CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST
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FIELD OF STUDY: MEDICINE

DOPPLER ASSESSMENT OF THE OPHTHALMIC ARTERY IN THE PREDICTION OF PREECLAMPSIA

SUMMARY OF THE DOCTORAL THESIS

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Contents

Acknowledgements……………………………………………………………….…page 4

List of published scientific papers………………………………………….................page 5

Abbreviations……………………………………………………………………….page 8

Introduction…………………………………………….……………….…….…......page 10

I. General Part ……………………………………………………………............page 11

1a. Preeclampsia

I.1a.1 Definition………………………………….…………………………........page 12

I.1a.2 Risk factors…………………..…...………….……………………….........page 12

I.1a.3 Pathogenesis……………………………………………………………......page 12

I.1a.4 Clinical and paraclinical diagnosis….....……………………………………....page 12

I.1a.5 Management…....…………..………………………………………............page 13

I.1a.6 Preeclampsia screening…………………………………………….............page 13

I.1a.7 Long-term complications……..……………………………………….......page 14

1b. Gestational diabetes

I.1b.1 Definition…………………………………………………...…………….…page 14

I.1b.2 Risk factors…………………..…...…………………………………….........page 14

I.1b.3 Pathogenesis………………………………….……………………...page 15

I.1b.4 Gestational diabetes screening. Clinical and paraclinical

diagnosis…...…………………………………………………….……………......page 15

I.1b.5 Management…....…………..…………………………………………........page 15

I.1b.6 Complications ……………………………..……..……………….……......page 16

2.Ophthalmic artery

I.2.1 Anatomy…………………………………..……………………………........page 16

I.2.2 Doppler assessment of the ophthalmic artery……….……..…………………….…page 16

I.2.3 Doppler assessment of the ophthalmic artery in the first trimester……............page 17

I.2.4 Doppler assessment of the ophthalmic artery in the second trimester……..….page 17

I.2.5 Doppler assessment of the ophthalmic artery in the third trimester…...….page 18

II. Personal contributions…………………………………….…………….......page 19

3. Working hypothesis and general objectives..page 20

4. General research methodology..page 20

5. Ophthalmic artery at 11–13 weeks in the prediction of preeclampsia

5.1. Introduction (working hypothesis and specific objectives)...............................page 21

5.2. Material and method or Patients and methods..page 21
5.3. Results..page 22
5.4. Discussions ....page 22
5.5. Conclusions ………...page 23
6. Usefulness of the ophthalmic artery in gestational diabetes in the first trimester
6.1. Introduction (working hypothesis and specific objectives)................................page 23
6.2. Material and method or Patients and methods..page 23
6.3. Results..page 24
6.4. Discussions..page 25
6.5. Conclusions ………...page 27
7. Doppler indices of the ophthalmic artery in relation to early and late preeclampsia at 11–13 weeks
7.1. Introduction (working hypothesis and specific objectives)………………........page 27
7.2. Material and method or Patients and methods..page 28
7.3. Results..page 28
7.4. Discussions ....page 29
7.5. Conclusions ....page 29
8. Evaluation of the ophthalmic artery in relation to the birth of small-for-gestational-age newborns
8.1. Introduction (working hypothesis and specific objectives)................................page 30
8.2. Material and method or Patients and methods..page 30
8.3. Results..page 31
8.4. Discussions ....page 32
8.5. Conclusions ....page 33
9. Conclusions and personal contributions……………………………………......page 33
Bibliography………………………………………………………………......page 36

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List of Published Scientific Papers

1. **Gana N, Sarno M, Vieira N, Wright A, Charakida M, Nicolaides KH. Ophthalmic artery Doppler at 11-13 weeks' gestation in prediction of pre-eclampsia. Ultrasound Obstet Gynecol. 2022 Jun;59(6):731-736. doi: 10.1002/uog.24914. PMID: 35642909.**

Revista: Ultrasound in Obstetrics and Gynaecology (ISUOG), 2022, Volumul 59(6), Paginile: 731-736, Indexare ISI, FI: 8.67

Link: Ophthalmic artery Doppler at 11–13 weeks' gestation in prediction of pre-eclampsia - Gana - 2022 - Ultrasound in Obstetrics & Gynecology - Wiley Online Library
(Capitolul II.5)

2. **Gana N, Chatzakis C, Sarno M, Charakida M, Nicolaides KH. Evidence that systemic vascular resistance is increased before the development of gestational diabetes mellitus. Am J Obstet Gynecol. 2025 Apr;232(4):398.e1-398.e9. doi: 10.1016/j.ajog.2024.08.039. Epub 2024 Aug 30.**

Revista: American Journal of Obstetrics and Gynecology (AJOG), 2025 Apr;Volumul: 232(4)Paginile:398.e1-398.e9. Published online: August 29, 2024 , Indexare ISI, FI: 8.4

Link: Evidence that systemic vascular resistance is increased before the development of gestational diabetes mellitus - PubMed
(Capitolul II.6)

3. **Gana N, Pittokopitou S, Solonos F, Perdeica A, Fitiri M, Nicolaides KH. Ophthalmic Artery Doppler Indices at 11-13 Weeks of Gestation in Relation to Early and Late Preeclampsia. J Clin Med. 2025 Jul 7;14(13):4811. doi: 10.3390/jcm14134811. PMID: 40649185; PMCID: PMC12251155.**

Revista: Journal of Clinical Medicine , an 2025 , Volumul 14 (13), Paginile:4811 , Indexare ISI, FI: 2.9

Link: Ophthalmic Artery Doppler Indices at 11-13 Weeks of Gestation in Relation to Early and Late Preeclampsia - PubMed

(Capitolul II.7)

4. **Gana N, Ianosev D, Allafi N, Impis Oglou M, Nicolaides KH. Ophthalmic Artery Doppler at 11-13 Weeks' Gestation and Birth of Small-for-Gestational-Age Neonates. J Clin Med. 2025 Jun 21;14(13):4425. doi: 10.3390/jcm14134425. PMID: 40648799; PMCID: PMC12249861.**

Revista: Journal of Clinical Medicine, an 2025, Volumul 14(13), Paginile:4425 , Indexare ISI, FI: 2.9

Link: Ophthalmic Artery Doppler at 11–13 Weeks' Gestation and Birth of Small-for- Gestational-Age Neonates - PMC

(Capitolul II.8)

