Dynamic cerebral autoregulation and endothelial dysfunction in preeclampsia

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“preeclampsia represents a spectrum of signs and symptoms
reflective of a long-standing and insidious developing disease
process that is not inherently a hypertensive condition”

James Martin Jr

ABSTRACT

Background: Preeclampsia affects approximately 1 in 20 pregnant women and may cause severe morbidity and mortality in both mother and fetus. The pathophysiology remains partly unclear, and the clinical course is highly variable. Reliable tools to predict organ dysfunction are currently lacking.

Aim: The overarching aim of this thesis was to investigate whether autoregulation index, angiogenic markers, and glycocalyx degradation products may serve as predictors and indicators of organ dysfunction in preeclampsia, at the time of diagnosis, in the early postpartum period, and 1 year postpartum.

Method: We assessed cerebral autoregulation in normotensive pregnancies, preeclampsia, and eclampsia, using transcranial Doppler and non-invasive continuous blood pressure monitoring to calculate the autoregulatory index. In normotensive pregnancies and preeclampsia, we investigated whether plasma concentrations of the glycocalyx degradation products syndecan-1, hyaluronic acid, and thrombomodulin correlated with disease severity, using blood samples collected at inclusion and information on organ dysfunction. We examined whether plasma levels of angiogenic markers and glycocalyx degradation products could predict subsequent organ dysfunction in women with preeclampsia. Blood samples were collected at diagnosis, and clinical outcomes were monitored.

Results: Cerebral autoregulation was found to be enhanced in normotensive pregnancies but depressed in preeclampsia. No differences were observed between preeclampsia with and without organ dysfunction. One year postpartum, autoregulation was comparable across groups. Cerebral autoregulation was depressed in eclampsia in the early postpartum period. Syndecan-1 levels were equal regardless of disease and disease severity. Hyaluronic acid was increased in preeclampsia but did not correlate with extent of organ dysfunction. Thrombomodulin levels were elevated in preeclampsia and even more so in cases with multiple organ dysfunctions. None of the glycocalyx markers reliably predicted overall organ dysfunction, though hyaluronic acid predicted thrombocytopenia and liver injury. sFlt-1 concentrations predicted thrombocytopenia, liver, and kidney injury, while PlGF and the sFlt-1/PlGF ratio showed limited predictive value.

Conclusion: Cerebral autoregulation is depressed in preeclampsia and eclampsia, underscoring the importance of blood pressure management to prevent cerebral complications. Although sFlt-1 dysregulation and glycocalyx degradation appear involved in preeclampsia pathophysiology, their utility in predicting organ dysfunction in women with a preeclampsia diagnosis is limited.

Keywords: preeclampsia, eclampsia, cerebral autoregulation, autoregulation index, syndecan-1, hyaluronic acid, thrombomodulin, soluble fms-like tyrosine kinase, placental growth factor

SAMMANFATTNING PÅ SVENSKA

Preeklampsi drabbar cirka fem procent av gravida kvinnor och kan leda till allvarlig sjukdom och död hos både mor och foster. Patofysiologin är till stora delar oklar och sjukdomsförloppet varierar avsevärt. Det saknas tillförlitliga verktyg för att prognostisera svår sjukdom med organdysfunktion.

Syftet med denna avhandling har varit att utvärdera autoregleringsindex, angiogena markörer (lösligt fms-likt tyrosinkinas [sFlt-1] och placentatillväxtfaktor [PlGF]) samt glykokalyxnedbrytningsprodukter (syndecan-1, hyaluronsyra och trombomodulin) som potentiella markörer för prediktion och bedömning av organdysfunktion vid preeklampsi.

I studierna I och V undersöktes normotensiva gravida kvinnor samt kvinnor med preeklampsi eller eklampsi med transkraniell doppler och icke-invasiv, kontinuerlig blodtrycksmätning. Autoregleringsindex beräknades för att värdera cerebral autoreglering. I studie I genomfördes undersökningen postpartum, medan studie V inkluderade mätningar vid diagnos och ett år efter förlossning.

Studie II analyserade plasmanivåer av glykokalyxnedbrytnings-produkter hos normotensiva gravida och kvinnor med preeklampsi, med syfte att undersöka korrelation med sjukdomens svårighetsgrad. Blodprov togs vid diagnos och antalet påverkade organ registrerades.

Studierna III och IV fokuserade på huruvida plasmanivåer av angiogena markörer och glykokalyxnedbrytningsprodukter kunde förutsäga utveckling av organdysfunktion hos kvinnor med diagnostiserad preeklampsi. Blodprov togs vid diagnos och patienterna följdes med avseende på komplikationer.

Gravida kvinnor uppvisade förbättrad cerebral autoreglering, som var nedsatt vid preeklampsi. Ingen skillnad i autoreglering kunde påvisas mellan preeklampsi med och utan organdysfunktion. Ett år efter förlossning förelåg ingen skillnad mellan kvinnor med tidigare normotensiv graviditet och de med preeklampsi, oavsett organdysfunktion. Kvinnor med eklampsi, undersökta postpartum, uppvisade nedsatt cerebral autoreglering med lägre autoregleringsindex än både preeklampsi och normotensiva graviditeter.

Plasmanivåer av syndecan-1 var förhöjda oberoende av preeklampsistatus och förekomst av organdysfunktion. Hyaluronsyra var förhöjt vid preeklampsi men korrelerade inte med antalet dysfunktionella organ. Trombomodulin var förhöjt vid preeklampsi och vid multipel organdysfunktion. Ingen av dessa markörer visade god förmåga att förutsäga organdysfunktion generellt, men hyaluronsyra kunde förutsäga trombocytopeni och leverskada.

sFlt-1 kunde förutsäga trombocytopeni, leverskada och njurpåverkan. PlGF och kvoten sFlt-1/PlGF hade begränsad prediktiv förmåga avseende organdysfunktion.

Sammanfattningsvis är cerebral autoreglering nedsatt vid preeklampsi och eklampsi, vilket understryker vikten av adekvat blodtrycksbehandling för att förebygga cerebrala komplikationer. Vid intubation bör blodtryckshöjning undvikas farmakologiskt. Ökad produktion av sFlt-1 och nedbrytning av glykokalyx tycks ingå i den patofysiologiska processen vid preeklampsi, men varken angiogena markörer eller glykokalyxnedbrytningsprodukter är tillräckligt tillförlitliga för att förutsäga organdysfunktion hos kvinnor med diagnostiserad preeklampsi.

LIST OF PAPERS

This thesis is based on the following studies, which are referred to in the text by their Roman numerals.

I. Bergman L, Cluver C, Carlberg N, Belfort M, Tolcher, MC, Panerai RB, van Veen T. Cerebral perfusion pressure and autoregulation in eclampsia—A case control study. Am J Obstet Gynecol 2021;225:185.e1-9.

II. Carlberg N, Cluver C, Hesse C, Thörn S-E, Gandley R, Damén T, Bergman L. Circulating concentrations of glycocalyx degradation products in preeclampsia. Front Physiol 2022;13:1022770.

III. Carlberg N, Hesse C, Thörn SE, Imberg H, Wallin N, Andersson M, Sengpiel V, Damén T, Bergman L. Soluble fms-like tyrosine kinase and placental growth factor as predictors of adverse maternal events in women with a confirmed diagnosis of preeclampsia. Manuscript.

IV. Carlberg N, Wesslén E, Gandley R, Sengpiel V, Imberg H, Thörn S-E, Bergman L, Hesse C, Damén T. Prediction of organ complications in women with a confirmed diagnosis of preeclampsia by glycocalyx degradation products. Manuscript.

