ORIGINAL RESEARCH ARTICLE

Challenges in Diagnosis and Risk Factors of Preeclampsia and HELLP Syndrome

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Keywords: Pre-eclampsia, HELLP syndrome, Pregnancy, Obstetric complications, Gestational hypertension.

ABSTRACT

Introduction: Preeclampsia and HELLP syndrome are serious complications of pregnancy associated with high rates of maternal and fetal morbidity and mortality. These conditions pose diagnostic challenges due to the variability of their symptoms and the complexity of risk factors, compromising early identification and appropriate management.

Methods: The study used a literature review. Data analysis prioritised identifying gaps in diagnostic protocols and the relevance of identified risk factors.

Results: The results indicated that the absence of specific symptoms in the early stages, such as oedema and mild hypertension, makes it difficult to identify preeclampsia. In addition, HELLP syndrome presents nonspecific symptoms, such as epigastric pain and nausea, which are often confused with other conditions. The variability in diagnostic criteria, especially the absence of proteinuria in some cases, aggravates the problem. Regarding risk factors, the most important are family history, pre-existing conditions such as chronic hypertension and obesity, and individual characteristics, such as advanced maternal age and multiple pregnancy.

Conclusion: The complexity of these conditions requires a multidisciplinary and ongoing approach. Preventive strategies, such as the use of low-dose aspirin and calcium supplementation, have been shown to be effective in reducing complications. In addition, improvements in access to diagnostic technologies and the implementation of uniform clinical protocols are essential to reduce the impacts of preeclampsia and HELLP syndrome.

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What do we already know about this topic?
Preeclampsia and HELLP syndrome are serious obstetric conditions that pose significant challenges in clinical practice due to their variable presentation and high risk of maternal and fetal complications. Studies indicate that preeclampsia is associated with endothelial dysfunction and systemic inflammation, and may progress to HELLP syndrome, characterized by hemolysis, elevated liver enzymes, and low platelet counts. Early identification of risk factors is essential to improve the management of these conditions. A review published in BMJ Open highlights the importance of prognostic models to predict adverse maternal outcomes in patients with preeclampsia. In addition, research indicates that HELLP syndrome may occur in 10–20% of cases of severe preeclampsia, requiring close monitoring during pregnancy.Diagnosis of these conditions remains challenging, as symptoms can be nonspecific and vary between patients. A recent review addresses advances in the diagnosis, treatment and prognosis of HELLP syndrome, reinforcing the need for effective strategies to reduce maternal and neonatal morbidity and mortality

What is the main contribution to Evidence-Based Practice from this article?
The article "Challenges in Diagnosis and Risk Factors of Preeclampsia and HELLP Syndrome" contributes significantly to evidence-based practice by providing an in-depth analysis of the diagnostic challenges and risk factors for these serious obstetric conditions.
The research highlights the need to improve methods for early identification of preeclampsia and HELLP syndrome, allowing for more effective interventions and reducing maternal and fetal complications. In addition, the article explores recent advances in biomarkers and imaging techniques that can improve diagnostic accuracy, assisting clinicians in making informed clinical decisions.Another relevant aspect is the discussion of evidence-based management strategies, including treatment protocols that can optimize maternal and neonatal outcomes. This information is essential for healthcare professionals who manage high-risk pregnancies, helping to reduce morbidity and mortality associated with these conditions.

What are this research's implications towards health policy?
The article "Challenges in Diagnosis and Risk Factors of Preeclampsia and HELLP Syndrome" has important implications for theory, clinical practice and public health policies, contributing to the advancement of maternal-fetal medicine and the improvement of obstetric care protocols.In the theoretical field, the research deepens knowledge about the pathophysiological mechanisms of preeclampsia and HELLP syndrome, analyzing genetic, environmental and behavioral factors that influence the development of these conditions. Research on emerging biomarkers and early diagnosis strategies also strengthens epidemiological models, enabling future studies aimed at more effective interventions.In clinical practice, the article highlights challenges in the diagnosis of these syndromes, emphasizing the importance of more refined protocols for early identification. The research suggests approaches that can optimize the management of high-risk pregnancies, helping in medical decision-making to avoid serious complications. In addition, by discussing evidence-based strategies, the study guides health professionals on practices that can improve maternal and fetal outcomes.In the context of health policies, the article reinforces the need for more rigorous prenatal screening and monitoring programs, ensuring that pregnant women with risk factors are adequately monitored. In addition, it highlights the importance of medical training to improve the recognition and clinical management of these syndromes, influencing government guidelines aimed at reducing maternal and neonatal morbidity and mortality. The study can also support investments in research and new technologies, favoring the development of more accurate diagnostic methods and effective treatments.By integrating theory, practice and health policies, this article becomes an essential reference for professionals in the obstetric field and health authorities, contributing to more qualified care for pregnant women and to reducing the impacts of these conditions on maternal and child health.
Authors' Contributions Statement:
Naddeo, Marcelo Lopes da Cruz was the sole author of the article, doing all the writing.

