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A Review of the Diagnosis, Risk Factors, and Role of Angiogenetic Factors in Hypertensive Disorders of Pregnancy

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Hypertensive disorders in pregnancy (HDPs) include chronic hypertension, gestational hypertension, preeclampsia, and chronic hypertension with superimposed preeclampsia and are major causes of maternal and fetal complications. Preeclampsia, in particular, poses significant risks, yet prevention and management remain challenging despite extensive research. Various risk factors have been identified, with obesity being a key contributor to preeclampsia. The role of angiogenic factors, specifically soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), has gained more attention in hopes of better understanding the pathogenesis of preeclampsia. Imbalances in these factors – increased sFlt-1 and decreased PlGF levels – can be observed before the clinical onset of the disease. The sFlt-1/PlGF ratio has been demonstrated to have strong predictive value in ruling out preeclampsia within the next 7 days for women with suspected cases, enhancing early diagnosis and screening mechanisms. Furthermore, women with a history of hypertensive disorders during pregnancy face a significantly higher risk of developing postpartum hypertension, especially within the first 2 years following childbirth. This article aims to provide a comprehensive review of HDPs, focusing on risk factors, diagnostic criteria, and the emerging role of angiogenic biomarkers. Specifically, it highlights the potential of the sFlt-1/PlGF ratio as a noninvasive tool to improve the early detection and diagnosis of preeclampsia.

Keywords: **Preeclampsia • Gestational Hypertension • PGF Protein, Human • FLT1 Protein, Human**

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Introduction

Hypertensive disorders in pregnancy (HDPs), including chronic hypertension, gestational hypertension, preeclampsia, and chronic hypertension with superimposed preeclampsia, are among the leading causes of morbidity and mortality in pregnant women [1-4]. Preeclampsia, in particular, is one of the most feared complications of pregnancy (6). According to data from the World Health Organization, HDPs are the cause of 12% of maternal deaths [1]. In recent years, many studies have attempted to explain this phenomenon, selecting pregnant women at risk of developing gestational hypertension and preeclampsia.

Bornstein et al conducted a retrospective cohort study spanning 30 years, from 1989 to 2018. The study analyzed approximately 120.7 million live births in the United States and found that the prevalence of gestational hypertension, mild and severe preeclampsia, eclampsia, and HELLP syndrome increased by 149%, while the prevalence of chronic hypertension increased by 182% [5]. This phenomenon is largely correlated with the obesity epidemic and increasing age of mothers [6].

Giorgione et al, in their systematic review and meta-analysis, found that women with a history of HDPs have a 6-fold higher risk of developing hypertension within 2 years postpartum, compared with women who had a normotensive pregnancy. In the first 6 months postpartum, the risk of developing hypertension is more than 10 times higher than in women with a normotensive pregnancy. The risk remains significantly elevated during the period from 6 months to 1 year (4 times higher) and from 1 year to 2 years (8 times higher) postpartum [7].

Due to the risk of complications for the mother and fetus/newborn in a pregnancy complicated by preeclampsia, it is necessary to define more precise methods to diagnose this clinical problem. The high prevalence highlights the importance of researching noninvasive, blood-borne, or urinary biochemical markers that could be used for screening, presymptomatic diagnosing, and predicting the development of preeclampsia.

Angiogenic factors play a key role in the pathophysiology of preeclampsia [8]. The soluble fms-like tyrosine kinase 1 (sFlt-1), an anti-angiogenic factor, and placental growth factor (PlGF), a pro-angiogenic factor, are commonly expressed as a ratio that correlates with the onset and severity of preeclampsia. The sFlt-1/PlGF ratio demonstrates a significantly high negative predictive value for excluding the progression of preeclampsia within a week in women who are suspected of having the condition [9]. This article aims to review the diagnosis, risk factors, and role of angiogenetic factors in HDPs.