V. Carlberg N, Junus K, Bergman L, Imberg H, Kniepe K, Panerai R, Hesse C, Damén T, van Veen T. Cerebral autoregulation in normal pregnancy, preeclampsia and one year postpartum. Manuscript.

CONTENTS

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
ASPRE	Combined Multimarker Screening and Randomised Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention
$ETCO_2$	End-tidal carbon dioxide
GDP	Glycocalyx degradation products
GoPROVE	Gothenburg Preeclampsia Obstetric Adverse Events
HELLP	Hemolysis, elevated liver enzymes, and low platelets
ICU	Intensive care unit
ISSHP	International Society of the Study of Hypertension in Pregnancy
MBRRACE	Mothers and Babies: Reducing Risks through Audits and Confidential Inquiries
MCA	Arteria cerebri media
PROVE	Preeclampsia Obstetric Adverse Events
TCD	Transcranial Doppler
UPMOST	Uppsala Pregnancy Complication Study

DEFINITIONS IN SHORT

Adverse maternal events, organ complications, organ dysfunction, or severe features	Definitions and terminology regarding complications of preeclampsia vary between studies, making it difficult to provide a concise definition. Definitions often follow American College of Obstetricians and Gynecologists (ACOG) or International Society of the Study of Hypertension in pregnancy (ISSHP) criteria. Terms are often used interchangeably.
Composite outcome	A composite of any one of 14 defined core outcomes included in a core set of outcomes for preeclampsia research. The outcomes are maternal mortality, eclampsia, stroke, cortical blindness, retinal detachment, pulmonary edema, acute kidney injury, liver capsule hematoma or rupture, placental abruption, postpartum hemorrhage, raised liver enzymes, low platelets, admission to intensive care unit (ICU) required, and intubation and mechanical ventilation (not for childbirth).
Single outcome	Any one of the 14 defined core outcomes being part of the composite outcome with more than 10 events, as reported in each study.

INTRODUCTION

Pregnancy and childbirth pose significant health risks for women globally, particularly in low- and middle-income countries. As an anesthesiologist in Gothenburg, Sweden, with a dedicated focus on obstetric anesthesia, I have encountered many women with preeclampsia and developed a strong interest in this complex condition. My PhD studies supervisor is affiliated with Stellenbosch University in Stellenbosch and Tygerberg University Hospital, Cape Town, both in South Africa, granting me valuable insight into the diverse clinical and social challenges posed by preeclampsia across different healthcare settings. The designation "women with preeclampsia" is used throughout this thesis for consistency with clinical practice, with the understanding that preeclampsia may occur in any pregnant person, regardless of gender identity.

PREECLAMPSIA

Definition

Preeclampsia is a pregnancy-related disease. Although its definitions vary across time and space, a commonly agreed-upon definition today is that preeclampsia is the new onset of hypertension after 20 weeks of gestation, in combination with at least one of several defined organ dysfunctions (1). Figure 1 presents examples of defined dysfunctions, according to the International Society of the Study of Hypertension in Pregnancy (ISSHP).

Incidence

The incidence of preeclampsia is often reported as 3%–5% of all pregnancies, although it may vary in different populations and according to different definitions. In Sweden, 3.8% of pregnant women were diagnosed with preeclampsia in 2022 (2). Data from South Africa are subject to greater uncertainty; however, a systematic review of

1. Proteinuria (not required for diagnosis)
2. Other maternal organ dysfunction, including:
   - Acute kidney injury (AKI) (creatinine ≥ 90 µmol/L; 1 mg/dL)
   - Liver involvement (elevated transaminases, e.g. ALT or AST > 40 IU/L) with or without right upper quadrant or epigastric abdominal pain)
   - Neurological complications (e.g. eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata)
   - Haematological complications (thrombocytopenia–platelet count below 150 000/µL, DIC, hemolysis)
3. Uteroplacental dysfunction (e.g. fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth)

Figure 1. Examples of organ dysfunctions according to the ISSHP in 2018 (ALT, alanine aminotransferase; AST, aspartate aminotransferase; DIC, disseminated intravascular coagulation).

studies from 2000 to 2018 reported an incidence of preeclampsia in the sub-Sahara region of 4.1% (3).

Pathophysiology

Preeclampsia is a syndrome diagnosed by definitions, so its pathophysiology may be diverse. While numerous mechanisms have been proposed, the leading hypothesis is known as the "two-stage model."

Two-stage model

In 1989, Roberts et al. proposed the idea that "poorly perfused placental tissue releases a factor(s) into the systemic circulation that injures endothelial cells" (4). It was known at that time that spiral artery remodeling was impaired in hypertensive pregnancies. Today, we know that the invasion of trophoblasts into spiral arteries, leading to remodeling and adapted blood flow, is essential to healthy pregnancy (5). Vascular malperfusion and placental maldevelopment lead to pathological changes in both fetal growth restriction and early-onset preeclampsia, whereas placental stress and aging leads to a pathology common to both early and late-onset preeclampsia (6).

The cardiovascular stress test

A problem with the two-stage model is that not all women with preeclampsia have signs of defect placentation. Some researchers have suggested that a vulnerable cardiovascular system is the culprit behind preeclampsia, regardless of placental lesions, such that some women enter their pregnancy already destined to develop preeclampsia (7). Pregnancy is a stress test on the maternal cardiovascular system, and limited capability to handle hemodynamic changes may be the underlying pathophysiological mechanism causing some women to develop hypertension and organ complications during pregnancy. Nevertheless, although a high body mass index, chronic hypertension, and diabetes are known risk factors for preeclampsia, heart failure is not, which presents a strong argument against the hypothesis that reduced pre-pregnancy cardiovascular function is the primary culprit for preeclampsia (8).

Placenta in a pot

The "placenta in a pot"-hypothesis states that every pregnant woman would have developed preeclampsia eventually if the pregnancy had continued, because of an aging placenta. For most women, this timepoint is thought to be beyond birth; however, for those with an unfavorable outcome, the aging placenta becomes a source of factors that are toxic to the mother (9). In some women, placental pathology is apparent early in pregnancy; senescent changes can often be found in these relatively young placentas, which also release toxic factors (9).

A CORE OUTCOME SET FOR PREECLAMPSIA RESEARCH

The organ dysfunctions seen in the clinical presentation of preeclampsia differ considerably, as do the definitions of outcomes in studies on preeclampsia. To enable meta-analyses and to focus on relevant issues, researchers, clinicians, and patients have established a core set of outcomes for preeclampsia research via a Delphi process (10). As this set of outcomes provides a representative description of preeclampsia, its individual components are reviewed here in detail. (Table 1) Cerebral and neurological complications will be discussed separately, in the section titled "Cerebral complications in preeclampsia."

Maternal death

At the global scale, at least 40 000 women die from complications of preeclampsia every year. In sub-Saharan Africa, the risk of maternal mortality is 17 times higher in women with hypertensive disorders in pregnancy than in women with normotensive pregnancies, and 15.7% of maternal mortality is attributed to hypertensive diseases (3, 11). A South African study on adverse maternal outcomes in preeclampsia from three tertiary care hospitals reported 1% maternal mortality among the study population, of which 9.5% had eclampsia and 17.6% had kidney injury due to preeclampsia (12). Between 2014 and 2016, 47 teenagers died from eclampsia in South Africa, although most of these cases involved avoidable factors, such as referral to the wrong level of care or a long ambulance arrival time (13). In Sweden, new national recommendations were published in 2019 emphasizing blood pressure control and suggesting the immediate induction of birth in women with preeclampsia after 37 gestational weeks, and only one woman has died of preeclampsia in Sweden during the last 5 years. Similarly, maternity care in the UK exerts considerable effort to reduce mortality in women with preeclampsia, with good results: (14) In the last Mothers and Babies: Reducing Risks through Audits and Confidential Inquiries (MBRRACE) report, confidential inquiries into mothers' deaths during 2020–2022 revealed that seven women had died from preeclampsia in the UK, constituting just 3% of maternal deaths in that report, in comparison with the three-year period 1985–1987, when 27 women died, constituting 12% of the total maternal mortality in those years (14).