5. **Gana, N.; Năstac, A.; Apostol, L.M.; Huluță, I.; Gica, C.; Peltecu, G.; Gica, N. The Role of Ophthalmic Artery Doppler in Predicting Preeclampsia: A Review of the Literature. *Medicina* 2026, *62*, 186. https://doi.org/10.3390/medicina62010186**

Revista: Medicina, an 2026, Volumul 62(1), Paginile:168 , Indexare ISI, FI: 2.4

Link: https://www.mdpi.com/1648-9144/62/1/186

(Capitolul II.9)

Abbreviations

HbA1c – Glycated Hemoglobin

3D – Three-dimensional

ACC/AHA – American College of Cardiology / American Heart Association

ACOG – American College of Obstetricians and Gynecologists

ADA – American Diabetes Association

ADHD – Attention Deficit Hyperactivity Disorder

ALT – Alanine Aminotransferase

ANG-II – Angiotensin II

APS – Antiphospholipid Syndrome

AST – Aspartate Aminotransferase

AUC – Area Under the Curve

AVC – Stroke (Cerebrovascular Accident)

b-HCG – Beta Human Chorionic Gonadotropin

CI – Confidence Interval

COX-1/2 – Cyclooxygenase 1 and 2

CRL – Crown-Rump Length

dNK – Decidual Natural Killer Cells

DR – Detection Rate EDV – End-Diastolic Velocity

FDA – Food and Drug Administration

FIGO – International Federation of Gynecology and Obstetrics

FMF – Fetal Medicine Foundation

FP – False Positive

FPR – False Positive Rate

GDM – Gestational Diabetes Mellitus

GGT – Gamma-Glutamyl Transferase

GLUT4 – Glucose Transporter Type 4

HELLP – Hemolysis, Elevated Liver Enzymes, Low Platelets Syndrome

HDP – Hypertensive Disorders of Pregnancy

HLG – Complete Blood Count

IADPSG – International Association of Diabetes and Pregnancy Study Groups

IGF – Insulin-Like Growth Factor

IMC – Body Mass Index (BMI)

ISSHP – International Society for the Study of Hypertension in Pregnancy

IVF – In Vitro Fertilization

L – Liter

MAP – Mean Arterial Pressure

MoM – Multiples of the Median

MV – Mean Velocity Peaks

NHS – National Health System (UK)

NICE – National Institute for Health and Care Excellence

NO – Nitric Oxide

NOS – Nitric Oxide Synthase

NPH – Neutral Protamine Hagedorn

OGTT – Oral Glucose Tolerance Test

OMS – World Health Organization (WHO)

PAPP-A – Pregnancy-Associated Plasma Protein A

PE – Preeclampsia

PI – Pulsatility Index

PlGF – Placental Growth Factor

PMDV – Peak Mid-Diastolic Velocity

PR – Ratio between First End-Diastolic Flow and First Systolic Peak

PRF – Pulse Repetition Frequency

PSV – Peak Systolic Velocity

RCIU – Intrauterine Growth Restriction (IUGR)

RI – Resistance Index

ROC – Receiver Operating Characteristic

ROS – Reactive Oxygen Species

sEng – Soluble Endoglin

sFLT – Soluble fms-like Tyrosine Kinase-1

SLE – Systemic Lupus Erythematosus

SOGC – Society of Obstetricians and Gynaecologists of Canada

Introduction

Preeclampsia (PE) is one of the most severe obstetric complications, contributing significantly to maternal and fetal morbidity and mortality.[1,2] It affects 2–8% of pregnancies, with a higher incidence in developing countries,[3,4] and usually occurs after 20 weeks of gestation in women with previously normal blood pressure, potentially leading to serious or fatal complications for both mother and fetus.[5–11] PE and fetal growth restriction are major causes of neonatal mortality and long-term disability, and are also associated with an increased cardiovascular risk later in life.[12–14] Delivery is the only treatment option, often resulting in iatrogenic prematurity, with PE accounting for 17% of preterm births.[4,15]

Despite advances in understanding its pathophysiology, PE remains incompletely elucidated,[4] and research focuses on early identification and prevention of maternal and fetal complications.

Another common complication is gestational diabetes (GDM), with a global prevalence of 6%, increasing with obesity,[16] ranging from 5.8% in Europe to up to 13% in the Middle East and North Africa.[17] Screening is not standardized internationally, being recommended either universally or only for patients with risk factors, usually in the second trimester. In Romania, universal screening with a 75 g glucose test is recommended, with diagnostic serum values >92 mg/dl (0 h), >180 mg/dl (1 h), and >153 mg/dl (2 h).[18,19]

This thesis evaluates the usefulness of ophthalmic artery Doppler, combined with other biomarkers (UtA-PI, MAP, PlGF, sFLT), in predicting PE and in the early screening of GDM. The studies are prospective and observational, including all women presenting for first-trimester morphology. The ophthalmic artery reflects intracranial vascularization, and early maternal cardiovascular changes, including increased peripheral vascular resistance, are translated into alterations in Doppler waveforms.[20] Women at risk of GDM exhibit a similar cardiovascular profile.[21]

I. GENERAL PART

Chapter I.1a Preeclampsia

I.1a.1. Definition

Hypertensive disorders in pregnancy are a heterogeneous group of clinical and paraclinical manifestations and include chronic hypertension preceding pregnancy or occurring within the first 20 weeks of gestation with values ≥140/90 mmHg; gestational hypertension, which is hypertension appearing after 20 weeks of gestation without proteinuria; preeclampsia–eclampsia, characterized by newly onset hypertension accompanied by new-onset proteinuria; and chronic hypertension with superimposed preeclampsia, defined as chronic hypertension with de novo appearance of proteinuria or other signs and symptoms associated with preeclampsia after 20 weeks, or chronic proteinuria with newly onset hypertension.[22,23]

I.1a.2. Risk Factors

Several maternal risk factors are known to be associated with the development of preeclampsia.[24] These include: maternal age [25], parity [26,27], history of preeclampsia [28,29], interpregnancy interval [30,31,32], assisted reproductive technologies [33,34,35,36], family history [37,38,39], obesity [40,41], race and ethnicity [24,42,43], comorbidities [24,44,45], and fetal sex [46].