Definition and Diagnostic Criteria for Hypertension in Pregnancy

Specific HDPs are named based on the context in which the hypertension is initially identified. Based on international guidelines, hypertensive conditions during pregnancy are broken down into 4 categories. Chronic/pre-existing hypertension is defined as hypertension diagnosed preconception or before 20 weeks of gestation. Gestational hypertension is defined when the initial diagnosis of hypertension is made after 20 weeks of gestation, and the blood pressure abnormalities normalize after pregnancy [10].

The International Society for the Study of Hypertension in Pregnancy (ISSHP) defines preeclampsia-eclampsia as gestational hypertension accompanied by proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, neurologic signs, or fetal growth restriction [10,11]. Chronic/pre-existing hypertension with superimposed preeclampsia-eclampsia is defined as hypertension diagnosed before 20 weeks of gestation that develops signs and symptoms of preeclampsia or eclampsia after 20 weeks of gestation [11-13]. **Figure 1** presents a flowchart for diagnosing the various HDPs.

When defining the complications of preeclampsia, the following diagnostic guidelines should be used. Proteinuria is typically

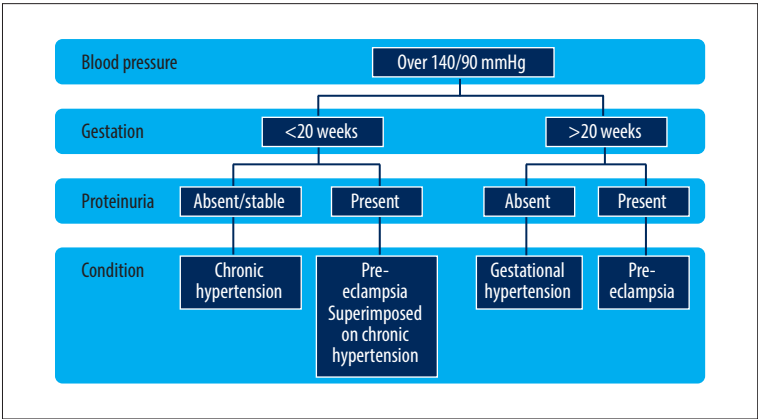


Figure 1. Hypertensive disorders of pregnancy [12]. Source: Own elaboration based on data from: Portelli M, Baron B. Clinical presentation of preeclampsia and the diagnostic value of proteins and their methylation products as biomarkers in pregnant women with preeclampsia and their newborns. *J Pregnancy.* 2018;2018:2632637.

diagnosed by 24-h urine collection or extrapolated from timed collections in which ≥ 300 mg of protein is obtained within the urine. Proteinuria can also be confirmed by a protein/creatinine ratio of ≥ 0.3 mg/dL in the urine or a dipstick reading of 2+ protein when no other methods are available to obtain the diagnosis [11-13].

Thrombocytopenia is defined as a platelet count of $< 100\,000/\text{mm}^3$. Renal insufficiency is defined as a serum creatinine concentration > 1.1 mg/dL or a doubling of serum creatinine concentrations in the absence of pre-existing renal disease. Similarly, impaired liver function is defined by elevated concentrations of liver transaminases that are 2 times normal values or the presence of severe persistent right upper quadrant or epigastric pain unresponsive to medication [11-13].

When a diagnosis of pulmonary edema is suspected, it should be confirmed on physical examination and a chest X-ray when possible. Neurologic signs often seen with preeclampsia include new-onset headaches unresponsive to medications, and not accounted for by an alternative diagnosis or visual symptoms. Finally, if hypertension is present during pregnancy and fetal growth restriction, as defined as a fetal weight less than the 10th percentile, is present, then a diagnosis of preeclampsia can be made [11-13].

Definition and Diagnosis of Preeclampsia

The ISSHP defines preeclampsia as gestational hypertension that occurs alongside at least one of the following newly developed conditions after 20 weeks of gestation: proteinuria, dysfunction of maternal organs (which can include acute kidney injury, liver involvement, neurological issues, or hematological complications), or dysfunction of the uteroplacental unit [10,11].