Table 1: A list of all maternal outcomes suggested as a core set of outcomes for preeclampsia research, established using a Delphi process and published by Duffy et al., with the definitions employed in Studies III–V to classify outcomes during medical chart analysis (10).

Organ dysfunction/core outcome	Definitions
Maternal death	Medical chart information on maternal death
Eclampsia	Generalized tonic-clonic seizures in a woman with preeclampsia (ICD code O15)
Stroke	ICD codes I60, I61, I63, and I64
Cortical blindness	PRES diagnosed in medical charts, OR radiological evidence of PRES, OR diagnosis I67.83
Retinal detachment	ICD code H33.0
Pulmonary edema	Pulse oximetry ≤ 90 AND auscultatory crackles OR *x*-ray signs of pulmonary edema OR ultrasound signs of pulmonary edema
Acute kidney injury	Creatinine ≥ 90 μmol/L or oliguria < 500 mL/day
Liver capsule hematoma or rupture	Radiological or surgical evidence of hematoma or rupture
Placental abruption	Placental abruption diagnosed in medical charts OR ICD code O45
Postpartum hemorrhage	More than 500 mL bleeding if vaginal birth OR more than 1000 mL if cesarean section
Raised liver enzymes	ALT or AST ≥ 2 times highest normal value (ALT > 1.5 μkat/L and AST < 1.2 μkat/L)
Low platelets	Platelet particle concentration < 100×10^9/L
Admission to ICU	Admission to ICU
Intubation and mechanical ventilation	Intubation (not for childbirth)

Notes: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICD, international classification of diseases; ICU, intensive care unit; PRES, posterior reversible encephalopathy syndrome

Pulmonary edema

Pulmonary edema is a life-threatening complication that is rare in high-income settings. In a study from the United States with 15 000 000 pregnancies, the incidence of pulmonary edema was only 0.08%; however, at a tertiary referral center in South Africa, pulmonary edema constituted 0.2% of all pregnancies and 18.1% of all severe maternal outcomes, with a case fatality rate of 5.6% (15, 16).

A study investigating pulmonary ultrasound in women with severe preeclampsia found B-lines—that is, signs of interstitial fluid in the lungs—in 64.3% of the participants and in 100% of those with dyspnea. Diastolic heart dysfunction was found in 47.1% of the participants and was strongly correlated with B-lines (17). Subclinical pulmonary edema may therefore be common in severe preeclampsia.

Acute kidney injury

Proteinuria is present in approximately 90% of all women with preeclampsia and was formerly considered a mandatory diagnostic criterion (18). Endothelial glomerulosis and a reduced glomerular filtration rate may result in proteinuria and oliguria (19). Podocyte injury and kidney tubular injury have also been demonstrated (20). Oliguria (<500 mL per day) or at least a 1.5-fold increase in plasma creatinine are common diagnostic criteria for acute kidney injury. In Africa, preeclampsia in combination with obstetric hemorrhage and sepsis is a leading cause of pregnancy-related acute kidney failure (21). Preeclampsia may even result in end-stage kidney disease and a need for dialysis, although kidney function usually resolves postpartum (19).

Liver capsule hematoma or rupture and HELLP syndrome

Hemolysis, elevated liver values, and low platelets (HELLP) syndrome is a serious manifestation of preeclampsia. Although HELLP syndrome is not included in the core set of outcomes for preeclampsia research, it is described here because of its association with liver capsule hematoma or rupture. While definitions of HELLP syndrome differ, common diagnostic criteria include elevated lactate dehydrogenase (e.g., ≥10 μkat/L), haptoglobin (e.g., ≤0.25 g/L), or schistocytes as a sign of hemolysis; aspartate or alanine transferase twice the upper reference limit as a sign of hepatic involvement; and a thrombocyte level ≤ 100 × 10^9/L as a sign of thrombocytopenia. HELLP syndrome sometimes is associated with upper-right-quadrant abdominal pain. In Sweden, the incidence of HELLP syndrome was 0.12% of all pregnancies in 2022 (2). In Africa, it has been reported to be 0.22% (22). Liver capsule hematoma or rupture is a rare complication of HELLP syndrome, with an incidence of less than 0.004% of all pregnancies (23). Liver capsule hematoma or rupture is included in the core set of outcomes for preeclampsia research. The pathophysiology remains unclear, but sinusoidal fibrin deposits, liver cell necrosis and friable neovascularization have been suggested as mechanisms (23, 24).

Placental abruption and uteroplacental dysfunction

Uteroplacental dysfunction are common in preeclampsia (25). The birthweight of neonates of mothers affected by preeclampsia was found to be reduced by 5% relative to expected norms, with neonates of mothers with early-onset preeclampsia exhibiting a more pronounced decrease of 23% in a Norwegian population (26). Almost one in four women with preeclampsia give birth preterm; in one study, the odds ratio for preterm birth was 4.51 (4.23–4.80) times higher in women with preeclampsia than in those without (27, 28). The incidence of abruptio placentae is approximately 0.4%–1% in Sweden, with a two-fold increase in risk for women with preeclampsia without severe features and a more than five-fold increase in risk for women with preeclampsia with severe features, compared with normotensive pregnancies (25, 29). In South Africa, the overall incidence of placental abruption has been reported to be 1.1% (30). Notably, magnesium sulfate lowers the risk for placental abruption (31).

Postpartum hemorrhage

Preeclampsia is considered a risk factor for postpartum hemorrhage. In a recent large systematic review and meta-analysis, the adjusted odds ratio for postpartum bleeding in preeclampsia was 1.54 (95% confidence interval (CI): 1.48–1.60) (32). Interrelated factors such as induction of labor and cesarean section might explain part of this increased risk; the coagulopathy seen in preeclampsia and an increased risk of placenta abruption may also contribute (33, 34). Magnesium sulfate probably does not contribute to an increased risk of postpartum hemorrhage in preeclampsia (35, 36).

Raised liver enzymes

Elevated liver enzymes can occur without the other components of HELLP syndrome. The pathophysiology is the same as in HELLP syndrome, with sinusoidal fibrin deposition and periportal liver cell necrosis (24, 37).

Low platelets

The incidence of thrombocytopenia—commonly defined as a platelet count < 150×10^9/L—in pregnancy is 7%–12% (38). The most common cause of thrombocytopenia is not preeclampsia but gestational thrombocytopenia (39). According to the American College of Obstetricians and Gynecologists (ACOG), a diagnostic criterion for preeclampsia is a platelet count < 100×10^9/L (38). The decline in platelet count is considered to reflect consumptive processes (38). Thrombocytopenia increases the risk of postpartum hemorrhage by 40% (95% CI: 4%–89%) (32).

Admission to intensive care unit

In Sweden in 2023, a total of 117 women were admitted to an intensive care unit (ICU) due to preeclampsia, HELLP syndrome, or eclampsia, corresponding to an incidence of 0.12% (166). This finding is in line with several studies from high-income countries that reported an incidence of 0.24%–0.42% (40). The utility of intensive care in this population has been emphasized by the favorable long-term outcome among survivors and by confidential enquiries into maternal deaths, suggesting that delayed access to appropriate care levels may have contributed to preventable mortality (40).