The physiological state of pregnancy can result in direct and indirect alterations in hematologic indices. Although many of these alterations are normal and necessary, pregnancy can predispose women to certain hematologic disorders and exacerbate preexisting conditions, resulting in increased maternal and fetal morbidity and mortality. Conditions such as iron deficiency anaemia, thrombocytopenia, and bleeding disorders can increase the risk of preterm birth, fetal growth restriction, and postpartum haemorrhage. The estimated prevalence of anaemia in pregnancy ranges from 17% to 31% in Europe and North America and up to 44%–61% in Southeast Asia and Africa (Karami, Chaleshgar, Salari, Akbari, & Mohammadi, 2022). The most common hematologic complication in pregnancy is iron deficiency anaemia, followed by thrombocytopenia, affecting 7%–12% of all pregnancies (Karami, Chaleshgar, Salari, Akbari, & Mohammadi, 2022). Although hematologic conditions are common in pregnancy and associated with adverse outcomes, there are

limited data on risk factors, assessment, management, and treatment (WHO, 2001). This is because pregnant women are often excluded from clinical trials, so assessment and treatment of hematologic complications are often extrapolated from nonpregnant populations.

Pre-eclampsia (PE) and Hemolysis, Elevated Liver Enzyme, and Low Platelet Count (HELLP) syndrome are serious obstetric conditions that can significantly compromise the health of the pregnant woman and fetus. PE is a multisystem disorder that typically affects 2% to 5% of pregnant women and is a major cause of maternal and perinatal morbidity and mortality, especially when the condition has an early onset. When it begins after 20 weeks of gestation or within 6 weeks postpartum, it is usually associated with at least one other manifestation, including thrombocytopenia, impaired liver function or injury, new-onset renal failure, pulmonary oedema, and cerebral or visual disturbances (Stein & Martin, 2019). PE is characterised by arterial hypertension (AH) associated with endothelial dysfunction and organ damage, and in extreme cases, the condition can progress to eclampsia, involving maternal seizures and increasing the risk of morbidity and mortality. Persistent hypertension is defined as systolic blood pressures greater than 160 mmHg or diastolic blood pressures greater than 110 mmHg during pregnancy (ACOG, 2019).

Thrombocytopenia is present in half of patients with PE, and signs of low platelets and elevated liver enzymes may occur before symptoms of headache, proteinuria, and elevated blood pressures, leading to delays in diagnosis and treatment (Stein & Martin, 2019). Patients with PE are categorised as those with or without severe features. The presence of proteinuria (urine collection of 300 mg/24 h) defines PE without severe features. Severe features may present as new-onset thrombocytopenia (<100 × 109/L), impaired liver function (twice the upper limit of normal), renal insufficiency (serum creatinine >1.1 mg/dL or doubling of serum creatinine concentration), and evidence of pulmonary edema or new-onset headache unresponsive to medication (American College of Obstetricians and Gynecologists, 2020). Women with any of these high-risk features should receive aspirin (81 mg/day) initiated between 12 and 28 weeks of gestation and continued until delivery. Delivery rather than expectant management is recommended at 37 weeks of gestation or beyond. If delivery is indicated at less than 34 weeks of gestation, administration of corticosteroids for fetal lung maturation is recommended. Management is directed at preventing seizures and controlling AH. Magnesium sulfate is the mainstay of treatment to prevent seizures in women with PE with severe features. However, there is no consensus on the prophylactic use of magnesium sulfate for the prevention of seizures. The goal of treatment for severe hypertension is to prevent congestive heart failure (CHF), renal injury or failure, and ischemic or hemorrhagic stroke, and antihypertensive therapy is recommended (ACOG, 2019). For gestational hypertension or PE without severe features, vaginal delivery is preferred. For PE with severe features, vaginal delivery is possible but is less likely with decreasing gestational age at diagnosis (ACOG, 2019).

Globally, 76,000 women and 500,000 infants die each year from this disorder. Furthermore, women in resource-poor countries are at higher risk of developing PE compared to those in resource-rich countries.

