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Maksimovich Yelizaveta *

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Review Article

The Evolving Landscape: From Proteinuria to Biomarkers in the Differential Diagnosis of Chronic Hypertension and Preeclampsia

Maksimovich Yelizaveta *, Lala Mukhtarzade

Department of 1 Internal Medicine, Grodno State Medical University, Grodno, Belarus.

***Corresponding Author:** Maksimovich Yelizaveta., Department of 1 Internal Medicine, Grodno State Medical University, Grodno, Belarus.

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Abstract:

The stakes are high: while CH requires careful monitoring, PE necessitates timely delivery to prevent progression to eclampsia or HELLP syndrome. The diagnostic dilemma is particularly pronounced in superimposed PE, where worsening hypertension may represent either poor control or evolving placental dysfunction

keywords: preeclampsia; chronic hypertension; diagnosis; sFlt-1; PlGF; ISSHP; ACOG; biomarkers

Introduction

Hypertensive disorders complicate approximately 10% of pregnancies globally and remain a leading cause of maternal and perinatal morbidity and mortality. The differential diagnosis between chronic hypertension (CH) and preeclampsia (PE) represents a daily clinical challenge, particularly in cases of superimposed PE, which affects 20-30% of pregnancies with CH. For decades, clinicians relied on rigid criteria centered on blood pressure thresholds and proteinuria. However, the understanding of PE has evolved from a simple hypertensive disorder to a multisystemic condition driven by placental anti-angiogenic factors. This review traces the evolution of diagnostic approaches and evaluates the integration of novel biomarkers—particularly the sFlt-1/PlGF ratio—into clinical practice. The landscape of hypertensive disorders in pregnancy has been transformed over the past two decades. Where once the diagnosis of PE required hypertension and proteinuria, today we recognize it as a complex systemic syndrome of endothelial dysfunction. This paradigm shift, validated by updated guidelines from the International Society for the Study of Hypertension in Pregnancy (ISSHP) and the American College of Obstetricians and Gynecologists (ACOG), has improved our ability to identify severe disease earlier [1]. The stakes are high: while CH requires careful monitoring, PE necessitates timely delivery to prevent progression to eclampsia or HELLP syndrome. The diagnostic dilemma is particularly pronounced in superimposed PE, where worsening hypertension may represent either poor control or evolving placental dysfunction.

The Traditional Paradigm: Blood Pressure and Proteinuria

For most of the 20th century, the diagnosis of preeclampsia was codified by two cardinal features: new-onset hypertension (≥140/90 mm Hg) and new-onset proteinuria (≥300 mg/24h) after 20 weeks of gestation [3]. Chronic hypertension was defined by elevated blood pressure predating pregnancy or diagnosed before 20 weeks.

Limitations of the Traditional Model

While straightforward, this model had significant shortcomings:

· Proteinuria as a Late Marker: Significant proteinuria often appears late in the disease course, delaying diagnosis.

· Lack of Sensitivity for Atypical PE: Many women present with severe features (e.g., HELLP syndrome) without significant proteinuria.

· The "Gray Zone" of Superimposed PE: In women with CH, it was challenging to determine if worsening hypertension represented poor control or evolving PE. Old criteria offered little guidance for this common dilemma [4].

The Modern Shift: Preeclampsia as a Systemic Syndrome

Recognizing these flaws, major societies revised their definitions, moving towards a broader, pathophysiologically grounded model.

The ACOG (2013) and ISSHP (2018, 2021) Criteria

The revised definitions de-emphasized proteinuria as an absolute requirement. Preeclampsia can now be diagnosed with new-onset hypertension AND any of the following [1, 5]:

· Thrombocytopenia (platelet count <100 x 10^9/L)

· Impaired liver function (elevated transaminases to twice normal)

· New renal insufficiency (creatinine >1.1 mg/dL)

· Pulmonary edema

· New-onset cerebral or visual disturbances

For superimposed PE, the diagnosis hinges on the new development of these systemic signs or sudden worsening of hypertension in a woman with known CH, particularly if requiring intensified therapy [5].

The Biomarker Revolution: The sFlt-1/PlGF Ratio

The most significant recent advancement is the clinical incorporation of angiogenic biomarkers, specifically the ratio of soluble fms-like tyrosine kinase-1 (sFlt-1, anti-angiogenic) to placental growth factor (PlGF, pro-angiogenic).