Intubation

Intubation for respiratory failure is a sign of severe illness. This procedure requires anesthesia and thus carries a substantial risk, as upper airway edema, rapid desaturation, and increased risk of aspiration make anesthesia-related complications more common in obstetric anesthesia (41). Apart from airway difficulties, intubation in preeclampsia carries a risk of cerebral hemorrhage (41).

CEREBRAL COMPLICATIONS IN PREECLAMPSIA

Preeclampsia affects the central and peripheral nervous system, and its symptoms range from mild to fatal. Headache and hyperreflexia are common, and impaired cognitive function has been reported in eclampsia and preeclampsia with pulmonary edema, compared with normotensive pregnancies (42). Given the relevance of cerebral complications to this thesis, they are outlined separately in this section.

Eclampsia

Generalized tonic-clonic fits during pregnancy have been recognized by doctors for more than two thousand years and are named for the ancient Greek word *eclampsias*, meaning “a sudden flash.” Eclampsia is a rare complication in Sweden today, with an incidence of just 0.035% in Sweden in 2022 (2). In sub-Saharan Africa, however, it is much more common, with an incidence of 1.5%, and other regions in Africa show a similar incidence (3, 22). Women with eclampsia are 42 times more likely to die during pregnancy, compared with those without (28). Eclampsia sometimes presents as the first symptom of preeclampsia (the “sudden flash”), but prodromal symptoms are often present (as evidenced by the term “preeclampsia”). In many women, a feeling of restlessness and unease may deteriorate to neurologic complications with severe headache, visual disturbances, and clonus before the fit, but there are no reliable clinical symptoms that predict eclampsia (43). Seizures are typically self-terminating, but vital functions require supportive management. Magnesium sulfate remains the treatment of choice for controlling seizures and preventing recurrence, as discussed further below (44).

Stroke

Stroke is uncommon in women of childbearing age. A Swedish study found an incidence of 15 per 100 000 person-years in women that were not pregnant, but this increased to 314 and 64 per 100 000 person-years in the peripartum and early postpartum period, respectively (45). Preeclampsia increases the risk of stroke in pregnancy more than five-fold (46, 47). In a South African study on mortality in teenage pregnancies with eclampsia, intracerebral hemorrhage was the most common cause of death (12).

Posterior reversible encephalopathy syndrome

Eclampsia is often accompanied by radiologic findings of posterior reversible encephalopathy syndrome (PRES) (48, 163). Severe preeclampsia is also associated with PRES. The radiologic findings are most often localized in the occipital lobe (84.2%), but they are also found in the parietal lobe (67.9%) and the frontal area (32.2%). Symptoms associated with PRES include seizures, headache, visual disturbances, and altered mental status; in a systematic review and meta-analysis, intracranial hemorrhage was reported in 11.2% and maternal death in 5.3% of available cases (48).

Cortical blindness

Cortical blindness is defined as a loss of vision associated with an intact visual pathway from the eye to the lateral geniculate bodies, while the pupillary reflex and ocular motility are preserved. Cortical blindness is usually associated with PRES (49).

Retinal detachment

Although a study employing routine ophthalmoscopy in women with severe preeclampsia or eclampsia revealed a retinal detachment incidence of 32%, the incidence is commonly reported as <1% in published data (49). Edema accumulates in the subretinal space, resulting in loss of visual acuity and visual field defects.

Other neurological signs and symptoms

Headache is a common symptom in preeclampsia and may, albeit unspecific, precede eclampsia and stroke (43). In two different case series, 56% of women with subsequent eclampsia and 96% of women with subsequent stroke had headache. Headache in preeclampsia is often unresponsive to non-opioid analgesics (50–52).

Altered level of consciousness, hyperreflexia (often defined as clonus in the Achilles-tendon reflex), and visual disturbances are often considered prodromal to more serious neurologic complications and an indication for treatment with magnesium sulfate as prophylaxis against eclampsia (44, 53).

Magnesium sulfate

Magnesium sulfate is well established as the drug of choice for eclampsia, in which it more than halves the risk of recurrent seizures (31). It can be given prophylactically to prevent seizures and lowers the risk of eclampsia by 58% (95% CI: 40%–71%; number needed to treat if given to preeclampsia with severe features is 63 (95% CI: 38–181)), without harmful side effects (53). The relative risk of death was 0·55, (95% CI 0.26–1.14) among women receiving magnesium sulphate.

CEREBRAL AUTOREGULATION

Autoregulation is classically viewed as a mechanism that protects organs from both high and low blood pressure (54). Several different organs are believed to possess this mechanism, with the brain and kidneys being the most studied of these. In 1959, Lassen wrote a paper titled "Cerebral blood flow and oxygen consumption in man" and presented a figure that has since become well known to all medical students, albeit slightly revised (Figure 2) (55).

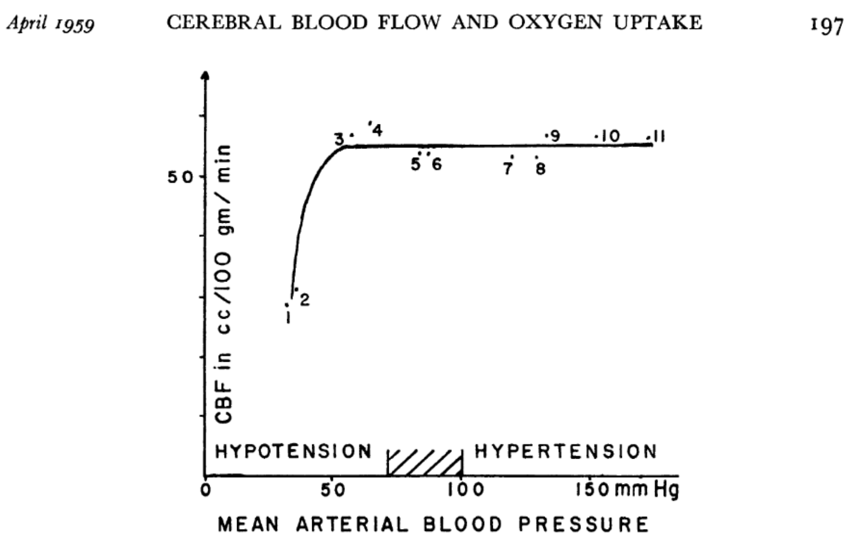


Figure 2. Cerebral blood flow and blood pressure, with the mean values of 11 groups of subjects reported in seven studies plotted. Among these groups are normal pregnant women (5) and "hypertensive toxemic pregnancy", i.e., preeclampsia (8). N. A. (Source: Lassen (55) pp. 183-238; reproduced with permission from the American Physiological Society.)

Static cerebral autoregulation

Modern reproductions commonly illustrate an upper level of cerebral autoregulation, above which the blood flow increase is proportional to the blood pressure. The plateau at which blood flow is constant at around 50 mL/100 g tissue/min is regarded as the range of autoregulation and is usually depicted as horizontal within the mean arterial blood pressure range of 50–150 mmHg. However, the plateau might be a slope, and the range is controversial (54, 56). In pregnancy, this plateau is probably wider, as shown in rats, but no studies in humans confirm this (57-59). To study cerebral autoregulation, changes in blood pressure are experimentally induced through the infusion of vasopressors, cuffing of limbs, or changes in posture. Cerebral blood flow is measured before and after the hemodynamic changes, using radioactively labeled substances or Fick's principle—that is, the uptake of a substance by an organ is equal to the product of blood flow and the arteriovenous concentration difference of that substance—applied to nitric oxide or some other, presumed inert inhaled gas. These measurements take at least a few minutes, hence their name "static measurements"; however, vasomotor reactions to changes in blood pressure are much faster than such measurements (54).

