OPHTHALMIC ARTERY DOPPLER AND ANGIOGENIC BIOMARKERS IN THE PREDICTION OF PREECLAMPSIA: CURRENT EVIDENCE AND FUTURE PERSPECTIVES

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Abstract. *In this review, current evidence on the pathogenesis, prediction, and potential role of ophthalmic artery Doppler and angiogenic biomarkers in pre-eclampsia is considered. Analysis of the available data indicates that one of the main trends in modern obstetrics is the search for reliable, non-invasive predictors capable of identifying women at increased risk of developing pre-eclampsia before the onset of clinical manifestations. Particular attention is given to ophthalmic artery Doppler parameters, especially the second systolic peak and peak systolic velocity ratio, which may reflect maternal cerebrovascular maladaptation associated with pre-eclampsia. At the same time, angiogenic biomarkers, including placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), and soluble endoglin (sEng), provide important information about placental and endothelial dysfunction. Current evidence suggests that the most promising direction is a multifactorial approach combining maternal clinical characteristics, Doppler parameters, and angiogenic biomarkers rather than the use of a single predictor. The combined assessment of ophthalmic artery Doppler and soluble endoglin may provide complementary information on maternal vascular and antiangiogenic dysfunction; however, its additional prognostic value has not yet been sufficiently established. Based on the analysis of the available literature, it can be concluded that further prospective studies, standardization of Doppler measurements, simultaneous assessment of biomarkers, and external validation of multimarker models are required before these approaches can be recommended for routine clinical prediction and risk stratification of pre-eclampsia.*

Keywords: *pre-eclampsia; ophthalmic artery Doppler; angiogenic biomarkers; soluble endoglin; PlGF; sFlt-1; prediction; risk stratification.*

ДОППЛЕРОМЕТРИЯ ГЛАЗНОЙ АРТЕРИИ И АНГИОГЕННЫЕ БИОМАРКЕРЫ В ПРОГНОЗИРОВАНИИ ПРЕЭКЛАМПСИИ: СОВРЕМЕННЫЕ ДАННЫЕ И ПЕРСПЕКТИВЫ

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Аннотация. *В данном обзоре рассмотрены современные данные о патогенезе, прогнозировании и потенциальной роли допплерометрии глазной артерии и ангиогенных биомаркеров при преэклампсии. Анализ имеющихся данных показывает, что одним из основных направлений современной акушерской науки является поиск надежных неинвазивных предикторов, позволяющих выявлять женщин с повышенным риском развития преэклампсии до появления клинических проявлений заболевания. Особое внимание уделяется параметрам допплерометрии глазной артерии, в частности второму систолическому пику и отношению пиковых систолических скоростей, которые могут отражать цереброваскулярную дезадаптацию материнского организма, связанную с преэклампсией. В то же время ангиогенные биомаркеры, включая плацентарный фактор роста (PlGF), растворимую fms-подобную тирозинкиназу-1 (sFlt-1) и растворимый эндоглин (sEng), предоставляют важную информацию о плацентарной и эндотелиальной дисфункции. Современные данные свидетельствуют о том, что наиболее перспективным направлением является мультифакторный подход, объединяющий клинические характеристики матери, допплерометрические показатели и ангиогенные биомаркеры, а не использование одного изолированного предиктора. Комбинированная оценка показателей допплерометрии глазной артерии и растворимого эндоглина может предоставить взаимодополняющую информацию о сосудистой и антиангиогенной дисфункции материнского организма, однако ее дополнительная прогностическая ценность пока недостаточно изучена. На основании анализа доступной литературы можно сделать вывод о необходимости дальнейших проспективных исследований, стандартизации допплерометрических измерений, одновременной оценки биомаркеров и внешней валидации мультимаркерных моделей до их внедрения в рутинную клиническую практику для прогнозирования и стратификации риска преэклампсии.*

Ключевые слова: *преэклампсия; допплерометрия глазной артерии; ангиогенные биомаркеры; растворимый эндоглин; PlGF; sFlt-1; прогнозирование; стратификация риска.*

PREEKLAMPSIYANI PROGNOZLASHDA OFTALMIK ARTERIYA DOPPLEROMETRIYASI VA ANGIOGEN BIOMARKERLAR: ZAMONAVIY DALILLAR VA KELAJAK ISTIQBOLLARI