I.1a.3. Pathogenesis

The pathogenesis of PE is not completely understood; however, significant progress has been made in recent years in understanding the mechanisms underlying preeclampsia. The placenta is the central element involved in the etiology of preeclampsia, as its removal leads to the improvement and resolution of symptoms.[47,28] Multiple studies have highlighted new mechanisms, although this is a vast topic beyond the scope of this thesis. The hypothesis that deficient trophoblast invasion associated with placental hypoperfusion may lead to PE has been supported by both human and animal studies.[49,50]

I.1a.4. Clinical and Paraclinical Diagnosis

The first mentions of eclampsia date back to the era of Hippocrates, who associated headache, dizziness, and convulsions with pregnancy, with the first written description appearing in 1619. In the 19th–20th centuries, various theories regarding etiology were proposed, including renal, uterine, epileptic, or infectious origins. In 1894, the effect of placental toxins was described, and as the pathophysiology of PE became better understood, diagnostic criteria evolved.[51]
According to ISSHP and ACOG, PE is gestational hypertension accompanied by hepatic or renal dysfunction, thrombocytopenia, neurological symptoms, or uteroplacental dysfunction (growth restriction, abnormal Doppler, or fetal death).[52,53,54,55]
Clinical manifestations:

- Typical: Most patients are nulliparous or have risk factors (obesity, chronic kidney disease, history of PE, chronic hypertension, pregestational diabetes).[56]
- Warning symptoms: Severe headache, visual disturbances, photophobia, upper abdominal pain, confusion, dyspnea.[56]
- Atypical presentation: Onset before 20 weeks (associated with molar pregnancy or APS).[56]
- Postpartum: Appears within the first 48 hours.[56]
- Rare forms: PE without hypertension, isolated hypertension (15–25%), isolated proteinuria.[56]

Investigations: Complete blood count, serum creatinine, transaminases (AST, ALT), bilirubin, proteinuria (24 h or protein/creatinine ratio); coagulation tests only in complications. Fetal evaluation includes NST, biophysical profile, growth ultrasound, and amniotic fluid assessment.[56]

I.1a.5. Preeclampsia Screening Methods

Combined risk screening for preeclampsia, which includes maternal characteristics, UtA-PI, PlGF, and PAPP-A, allows early identification of high-risk pregnancies, detecting 75% of early-onset and 45% of late-onset cases.[46,57,28,59] The sFLT/PlGF ratio can predict the onset of PE in the following week.[46,60] These methods improve individualized follow-up and allow early interventions to reduce maternal and fetal complications.

I.1a.6. Management

a. Prevention

ACOG, NICE, and SOGC recommend starting aspirin treatment before 16 weeks in all women identified at risk for placental insufficiency.[1] The ASPRE study administered 150 mg daily from 11–13 weeks until 36 weeks of gestation.[61] Multiple other studies have shown the ineffectiveness of treatments such as folic acid, fish oil, sodium restriction, and vitamins C, D, and E.[62]

b. Treatment

The only definitive treatment for preeclampsia is delivery of the fetus and placenta.[2] Antihypertensive treatment aims to reduce maternal and fetal complications and is indicated by ACOG when BP ≥160/110 mmHg. Fetal monitoring includes ultrasound every 3–4 weeks and weekly amniotic fluid assessment. Delivery is recommended at 37 weeks in cases of gestational hypertension or PE without severe signs, and at 34 weeks for PE with severe manifestations or complications (uncontrolled BP, refractory headache, abdominal pain, stroke, visual symptoms, myocardial infarction, HELLP, renal failure, pulmonary edema, eclampsia, or fetal distress). Magnesium sulfate is administered for eclampsia prophylaxis in severe PE, during labor, and 24 hours postpartum.[63]

I.1a.7. Long-Term Complications

Normal pregnancy induces a pro-atherogenic metabolic status. Immediately after conception, cardiac output and hypercoagulability increase. After 20 weeks, insulin resistance and dyslipidemia appear. These changes are more pronounced in women who develop preeclampsia. Although blood pressure returns to normal after delivery, there is evidence of endothelial dysfunction, and affected women remain at increased risk of cardiovascular disease.

Chapter I.1b. Gestational Diabetes

I.1b.1. Definition

Gestational diabetes affects 6% of pregnant women and has a rising trend due to increasing obesity rates.[16] Gestational diabetes (GDM) is defined as glucose intolerance diagnosed for the first time during pregnancy.[64]

I.1b.2. Risk Factors

The most well-known risk factors for gestational diabetes include: maternal age, family history of diabetes, previous gestational diabetes, macrosomic fetus, non-Caucasian ethnicity, elevated body mass index or obesity, and smoking.[17] Some studies have evaluated whether genes involved in type 2 diabetes are also implicated in gestational diabetes.[64] The most common risk factor is considered maternal obesity. Additionally, polycystic ovary syndrome has been implicated in the development of gestational diabetes.[66]

I.1b.3. Pathogenesis

During pregnancy, multiple adaptive changes occur in the maternal cardiovascular, renal, respiratory, hematologic, and metabolic systems to support normal fetal development. An important metabolic change is insulin sensitivity. Throughout pregnancy, insulin sensitivity varies according to the trimester: in the first trimester, insulin sensitivity increases to store glucose in adipose tissue as energy for later use.[67]

I.1b.4. Gestational Diabetes Screening. Clinical and Paraclinical Diagnosis

There is no international consensus regarding screening for gestational diabetes. Different international societies have proposed screening either only for women with risk factors or as universal screening.[18]
The study groups of the International Association of Diabetes and Pregnancy Study Groups (IADPSG), together with the American Diabetes Association, recommend testing at-risk women at the first prenatal visit using the following diagnostic criteria: glycated hemoglobin ≥6.5% or fasting serum glucose ≥126 mg/dl (7.0 mmol/L) after 8 hours of fasting, or after a 75 g oral glucose tolerance test (OGTT) dissolved in water, with 2-hour serum glucose values above 200 mg/dl (11.1 mmol/L), or in a patient with hyperglycemia symptoms, a serum glucose value at any time ≥200 mg/dl (11.1 mmol/L).[68]

I.1b.5. Management

Once gestational diabetes is diagnosed, the pregnant woman should be counseled and warned about the consequences of uncontrolled high blood glucose for herself and the fetus. Nutritional therapy is the first step. The patient is advised to follow a nutritional plan that lowers blood

glucose levels, primarily by limiting carbohydrates. She is taught to monitor her blood glucose at 1 hour and 2 hours postprandial.[69]
Insulin is the treatment of choice if initial measures are ineffective. Additionally, in some countries, Metformin is considered safe and administered during pregnancy.[70] Pharmacologic therapy is used when dietary modifications and lifestyle changes fail to maintain glucose balance. Insulin is considered safe in pregnancy, as only a small amount crosses the placenta.[70]