Dynamic cerebral autoregulation

Dynamic cerebral autoregulation refers to the almost instantaneous reaction to a sudden change in blood pressure. After a sudden drop or elevation in blood pressure, blood flow velocities follow the decrease or increase but return to previous flow velocities in a few seconds (54). Transcranial Doppler (TCD) examinations with low-frequency (2 MHz) ultrasound, initially developed by Aaslid et al., offer a high temporal resolution and a non-invasive way of measuring cerebral blood velocities (60). The temporal profile of cerebral arterial blood velocities, as measured by TCD ultrasound, can be graphically represented as a time series envelope curve. Similarly, non-invasive continuous blood pressure measurements, typically obtained from the index finger, yield a corresponding temporal waveform. Tiecks et al. developed a method for assessing autoregulatory changes in the cerebral circulation by mathematically analyzing and comparing the spectral contents from these two curves (61).

This method is described in detail in the section titled "Patients and Methods." Tiecks et al. proposed 10 templates, each corresponding to a value from 0 to 9, for assessing autoregulation (Figure 3): the so-called autoregulation index (ARI). If the blood flow velocity curve follows the blood pressure curve perfectly, autoregulation is absent, and the autoregulation index is 0. If autoregulation ensues instead, and the blood flow velocity returns to previous values, the situation can be illustrated by a step response curve, with the fastest and most

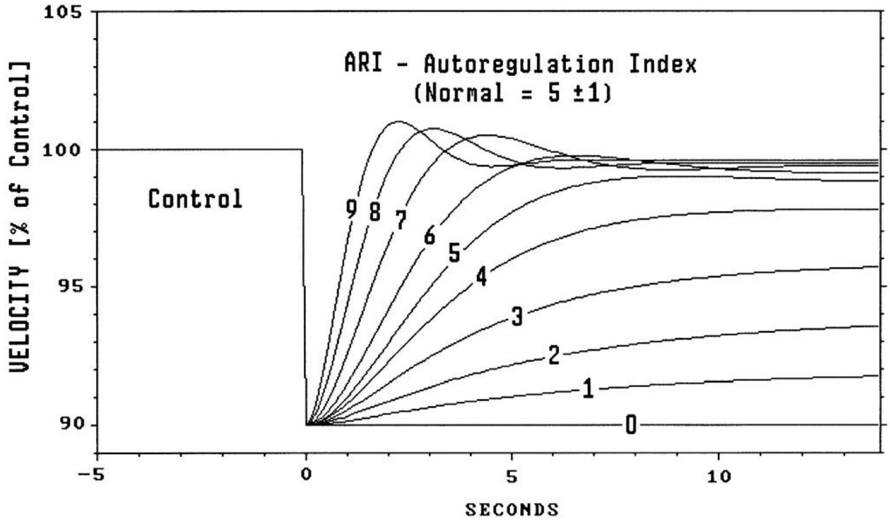


Figure 3. Template curves for the autoregulation index, proposed by Tiecks et al. (Source: Tiecks et al. (61), pp. 1014–9; reproduced with permission from Wolters Kluver Health Inc.)

comprehensive return to previous values corresponding to autoregulation index 9. Any step response curve in between these extremes can be translated into an autoregulation index value corresponding to the closest template curve. This method has been validated: A study with 120 measurements in 10 healthy volunteers showed a correlation variance of 12.3% and 13.3% for left- and right-sided measurements, respectively (62).

Another common way of expressing cerebral autoregulation is through phase, gain, and coherence. Instead of applying Tieck's templates as a unifying measure, the *phase* expresses how quickly the cerebral blood flow follows the mean arterial blood pressure. The *gain* expresses how comprehensive the return to baseline of the cerebral blood flow velocity is, and the *coherence* gives a measure of the strength of the relationship between the blood velocity and the blood pressure, described over a range of frequencies. Phase is expressed in degrees or sometimes radians; gain is described in centimeters per second per millimeters of mercury; and coherence is a value ranging from 0 (no coherence) to 1 (perfect coherence). High phase, low gain, and low coherence are signs of good cerebral autoregulation (54).

Cerebral autoregulation in pregnancy

A study on cerebral autoregulation in pregnancy, at gestational ages of both 20–30 weeks and 31–41 weeks, found that the autoregulation index is higher in pregnant versus non-pregnant women, with a mean ARI of 6.7, standard deviation (SD) 0.9 and 6.6, SD 0.9 vs. 5.3, SD 1.4 (63). Another study showed increased phase in normotensive pregnant women with mean values of 45.5°, SD 23.4° compared with non-pregnant women 31.5°, SD 11.9° but no difference in gain (64). Measurements in the posterior cerebral artery showed similar results (64).

The postpartum period is a time of great hemodynamic changes, and cerebral blood flow and autoregulation are likewise affected. In a study investigating the first week postpartum (although 80% of the participants were examined within 48 h), women with normotensive pregnancies (n = 20) had higher phase and gain compared with non-pregnant historical controls (n = 28) (65). Another study instead found lower phase in 35 normotensive women within 10 days postpartum, compared with the same women 6 months postpartum. Gain was unaltered. These women were examined on average 4.5, SD 2.7 days postpartum (66). In summary, pregnancy and the early postpartum period seem to align with enhanced cerebral autoregulation, but studies are inconsistent.

Cerebral autoregulation in preeclampsia

It has been shown that the mean autoregulation index is lower in women with preeclampsia (5.5, SD 1.7, n = 20) compared with normotensive controls (6.7, SD 0.6, n = 20) (67). The same research group, using the same methods, investigated the mean autoregulation index in 30 women with preeclampsia (5.5, SD 1.6), 30 women with chronic hypertension (5.6, SD 1.7), 20 women with gestational hypertension (6.7, SD 0.8), and 30 normotensive controls (6.7, SD 0.8) (Figure 4). In seven of the women with chronic hypertension who subsequently developed superimposed preeclampsia, the mean autoregulation index was 3.9, SD 1.9 compared with 6.1, SD 1.2 in the 23 women with chronic hypertension who did not develop superimposed preeclampsia (68).

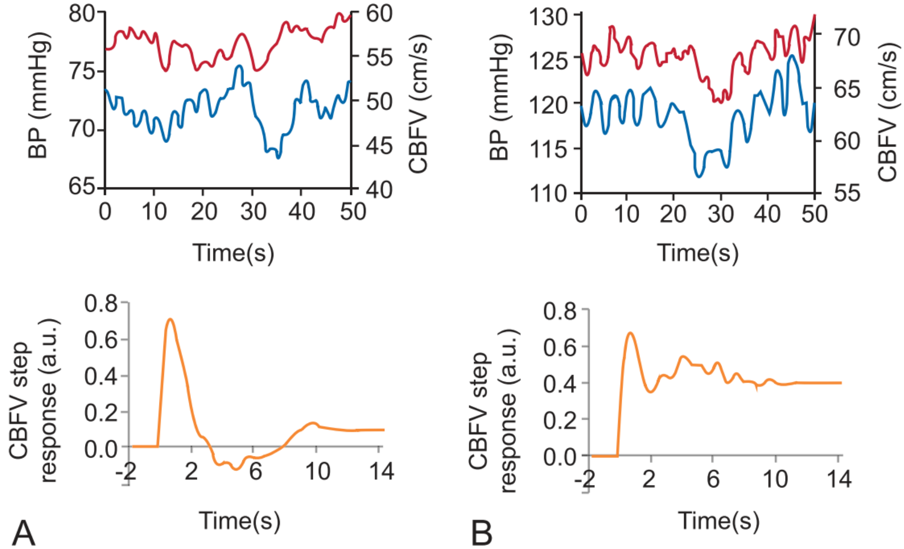


Figure 4. Dynamic cerebral autoregulation in normotensive pregnant control and women with preeclampsia. (A) An example of enhanced cerebral autoregulation: autoregulation index 7.0 (B) An example of depressed cerebral autoregulation: autoregulation index 2.6. Blue lines are continuous readings of blood pressure, red lines are cerebral blood velocities, and yellow lines are step response curves. (Source: van Veen et al. (67), pp. 1064–9; reproduced with permission from Wolters Kluver Health Inc.)