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Annotatsiya. *Ushbu sharhda preeklampsiyaning patogenezi, prognozlash imkoniyatlari, shuningdek, oftalmik arteriya dopplerometriyasi va angiogen biomarkerlarning potensial ahamiyati haqidagi zamonaviy ma'lumotlar ko'rib chiqilgan. Mavjud ma'lumotlarning tahlili shuni ko'rsatadiki, zamonaviy akusherlikning asosiy yo'nalishlaridan biri preeklampsiyaning klinik belgilari paydo bo'lishidan oldin uning rivojlanish xavfi yuqori bo'lgan ayollarni aniqlash imkonini beruvchi ishonchli va noinvaziv prognostik markerlarni izlashdan iborat. Oftalmik arteriya dopplerometriyasining, ayniqsa ikkinchi sistolik cho'qqi va sistolik cho'qqi tezliklari nisbatining ko'rsatkichlariga alohida e'tibor qaratilmoqda, chunki ular preeklampsiya bilan bog'liq ona organizmidagi serebrovaskulyar maladaptatsiyani aks ettirishi mumkin. Shu bilan birga, platsentar o'sish omili (PlGF), sFlt-1 va sEng kabi angiogen biomarkerlar platsentar va endotelial disfunksiya haqida muhim ma'lumot beradi. Zamonaviy dalillar bitta alohida prediktordan foydalanishdan ko'ra, onaning klinik xususiyatlari, Doppler ko'rsatkichlari va angiogen biomarkerlarni birlashtiruvchi multifaktorial yondashuv eng istiqbolli yo'nalish ekanligini ko'rsatmoqda. Oftalmik arteriya dopplerometriyasi va soluble endoglinni birgalikda baholash ona organizmidagi qon-tomir va antiangiogen disfunksiya haqida bir-birini to'ldiruvchi ma'lumot berishi mumkin, biroq ushbu yondashuvning qo'shimcha prognostik ahamiyati hali yetarlicha aniqlanmagan. Mavjud adabiyotlar tahlili asosida ushbu usullarni preeklampsiyani klinik prognozlash va xavfni stratifikatsiyalashda muntazam qo'llashdan oldin qo'shimcha prospektiv tadqiqotlar o'tkazish, Doppler o'lchovlarini standartlashtirish, biomarkerlarni bir vaqtda baholash hamda multimarkerli modellarni tashqi validatsiyadan o'tkazish zarur degan xulosaga kelish mumkin.*

Kalit so'zlar: *preeklampsiya; oftalmik arteriya dopplerometriyasi; angiogen biomarkerlar; soluble endoglin; PlGF; sFlt-1; prognozlash; xavfni stratifikatsiyalash.*

Introduction. Hypertensive disorders of pregnancy encompass chronic hypertension, gestational hypertension, preeclampsia and eclampsia and remain among the most important causes of preventable maternal and perinatal complications. Preeclampsia is a multisystem pregnancy disorder characterized by new-onset hypertension after 20 weeks of gestation together with proteinuria and/or evidence of maternal organ or uteroplacental dysfunction. Its clinical spectrum ranges from relatively mild late-onset disease to rapidly progressive early-onset disease associated with severe maternal complications, fetal growth restriction, indicated preterm delivery and substantial neonatal morbidity. The heterogeneity of the syndrome is one reason why a single biomarker is unlikely to provide adequate prediction across all gestational ages and clinical phenotypes. [2,20]

The modern approach to prediction increasingly relies on combinations of maternal characteristics, biophysical measurements and biochemical biomarkers. The Fetal Medicine Foundation competing-risks model, for example, combines maternal factors with mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and placental growth factor (PlGF). FIGO and ISUOG guidance has recognized this combined approach as the best validated first-trimester strategy for prediction of preterm preeclampsia. Nevertheless, screening performance is lower for term preeclampsia, access to biochemical assays is unequal, and there remains interest in additional inexpensive, reproducible and non-invasive vascular markers. [13,19]

Maternal ophthalmic artery Doppler (OAD) is attractive in this context because the ophthalmic artery originates from the internal carotid circulation and can provide an indirect window into maternal cerebral vascular adaptation. Preeclampsia is associated with endothelial dysfunction, altered vascular tone, impaired cerebral autoregulation and, in severe cases, cerebral hyperperfusion, edema, seizures and stroke. These pathophysiologic changes can alter the ophthalmic artery waveform before or during clinical disease. During the past decade, research has therefore moved from descriptive studies of ophthalmic hemodynamics toward prediction models and integration with established biomarkers.