Pathophysiological Rationale

PE is characterized by an imbalance in these factors: excessive placental release of sFlt-1 "mops up" circulating PlGF and VEGF, leading to widespread endothelial dysfunction—the hallmark of the clinical syndrome [6]. This imbalance precedes clinical symptoms by weeks.

Clinical Utility in Differential Diagnosis

The sFlt-1/PlGF ratio has emerged as a powerful adjunctive tool:

· Rule-Out Value: A low ratio (<38) has a high negative predictive value (>95%) for ruling out PE within the next week, helping avoid unnecessary hospitalization [7].

· Rule-In Value: A high ratio (>85) supports the diagnosis of PE and correlates with disease severity [7].

· In Superimposed PE: It shows particular promise in differentiating CH exacerbation from true superimposed PE. Rising serial ratios can signal placental dysfunction before overt clinical signs [8].

Management and Monitoring

Once the diagnosis is established, care shifts to vigilant surveillance.

Key Investigative Modalities

· Serial blood pressure monitoring

· Laboratory surveillance (platelets, liver enzymes, renal function)

· Fetal ultrasound for growth assessment and umbilical artery Doppler

· Biomarker trending when indicated

Management of Common Complications

· Severe Hypertension: First-line therapy includes labetalol, nifedipine, or hydralazine [2].

· HELLP Syndrome: Requires prompt delivery and magnesium sulfate for seizure prophylaxis.

· Pulmonary Edema: Managed with diuresis (furosemide) and afterload reduction.

Delivery Planning and Postpartum Care

Mode and Timing of Delivery

· Vaginal Delivery: Generally preferred for stable patients without severe features.

· Cesarean Section: Reserved for obstetric indications or severe disease with unfavorable cervical status.

· Timing: At term (>37 weeks), delivery is generally indicated. Preterm delivery may be necessitated by severe features refractory to management [5].

Intrapartum and Postpartum Management

· Magnesium sulfate for severe features during labor and 24 hours postpartum [4]

· Invasive monitoring for pulmonary edema or refractory hypertension

· The "Fourth Trimester": Hypertension can peak 3-6 days postpartum; continued vigilance is essential

A Contemporary Stepwise Diagnostic Algorithm

Step 1: Establish Chronology. Hypertension before 20 weeks = CH. New onset after 20 weeks = gestational hypertension or PE.

Step 2: Search for Systemic Features. Perform full blood count, liver enzymes, and renal function tests. Identify end-organ dysfunction per ISSHP/ACOG criteria.

Step 3: Utilize Biomarker Testing. In diagnostic uncertainty—suspected superimposed PE, atypical presentations, or new-onset hypertension without proteinuria—measure the sFlt-1/PlGF ratio.

· Low ratio: Favors CH or gestational hypertension; closer outpatient monitoring

· High ratio: Strongly supports PE; intensified surveillance and preparation for delivery

Step 4: Continuous Reassessment. Both CH and PE are dynamic. Reassess at each visit for new symptoms or laboratory abnormalities.

Conclusion

The differential diagnosis between chronic hypertension and preeclampsia has evolved from a proteinuria-centric model to a sophisticated multi-parameter assessment. The understanding of preeclampsia as a systemic syndrome of endothelial dysfunction, validated by ISSHP and ACOG criteria, has improved our ability to identify severe disease earlier. The integration of the sFlt-1/PlGF ratio represents a true breakthrough, providing an objective tool to navigate diagnostic gray zones, particularly in superimposed preeclampsia. Success in managing these patients is the product of structured, proactive care that begins with accurate diagnosis and continues through the critical postpartum period. The modern clinician must synthesize traditional clinical acumen with these advanced diagnostic insights to optimize timing of intervention and improve outcomes for both mother and fetus.

Abbreviations:

CH (chronic hypertension)

PE (preeclampsia)

sFlt-1 (soluble fms-like tyrosine kinase-1)

PlGF (placental growth factor)

ISSHP (International Society for the Study of Hypertension in Pregnancy)

ACOG (American College of Obstetricians and Gynecologists)

Conflict of Interest: The authors declare no conflicts of interest.

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