A small study comprising five women with preeclampsia and five normotensive controls found that the phase was higher and the gain lower in the women with preeclampsia (129°, SD 31° vs. 59°, SD 12°; 0.10, SD 0.4 vs. 0.29, SD 0.07), indicating enhanced autoregulation in women with preeclampsia, unlike the findings of other studies. (69) In the first week postpartum, women with preeclampsia do not differ in phase and gain compared with women who have had normotensive pregnancies (65, 66). In 25 women with a history of preeclampsia and 25 with normotensive pregnancies, examined 2–3 years postpartum, the phase and gain did not differ between groups; however, in another study by the same author, the median phase in pregnant women at 25–28 weeks gestation with a history of preeclampsia was lower than that in those with no history of preeclampsia (64, 70). In summary, preeclampsia seems to align with depressed autoregulation in comparison with normotensive pregnancies, and this change seems to be reversible, although findings across studies are inconsistent.

Knowledge gaps study I and V

It is unknown whether the severity of disease and development of organ dysfunctions in preeclampsia are associated with depressed autoregulation and whether specific severe neurological complications such as eclampsia depress autoregulation. It also remains unclear how cerebral autoregulation in preeclampsia and normotensive pregnancies changes postpartum. No study has investigated the autoregulation index in a cohort both during pregnancy and at 1-year follow-up.

GLYCOCALYX DEGRADATION PRODUCTS

The endothelial glycocalyx

The luminal side of the endothelial cells is covered by a thin lining of proteoglycans (e.g., syndecan-1), glycosaminoglycans (e.g., hyaluronic acid), and glycoproteins (e.g., thrombomodulin). These form a gel-like coat that helps regulate capillary permeability, vessel tone, coagulation, and inflammation. This structure is called the endothelial glycocalyx (71). (Figure 5, next page)

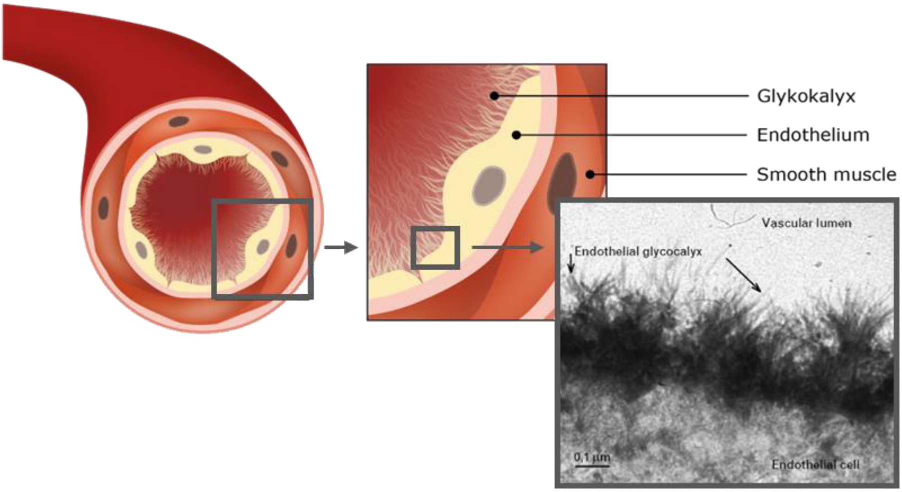


Figure 5. Schematic drawing of a part of the wall of an arteriole. Glycocalyx can be seen on the luminal surface of the endothelial cells. (Drawing by Lisa Vukovic Karlsson; photo from Chappell et al. (157), pp 155–162; reproduced with permission from Wolters Kluver Health Inc.).

Proteoglycans (syndecan-1)

The syndecans are a family of proteoglycans, all of which are membrane bound and part of the extracellular matrix (72). Syndecans play a key role in cell-to-cell adhesion, the activity of heparan sulfate-binding growth factors, and cell-matrix adhesion, and have numerous functions in health and disease (73, 74). Syndecan-1 (also known as CD-138) is mainly expressed by keratocytes, squamous epithelial cells, type-1 alveolar cells, hepatocytes, cholangiocytes, plasma cells, and the syncytiotrophoblast; to a lesser but still biologically relevant extent, it is also expressed by endothelial cells (75). It is an important constituent of the endothelial glycocalyx and essential for the regulation of angiogenesis and coagulation and as a cofactor for cytokines and angiogenic factors (71). Elimination of syndecan-1 is dependent on kidney function (76).

Glycosaminoglycans (hyaluronic acid)

Glycosaminoglycans are highly hydrophilic and form gels in most connective tissues throughout the body. Hyaluronic acid is a repeating sequence of glucuronic acid and N-acetylglucosamine that forms molecules of 4000–8 000 000 Daltons (77). Hyaluronic acid synthetase is highly expressed in mesothelial cells, pancreatic endocrine cells, and fibroblasts; to a lesser but biologically relevant extent, it is also expressed in endothelial cells (75). Daily turnover of hyaluronic acid has been calculated to be 150 mg, with a plasma half-life of 2.5–5 minutes (78). Elimination of hyaluronic acid is mostly hepatic (79). Hyaluronic acid is found in the endothelial glycocalyx, together with the membrane-bound hyaluronic acid binding protein CD 44 (80).

Alongside hyaluronic acid, heparan sulfate is the most abundant glycosaminoglycan of the endothelial glycocalyx and binds to syndecan-1; chondroitin sulfate, dermatan sulfate, and keratin sulfate are also found here (71, 81). Many heparin-binding proteins bind to heparan sulfate and have key functions within the endothelial glycocalyx (82).

Glycoproteins (thrombomodulin)

Numerous glycoproteins are expressed on the surface of endothelial cells, and thrombomodulin (also known as CD-141 or BDCA3) is one of them. Thrombomodulin helps regulate coagulation and inflammation through the activation of protein C (83). It is highly expressed in squamous epithelial cells, Schwann cells, endothelial cells, adipocytes, and peritubular cells; to some extent, it is also expressed in the syncytiotrophoblast and in macrophages and monocytes (75). Its plasma half-life is 10 minutes and depends on renal secretion (84).

Glycocalyx degradation

In mice subjected to lipopolysaccharide injection, it has been shown that the glycocalyx is degraded and glycocalyx degradation products (GDPs) are found in elevated plasma concentrations compared with controls (85). In patients with sepsis, GDPs can be found in the circulation, and elevated plasma levels correlate to increased mortality (86). In recent years, the significance of the endothelial glycocalyx in the pathophysiology of post-ischemic organ damage, trauma, sepsis, renal disease, diabetic vasculopathy, atherosclerosis, and preeclampsia has been recognized, and there are reviews discussing this topic (87, 88).