The field has evolved particularly rapidly since 2023. A systematic review and meta-analysis demonstrated strong diagnostic performance for waveform parameters such as peak ratio (PR) and the second systolic peak (P2). A 2025 systematic review then evaluated both stand-alone and incremental predictive performance of OAD. In July 2026, a systematic review focused specifically on first-trimester prediction of early-onset and preterm preeclampsia and concluded that stand-alone performance in large unselected cohorts is limited and incremental benefit remains uncertain. Meanwhile, 2025–2026 studies have provided new gestational reference ranges and a 2026 investigation demonstrated an association between OAD parameters and

the sFlt-1/PlGF ratio, suggesting that OAD may reflect angiogenic imbalance. These developments make it timely to reassess how OAD should be positioned within multimarker prediction rather than as an isolated screening test. [8]

Pathophysiology of Preeclampsia. Preeclampsia is commonly conceptualized as a two-stage disorder, although the underlying biology is more complex. In susceptible pregnancies, abnormal placentation and incomplete remodeling of the spiral arteries contribute to placental malperfusion, oxidative stress and release of circulating factors that disturb maternal endothelial homeostasis. An imbalance between proangiogenic and antiangiogenic signaling is central to this process. Increased circulating soluble fms-like tyrosine kinase-1 (sFlt-1) binds vascular endothelial growth factor and PlGF, reducing their bioavailability, while soluble endoglin (sEng) interferes with transforming growth factor-beta signaling. The resulting endothelial dysfunction contributes to hypertension, increased vascular permeability and multisystem organ injury.

The maternal brain is particularly important because neurologic complications are responsible for a substantial component of severe maternal morbidity. Normal pregnancy is accompanied by marked cardiovascular and vascular adaptation. In preeclampsia, cerebral autoregulation may become impaired, exposing the microcirculation to excessive pressure and flow. Cerebral hyperperfusion, blood-brain barrier disruption and vasogenic edema are relevant to headache, visual symptoms, posterior reversible encephalopathy syndrome and eclampsia. Direct assessment of cerebral vessels is possible but is not always practical in routine obstetric care. The ophthalmic artery offers an anatomically related and technically accessible vascular bed that can be examined with conventional Doppler ultrasound. [14]

The characteristic OAD pattern reported in preeclampsia is generally consistent with reduced downstream resistance and enhanced reflected systolic flow. Earlier studies emphasized reductions in resistance index (RI) and pulsatility index (PI). More recent work has highlighted the morphology of the systolic waveform, particularly the amplitude of the second systolic peak relative to the first. This shift is important because PR may capture changes in wave reflection and central vascular compliance that are not fully represented by conventional resistance indices.

Current standards for preeclampsia prediction: Risk-factor approaches based on maternal history remain clinically useful but have limited specificity. Important factors include previous preeclampsia, chronic hypertension, renal disease, autoimmune disease, diabetes, multifetal pregnancy, obesity, advanced maternal age and family history. However, modern prediction models perform better when maternal characteristics are combined with objective biophysical and biochemical measurements.

At 11–13+6 weeks, the most established multimarker model combines maternal factors, MAP, UtA-PI and PlGF. FIGO has recommended this combined test for first-trimester screening for preterm preeclampsia where feasible. ISUOG similarly identifies maternal factors plus MAP, UtA-PI and PlGF as the best combined test. The rationale is mechanistically coherent: MAP reflects maternal cardiovascular adaptation, UtA-PI reflects uteroplacental vascular resistance, and PlGF reflects placental angiogenic function. This model performs substantially better for preterm than term disease.