The diagnosis of preeclampsia can be made after 20 weeks of gestation when the following parameters are met: systolic blood pressure of 140 mmHg or more or a diastolic blood pressure of 90 mmHg or more on 2 occasions at least 4 h apart. In situations in which the systolic blood pressure is 160 mmHg or more or the diastolic blood pressure is 110 mmHg or more, a shorter interval between measurements can be used [12,13]. HDPs affect approximately 10% of pregnancies and include chronic hypertension, gestational hypertension, and preeclampsia (de novo or superimposed on chronic hypertension) [11,14].

Health Impact on the Mother and Fetus

These conditions can significantly impact maternal and fetal health in the short and long term. For the mother, this entails

a 2- to 4-fold increased risk of long-term hypertension, a doubling of the risk of cardiovascular mortality and major adverse cardiovascular events, and a 1.5-fold increased risk of stroke [15]. Numerous epidemiological studies have indicated that women experiencing both gestational hypertension and preeclampsia are associated with a higher incidence of low birthweight or small-for-gestational-age infants [16-19].

Role of Echocardiography in Evaluating Hypertensive Disorders

Sonaglioni et al conducted a meta-analysis summarizing the current knowledge on the impact of HDP on the mechanics of the left atrium using speckle tracking echocardiography. The analysis included echocardiographic studies evaluating parameters for left atrium deformation in women with HDP compared with healthy controls. The results demonstrated that HDP is independently associated with impaired function of the left atrium during pregnancy. The authors concluded that speckle tracking echocardiography analysis can help identify women with HDP who might benefit from more aggressive antihypertensive treatment and/or more thorough clinical monitoring, aimed at reducing the risk of adverse outcomes for the mother and preventing cardiovascular complications later in life [20].

Risk Factors Associated with Gestational Hypertension and Preeclampsia

Many different conditions and health-related behaviors are thought to predispose to preeclampsia [21]. Recently, a group of research specialists conducted an extensive study, published in the BJOG International Journal of Obstetrics and Gynaecology, examining 78 distinct risk factors associated with the likelihood of developing preeclampsia. These factors were sourced from clinical practice guidelines provided by 17 obstetric organizations worldwide, such as the American College of Obstetrics and Gynecology in the United States and the Society of Obstetricians and Gynaecologists of Canada [22].

Identified Risk Factors

Eight risk factors were identified as having a clear association with preeclampsia, which included demographic factors, such as adolescence; a past medical history of obesity, chronic hypertension, pre-gestational diabetes mellitus, considering type-1 and type-2 diabetes separately, and severe anemia; a past obstetric history of preeclampsia; and current pregnancy factors, such as fetal trisomy 13. Obesity (body mass index [BMI] ≥ 30 kg/m²) was the only risk factor with a 'definite' association with preeclampsia based on high-quality evidence.

High-quality evidence also supported the risk factors of being overweight (BMI=25.0-29.9 kg/m²) and having stage-1 hypertension (defined as systolic blood pressure of 130-139 mmHg and/or diastolic blood pressure 80-89 mmHg diagnosed at <20 weeks of gestation) [21,22].

Poon et al found that women who have previously had preeclampsia have a 4-times higher risk of early-onset preeclampsia, and the risk of late-onset preeclampsia is doubled compared with that of women who have never given birth. Conversely, when compared with women who have given birth but have not experienced preeclampsia, the risk of early and late-onset disease is 3 to 4 times higher in women having had preeclampsia [23].

Additional Risk Factors

Other risk factors associated with the occurrence of preeclampsia discussed in the literature include hypercholesterolemia [24,25], chronic kidney disease [26], advanced age [27], autoimmune diseases [28], family history of preeclampsia [21], multiple pregnancies [29], antiphospholipid syndrome [29], and in vitro fertilization [28]. Additionally, low educational attainment was significantly associated with a higher risk of preeclampsia/eclampsia [30]. While no association with preeclampsia is demonstrable for other risk factors (ie, HIV, tuberculosis, and malaria), the quality of available evidence is very low [22].

