain and rate of late-onset preeclampsia: a retrospective analysis on 57 000 singleton pregnancies in Reunion Island. BMJ Open 10: e036549.
Robillard P-Y, Dekker G, Chaouat G, Elliot MG, Scioscia M. 2019. High incidence of early onset preeclampsia is probably the rule and not the exception worldwide. 20th anniversary of the reunion workshop. A summary. Journal of Reproductive Immunology 133:30–36.
Robillard P-Y, Dekker G, Iacobelli S, Chaouat G. 2016. An essay of reflection: why does preeclampsia exist in humans, and why are there such huge geographical differences in epidemiology? Journal of Reproductive Immunology 114:44–47.
Robillard P-Y, Dekker G, Scioscia M, Bonsante F, Iacobelli S, Boukerrou M, Hulsey TC. 2019. Increased BMI has a linear association with late-onset preeclampsia: a population-based study. PLOS One 14: e0223888.
Robillard P-Y, Dekker G, Boukerrou M, Boumahni B, Hulsey T, Scioscia M. 2020b. The urgent need to optimize gestational weight in overweight/obese women to lower maternal–fetal morbidities: a retrospective analysis on 59,000 singleton term pregnancies. Archives of Women Health and Care 3:1–9.
Rolnik DL, Nicolaides KH, Poon LC. 2020. Prevention of preeclampsia with aspirin. American Journal of Obstetrics and Gynecology 9378: 30873–30875.
Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, et al. 2017. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. The New England Journal of Medicine 377:613–622.
Rye K-A, Barter PJ, Cochran BJ. 2016. Apolipoprotein A–I interactions with insulin secretion and production. Current Opinion in Lipidology 27:8–13.
Salimi S, Yaghmaei M, Tabatabaei E, Mokhtari M, Naghavi A. 2015. Vascular endothelial growth factor (VEGF)-634G/C polymorphism was

Salman H, Shah M, Ali A, Aziz A, Vitale SG. 2018. Assessment of relationship of serum neurokinin-B level in the pathophysiology of pre-eclampsia: a case-control study. Advances in Therapy 35:1114–1121.

Schiattarella A, Lombardo M, Morlando M, Rizzo G. 2021. The impact of a plant-based diet on gestational diabetes: a review. Antioxidants 10: 557.

Schiattarella A, Riemma G, Sisti G, Savoia F, Rapisarda A, De Franciscis P, Morlando M. 2021. Efficacy of phloroglucinol in shortening the first stage of labor: systematic review and meta-analysis of randomized controlled trials. The Journal of Maternal-Fetal & Neonatal Medicine 2021:1–7.

Scioscia M, Dekker GA, Chaouat G, Dawonauth L, Dechend R, Goldman-Wohl D, et al. 2019. A top priority in pre-eclampsia research: development of a reliable and inexpensive urinary screening test. The Lancet. Global Health 7:e1312–e1313.

Scioscia M, Karumanchi SA, Goldman-Wohl D, Robillard P-Y. 2015. Endothelial dysfunction and metabolic syndrome in preeclampsia: an alternative viewpoint. Journal of Reproductive Immunology 108:42–47.

Scioscia M, Noventa M, Cavallin F, Straface G, Pontrelli G, Fattizzi N, et al. 2019. Exploring strengths and limits of urinary D-chiro inositol phosphoglycans (IPG-P) as a screening test for preeclampsia: a systematic review and meta-analysis. Journal of Reproductive Immunology 134–135:21–27.

Sibai BM. 2004. Magnesium sulfate prophylaxis in preeclampsia: lessons learned from recent trials. American Journal of Obstetrics and Gynecology 190:1520–1526.

Sibai BM, Mercer BM, Schiff E, Friedman SA. 1994. Aggressive versus expectant management of severe preeclampsia at 28 to 32 weeks' gestation: a randomized controlled trial. American Journal of Obstetrics and Gynecology 171:818–822.

Silasi M, Cohen B, Karumanchi SA, Rana S. 2010. Abnormal placentation, angiogenic factors, and the pathogenesis of preeclampsia. Obstetrics and Gynecology Clinics of North America 37:239–253.