I.1b.6. Complications

Gestational diabetes is associated with multiple complications. In the short term, these include: preterm birth, admission to neonatal intensive care, brain injury, respiratory distress syndrome, hypertension, preeclampsia, and cesarean delivery. Maternal hyperglycemia causes fetal hyperinsulinemia, increasing the risk of neonatal hypoglycemia, hyperbilirubinemia, macrosomia, and polyhydramnios, with possible obstetric complications such as shoulder dystocia and severe perineal tears.[71,72,73].
In the long term, it increases maternal risk of type 2 diabetes, cardiovascular disease, metabolic syndrome, kidney, liver, and retinal disorders.[72]

Chapter 2. Ophthalmic Artery

I.2.1. Anatomy

The eyes are specialized organs of the visual system located within the orbits, consisting of the eyeballs and their accessories: nerves, arteries, veins, and muscles.[174]

I.2.2. Doppler Evaluation of the Ophthalmic Artery

The ophthalmic artery, a branch of the internal carotid artery, is accessible via ultrasound due to the peripheral position of the eyeball and reflects cerebral vascularization.[75] Doppler ultrasound is non-invasive, safe, and rapid.[76]
Preeclampsia involves placental dysfunction through defective spiral artery remodeling and oxidative stress with systemic inflammation.[77] The ophthalmic artery provides an inexpensive and reproducible method to assess cerebral vascular changes.[77] Cardiac contraction generates flow waves: the first systolic peak (PSV1) represents the direct wave, and the second (PSV2) the reflected wave, influenced by vasoconstriction or vasodilation; the PSV2/PSV1 ratio reflects these changes.[78]

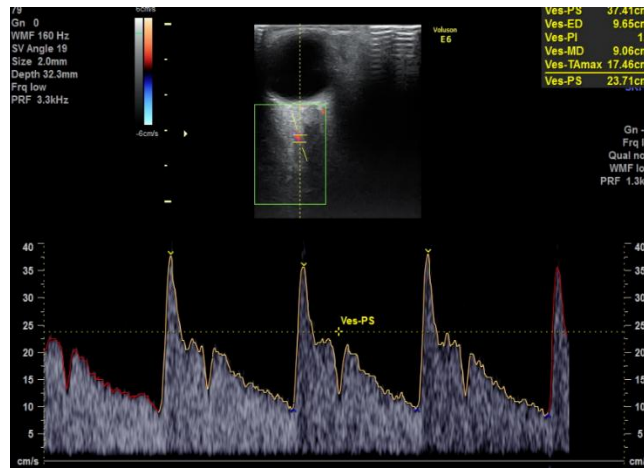

Figure 2.2 Doppler Indices of the Uterine Artery (personal collection)

I.2.3. Doppler Evaluation of the Ophthalmic Artery in the First Trimester

A small study was conducted on 440 pregnant women in the first trimester, between 11 and 14 weeks. The authors reported an increase in the second PSV in pregnancies affected by preeclampsia compared to unaffected pregnancies. All other ultrasound parameters did not differ significantly.[79]

I.2.4. Doppler Evaluation of the Ophthalmic Artery in the Second Trimester

Recently, a prospective observational cohort study examined a larger number of women with singleton pregnancies in the second trimester. A total of 2,853 pregnancies were assessed, recording maternal characteristics, MAP, UtA-PI, PlGF, sFLT, and Doppler examination of the ophthalmic arteries. Four indices of the ophthalmic artery were investigated: first PSV, second PSV, PSV2/PSV1 ratio, and PI. It was found that the PSV ratio improved prediction from 56% to 80% for preterm PE and from 34% to 46% for term PE, at a 10% false-positive rate. The ophthalmic artery, in combination with other biomarkers, proved effective in predicting PE, especially before 37 weeks.[80]

I.2.5. Doppler Evaluation of the Ophthalmic Artery in the Third Trimester

A larger study, conducted on 2,287 singleton pregnancies in the third trimester, analyzed the ophthalmic artery for PE prediction.[81] Using maternal factors, MAP, PlGF, and sFLT, the overall detection rate of PE was improved from 75.7% to 76.7%, at a 10% false-positive rate, by adding the PSV2/PSV1 ratio. The prediction rate of PE in the next three weeks from the time of examination improved from 84.8% to 88.6% using the combination of maternal characteristics, MAP, and PlGF.[82]

II. PERSONAL CONTRIBUTIONS

II.3. Working Hypothesis and General Objectives

Preeclampsia and gestational diabetes are obstetric complications with significant impact on both mother and fetus, associated with preterm birth, abnormal birth weight, neonatal hypoglycemia, and hospitalization. This thesis evaluates methods for early prediction of these complications to individualize maternal monitoring and counseling.

The ophthalmic artery, accessible via ultrasound and reproducible, can be incorporated into first-trimester screening for preeclampsia and gestational diabetes. The working hypothesis is that the PSV2/PSV1 ratio, alone or combined with other markers, can identify patients at risk of early preeclampsia and gestational diabetes.

The studies are prospective and observational, including all women presenting for first-trimester morphology, with collection of demographic data, maternal history, fetal ultrasound assessment, blood pressure, UtA-PI, and Doppler measurements of the ophthalmic artery (PSV1, PSV2, PI, and PSV2/PSV1 ratio).

II.4. General Research Methodology

Medical studies are divided into descriptive (case reports, case series, cross-sectional studies) and analytical (observational and experimental), with observational studies including case-control and cohort studies, retrospective or prospective.[83]

In this prospective, observational study, all patients between 11 and 13+6 weeks of gestation, with singleton pregnancies presenting for first-trimester morphology, were recruited at King’s College Hospital, London (n=4,200, June–August 2019 and May 2020–February 2021). Multiple pregnancies and fetuses with major malformations were excluded.

Ophthalmic artery assessment was performed using color pulsed Doppler with a 7.5 MHz linear transducer, applied over the upper eyelid, incidence angle $<20°$, gate 2 mm, depth 3–4.5 cm, filter 50 Hz, and PRF 125 kHz. Examination time for each eye was brief, a few seconds, with maximum mechanical index 0.4.[84]

II.5. Study 1
Ophthalmic Artery at 11–13 Weeks in Preeclampsia Prediction

II.5.1. Introduction

The ophthalmic artery, similar to small-caliber intracranial vasculature, allows evaluation of cerebral hemodynamics.[85] This study aimed to evaluate the Doppler value of the ophthalmic artery at 11–13 weeks, alone and in combination with first-trimester biomarkers (UtA-PI, MAP, PlGF, PAPP-A), for the prediction of preeclampsia.