Preeclampsia and Maternal Immune Tolerance

While pregnancy is a natural physiological phenomenon, the presence of the fetus presents a challenge to maternal immune tolerance. In a healthy pregnancy, maternal systems must accommodate the semi-allogenic fetus while simultaneously shielding it from rejection by the maternal immune response [31]. Preeclampsia is believed to arise due to inadequate invasion of trophoblast cells into the maternal decidua during placental implantation, leading to compromised remodeling of spiral arteries and reduced perfusion to the developing fetal-placental unit [32,33].

Role of Angiogenic and Anti-Angiogenic Factors

It is hypothesized that placental ischemia initiates the secretion of anti-angiogenic factors such as soluble sFlt-1 and soluble endoglin (sEng), leading to elevated plasma levels, compared with pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and PlGF [34]. Impaired remodeling of the maternal spiral arteries and placental underperfusion can

occur secondary to abnormal angiogenesis, leading to fetal growth restriction and maternal preeclampsia. Research indicates that angiogenic factors play a significant role in modulating placental vasculogenesis [35].

PlGF stimulates endothelial cell proliferation and placental vasculogenesis and induces vasodilation of uterine vessels [36]. sFlt-1 is an alternatively spliced version of VEGF-receptor 1 (Flt1) and is an anti-angiogenic factor. sFlt-1 binds VEGF and PlGF and blocks the angiogenic stimulatory effects on VEGF receptors [15,22]. PlGF and elevated sFlt-1 levels in the placenta are increasingly important in the clinical management of preeclampsia [37,38].

Imbalance of Angiogenic Factors in Hypertensive Disorders

While the etiology of HDP is not fully understood, mounting evidence indicates that these conditions stem from an imbalance between the equilibrium of pro- and anti-angiogenic factors damaging the maternal vascular endothelium, leading to the clinical manifestations of these conditions [39,40]. Theories suggest poor placental perfusion due to insufficient cytotrophoblastic invasion of the uterine arteries. This triggers an imbalance between anti-angiogenic factors like sFlt-1 and pro-angiogenic factors like PlGF [41].

In women diagnosed with preeclampsia, the maternal serum concentration of PlGF is decreased, and the level of sFlt-1 is increased [42-45]. Evidence suggests that the changes in PlGF and sFlt-1 levels occur before the clinical manifestations of the disease. Furthermore, the ratio of sFlt-1 to PlGF can aid in evaluating women attending specialty clinics with symptoms or signs of hypertensive disorders, helping differentiate those who may develop preeclampsia within the next 1 to 4 weeks from those who will not [46,47].

Timing of Changes in Angiogenic Factors

In a study conducted by Richard et al, it was found that the levels of sFlt-1, which were previously found to be elevated in women diagnosed with preeclampsia, began to rise significantly about 5 weeks before clinical symptoms become evident. Women who experience preterm preeclampsia or preeclampsia alongside the birth of a small-for-gestational-age infant tend to exhibit higher sFlt-1 and lower PlGF concentrations between weeks 21 and 32, as well as between weeks 33 and 41, than do those who develop preeclampsia at term or have preeclampsia without delivering a small-for-gestational-age infant [48].

Angiogenic Factors in Twin vs Singleton Pregnancies

In a study conducted by Faupel-Badger et al, which examined differences in maternal circulating angiogenic factors in twin and singleton pregnancies, it was found that maternal sFlt-1 concentrations and the sFlt-1/PIGF ratio were higher in twins than in singletons throughout pregnancy and at delivery, with the greatest disparities observed at week 35 [49].

Predictive Value of Angiogenic Imbalance

Previous studies have shown that during the first trimester of pregnancy, detecting angiogenic imbalance is not sensitive enough to predict preeclampsia [50]. However, later in pregnancy, the degree of angiogenic imbalance becomes a reliable indicator for anticipating the onset of preeclampsia. In cases of “suspected” preeclampsia, the level of angiogenic imbalance was found to have a stronger correlation with maternal and neonatal complications than brachial blood pressures, suggesting that evaluating the extent of angiogenic imbalance could address the limitations of traditional diagnostic criteria for preeclampsia [51].