Biomarker testing also has a role later in pregnancy. The sFlt-1/PlGF ratio has become an important tool for risk stratification in women with suspected disease in several settings, and ACOG issued a 2024 clinical practice update concerning biomarker-assisted assessment of progression to preeclampsia with severe features in selected hospitalized patients. Importantly, such use is not equivalent to universal population screening. The distinction between screening asymptomatic women, predicting disease among high-risk women, diagnosing established preeclampsia and forecasting adverse outcomes after hypertension develops must be preserved when interpreting OAD studies as well. [3]

Ophthalmic artery doppler. OAD is usually performed with a high-frequency linear transducer placed gently over the closed eyelid with minimal pressure. Color Doppler is used to identify the ophthalmic artery posterior to the globe, and pulsed-wave Doppler is then used to obtain reproducible waveforms. Because excessive probe pressure, insonation angle, sampling location and machine settings can affect measurements, standardization is essential. A 2026 practical review specifically addressing how to measure OAD for preeclampsia screening reflects the growing recognition that technical harmonization is a prerequisite for clinical translation. [12]

The conventional indices include PI and RI. PI is derived from the difference between peak systolic and end-diastolic velocities relative to mean velocity, while RI expresses the systolic-diastolic velocity difference relative to peak systolic velocity. End-diastolic velocity (EDV) and absolute peak systolic velocities may also be recorded. However, the ophthalmic artery waveform often has two systolic peaks. The first systolic peak (P1 or PSV1) is followed by a second systolic peak (P2 or PSV2). The peak ratio is generally calculated as PSV2/PSV1. In preeclampsia, the second peak becomes relatively prominent and PR tends to increase.

The emphasis on PR has several advantages. It is dimensionless, potentially reducing dependence

on absolute velocity calibration, and it reflects waveform morphology. Meta-analytic evidence has suggested that PR and P2 outperform PI and RI for complementary diagnosis of preeclampsia. Nevertheless, cut-offs vary among studies, and technical definitions must be standardized before a universal threshold can be adopted.

Reference values are also being refined. A 2026 prospective European cohort of 255 low-risk pregnant women evaluated OAD at 11–14, 20–24, 30–34 weeks and at term. The average PR was approximately 0.56 and did not differ significantly across these intervals or between eyes. The relative stability of PR across gestation is potentially useful, but reference ranges may still vary by population, equipment and acquisition protocol. Additional reference-range work published in 2025 further illustrates the transition from exploratory research toward standardization. [6]

Diagnostic Evidence in Established Preeclampsia:The diagnostic literature provides strong proof of biological signal but should not be confused with prediction. Women who already have preeclampsia frequently demonstrate lower vascular resistance and altered ophthalmic waveforms compared with normotensive pregnant women. A 2023 systematic review and meta-analysis of OAD for complementary diagnosis found particularly favorable sensitivity and specificity for PR and P2. These findings support the concept that maternal cerebral and orbital hemodynamics are measurably altered in clinical preeclampsia. [8]

However, diagnostic separation between established cases and healthy controls can overestimate the performance expected in prospective screening. Prediction requires measurement before disease becomes clinically apparent, ideally in an unselected or clearly defined at-risk population, followed by blinded ascertainment of outcomes. This methodological distinction explains why impressive diagnostic accuracy does not automatically translate into equally strong screening performance.

First-Trimester Prediction. First-trimester OAD is appealing because early identification of women at risk for preterm preeclampsia may permit timely preventive interventions. Initial studies reported associations between OAD indices and later disease, and subsequent work explored integration with maternal factors, MAP, UtA-PI and PlGF. Nevertheless, the most recent evidence urges caution.

The 2026 systematic review and critical appraisal by Ali and colleagues identified five prospective cohort reports representing four unique cohorts. In large unselected populations, stand-alone OAD had limited predictive value. Within multivariable models, detection rates for preterm preeclampsia were approximately 56–59% at a 10% false-positive rate. Smaller selected or mixed-risk cohorts reported much higher discrimination, including AUROC values approaching 0.98, but these estimates were sensitive to population selection and model structure. The authors concluded that incremental benefit beyond established screening remains uncertain and emphasized standardized acquisition, consistent outcome definitions and prespecified validation. [1]

These findings have two implications. First, OAD should not currently replace established first-trimester screening components. Second, future studies should test whether OAD provides clinically meaningful incremental information, rather than merely demonstrating a statistically significant association. Appropriate comparisons include a baseline model of maternal factors and MAP, an established model including UtA-PI and PlGF, and an expanded model adding OAD. Changes in AUC should be accompanied by calibration assessment and, where appropriate, decision-curve or reclassification analyses.