II.5.2. Patients and Methods

This prospective observational study included pregnant women between 11+0 and 13+6 weeks at King's College Hospital, London, from 2019–2021. Routine visit data included demographics, personal and family history, ultrasound measurements following ISUOG first-trimester guidelines [86,87], double test analyses (PAPP-A, β-HCG) [88], and additional samples for research.

Doppler waves of the bilateral ophthalmic arteries were measured using a standardized technique, and the mean PSV2/PSV1 ratio was calculated. Blood pressure and uterine artery Doppler indices (UtA-PI) were recorded, and serum was used to assay PAPP-A, β-HCG, and PlGF. Gestational age was determined by crown-rump length or embryo transfer date in IVF [89].

Only singleton pregnancies resulting in birth ≥24 weeks were included; pregnancies with aneuploidy or major anomalies were excluded. Preeclampsia diagnosis followed standard criteria [90]. Missing data were completed by phone or excluded.

Statistical analyses used median/IQR for continuous variables and n (%) for categorical variables, with Student t, χ^2, or Fisher tests, and multivariate linear regressions to assess the relationship between PSV ratio, maternal characteristics, and PE occurrence [84]. MAP, UtA-PI, PlGF, and PAPP-A values were converted to MoM. Individual PE risk was estimated using Bayesian models combining biomarkers and maternal factors, evaluating screening performance via AUC and detection rates at 10% FPR.

To eliminate aspirin effects, simulated datasets without aspirin administration were created using Monte Carlo methods and the hypothesis of a 0.62 reduction in preterm PE risk; multiple imputation was performed with WinBUGS, and the rest of the analyses in R [84,91,92].

II.5.3. Results

A part of the results were previously puplished by the author. A total of 4,113 patients consented to participate. Among them, 4,066 had live births, and the remaining 47 had miscarriage, intrauterine fetal death, feticide, or pregnancy termination.

Study Population

The study included 4,066 pregnancies, of which 114 (2.8%) developed preeclampsia (PE). 25 (0.6%) cases of PE delivered before 37 weeks.

Multivariate linear regression models were applied to the PSV2/PSV1 ratio of the ophthalmic artery. Factors significantly influencing the ratio included maternal weight, age, height, East and South Asian ethnicity, smoking, chronic hypertension, and multiparity without PE [84]. Data were standardized into Delta values, accounting for maternal characteristics and medical history. The PSV ratio was significantly higher in pregnancies with PE, and the effect of PE depended on gestational age at delivery [84].

Modeled results showed that including the PSV ratio improved preterm PE prediction compared with models based only on maternal risk factors (46.3% → 58.4%), as well as combinations with biomarkers:

Maternal factors + MAP + UtA-PI (65.9% → 70.6%)

Maternal factors + MAP + UtA-PI + PlGF (74.6% → 76.7%)

Maternal factors + MAP + UtA-PI + PAPP-A (67.6% → 71.8%) [84]

However, the PSV ratio did not improve term PE prediction for any biomarker combination [84].

Adjustments for Aspirin Use

For aspirin adjustments, only cases receiving aspirin were considered. In the studied population, 3.2% of women in the unaffected group and 4.4% in the PE group were on aspirin.

II.5.4. Discussion

A previous study showed that ophthalmic artery Doppler at 11–14 weeks can predict PE: in a cohort of 440 pregnancies, 7% developed PE and 2% early PE, with the second systolic peak (PSV2) higher in PE pregnancies [85]. Screening based only on maternal factors detected 63% of early PE and 45% overall, at 10% false-positive rate, and adding PSV2 increased detection to 67% and 48%, without improvement when combined with UtA-PI.

The current study shows that PSV ratio combined with UtA-PI improves screening performance [84].

Key findings:

PSV ratio is significantly increased in pregnancies with PE, especially early PE.

Small numbers of early PE cases introduce uncertainty in estimates.

Results confirm the utility of maternal factors combined with MAP, UtA-PI, PlGF, and PAPP-A [12,93,94,95].

Integration of PSV2/PSV1 ratio improves early PE prediction, but not term PE.

Strengths: Prospective design, standardized Doppler technique, extensive biomarker analysis, and use of an advanced concurrent risk model [84]. Limitation: Small number of early PE cases; future larger studies are needed to fully evaluate the utility of the PSV ratio.

II.5.5. Conclusions

Larger future studies are needed to confirm that ophthalmic artery Doppler at 11–13 weeks can be incorporated as a marker for early preeclampsia prediction. This could enable earlier interventions and closer monitoring, reducing prematurity and maternal, fetal, and neonatal complications associated with preterm PE.

II.6. Study II

Utility of the Ophthalmic Artery in First-Trimester Gestational Diabetes

II.6.1–II.6.2. Introduction and Patients & Methods (Working Hypothesis, Specific Objectives, Patients, and Methods)

Gestational diabetes (GDM) affects approximately 6% of pregnant women, with prevalence increasing due to obesity [16]. It is defined as glucose intolerance diagnosed for the first time during pregnancy [64]. Recent studies have shown that women who develop GDM or preeclampsia (PE) have a significantly increased cardiovascular risk during the first 10 years postpartum [96]. Pregnancy thus represents a key window for identifying women at

cardiovascular risk, as early changes—endothelial dysfunction, arterial stiffness, and increased vascular resistance—may precede the onset of these pathologies. However, most studies have not analyzed first-trimester changes [96].

The aim of this study was to compare the PSV ratio of the ophthalmic artery measured at 11–13 weeks among women who later developed GDM, PE, or had uncomplicated pregnancies.

Study Design: Observational, prospective study conducted at King's College Hospital (London) between 2019 and 2021. Women were assessed at routine visits between 11+0 and 13+6 weeks. Doppler examinations followed standardized parameters (angle <20°, gate 2 mm, depth 3–4.5 cm, PRF 3–6 kHz), with short duration for ocular safety and emission reduction presets [96].

Inclusion criteria: singleton pregnancies evaluated at 11–13+6 weeks, resulting in birth >24 weeks, without major malformations.