Beyond distinguishing between pregnant women with and without preeclampsia, evaluating the angiogenic imbalance can also accurately differentiate preeclampsia from other conditions that resemble it, such as chronic and gestational hypertension, acute and chronic glomerulonephritis, lupus nephritis, and thrombocytopenia not related to HELLP syndrome [51,52].

This short review of the literature underscores the potential for sFlt-1/PIGF ratio measurements to serve as an additional tool in managing preeclampsia [53]. Proper application of angiogenic factor measurements could help lower the rate of iatrogenic preterm deliveries in women, with a low risk of adverse outcomes, thereby reducing resource use without heightening the risk of negative effects on mothers and newborns. Therefore, it seems justified to perform an assessment of the sFlt-1 to PIGF ratio in the third trimester of pregnancy in women at high risk for preeclampsia to minimize adverse perinatal events for those who develop preeclampsia, by determining the appropriate time and place for delivery [54].

Future Directions

Women with a history of HDPs face a significantly increased risk of postpartum hypertension, especially in the first 2 years after childbirth. This heightened risk underscores the importance of continuous health monitoring during the postpartum period [16].

Research is being conducted on a text message-based blood pressure monitoring program, which has shown promising results. A study involving postpartum patients with hypertensive disorders revealed high patient satisfaction and a high rate of participation, with 97% of participants submitting at least 1 blood pressure measurement via text message. Additionally, a systematic review indicated that home blood pressure monitoring improves the accuracy of readings in the first 10 days postpartum and can help reduce racial disparities in monitoring by approximately 50%. However, there is currently insufficient evidence to determine if this approach reduces severe maternal morbidity [55].

Emerging research in hypertensive disorders of pregnancy highlights the importance of continuous monitoring and innovative diagnostic approaches. One promising area of study is the use of remote blood pressure monitoring programs, particularly those using text messaging, which have shown high patient satisfaction and feasibility. Studies indicate that a significant majority of women in the postpartum period successfully engaged with these programs, facilitating better blood pressure management during the early postpartum period [55,56].

Furthermore, the measurement of angiogenic factors, specifically the sFlt-1/PIGF ratio, offers a noninvasive means of predicting and managing preeclampsia. This ratio can identify women at risk of developing the condition before clinical symptoms manifest, thereby allowing for timely interventions and potentially improving maternal and fetal outcomes [9]. Future research should focus on standardizing these monitoring methods and exploring their effectiveness across diverse populations.

Additionally, refining the use of angiogenic markers could enhance our understanding of the pathophysiology of HDPs and lead to the development of targeted therapies. Ultimately, these advancements may contribute to a reduction in maternal and neonatal morbidity associated with HDPs.

Conclusions

HDPs, including chronic hypertension, gestational hypertension, and preeclampsia, pose significant health challenges that contribute to the morbidity and mortality of pregnant women. Preeclampsia, in particular, is recognized as one of the most serious complications, with substantial implications for maternal and fetal health. The increasing prevalence of these disorders, linked to the obesity epidemic and rising maternal age, is alarming. Women with a history of hypertensive disorders during pregnancy are at a significantly heightened risk of developing postpartum hypertension, especially in the first 2 years following delivery. This ongoing elevated risk underscores

the urgent need for continuous health monitoring during the postpartum period.

To address the risks associated with preeclampsia for mothers and infants, the development of precise diagnostic tools is crucial. The sFlt-1/PlGF ratio has demonstrated a high predictive value for the early diagnosis and effective management of preeclampsia. Fluctuations in these biomarkers can indicate the onset of the condition prior to the manifestation of clinical symptoms, facilitating timely interventions. By measuring levels of sFlt-1 and PlGF, healthcare providers can better assess placental angiogenesis and predict preeclampsia, which may lead to the improved timing and location of delivery, a reduction in iatrogenic preterm births, and enhanced overall healthcare outcomes.

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Declaration of Figures' Authenticity

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