Glycocalyx degradation in preeclampsia

It has been shown that the plasma concentrations of the glycocalyx components hyaluronic acid and thrombomodulin are elevated in women with preeclampsia (89, 90). Syndecan-1 has complex pharmacokinetics as the placenta produces large amounts of syndecan-1 in normal pregnancy (91). Preeclampsia appears to be associated with subnormal plasma concentrations of syndecan-1 in the first stage of the disease (before the onset of symptoms), but plasma concentrations elevated severalfold were found in women with severe preeclampsia compared with normotensive pregnant women (92–94).

Glycocalyx degradation in preeclampsia of different severities

Previous studies have investigated the plasma concentrations of GDPs in women with preeclampsia of different severities. In HELLP, median plasma concentrations of both hyaluronic acid and thrombomodulin were found to be higher compared with those in preeclampsia both with and without organ dysfunction (95, 96). Median plasma concentrations of thrombomodulin have also been found to be higher in women with eclampsia or severe preeclampsia, compared with preeclampsia without organ dysfunction (97, 98). In women with preeclampsia admitted to an ICU, the median plasma concentrations of syndecan-1 and hyaluronic acid were higher compared with those in women with preeclampsia who were not admitted to an ICU (99).

Knowledge gaps study II and IV

It is not known whether the damage to the endothelial glycocalyx is proportional to the severity of disease and whether GDPs could predict organ dysfunction in women with a diagnosis of preeclampsia.

ANGIOGENIC MARKERS

Soluble fms-like tyrosine kinase

Soluble fms-like tyrosine kinase (sFlt-1) is the extracellular, ligand-binding part of vascular endothelial growth factor receptor-1 (VEGFR-1). It has endocrine and paracrine effects, mainly regulating angiogenesis through inhibition of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF); it also has an impact on endothelial health in general (100). VEGF inhibitors are used in oncology and ophthalmology for their anti-tumor and anti-angiogenic effects. Side effects of these treatments include hypertension and proteinuria (101–104).

Placental growth factor

PlGF is a member of the VEGF family; it binds tightly to sFlt-1 and VEGFR-1 but not to VEGF-binding receptor VEGFR-2 (also known as kinase insert domain receptor (KDR)). PlGF has four isoforms. (105) It is highly expressed by the syncytiotrophoblast and extravillous trophoblasts; it is also expressed to some extent in endothelial cells (75). sFlt-1 and PlGF are often referred to as angiogenic markers.

Angiogenic markers and preeclampsia

Maynard et al. were the first to investigate the association between sFlt-1, PlGF, and preeclampsia, publishing a landmark report based on a series of experiments (106). They showed that mRNA expressing sFlt-1 was upregulated in preeclamptic placentas and that the average serum level of sFlt-1 was almost five-fold higher in women with severe preeclampsia than in normotensive, pregnant women. They found decreased serum concentrations of free VEGF and PlGF in women with preeclampsia, and the decrease was proportional to increased levels of sFlt-1 in these women. They also found that sFlt-1 did not cause vasoconstriction in an *in vitro* assay for microvascular reactivity but obliterated the vasodilation of VEGF and PlGF. Finally, they infected mice with an adenovirus expressing sFlt-1 and found that the mice developed hypertension, proteinuria, and glomerular endotheliosis.

The first clinical study on angiogenic markers in preeclampsia

Levine et al., with Maynard as one of the coauthors, presented an important clinical case-control study, analyzing serum from 120 women with preeclampsia and 120 healthy pregnant women for sFlt-1, VEGF, and PlGF (107). Their results suggested that an increase in sFlt-1, accompanied by a decrease in VEGF and PlGF, preceded clinical symptoms of preeclampsia by several weeks, and that serum concentrations of sFlt-1 were severalfold higher in women with clinical symptoms of preeclampsia compared with normotensive controls (Figure 6).

Angiogenic markers as promising biomarkers

After the work by Levine et al., a multitude of studies confirmed their findings, and PlGF and the sFlt-1/PlGF ratio are now recognized as potentially useful biomarkers for the prediction of preeclampsia in women with suspected preeclampsia (108, 109). The National Institute for Health and Care Excellence in the UK recommends PlGF as a single test to rule in or rule out preeclampsia in preterm women with suspected preeclampsia (110).

PlGF has also emerged as a relevant biomarker of placental function as early as in the first trimester. In the Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) study, PlGF was part of the screening at a gestation age of 11–13 weeks for detecting high-risk women suitable for intervention with aspirin (111). Nevertheless, there is controversy on many aspects of testing, and most national or institutional recommendations do not include sFlt-1 or PlGF as a test for preeclampsia at any gestational age.

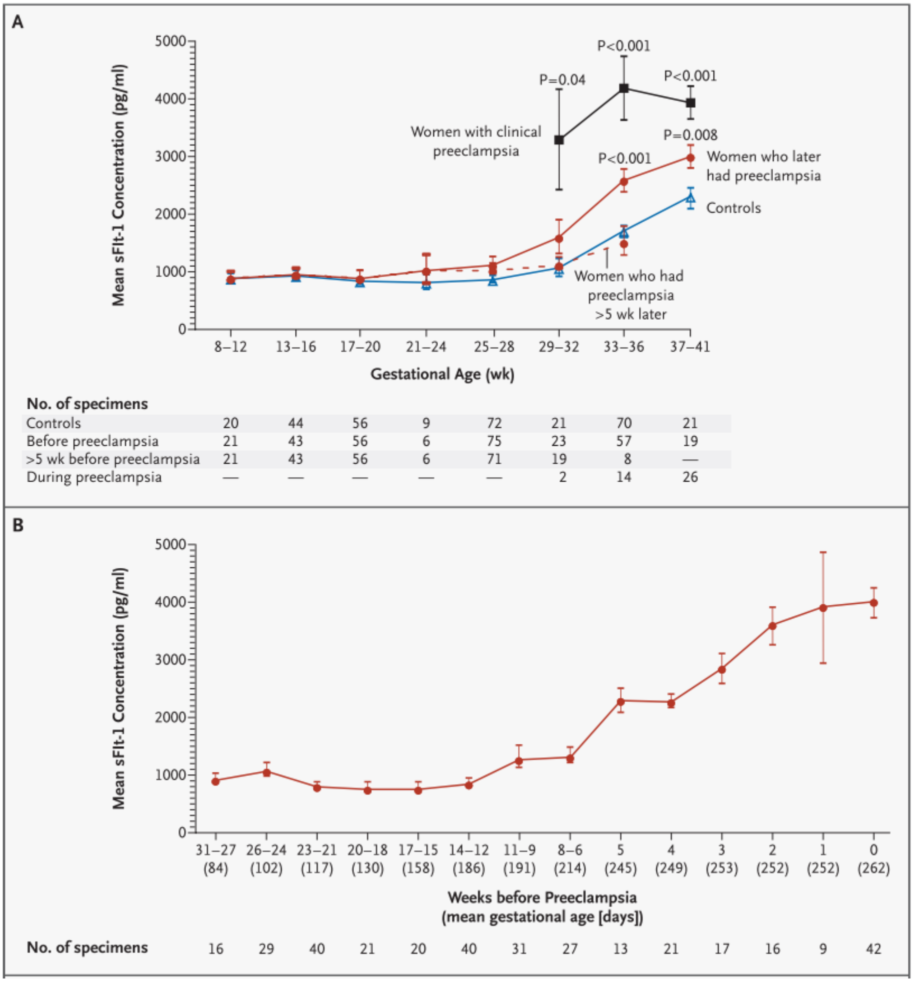


Figure 6. Mean sFlt-1 concentrations were found to be higher in women with preeclampsia compared with women who later developed preeclampsia and the controls. The lowest mean plasma concentration was found in controls. Mean sFlt-1 concentrations started rising several weeks before clinical symptoms of preeclampsia. (Source: Levine et al. (107); Reproduced with permission from (107), Copyright Massachusetts Medical Society.)