Exclusion criteria: coexistence of GDM+PE, major chromosomal/fetal anomalies, preexisting diabetes, chronic hypertension, lupus, or antiphospholipid syndrome. Data were drawn from the same population used in the previous PE prediction study.

Data Collection and Outcome Definitions: Obstetric outcomes (GDM, PE) were obtained from maternity records or direct patient contact. The GDM screening protocol included three levels:T1 testing for women with risk factors (BMI >30, prior macrosomia, history of GDM, first-degree relatives with diabetes). Early OGTT performed if HbA1c >5.7%.

Universal screening at 26–28 weeks using carbohydrate challenge test, followed by OGTT for values >6.7 mmol/L.Testing after 28 weeks in cases of polyhydramnios or macrosomia [194].GDM management included diet, glucose monitoring, and if needed, metformin/insulin for persistently elevated values.

Statistical Analysis: Variables were analyzed according to distribution (Kolmogorov-Smirnov, ANOVA, Kruskal-Wallis, chi-square, or Fisher tests). The PSV ratio was assessed using linear regression with maternal characteristics and biomarkers. GDM prediction was performed using logistic regression, and PSV values were compared between groups (GDM, PE, controls), including subgroup analysis by treatment [194]. All analyses were performed in R 2.15.1.

II.6.3. Results

A part of the results were previously puplished by the author.The study included 3,999 pregnancies, of which 375 women (9.8%) developed GDM and 101 (2.5%) developed PE. Characteristics of Women with GDM (vs. non-GDM/PE) included: higher age, weight, and

BMI; shorter height; increased incidence of Afro-Caribbean and Asian ethnicity; higher frequency of family history of diabetes and prior GDM.

Characteristics of Women with PE: higher weight and BMI; increased proportion of Afro-Caribbean and mixed ethnicity; nulliparity more frequent; history of PE more common. Direct Comparison GDM vs. PE: maternal age was higher in GDM; higher prevalence of Asian ethnicity, family diabetes history, and prior GDM in the GDM group; mixed ethnicity, nulliparity, and PE history were less common.

Factors Influencing Ophthalmic Artery PSV Ratio: Linear regression identified independent predictors: development of PE, maternal age, BMI, MAP (MoM), family history of PE, Asian origin, family diabetes history, and maternal smoking. GDM did not significantly influence the PSV ratio. PSV Value Comparison: Mean PSV ratio was higher in GDM (0.66 ± 0.10) than in women without GDM/PE (0.63 ± 0.10; $P < 0.001$), but lower than in PE (0.69 ± 0.10; $P = 0.012$). The observed increase in GDM appears related to maternal characteristics, not GDM as a pathophysiological mechanism.

Therapeutic Subgroups in GDM: Among 375 women with GDM: 43.3% diet only, 34.1% metformin, 22.6% insulin (± metformin).
In the insulin-treated subgroup, observed: higher weight and BMI, higher prevalence of Afro-Caribbean and Asian ethnicity, more family history of diabetes, and fewer nulliparas. Similar but less pronounced results were observed in the metformin group. The PSV ratio did not differ significantly between therapeutic subgroups.

Predictors of PSV in GDM: Insulin treatment, maternal age and weight, BMI, MAP (MoM), and nulliparity. In insulin-treated patients, PSV (0.67 ± 0.09) was higher than in unaffected pregnancies (0.63 ± 0.10), but similar to PE.

Clinical Relevance: PSV ratio of the ophthalmic artery was not a significant predictor of GDM development, suggesting that observed differences reflect maternal profile rather than GDM-specific pathophysiology.

II.6.4. Discussion

In this prospective first-trimester study, the maximal systolic velocity (PSV) ratio of the ophthalmic artery was assessed in women who later developed GDM, compared to PE and uncomplicated pregnancies.
PSV was higher in women who developed GDM than in unaffected women, but lower than in PE.

In GDM, PSV was highest in insulin-treated women, but PSV ratio was not predictive of GDM onset, limiting its utility as a first-trimester screening tool.

Women predisposed to GDM often have an unfavorable cardiovascular profile, placing them at increased long-term cardiovascular risk. The analyzed cohort reflects this profile: higher maternal age, increased weight, and higher proportion of women of African origin. Impaired hemodynamic adaptation during pregnancy may contribute to these risks.

Consistent with previous studies, an elevated PSV ratio appeared early in women who later developed severe GDM requiring insulin, suggesting a distinct phenotype characterized by early peripheral vascular resistance increase. This supports the notion that GDM is heterogeneous, with varying degrees of metabolic and vascular dysfunction.

Although PSV ratio is not useful for GDM prediction, it may help identify women at increased cardiovascular risk early in pregnancy, allowing closer monitoring and preventive strategies during pregnancy and postpartum.

Strengths and Limitations of the Study:

Strengths:

Prospective design with a large sample of singleton pregnancies evaluated at routine first-trimester visits.

Doppler assessment of the ophthalmic artery performed using standardized technique, with two recordings per eye, reducing measurement variability.

Direct comparison of PSV ratio between women who later developed GDM, PE, and uncomplicated pregnancies.

Limitations:

OGTT was performed only in a subgroup (~80%) considered at high risk for GDM, potentially leading to underdiagnosis of GDM and misclassification of some controls, possibly overestimating observed associations.

II.6.5. Conclusions

In women who developed severe GDM requiring insulin, peripheral vascular resistance was elevated as early as the first trimester. These results suggest that first-trimester PSV ratio assessment may help in the early identification of women at risk for severe GDM and PE. Furthermore, they confirm that an unfavorable maternal cardiovascular profile and impaired hemodynamic adaptation during pregnancy play a key role in the development of obstetric complications.

II.7. Study 3

Doppler indices of the ophthalmic artery in relation to early and late preeclampsia at 11–13 weeks

II.7.1. Introduction (Working Hypothesis and Specific Objectives)

Preeclampsia (PE) is a hypertensive disorder of pregnancy, characterized by endothelial dysfunction and organ involvement, posing a major risk to mother, fetus, and newborn [97,98]. Early identification of risk is essential, as it allows the application of preventive measures such as aspirin, which reduces the incidence of PE [99]. However, methods for early detection continue to be actively investigated.

The maternal ophthalmic artery has emerged as a promising tool in PE screening due to its accessibility, lack of need for additional equipment, and applicability even in resource-limited settings. The Doppler waveform of the ophthalmic artery exhibits two systolic peaks: the first corresponding to cardiac ejection, and the second influenced by peripheral vascular resistance reflection [75,100].