In Brazil, PE has an estimated prevalence of 6.7% of pregnancies, with significant regional variations due to socioeconomic factors and unequal access to health services. The

condition is one of the main causes of maternal mortality in the country, accounting for approximately 25% of registered maternal deaths. The north and northeast regions have high maternal mortality rates associated with PE, due to the difficulty in accessing specialised care and limited infrastructure (Brown et al., 2018). The estimate for the coming years suggests that, without significant interventions, the prevalence may remain high, especially in rural and isolated areas. The south and southeast regions have better medical resources and infrastructure, resulting in lower maternal mortality rates. However, the prevalence of PE is still significant in vulnerable populations, such as low-income pregnant women. For the coming years, it is expected that the prevalence of PE in Brazil can be reduced with the expansion of access to quality prenatal care, health education, and public policies aimed at reducing regional inequalities. Implementation of early surveillance and diagnosis programs will be essential to improve maternal and neonatal outcomes (Brown et al., 2018).

The pathogenesis of PE is not yet fully understood, but there is a two-stage process that can be understood to explain PE. The first stage is caused by superficial invasion of the trophoblast, resulting in inadequate remodelling of the spiral arteries (FIGO, 2019). This is presumed to lead to the second stage, which involves the maternal response to endothelial dysfunction and the imbalance between angiogenic and antiangiogenic factors, resulting in the clinical features of the disease (Brown et al., 2018).

PE can be subclassified into: early-onset PE (with delivery at <34 +0 weeks of gestation); preterm PE (with delivery at <37 +0 weeks of gestation); late-onset PE (with delivery at ⩾34 +0 weeks of gestation); and term PE (with delivery at ⩾37 +0 weeks of gestation). These subclassifications are not mutually exclusive. Early-onset PE is associated with a much higher risk of short- and long-term maternal and perinatal morbidity and mortality (Brown et al., 2018). Women who have suffered from PE may also face additional health problems in later life, as the condition is associated with an increased risk of death from future cardiovascular disease (CVD), hypertension, cerebrovadcular acidente (CVA), renal failure, metabolic syndrome (MS), and diabetes (DM). The life expectancy of women who develop premature PE is reduced by an average of 10 years. To prevent all potential complications, some measures should be taken, such as universal screening where all pregnant women should be screened for premature PE during early pregnancy by a first-trimester combined test with maternal risk factors and biomarkers, as a one-step procedure. FIGO encourages all countries and their member associations to adopt and promote strategies to ensure this (Brown et al., 2018). The best combined test is one that includes maternal risk factors, mean arterial pressure (MAP), serum placental growth factor (PLGF), and uterine artery pulsatility index (UTPI). When PLGF and/or UTPI cannot be measured, the baseline screening test should be a combination of maternal risk factors with MAP, not maternal risk factors alone. If maternal serum pregnancy-associated plasma protein-A (PAPP-A) is measured for routine first-trimester screening for fetal aneuploidy, the result can be included in the PE risk assessment. Variations in the complete combined test would lead to reduced screening performance. A woman is considered at high risk when the risk is 1 in 100 based on the first-trimester combined test with maternal risk factors, MAP, PLGF, and UTPI. Contingent screening, when resources are limited, can consider routine screening for premature PE by

maternal factors and MAP in all pregnancies and reserve PLGF and UTPI measurements for a subgroup of the population, selected based on the risk derived from screening by maternal factors and MAP (Brown et al., 2018).

Methodology

The diagnosis of PE and HELLP syndrome is fraught with clinical and laboratory challenges that can hinder early identification and appropriate management of these potentially serious conditions. Both are associated with pregnancy and involve significant risks to maternal and fetal health, requiring multidisciplinary care and well-defined criteria to avoid complications.

Challenges in Diagnosing Preeclampsia

The major challenges in diagnosing PE lie in the symptoms, which may be nonspecific or even absent in the early stages. PE may begin with subtle changes, such as swelling, mild increase in blood pressure, or malaise, which are often considered normal during pregnancy. This can lead to an underestimation of clinical signs, delaying diagnosis. Although proteinuria is a classic indicator, it is not present in all cases, especially in more severe PE. This requires physicians to rely on other criteria, such as liver dysfunction, changes in blood tests, or signs of neurological impairment. Preexisting diseases such as DM, chronic hypertension, or obesity may mask or intensify the symptoms of PE, making it difficult to distinguish between conditions aggravated by pregnancy and PE itself. In some patients, PE can rapidly progress to more serious conditions, such as eclampsia (seizures) or HELLP syndrome. The absence of clear warning signs makes early identification difficult (Poon et al., 2019).