Second-Trimester Prediction: The second trimester may be a particularly relevant window for OAD because placental dysfunction and maternal vascular maladaptation may be more developed while clinical preeclampsia has not yet emerged in most women. Studies at approximately 19–23 weeks have evaluated OAD in combination with other biomarkers. Earlier work by Sapantzoglou and colleagues demonstrated that ophthalmic artery Doppler could be incorporated into multimarker models at this gestational stage. [22]

Recent 2026 literature continues to support investigation of second-trimester OAD, but the same methodological concerns apply: case numbers are often modest, thresholds differ, and external validation is uncommon. For a new prospective study, performing OAD and biochemical sampling at the same visit is especially valuable because it allows direct comparison of vascular and angiogenic signals before the clinical outcome is known. A protocol at approximately 18–22 or 20–24 weeks can therefore provide a biologically and operationally coherent framework for evaluating OAD together with sEng or established angiogenic markers.

Third-Trimester and Near-Term Assessment: At 35–37 weeks, the clinical objective differs from first-trimester prevention. The focus shifts toward predicting imminent disease, deciding surveillance intensity and distinguishing women likely to remain stable from those approaching clinically significant preeclampsia. Studies have compared OAD with PlGF and the sFlt-1/PlGF ratio in this setting. Evidence suggests that OAD can capture hemodynamic abnormalities near term, although its added value for late and term preeclampsia has generally been less consistent than for early or preterm phenotypes. [15,23]

A particularly important development appeared in 2026. Tinajero and colleagues investigated whether the sFlt-1/PlGF ratio is associated with OAD

hemodynamic changes in near-term pregnancy and evaluated OAD for identifying angiogenic imbalance. The reported association, especially involving peak systolic velocity ratio, provides a mechanistic bridge between placental angiogenic dysfunction and maternal cerebral/orbital hemodynamics. This does not establish OAD as a substitute for biochemical testing, but it supports the hypothesis that OAD may function as a low-cost, non-invasive surrogate marker in settings where angiogenic assays are unavailable or expensive. [24]

Angiogenic Biomarkers: PlGF, sFlt-1 and Soluble Endoglin. PlGF and sFlt-1 are currently the best characterized angiogenic biomarkers in preeclampsia. PlGF promotes angiogenesis and placental vascular development, whereas sFlt-1 acts as a circulating decoy receptor that binds VEGF and PlGF. The characteristic antiangiogenic state of preeclampsia is therefore reflected by increased sFlt-1 and reduced PlGF, and the sFlt-1/PlGF ratio has substantial clinical value in selected diagnostic and prognostic contexts.

Soluble endoglin is another antiangiogenic factor with particular relevance to endothelial dysfunction. Endoglin is a co-receptor involved in transforming growth factor-beta signaling. The soluble circulating form can disrupt endothelial signaling and contribute to vascular dysfunction. Increased maternal sEng concentrations have been described before and during clinical preeclampsia. A meta-analysis evaluating sEng by trimester found higher concentrations in women with preeclampsia, with stronger evidence in the second and third trimesters than in the first. Thus, sEng is biologically attractive as a component of a multimarker strategy, although it is less established for routine clinical use than PlGF or the sFlt-1/PlGF ratio. [17]

For research purposes, sEng may be particularly informative because it captures a pathway that is related to but not identical with PlGF and sFlt-1. If OAD reflects maternal cerebrovascular consequences of endothelial and angiogenic disturbance, simultaneous measurement of sEng could help determine whether abnormal orbital hemodynamics parallel antiangiogenic activity. This relationship is plausible but remains insufficiently characterized, creating a relevant area for prospective investigation.