Silva VRS, Soardi FC, Tanaka SCSV, da Silva-Grecco RL, Paschoini MC, Balarin MAS. 2015. Investigation of polymorphisms in pre-eclampsia related genes VEGF and IL1A. Archives of Gynecology and Obstetrics 291:1029–1035.

Sisti G. 2019. Maternal outcomes associated with lower range stage 1 hypertension. Obstetrics and Gynecology 133:190.

Sisti G, Colombi I. 2019. New blood pressure cut off for preeclampsia definition: 130/80 mmHg. European Journal of Obstetrics, Gynecology, and Reproductive Biology 240:322–324.

Sisti G, Schiattarella A, Morlando M, Corwin A. 2021. Timing of delivery and blood pressure cut-off in chronic hypertension during pregnancy: state of art and new proposals. International Journal of Gynaecology and Obstetrics.

Sisti G, Williams B. 2019. Body of evidence in favor of adopting 130/80 mm Hg as new blood pressure cut-off for all the hypertensive disorders of pregnancy. Medicina 55:703.

Skjaerven R, Vatten LJ, Wilcox AJ, Rønning T, Irgens LM, Lie RT. 2005. Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort. British Medical Journal (Clinical Research ed.) 331:877.

Sonnaville CMW, Hukkelhoven CW, Vlemmix F, Groen H, Schutte JM, Mol BW, Pampus MG. 2020. Impact of hypertension and preeclampsia intervention trial at near term-I (HYPITAT-I) on obstetric management and outcome in The Netherlands. Ultrasound in Obstetrics & Gynecology 55:58–67.

Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, Ghi T, Glanc P, Khalil A, et al. 2019. ISUOG practice guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia. Ultrasound in Obstetrics & Gynecology 53:7–22.

Sturlese E, Triolo O, Grasso R, Laganà AS, Retto A, Rossetti D, et al. 2017. Thromboembolism prophylaxis in laparoscopic surgery for gynecologic benign diseases. Results of a single center experience in 922 procedures. Annali Italiani di Chirurgia 88:342–347.

333–347.

Tan MY, Syngelaki A, Poon LC, Rolnik DL, O'Gorman N, Delgado JL, et al. 2018. Screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation. Ultrasound in Obstetrics & Gynecology 52: 186–195.

Tannetta DS, Dragovic RA, Gardiner C, Redman CW, Sargent IL. 2013. Characterisation of syncytiotrophoblast vesicles in normal pregnancy and pre-eclampsia: expression of Flt-1 and endoglin. PLOS One 8: e56754.

Torella M, Bellini G, Punzo F, Argenziano M, Schiattarella A, Labriola D, et al. 2019. TNF-α effect on human delivery onset by CB1/TRPV1 cross-talk: new insights into endocannabinoid molecular signaling in preterm vs. term labor. Analysis of the EC/EV pathway and predictive biomarkers for early diagnosis of preterm delivery. Minerva Ginecologica 71:359–364.

Tranquilli AL, Brown MA, Zeeman GG, Dekker G, Sibai BM. 2013. The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Pregnancy Hypertension 3:44–47.

Vaka VR, Cunningham MW, Deer E, Franks M, Ibrahim T, Amaral LM, et al. 2020. Blockade of endogenous angiotensin II type I receptor agonistic autoantibody activity improves mitochondrial reactive oxygen species and hypertension in a rat model of preeclampsia. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology 318: R256–R262.

Vetvicka V, Laganà AS, Salmeri FM, Triolo O, Palmara VI, Vitale SG, et al. 2016. Regulation of apoptotic pathways during endometriosis: from the molecular basis to the future perspectives. Archives of Gynecology and Obstetrics 294:897–904.

Vijgen SMC, Koopmans CM, Opmeer BC, Groen H, Bijlenga D, Aarnoudse JG, et al. 2010. An economic analysis of induction of labour and expectant monitoring in women with gestational hypertension or pre-eclampsia at term (HYPITAT trial). British Journal of Gynecology 117: 1577–1585.