Challenges in Diagnosing HELLP Syndrome

Regarding HELLP syndrome, it can occur without the presence of some typical symptoms and signs, such as hypertension. Between 15% and 30% of patients with HELLP do not have significant hypertension, which can lead health professionals to ignore the possibility of this condition in its early stages. HELLP symptoms, such as epigastric pain, nausea, vomiting and fatigue, can be confused with gastritis, hepatitis or other diseases, making differentiation difficult. This similarity can delay diagnosis and treatment. The diagnosis of HELLP depends on laboratory tests that identify hemolysis, changes in liver enzymes and low platelet count. These tests are not always available promptly, especially in remote areas or with limited resources. Although HELLP usually occurs during pregnancy, there are cases in which symptoms develop after delivery, making it difficult to immediately connect with gestational complications and delaying treatment (Poon et al., 2019). Difficulty in diagnosing these conditions can lead to delays in proper management, increasing the risk of serious complications such as liver failure, haemorrhages, kidney dysfunction and even maternal and fetal mortality.

Risk Factors

There are several maternal risk factors that are associated with the development of PE, such as advanced maternal age, nulliparity, prior history of PE, short and long interpregnancy intervals, use of assisted reproductive technologies, family history of PE, obesity, Afro-Caribbean and South Asian racial origin, comorbid medical conditions including hyperglycemia in pregnancy, pre-existing

chronic hypertension, renal disease, autoimmune diseases such as systemic lupus erythematosus and antiphospholipid syndrome. These risk factors have been described by several professional organizations for the identification of women at risk for PE; however, this screening approach is inadequate for effective prediction of PE (Poon et al., 2019).

Maternal age

Advanced maternal age, defined as age ⩾ 35 years at delivery, is associated with a 1.2- to 3-fold increased risk of developing PE. The predictive probability of PE increases when maternal age is > 35 years, and the probability increases even more rapidly when maternal age is > 40 years. One study evaluated the risk associated with maternal age according to the severity of PE. Using multivariate logistic regression analysis, adjusting for confounders, the risk of late-onset PE was shown to increase by 4% with each 1-year increase in maternal age above 32 years. However, maternal age was not associated with an increased risk of early-onset PE (Poon et al., 2019).

Pregnancy interval

Short and long interpregnancy intervals are associated with an increased risk of PE. A recent study reported that interpregnancy intervals of <12 months or >72 months are associated with a higher risk of developing PE compared with interpregnancy intervals of 12 to 23 months. It was observed that the longer the interval, the higher the risk of developing PE. The reasons for the association between short interpregnancy interval and PE are unclear, but several hypotheses have been proposed, including factors related to socioeconomic status, postpartum stress, malnutrition, and inadequate access to health services. Meanwhile, the increased risk of PE in women with long interpregnancy intervals may be attributed to advanced maternal age, infertility, and underlying maternal medical conditions (Poon et al., 2019).

Assisted reproduction

Several studies have reported that the use of assisted reproductive technologies (ART) doubles the risk of PE. In one cohort study, the risk of PE was increased in women exposed to hyperestrogenic ovarian stimulation drugs, regardless of the type of ART, compared with those who conceived spontaneously. Women who conceive by intrauterine insemination, particularly with donor sperm, are at increased risk of developing PE. Those who have undergone in vitro fertilisation (IVF) with a donor egg appear to have a higher risk of PE than those who have had IVF with an autologous egg. Evidence from IVF pregnancies with egg donation suggests that there are alterations in the extravillous trophoblast and immunological alterations in the decidua basalis, which may prevent modification of the spiral arteries (Roberge et al., 2017).

Family history of PE

Although most cases of PE are sporadic, a familial susceptibility to PE has been documented. Daughters or sisters of women with PE are 3 to 4 times more likely to develop the condition than women with no family history. The mode of inheritance appears to be complex, including numerous variants, which individually have small effects but collectively contribute to an individual's susceptibility to the disorder. Genome-wide association studies (GWAS) using sib-pair analysis have identified

plausible, yet conflicting, positional candidate genes for maternal susceptibility to PE. GWAS of families affected by PE have demonstrated significant linkage to chromosomes 2p, 2q, 4p, 7p, 9p, 10q, 11q, and 22q. However, no other studies have replicated these significant or suggestive loci (Roberge et al., 2017).