Integrating Ophthalmic Artery Doppler with Angiogenic Biomarkers: The central question for the next generation of studies is not whether OAD is statistically associated with preeclampsia, but whether it contributes information that changes risk estimation beyond established predictors. The 2025 systematic review of predictive accuracy explicitly considered stand-alone and incremental performance. Its findings indicate substantial heterogeneity and insufficient evidence for routine clinical implementation. The 2026 first-trimester review reached a similar conclusion: OAD may be informative, but the magnitude and clinical relevance of incremental benefit remain uncertain. [4]

A rational multimarker model should represent different components of disease biology. Maternal history captures baseline susceptibility; MAP reflects cardiovascular phenotype; UtA-PI reflects uteroplacental vascular resistance; PlGF and sFlt-1 reflect placental angiogenic balance; sEng reflects antiangiogenic endothelial disturbance; and OAD may reflect maternal cerebral vascular adaptation. Combining non-redundant signals could theoretically improve discrimination and risk stratification, but adding correlated markers can also increase complexity without meaningful gain. Therefore, incremental value must be demonstrated empirically.

One clinically relevant model-development strategy would compare: (1) clinical-anamnestic factors alone; (2) clinical factors plus OAD; (3) clinical factors plus sEng; and (4) clinical factors plus OAD and sEng. If resources permit, an established comparator including MAP, UtA-PI and/or PlGF should also be evaluated. Such a design would clarify whether OAD and sEng are independent predictors, whether they interact, and whether the combined model improves discrimination and calibration. Internal validation using bootstrapping and subsequent external validation in a separate cohort are essential before clinical implementation.

The literature contains extensive evidence on OAD and preeclampsia, extensive evidence on angiogenic imbalance, and emerging evidence directly comparing OAD with PlGF or the sFlt-1/PlGF ratio. In contrast, the specific combination of OAD with soluble endoglin appears much less developed. This distinction is important when defining scientific novelty. Neither OAD nor sEng should be presented as newly discovered predictors. A more defensible research question is whether their combined assessment captures complementary aspects of maternal vascular and antiangiogenic dysfunction and improves individualized prediction compared with either component alone.

A prospective cohort design is preferable for answering this question. Women should be enrolled before the development of the primary outcome, OAD and sEng should be measured according to prespecified protocols, and participants should be followed until delivery. The primary outcome should be clearly defined, preferably preeclampsia, with gestational hypertension, preterm preeclampsia, severe disease and adverse perinatal outcomes considered secondary outcomes. Group assignment should occur after follow-up according to observed outcomes rather than by preselecting fixed numbers of future cases and controls.

Methodological Limitations of the Current Evidence. Several limitations repeatedly appear in the OAD literature. First, sample sizes and numbers of preeclampsia events are often small. Prediction models developed with too few events relative to the number of candidate predictors are vulnerable to overfitting and exaggerated performance. Second, study populations differ markedly, ranging from unselected screening cohorts to high-risk referrals and women already presenting with hypertension. Performance estimates from these settings are not directly interchangeable.

Third, Doppler acquisition and reporting have not been fully standardized. Differences in transducer pressure, sampling location, insonation angle, waveform selection, unilateral versus bilateral measurements and parameter definitions can introduce heterogeneity. The publication of measurement guidance and gestational reference ranges in 2025–2026 is therefore an important advance. Fourth, outcome definitions differ, especially for early-onset, preterm, severe and term preeclampsia. Fifth, many studies report discrimination but provide limited information on calibration, clinical utility or external validation.

Finally, statistical significance is not synonymous with clinical usefulness. A new marker that changes AUC only minimally may not justify added complexity, whereas a modest statistical improvement could still be valuable if the test is inexpensive, reproducible and accessible in low-resource settings. Because OAD uses ultrasound equipment already available in many obstetric services, cost-effectiveness and implementation research should accompany future accuracy studies. The potential appeal of OAD is particularly strong in settings where advanced biochemical assays are not routinely available. A non-invasive ultrasound marker that can be acquired during an existing antenatal visit could expand vascular phenotyping without requiring additional laboratory infrastructure. However, low cost alone cannot compensate for inadequate accuracy or poor reproducibility. Training requirements, interobserver variability, machine dependence and quality assurance must be considered.

The 2026 evidence linking OAD with angiogenic imbalance is especially relevant to this discussion. If validated, OAD could potentially identify women whose vascular phenotype resembles an antiangiogenic state and help determine who requires biochemical testing or intensified surveillance. Such a contingent strategy may be more realistic than replacing established biomarkers altogether. Prospective health-economic evaluation would be required before recommending this approach.