This prospective study evaluated first-trimester Doppler parameters of the ophthalmic artery—maximal systolic velocities (PSV1 and PSV2) and pulsatility index (PI)—to determine whether they can contribute to the early identification of early-onset PE (<37 weeks) and late-onset PE (>37 weeks) in women presenting for first-trimester screening.

II.7.2. Materials and Methods

This prospective study recruited 4,054 pregnant women at 11–13+6 weeks gestation at King's College Hospital, London, between June 2019 and February 2022 to assess PE risk. Among these, 114 developed early (<37 weeks) or late (>37 weeks) PE. The study was approved by the NHS Ethics Committee, and all participants provided written informed consent.

In a subset of 336 patients, plasma levels of placental growth factor (PlGF) were measured. Only singleton pregnancies were included; cases with fetal malformations or intrauterine death were excluded. [101]

Ophthalmic artery examination was performed using a 7–15 MHz linear probe, with color and pulsed Doppler, recording 3–5 waveforms. The first and second systolic peaks (PSV1, PSV2) and pulsatility index (PI) were measured, and the mean of four measurements was saved for analysis.

Statistical Analysis: Microsoft Excel and IBM SPSS 30 were used. Continuous variables were expressed as mean ± standard deviation, and categorical variables as number and percentage. Groups included: control, early PE, and late PE. Group comparisons used Student's t-test, ANOVA, and Chi-square tests.

ROC curves assessed the predictive capacity of ophthalmic and uterine artery indices, mean arterial pressure (MAP), and PlGF for early and late PE. Binary logistic regression determined independent associations between Doppler indices, PlGF, uterine artery PI, and MAP, reporting OR with 95% CI. Inverse values (1/x) were used for PlGF and PI due to their inverse relationship with PE risk.

II.7.3. Results

A part of the results were previously puplished by the author. Of the 4,054 pregnant women, 114 developed PE (25 early, 89 late). In the PlGF subset (n=336), there were 23 early, 89 late, and 224 control cases.

Significant differences were observed for BMI, race, personal and family history of PE, MAP, and uterine artery PI, while maternal age, height, conception method, smoking, and aspirin use showed no significant differences.

The PSV ratio of the ophthalmic artery was higher in both PE groups compared to controls, while the ophthalmic artery PI showed a slight decreasing trend in early PE. ROC curves and AUC assessed predictive performance of ophthalmic and uterine artery indices, MAP, and PlGF for early and late PE.

Logistic regression identified independent predictors:

- Early PE: ophthalmic artery PSV ratio, uterine artery PI, and PlGF (subset)
- Late PE: MAP (MoM), PlGF (MoM), and in some analyses, PSV ratio and uterine artery PI

Thus, ophthalmic and uterine Doppler indices, along with PlGF, have predictive value in the first trimester for PE development.

II.7.4. Discussion

The study demonstrates that first-trimester ophthalmic artery Doppler assessment can contribute to PE prediction, providing information on cerebral and peripheral circulation, complementary to traditional markers (uterine arteries, MAP, PlGF).

The PSV ratio was higher in early PE, suggesting distinct hemodynamic mechanisms compared to late PE. Integrating this measurement into existing prediction models could allow early identification of at-risk women and the implementation of preventive strategies such as aspirin 150 mg/day until 36 weeks.

Limitations include a single-center design and small number of early PE cases (n=25), limiting statistical power. Multicenter studies and standardization of ophthalmic artery measurements are needed to validate and generalize these findings.

II.7.5. Conclusions

This study highlights the promising role of ophthalmic artery Doppler (OA) assessment as a tool for early identification of women at risk of PE. Specific Doppler waveform changes reflect the heterogeneity of pathophysiological mechanisms underlying this hypertensive disorder and underscore the importance of developing personalized prevention and management strategies.

Recent studies have shown that the ophthalmic artery PSV ratio, both in the first and third trimesters, is a significant predictor of PE. These findings suggest that integrating OA Doppler assessment into prenatal screening protocols could improve early detection and targeted management of PE. However, validation through large prospective studies, standardization of measurements, and assessment of feasibility across different healthcare systems are essential to maximize clinical benefit for mother and fetus.

II.8. Study 4

Evaluation of the ophthalmic artery in relation to birth of small-for-gestational-age (SGA) neonates

II.8.1. Introduction

This prospective observational study evaluates the ophthalmic arteries in the first trimester and their association with the risk of low birth weight. The ophthalmic artery, a branch of the internal carotid artery, reflects cerebral blood flow via the eye. The first systolic peak corresponds to cardiac systole, while the second systolic peak reflects peripheral vascular resistance, and the PSV2/PSV1 ratio serves as a marker of this resistance.

Mechanisms underlying hypertension, preeclampsia, and intrauterine growth restriction (IUGR) involve abnormal placentation and endothelial dysfunction. Therefore, ophthalmic artery assessment may serve as an early, non-invasive marker of low birth weight risk, complementing the established role of uterine artery evaluation. First-trimester screening already includes uterine artery Doppler indices and biochemical markers such as PAPP-A and PlGF, but ophthalmic artery Doppler, being more accessible and inexpensive, can provide additional fetal risk information.

This study focuses on systolic peak ratios (PSV) and pulsatility index (PI) of the ophthalmic artery.

II.8.2. Materials and Methods

This prospective observational study included 4,054 women who provided anonymous consent, recruited for routine first-trimester screening in the UK at King's College Hospital, London, between June 2019 and February 2022. The study was approved by the NHS Ethics Committee.

All participants underwent ophthalmic artery Doppler, recording the two systolic peaks and PI, calculating the mean of four measurements (left and right eye) and the PSV2/PSV1 ratio [84]. Blood samples were also collected for PAPP-A and β-hCG [97]. Doppler evaluation took under 1 minute [102].

The study analyzed two outcomes: birth weight ≤3rd percentile vs. >3rd percentile and ≤10th percentile vs. >10th percentile, according to FMF charts [103].

Inclusion criteria: attendance at first-trimester screening, consent, singleton pregnancy. Exclusion criteria: malformations, intrauterine death.

Statistical analysis: Microsoft Excel and IBM SPSS 30.0. Normality was tested with Kolmogorov-Smirnov and Shapiro-Wilk. Continuous variables (maternal age, height, weight, BMI, MAP, uterine artery PI, PAPP-A, gestational age, birth weight) were expressed as mean ± SD, with PAPP-A, uterine PI, and MAP transformed into MoM [104]. t-test was used for comparing two groups.