Race and ethnicity

There is ample evidence in the literature demonstrating the association between race and ethnicity and PE. Large population-based studies suggest that the risk of PE in Afro-Caribbean women is increased by 20%–50 %. The risk of PE is also higher in women of South Asian origin than in those of non-Hispanic white women. The increased risk of PE reflects the metabolic profiles of non-pregnant women associated with an increased susceptibility to cardiovascular disease. Both Afro-Caribbean and South Asian women are more susceptible to developing chronic hypertension, DM, and CVD. In a large prospective observational cohort study of over 79,000 singleton pregnancies recruited in London, UK, the risk of PE was significantly higher in women of African-Caribbean and South Asian racial origins compared with white women. The increased risk remains significant even after adjustment for other confounding risk factors for PE (Rondeau et al., 2022).

Uteroplacental ischemia

The main disease mechanism implicated in the aetiology of PE is uteroplacental ischemia. The cause of placental ischemia in women with PE may be a defect in placentation leading to ischemia, but more recently, a dysfunctional maternal cardiovascular system has been implicated (Melchiorre, Giorgione, & Thilaganathan, 2022).

The case for ischemia as an etiologic factor would be even more convincing if treatment of ischemia could prevent PE. Such evidence is difficult to generate in pregnant women. However, it could be argued that the efficacy of aspirin in reducing the rate of preterm PE is achieved through prevention of arterial thrombosis in the spiral arteries and intervillous space, since this is the proposed mechanism for aspirin in preventing myocardial infarction in atherosclerosis. This interpretation would also explain the lack of efficacy of aspirin in preventing preeclampsia at term, since ischemia appears to play a minor role (Melchiorre, Giorgione, & Thilaganathan, 2022).

Maternal infection

Maternal infection has been implicated in the aetiology of PE since the early 20th century. One study proposed that the "toxins" responsible for eclampsia were the product of putrefactive changes in the uterine cavity caused by the action of bacteria ("a latent microbial endometritis"). Indeed, a microorganism, Bacillus eclampsiae, was proposed as the cause. This view has progressively fallen into disuse because PE and eclampsia do not present the typical features, e.g. fever, of an infectious disease. However, the idea that microorganisms may be involved in the genesis of PE and eclampsia recurs in the literature every few years and has recently resurfaced based on the relationship between periodontal disease, urinary tract infection, SARS-Cov-2 infection and maternal intestinal dysbiosis (Sen et al., 2021).

Periodontal disease

It refers to an inflammatory condition caused by immune dysfunction initiated by bacteria within the oral cavity (Sen et al., 2021). The

spectrum of the disease ranges from gingivitis (inflammation of soft tissues only) to destruction of the connective tissue attachment and alveolar bone, which can eventually lead to tooth loss. Bacteria in the periodontal space can be released during dental procedures or in the course of severe disease, leading to a systemic inflammatory response that can cause damage and seed sites in the cardiovascular system. Indeed, strong evidence indicates that periodontal disease is a risk factor for atherosclerotic cardiovascular diseases, including atherosclerosis, coronary artery disease, stroke, and atrial fibrillation (Sen et al., 2021). In summary, such evidence denotes that 1) microorganisms found in the periodontal space can cause bacteremia; 2) oral cavity bacteria have been found in atheromatous plaques; and 3) periodontal infections can induce vascular lesions in the aorta and coronary arteries.

Urinary tract infectio

The relationship between microbial colonisation of the maternal urinary tract and PE has also been reported. A systematic review noted that urinary tract infections are associated with PE, such as pyelonephritis, lower urinary tract infections, and asymptomatic bacteriuria as a group. When subgroup analysis is performed, the evidence for the association with PE weakens or disappears. We have doubts that asymptomatic bacteriuria, which is not associated with a systemic inflammatory response, can cause PE (Sen et al., 2021).
Bacterial endotoxin is a method used to induce a systemic inflammatory response and thrombin activation through the release of tissue factor. These mechanisms are implicated in the pathogenesis of PE (Sen et al., 2021).

SARS-CoV-2 infection

Early in the COVID-19 pandemic, it was recognised that a subset of non-pregnant patients developed AH, proteinuria, thrombocytopenia, and elevated liver enzymes, which resemble preeclampsia and hemolysis, elevated liver enzymes, and HELLP syndrome. A recent meta-analysis demonstrated that SARS-Cov-2 infection during pregnancy is associated with a significant increase in the odds of developing PE, PE with severe features, eclampsia, and HELLP syndrome (Conde-Agudelo & Romero, 2022).
A mechanism by which SARS-Cov-2 infection may be causally linked to PE has been proposed to involve endothelial dysfunction. An infectious process, which targets the endothelium, may lead to a syndrome resembling PE and eclampsia. Of interest, pregnant women with COVID-19 infection who developed PE-like symptoms: their recovery from SARS-Cov-2 infection, followed by resolution of HA, occurred without delivery of the fetus and placenta. Genetic susceptibility may explain why some women with COVID-19 infection develop PE but others do not (Choudhary, Sreenivasulu, Mitra, Misra, & Sharma, 2021).