Future Research Priorities. Future studies should prioritize large prospective cohorts with prespecified protocols and sufficient numbers of preeclampsia events. Recruitment should occur before outcome development, and investigators should clearly distinguish prediction from diagnosis. OAD acquisition should follow standardized methodology, ideally using bilateral measurements and predefined waveform-quality criteria. P1, P2, PR, PI, RI and EDV should be reported consistently, while investigators should avoid data-driven selection of cut-offs without validation.

Biomarker sampling and OAD should be performed at the same gestational visit when their relationship is a research objective. For studies focused on sEng, the second trimester is attractive because meta-analytic evidence for sEng differences is stronger than in the first trimester and because this timing precedes many clinical presentations of preeclampsia. Serial assessment may reveal whether changes over time are more informative than a single measurement. Model development should be conservative and transparent. Candidate predictors should be limited relative to the number of outcome events; missing data should be handled appropriately; continuous variables should generally remain continuous rather than being prematurely dichotomized; and internal validation should quantify optimism. Reporting should include AUC with confidence intervals, sensitivity and specificity at clinically relevant thresholds, calibration plots or statistics and, where possible, decision-curve analysis. External validation in geographically and ethnically distinct populations is essential.

An especially valuable future question is whether a model combining clinical factors, OAD and sEng performs better than clinical factors plus either OAD or sEng alone. A second question is how such a model compares with established combinations incorporating MAP, UtA-PI and PlGF. These comparisons would position the new approach within current clinical practice rather than evaluating it in isolation.

Conclusions: Ophthalmic artery Doppler has progressed from a physiologic research technique to a promising candidate marker of maternal vascular maladaptation in preeclampsia. The strongest waveform signals appear to be the second systolic peak and the peak systolic velocity ratio, while conventional PI and RI remain useful but generally less discriminative. Evidence through 2026 confirms associations between OAD abnormalities and preeclampsia, yet recent systematic reviews caution that standalone first-trimester prediction is limited in large unselected cohorts and that incremental benefit beyond established screening models has not been conclusively demonstrated.

The emerging link between OAD and angiogenic imbalance provides an important new direction. PlGF and sFlt-1 are established components of the angiogenic pathway, while soluble endoglin represents an additional antiangiogenic mechanism associated with endothelial dysfunction. Combining OAD with sEng is therefore biologically plausible and may capture complementary maternal vascular and biochemical information. However, this concept requires prospective validation and should not yet be presented as an established clinical algorithm.

Future research should focus on standardized OAD acquisition, simultaneous biomarker assessment, adequately powered prospective cohorts, rigorous model development and validation, and direct comparison with established screening strategies. If these requirements are met, multimarker approaches integrating maternal clinical characteristics, ophthalmic artery hemodynamics and angiogenic biomarkers may contribute to more individualized prediction and risk stratification of preeclampsia.

REFERENCES

1. Ali S, Mustafa Z, Jibran H et al. First-trimester ophthalmic artery Doppler for prediction of early-onset and preterm preeclampsia: a systematic review and critical appraisal. BMC Pregnancy Childbirth. 2026. doi:10.1186/s12884-026-09618-9. Online ahead of print.

2. American College of Obstetricians and Gynecologists. Gestational Hypertension and Preeclampsia. ACOG Practice Bulletin No. 222. Obstet Gynecol. 2020;135: e237-e260. Reaffirmed 2026.

3. American College of Obstetricians and Gynecologists. Clinical Practice Update: Biomarker Prediction of Preeclampsia With Severe Features. Obstet Gynecol. 2024;143:e153-e154.

4. Arkorful J, Browne JL, Adu-Bonsaffoh K, Ali S, Srofenyoh E, Bloemenkamp KWM. Predictive accuracy of ophthalmic artery Doppler for pre-eclampsia: a systematic review. BMJ Open. 2025;15:e094348.

5. Brandão AHF, Barbosa AS, Lopes APBM, Leite HV, Cabral ACV. Dopplerfluxometria de artérias oftálmicas e avaliação da função endotelial nas formas precoce e tardia da pré-eclâmpsia. Radiol Bras. 2012;45(1):20-23.