Villa PM, Marttinen P, Gillberg J, Lokki AI, Majander K, Ordén M-R, et al. 2017. Cluster analysis to estimate the risk of preeclampsia in the high-risk Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) study. PLOS One 12:e0174399.

Vitale SG, Capriglione S, Peterlunger I, La Rosa VL, Vitagliano A, Noventa M, et al. 2018. The role of oxidative stress and membrane transport systems during endometriosis: a fresh look at a busy corner. Oxidative Medicine and Cellular Longevity 2018:7924021.

Vitale SG, Corrado F, Caruso S, Di Benedetto A, Giunta L, Cianci A, D'Anna R. 2021. Myo-inositol supplementation to prevent gestational diabetes in overweight non-obese women: bioelectrical impedance analysis, metabolic aspects, obstetric and neonatal outcomes – a randomized and open-label, placebo-controlled clinical trial. International Journal of Food Sciences and Nutrition 72:670–679.

Vitale SG, Fiore M, La Rosa VL, Rapisarda AMC, Mazza G, Paratore M, et al. 2022. Liposomal ferric pyrophosphate and ascorbic acid supplementation in pregnant women with iron deficiency anaemia: haematochemical, obstetric, neonatal and psychological outcomes in a prospective observational study. International Journal of Food Sciences and Nutrition 73:221–229.

Vitale SG, Marilli I, Rapisarda AM, Iapichino V, Stancanelli F, Cianci A. 2015. Diagnosis, antenatal surveillance and management of prolonged pregnancy: current perspectives. Minerva Ginecologica 67:365–373.

Vitale SG, Marilli I, Rapisarda AM, Rossetti D, Belluomo G, Iapichino V, et al. 2014. Cellular and biochemical mechanisms, risk factors and management of preterm birth: state of the art. Minerva Ginecologica 66:589–595.

Wang J, Dong X, Wu H, Wu N, Zhang X, Wang X, Shang L. 2016. Relationship of liver X receptors α and endoglin levels in serum and placenta with preeclampsia. PLOS One 11:e0163742.

Watanabe N, Fujiwara T, Suzuki T, Jwa SC, Taniguchi K, Yamanobe Y, et al. 2014. Is in vitro fertilization associated with preeclampsia? A propensity score matched study. BMC Pregnancy and Childbirth 14:69.

World Health Organization. 2011. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia [online]. Available from: http://apps.who.int/iris/bitstream/10665/44703/1/9789241548335_eng.pdf

World Health Organization. 2013. Guideline: calcium supplementation in pregnant women. https://apps.who.int/iris/handle/10665/85120

Wright D, Nicolaides KH. 2019. Aspirin delays the development of preeclampsia. American Journal of Obstetrics and Gynecology 220: 580.e1–580.e6.

Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. 2015. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. American Journal of Obstetrics and Gynecology 213:62.e1–62.e10.

Wyatt-Ashmead J. 2011. Antenatal closure of the ductus arteriosus and hydrops fetalis. Pediatric and Developmental Pathology 14:469–474.

ratio: ruling out pre-eclampsia for up to 4 weeks and value of retesting. Ultrasound in Obstetrics & Gynecology 53:367–375.

Zhang P. 2021. Phenotypic switch of endovascular trophoblasts in decidual vasculopathy with implication for preeclampsia and other pregnancy complications. Fetal and Pediatric Pathology 40:543–520.

Zhou Y, Damsky CH, Fisher SJ. 1997. Preeclampsia is associated with failure of human cytotrophoblasts to mimic a vascular adhesion phenotype. One cause of defective endovascular invasion in this syndrome? The Journal of Clinical Investigation 99:2152–2164.

Zhou Y, Gormley MJ, Hunkapiller NM, Kapidzic M, Stolyarov Y, Feng V, et al. 2013. Reversal of gene dysregulation in cultured cytotrophoblasts reveals possible causes of preeclampsia. The Journal of Clinical Investigation 123:2862–2872.