Maternal intestinal dysbiosis

Gut dysbiosis, or an imbalance between the microbial communities of the human gut, is implicated in the development of atherosclerosis, hypertension, proteinuria, cardiometabolic syndrome, and PE. A causal link between gut dysbiosis and cardiovascular disease was derived from an observation that transplantation of faecal material from nonpregnant hypertensive human subjects into germ-free mice led to hypertension. Similarly, faecal transplants from atherosclerosis-prone

mice can transmit the condition to susceptible mice (e.g., apolipoprotein E null mice). This effect has been attributed, at least in part, to trimethylamine-N-oxide (TMAO), a bacterially derived metabolite of choline and carnitine that is present in gut dysbiosis and has been shown to accelerate the development of atherosclerosis (Choudhary, Sreenivasulu, Mitra, Misra, & Sharma, 2021). Changes in the human gut microbiota have been reported in PE that persist 6 weeks postpartum. Changes include a reduction in microbial load with Firmicutes, Clostridia, Clostridiales, and Ruminococcus and an increase in Bacteroidetes, Proteobacteria, Actinobacteria, Bacteroidia, Gammaproteobacteria, and Enterobacteriaceae.

Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) has been associated with the development of PE. Furthermore, DM is considered to be strongly associated with late-onset PE rather than early-onset PE (Davenport et al., 2018).
A causal role has been supported by the observation that treatment of GDM with diet, insulin, and metformin reduces the risk of PE. Metformin is associated with a reduced risk of PE and prolonged gestation in women with preterm PE (median, 18 days). Prenatal exercise has also been reported to decrease the rate of GDM by 38% and PE by 41%, based on the results of a systematic review and meta-analysis (Davenport et al., 2018).

Maternal obesity

Obesity, defined as a body mass index (BMI) of 30.0 kg/m 2 or greater, is strongly associated with PE. Studies have shown that maternal obesity is significantly associated with the development of PE, and the risk was even higher in severe obesity (BMI $\geqslant$ 35 kg/m 2) (Schenkelaars et al., 2021).
In addition, a dose-dependent relationship was found between prepregnancy BMI and the risk of PE in nulliparous and multiparous women in an epidemiological study. Most studies consider obesity to primarily predispose to late-onset PE, but maternal obesity is associated with an increased risk of both early-onset and late-onset disease (e.g., BMI of 40 kg/m 2 or greater). Furthermore, preconception maternal weight loss, either through lifestyle modification or bariatric surgery, has been shown to be effective in reducing the risk of PE (Schenkelaars et al., 2021).

Metabolic Syndrome

The term “metabolic syndrome” (MetS) refers to a cluster of metabolic abnormalities that includes central obesity, insulin resistance, atherogenic dyslipidemia, and hypertension. This syndrome is strongly associated with systemic inflammation, oxidative stress, and endothelial dysfunction, all of which are hallmarks of PE. PE is also a risk factor for the subsequent development of MetS after delivery. Furthermore, bariatric surgery performed before pregnancy as a treatment for MetS has been associated with a lower rate of PE or eclampsia (Bennett et al., 2010).
The mechanisms by which insulin resistance predisposes to the development of PE are related to intravascular inflammation and endothelial cell dysfunction, which is the common pathway for the syndrome. However, insulin resistance is neither necessary nor sufficient for the development of PE. The reason why some, but not others, patients with insulin resistance develop PE is unknown (Bennett et al., 2010).

Sleep disorders

Sleep-disordered breathing, a term that encompasses obstructive sleep apnea, snoring, periodic episodes of hypoxia, central sleep apnea, and hypopnea, during pregnancy is a risk factor for PE.
Evidence supporting a causal relationship between snoring and PE indicated that treatment with nasal continuous positive airway pressure (CPAP) improved BP in women with PE (Bourjeily et al., 2015).
In normal pregnancy, blood pressure has a circadian rhythm and peaks during the day. A reversed diurnal blood pressure rhythm has been reported in PE. Sleep architecture, using polysomnography, showed that patients with PE had altered sleep patterns, specifically spending more time in slow-wave sleep, compared with those with a normal pregnancy. Collectively, the proposed mechanisms linking sleep disorders and PE involve intravascular inflammation and endothelial cell dysfunction (Bourjeily et al., 2015).