6. Campana-Rüegg L, Hofmann M, Wawrla-Zepf J et al. Ophthalmic artery Doppler: reference values in low-risk pregnant women. Arch Gynecol Obstet. 2026. doi:10.1007/s00404-026-08489-x. Online ahead of print.

7. Carneiro RS, Sass N, Diniz AL, Souza EV, Torloni MR, Moron AF. Ophthalmic artery Doppler velocimetry in healthy pregnancy. Int J Gynaecol Obstet. 2008;100(3):211-215.

8. de Melo PFMV, Roever L, Mendonça TMS et al. Ophthalmic artery Doppler in the complementary diagnosis of preeclampsia: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2023; 23:343.

9. de Souza PC, Alves JA, Júnior EA, Martins WP, Costa FD. Second trimester screening of preeclampsia using maternal characteristics and uterine and ophthalmic artery Doppler. Ultraschall Med. 2018;39:190-197.

10. Gana N, Sarno M, Vieira N, Wright A, Charakida M, Nicolaides KH. Ophthalmic artery Doppler at 11-13 weeks' gestation in prediction of preeclampsia. Ultrasound Obstet Gynecol. 2022;59:731-736.

11. Gurgel Alves JA, Praciano de Sousa PC, Bezerra Maia e Holanda Moura S, Kane SC, da Silva Costa F. First-trimester maternal ophthalmic artery Doppler analysis for prediction of pre-eclampsia. Ultrasound Obstet Gynecol. 2014;44:411-418.

12. Hanton T, Khalil A. How to measure ophthalmic artery Doppler for pre-eclampsia screening. Best Pract Res Clin Obstet Gynaecol. 2026; 108: 102760.

13. International Society of Ultrasound in Obstetrics and Gynecology, Bilardo CM, Chaoui R et al. ISUOG Practice Guidelines (updated): performance of 11-14-week ultrasound scan. Ultrasound Obstet Gynecol. 2023;61(1):127-143.

14. Kane SC, Brennecke SP, da Silva Costa F. Ophthalmic artery Doppler analysis: a window into the cerebrovasculature of women with pre-eclampsia. Ultrasound Obstet Gynecol. 2017;49:15-21.

15. Lau KGY, Kountouris E, Salazar-Rios L, Nicolaides KH, Kametas NA. Prediction of adverse outcome by ophthalmic artery Doppler and angiogenic markers in pregnancies with new onset hypertension. Pregnancy Hypertens. 2023;34:110-115.

16. Levine RJ, Lam C, Qian C et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. N Engl J Med. 2006;355:992-1005.

17. Margioula-Siarkou G, Margioula-Siarkou C, Petousis S et al. Soluble endoglin concentration in maternal blood as a diagnostic biomarker of preeclampsia: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2021;258:366-381.

18. Nicolaides KH, Sarno M, Wright A. Ophthalmic artery Doppler in the prediction of preeclampsia. Am J Obstet Gynecol. 2022;226:S1098-S1101.

19. Poon LC, Shennan A, Hyett JA et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet. 2019;145(Suppl 1):1-33.

20. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: pathophysiology, challenges, and perspectives. Circ Res. 2019;124:1094-1112.

21. Roberts JM, Rich-Edwards JW, McElrath TF, Garmire L, Myatt L. Subtypes of preeclampsia: recognition and determining clinical usefulness. Hypertension. 2021;77(5):1430-1441.

22. Sapantzoglou I, Wright A, Arozena MG et al. Ophthalmic artery Doppler in combination with other biomarkers in prediction of pre-eclampsia at 19-23 weeks' gestation. Ultrasound Obstet Gynecol. 2021;57:75-83.

23. Sarno M, Wright A, Vieira N et al. Ophthalmic artery Doppler in combination with other biomarkers in prediction of pre-eclampsia at 35-37 weeks' gestation. Ultrasound Obstet Gynecol. 2021; 57:600-606.

24. Tinajero MF, Faraci C, Cuenca M et al. Ophthalmic artery Doppler as potential surrogate marker of angiogenic imbalance in near-term pregnancy. Ultrasound Obstet Gynecol. 2026. doi:10. 1002/uog.70270. Online ahead of print.

25. Zeisler H, Llurba E, Chantraine F et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med. 2016;374:13-22.