Categorical variables (conception method, aspirin use, smoking, race, personal history of SGA) were expressed as frequencies and percentages, compared with Chi-square or Fisher's exact test. ROC curves assessed discriminatory capacity for SGA (≤3rd and ≤10th percentiles), calculating AUC and p-values (<0.05).

II.8.3. Results

A part of the results were previously puplished by the author. Of 4,054 cases, 485 (11.96%) had birth weight ≤10th percentile, and 3,569 (88.03%) >10th percentile. Additionally, 196 (4.83%) had birth weight ≤3rd percentile, and 3,858 (95.16%) >3rd percentile.

Comparative analysis was conducted in two stages: ≤3rd percentile vs. >3rd percentile and ≤10th percentile vs. >10th percentile. Significant differences ($p<0.05$) were observed in maternal age, weight, height, BMI, PAPP-A (MoM), uterine artery PI (MoM), MAP (MoM), race, smoking, history of SGA, and gestational age at birth.

Ophthalmic artery indices: the PSV ratio (PSV2/PSV1) was significantly higher in ≤3rd and ≤10th percentile groups compared with >3rd and >10th percentile groups ($p<0.05$), while PI showed no significant discrimination.

ROC curve analysis: ≤3rd percentile vs. >3rd percentile:

Ophthalmic artery PSV: AUC = 0.544 (95% CI: 0.502–0.585), p = 0.038 → weak discriminative ability. Ophthalmic artery PI: AUC = 0.492 (95% CI: 0.452–0.533), p = 0.715 → not significant. Uterine arteries: AUC = 0.581 (95% CI: 0.538–0.624), p < 0.001 → good discrimination. MAP: AUC = 0.469 (95% CI: 0.426–0.511), p = 0.150 → not significant
≤10th percentile vs. >10th percentile: Ophthalmic artery PSV: AUC = 0.560 (95% CI: 0.533–0.588), p < 0.0001 → good discrimination. Ophthalmic artery PI: AUC = 0.476 (95% CI: 0.488–0.504), p = 0.088 → not significant. Uterine arteries: AUC = 0.566 (95% CI: 0.528–0.584), p < 0.001 → good discrimination.MAP: AUC = 0.507 (95% CI: 0.479–0.536), p = 0.616 → not significant.

These results indicate that the ophthalmic artery PSV ratio has better discriminatory capacity for low birth weight, especially for the 10th percentile, compared with PI or MAP.

II.8.4. Discussion

First-trimester ophthalmic artery Doppler, particularly the PSV ratio, may be a useful tool to identify pregnancies at risk for SGA neonates. A higher PSV ratio likely reflects placental dysfunction and vascular adaptation to compromised perfusion, suggesting its role as an early non-invasive fetal growth marker [105,106].

SGA neonates represent a heterogeneous group, including constitutionally small and growth-restricted infants, without separation in this study [107].

These findings suggest that ophthalmic artery Doppler could be integrated into first-trimester screening protocols to identify high-risk pregnancies, allowing early monitoring and interventions. SGA neonates have higher risks of perinatal complications and long-term neurodevelopmental outcomes, so early detection may optimize timing of delivery and perinatal outcomes [108].

However, PSV ratio alone shows modest performance (AUC < 0.6), highlighting the need for integration with other established markers in prenatal evaluation.

II.8.5. Conclusions

The ophthalmic artery PSV ratio has potential as an additional marker for early identification of SGA pregnancies, but its highest clinical value is achieved when integrated with established screening methods. Ophthalmic artery Doppler provides a non-invasive, accessible approach to detect SGA risk; however, large multicenter studies are needed to validate results, standardize measurements, and establish optimal clinical cut-offs.

9. Conclusions and Personal Contributions

9.1. Conclusions

This thesis includes four studies highlighting the potential of maternal ophthalmic artery Doppler assessment during pregnancy, particularly for predicting common maternal-fetal complications such as preeclampsia (PE), gestational diabetes (GDM), and intrauterine growth restriction (IUGR/SGA). All studies assess blood flow in the ophthalmic artery in the first trimester (11–14 weeks), a critical period for early identification of high-risk pregnancies. The method is non-invasive, reflects maternal hemodynamic status, and detects early circulatory changes associated with pregnancy complications.

Technical and economic advantages:

- Non-invasive, rapid, reproducible, and easily integrated into routine ultrasound evaluation; [109]
- Does not require additional equipment and is available in most centers;
- More accessible and cost-effective than serum biomarkers, particularly useful in resource-limited settings; [109]
- Can be repeated in subsequent trimesters.

Disadvantages and limitations:

- Requires training, protocol standardization, and a learning curve;

- Inter- and intra-observer variability may affect measurement accuracy;
- Lack of a universally accepted cut-off limits clinical applicability;
- Larger, long-term studies are needed to evaluate impact and predictive performance.

Future research directions:

- Validation in diverse, multicenter populations;
- Integration of Doppler indices into algorithms combined with biomarkers to improve sensitivity and specificity;
- Assessment of economic impact on healthcare systems;
- Evaluation of the method's effect on maternal and neonatal morbidity and mortality;
- Investigation of links with other vascular and metabolic disorders;
- Development of AI systems for Doppler index analysis to reduce human variability.

9.2. Personal Contributions

Summary and contributions:

The included studies demonstrate the value of first-trimester maternal ophthalmic artery Doppler assessment for early identification of pregnancy complications.

- The PSV2/PSV1 ratio shows predictive potential for early-onset preeclampsia (<37 weeks), distinguishing early from late-onset forms (Studies II.5 and II.7).
- Increased hemodynamic changes are also observed before the onset of gestational diabetes, suggesting a role of endothelial dysfunction in GDM (Study II.6).
- Ophthalmic artery blood flow can anticipate births of small-for-gestational-age (SGA) infants, providing an early, non-invasive marker (Study II.8).

Practical contributions:

- Validation of the technique in the local population;
- Correlation of Doppler measurements with maternal clinical profile;
- Standardization of measurements and development of regional and multicenter databases;
- Integration of findings into screening algorithms for PE, GDM, and SGA;
- Demonstration that the ophthalmic artery can serve as a common marker of vascular dysfunction, supporting early identification of high-risk pregnancies.

In conclusion, ophthalmic artery Doppler is an accessible, non-invasive, and promising tool for integration into prenatal screening protocols, although further validation through large multicenter studies is needed for widespread clinical implementation.

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