Molar pregnancy

Hydatidiform mole, a gestational trophoblastic disease characterized by abnormal trophoblast proliferation and hydropic changes of the chorionic villi, is associated with PE and sometimes presents before 20 weeks of gestation. The frequency of PE in patients with hydatidiform mole ranges from 27% to 40% and is probably higher in patients who are not treated until the second trimester (Zilberman Sharon, Maymon, Melcer, & Jauniaux, 2020).

Fetal diseases

Specific fetal conditions associated with the development of PE include 1) Ballantyne or mirror syndrome; 2) trisomy 13 or triploidy; and 3) a unique complication of multiple gestations (e.g., twin-to-twin transfusion syndrome or selective fetal growth restriction). In mirror syndrome, the mother may develop proteinuria, AH, and even severe PE. The frequency of AH in patients with mirror syndrome is approximately 60%. Reversal of PE and Ballantyne syndrome can occur after intrauterine transfusion in parvovirus-induced hydrops without labour. All patients with mirror syndrome had increased maternal plasma concentrations of sFlt-1 (Goa et al., 2013).
Another example of PE with fetal disease is trisomy 13 or triploidy. Multiple gestations with twin-to-twin transfusion syndrome or selective fetal growth restriction may also predispose to the development of PE. PE can resolve without delivery, and studies suggest that fetal compromise may induce the syndrome in some cases (Goa et. al., 2013).

Placental Aging

Placental aging has been described for several decades, and premature aging has been implicated as a disease mechanism for obstetric outcomes, such as PE, fetal growth restriction, fetal death, and preterm birth. Placentas from patients with PE exhibit increased expression of p53, p21, and p16, shorter telomeres, and reduced telomerase activity. Redman et al. (2022) proposed that with advancing gestational age some patients develop a “twilight placenta,” a condition in which the organ is affected by senescence. A twilight placenta has been invoked as a potential cause of late pregnancy problems, such as late-onset PE (Redman, Sargent, & Staff, 2014).

Endocrine disorders

There is an association between several

endocrine disorders and PE, and two plausible explanations are: the low frequency of endocrine disorders in pregnancy and the scarcity of experimental evidence from animal studies on endocrine disorders. These investigations have not focused on the effect of such disorders on the development of PE (Kovacs, 2016).

Maternal morbidity and mortality

The most common cause of death in women with PE is intracranial hemorrhage. Other serious complications include placental abruption, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), acute pulmonary edema, respiratory distress syndrome, and acute renal failure. Although PE may not directly cause CAD in adulthood, pregnancy itself acts as a challenge test to reveal underlying metabolic risk factors for atherosclerosis and CAD. Evidence supporting this hypothesis is that PE and CAD share many risk factors, including obesity, insulin resistance, DM, underlying hypertension, and dyslipidemia. A meta-analysis demonstrated that women with earlier PE had a more severe condition and were at greater risk of developing subsequent CAD (Rathore, Pramanick, Regi, & Lionel, 2014).

Perinatal morbidity and mortality

The most important complication that requires major attention through effective prediction and prevention in PE is intrauterine fetal death (IFM). The risk of IFM varies widely depending on the population, the severity of PE, and the presence of comorbid factors. For women with PE, infant mortality is three times higher in low- and middle-income countries than in high-income countries. The underlying causes of IFM related to PE include acute and chronic hypoxia, placental insufficiency, FGR, and placental abruption (Villers, Jamison, De Castro, & James, 2008). Infants born to mothers with PE are at risk of being born preterm, as delivery is the only cure for PE. In women with early-onset or severe PE, the risk is much higher. Approximately 25% of PE cases require delivery before 37 weeks of gestation. It is estimated that approximately one-third of preterm births are medically indicated, and that PE is the leading indication for iatrogenic preterm birth. Infants born prematurely are at increased risk of neonatal mortality and morbidity, including necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, intraventricular hemorrhage, and neurodevelopmental impairments, compared with full-term infants. These tend to be inversely related to gestational age at birth.

HELLP syndrome

HELLP syndrome is considered a serious complication of PE, characterized by hematologic and hepatic changes that can lead to organ failure. In addition to hemolysis, the syndrome can cause progressive liver damage, resulting in necrosis and rupture of the liver in extreme cases. Thrombocytopenia also increases the risk of serious bleeding, making early diagnosis and immediate intervention essential. Studies indicate that 10% to 20% of pregnant women with severe PE develop HELLP syndrome, and it affects 0.5%–0.9% of all pregnancies, making early diagnosis and appropriate management essential. Symptoms include severe epigastric pain, nausea, vomiting, headache, and visual changes, requiring immediate intervention to avoid fatal complications. Treatment involves strict control of BP, administration of magnesium sulfate to prevent seizures, and, in many cases, termination of pregnancy. Risk factors include

multiparity, multiple gestation, personal or family history of preeclampsia or HELLP syndrome, high body mass index, and advanced maternal age (Stam et al., 2023). Management of these conditions involves close monitoring, blood pressure control, hematologic support, and, in many cases, termination of pregnancy to protect both mother and baby. Research indicates that genetic, immunologic, and vascular factors contribute to the development of these complications, reinforcing the need for careful prenatal care.

Results

The results reveal critical aspects that affect the management of these conditions during pregnancy. The studies indicate that both problems represent significant challenges for both healthcare professionals and patients, due to the complex and multifaceted nature of clinical manifestations and predisposing factors.

Regarding risk factors, the studies highlight that genetic predisposition, such as a family history of PE, plays an important role in increasing the chances of developing the condition. Pre-existing medical conditions, such as chronic hypertension, obesity, DM and kidney disease, also emerge as determining factors. Other elements, such as advanced maternal age and multiple pregnancies, are cited as factors that amplify the risk, showing that individual characteristics and comorbidities play a key role.

Diagnostic challenges are widely recognized as a significant obstacle in the early identification of PE and HELLP syndrome. Symptoms often manifest nonspecifically, especially in the early stages, which can lead to delayed diagnosis. Furthermore, diagnostic criteria are not always uniform, such as variability in the presence of proteinuria and hypertension, which may result in underestimation of the problem. HELLP syndrome, for example, may occur without significant hypertension, making recognition even more difficult.

There is evidence that the rapid progression of these conditions is a critical factor that increases the risk of maternal and fetal complications, such as liver failure, renal dysfunction, and premature placental abruption. In this context, early identification and timely management are considered essential to improve clinical outcomes.

In addition, preventive strategies, such as the use of low-dose aspirin and calcium supplementation, show promising results in reducing the incidence of complications in high-risk patients. On the other hand, the implementation of humanized prenatal care and rigorous monitoring is also indicated as an effective approach for the detection and monitoring of these conditions.

Conclusion

Genetic predisposition and family history play a central role in the risk of developing PE. In addition, pre-existing conditions such as chronic hypertension, DM, obesity and kidney disease are recognized as significant risk factors. Demographic factors, such as advanced maternal age and multiple pregnancies, also contribute to increasing the chances of these complications occurring. However, early diagnosis still faces several challenges. The initial symptoms of PE, such as edema and a slight increase in blood pressure, are often confused with normal physiological changes of pregnancy. In HELLP syndrome, the absence of significant hypertension in many cases and the similarity of symptoms with other conditions, such as gastritis and hepatitis, make diagnosis even more complex. In addition,

variability in diagnostic criteria, such as the presence or absence of proteinuria in PE, adds further difficulty in accurately identifying these conditions.

The lack of uniformity in diagnostic protocols and unequal access to medical care emerge as factors that limit appropriate management, especially in regions with fewer resources. On the other hand, the review highlights important advances in preventive strategies and therapeutic approaches. The use of low-dose aspirin and calcium supplementation, for example, have shown efficacy in reducing complications in high-risk pregnancies. In addition, humanized prenatal monitoring and rigorous follow-up are considered essential to improve clinical outcomes.

There is a need for future research and the implementation of more effective preventive measures, aiming to reduce maternal and fetal morbidity and mortality and improve obstetric care. These measures are essential to overcome the obstacles imposed by these conditions and ensure a safer pregnancy for women and their babies.

Abbreviations

CVA - Cerebrovascular Accident, CPAP - Nasal Continuous Positive Airway Pressure, CD - Cardiovascular Disease, DM - Diabetes, GDM - Gestational Diabetes Mellitus, IVF - In Vitro Fertilization, GWAS - Genome-Wide Association, HA - Arterial Hypertension, HELLP - Hemolysis, Elevated Liver Enzymes and Low Platelet Count, CHF - Congestive Heart Failure, BMI - Body Mass Index, MFI - Intrauterine Fetal Death, MAP - Mean Arterial Pressure, PAPP-A - Plasma Protein A, PE - Preeclampsia, PLGF - Serum Placental Growth Factor, MS - Metabolic Syndrome, TMAO - Trimethylamine-N-oxide, ART - Assisted Reproductive Technologies, UTPI - Uterine Artery Pulsatility Index.

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