PREDICTION OF ORGAN DYSFUNCION

A recent systematic review and meta-analysis on the prediction of both maternal and fetal organ dysfunctions in women with preeclampsia included 506 178 women in 110 studies (112). Despite the large number of subjects and studies, no meta-analysis could be done on the predictive value of any biomarker for adverse maternal outcomes, due to heterogeneity in populations, exposures, and outcomes.

A compilation of the results of this systematic review showed that sFlt-1, PlGF, and the sFlt-1/PlGF ratio were tested 99 times in 15 different studies, in which 19 distinct predictors (variants of sFlt-1, PlGF, and the sFlt-1/PlGF ratio with different cut-off values) were tested for 24 different outcomes. Seven of these tests showed better than poor performance (defined as a 95% CI for a negative likelihood ratio entirely below 0.5 or entirely above 2.0 for the positive likelihood ratio).

The conclusion from this systematic review was that it is too early to implement sFlt-1, PlGF, or the sFlt-1/PlGF ratio for risk stratification of women with preeclampsia in clinical practice. (112)

No studies investigating the plasma concentrations of GDPs for the prediction of organ dysfunction in preeclampsia were included in the systematic review (112).

Knowledge gaps study III

There is a lack of good prognostic tools for the prediction of subsequent organ dysfunction in women with preeclampsia. While sFlt-1 and PlGF may have prognostic value for organ dysfunction in women with preeclampsia, their predictive utility remains uncertain. There is a need for studies validating previous findings, and new studies should harmonize with previous works in terms of predictors and outcomes to enable future meta-analyses to be conducted.

AIM

The overall aim of this thesis was to evaluate the role of cerebral autoregulation and angiogenic and endothelial biomarkers as determinants of the presence and degree of organ dysfunction in general and cerebral dysfunction in particular in preeclampsia at diagnosis and 1 year postpartum.

The aim of Study I was to compare the autoregulation index and estimated cerebral perfusion pressure in women with eclampsia, preeclampsia of different severities, and normotensive pregnancies. The aim of Study II was to compare the circulating concentrations of the glycocalyx products syndecan-1, hyaluronic acid, and thrombomodulin in women with preeclampsia of different severities. The aims of Study III and IV were to investigate the predictive accuracy of sFlt-1, PlGF, the sFlt-1/PlGF ratio, syndecan-1, hyaluronic acid, and thrombomodulin for the development of a core set of preeclampsia-related organ dysfunction in women diagnosed with preeclampsia. The aim of Study V was to compare the autoregulation index in women with preeclampsia with that in women with normotensive pregnancies at diagnosis and 1 year postpartum. As a secondary outcome, it aimed to investigate whether the autoregulation index differs in women with preeclampsia with organ dysfunction versus women with preeclampsia without organ dysfunction at diagnosis and 1 year postpartum.

PATIENTS AND METHODS

ETHICAL CONSIDERATIONS

All women were recruited to one of the Preeclampsia Obstetric Adverse Events (PROVE), Uppsala Pregnancy Complication Study (UPMOST), or Gothenburg Preeclampsia Obstetric adverse events (GoPROVE) biobanks. Ethical permission for the PROVE biobank (N17/05/048) was obtained from the Health Research Ethics Committee at Stellenbosch University on 28 February 2018, and the study is registered as ISRCTN10623443 (113). Ethical permission for the GoPROVE biobank (No. 955-18) was obtained from the Regional Ethics Committee of Gothenburg on 28 December 2018 (114). Amendments for angiogenic markers and other biomarkers related to preeclampsia (GDPs) were obtained from Ethix, the Swedish Ethical Review Authority, on 4 April 2023 (2023-02271-02-391236). Ethical permission for the UPMOST biobank (No. 2019-00309) was obtained from the Swedish Ethical Review Authority on 27 February 2019. These encompassed the full ethical permissions for Studies III–V (114). GoPROVE and UPMOST are registered as ISRCTN13060768.

For Study I, additional ethical permission (Project ID 8786, HREC #N18/03/034) was obtained from the Health Research Ethics Committee at Stellenbosch University on 28 February 2019. For Study II, additional ethical permission (Project ID 24459, HREC #N22/02/011_Substudy_ N17/05/048) was obtained from the Health Research Ethics Committee at Stellenbosch University on 3 March 2022. For Studies III–V, no additional ethical permissions were needed.

All studies were conducted according to the Helsinki Declaration. All studies were observational. All women gave informed consent before entering the studies. Participants had the right to decline any examinations or assessments included in the studies at any time. Efforts were made to minimize harm, such as by combining clinically required blood sampling with the blood sampling for these studies. Patient confidentiality and General Data Protection Regulation (GDPR) compliance were consistently considered. Biobank materials were handled and stored using the services of Biobank Väst.

STUDY DESIGN

The studies in this thesis focus on the prediction of organ complications in women with preeclampsia. Study I was a case-control study. Cases and controls were identified in the PROVE population, and the participants' autoregulation index and cerebral perfusion pressure were measured on one occasion. All participants were examined postpartum. At the time of assessment, they were assigned to one of four groups–eclampsia, preeclampsia with organ dysfunction, preeclampsia without organ dysfunction, or normotensive pregnancies–based on clinical information available at that point. Study II had a similar design and was described as a cross-sectional study. Women enrolled in the PROVE biobank with a plasma sample taken before birth were eligible. Participants were divided into the following groups: normotensive pregnancy, preeclampsia without organ dysfunction, preeclampsia with a single organ dysfunction, and preeclampsia with multiple organ dysfunction. The participants were stratified according to the organ dysfunctions present at the time of blood sampling; if they developed organ dysfunction after blood sampling, they remained in their group.

Studies III and IV were prospective, observational cohort studies investigating the predictive value of angiogenic markers or GDPs for organ dysfunction. Women enrolled in the GoPROVE biobank with preeclampsia without organ dysfunction were eligible for these studies, and organ dysfunctions were recorded throughout the pregnancy and puerperium. Participants were divided into groups based on whether they experienced subsequent organ dysfunction or not.

Table 2. Study design

Paper	Study design	Study population	Period	Exposure	Outcome(s)
I	Case-control	PROVE 87 women included: 16 eclampsia, 18 PE w OD, 32 PE w/o OD, 21 normotensives	2018 to 2020	Eclampsia, PE w OD, PE w/o OD	ARI and CPP
II	Cross-sectional	PROVE 57 women included: 13 PE w multiple OD, 24 w single OD, 10 w/o OD and 10 normotensives	2018 to 2020	PE w multiple OD, PE w single OD, PE w/o OD	Plasma concentrations of SDC-1, HA, and TM
III	Cohort	GoPROVE 307 women included: 129 developed adverse maternal events	2019 to 2024	sFlt-1, PlGF, and the sFlt-1/PlGF ratio	The composite of the core set of outcomes for preeclampsia research and single outcomes with ≥10 events
IV	Cohort	GoPROVE 212 women included: 92 developed adverse maternal events	2019 to 2023	SDC-1, HA, and TM	The composite of the core set of outcomes for preeclampsia research and single outcomes with ≥10 events
V	Cohort	UPMOST and GoPROVE 124 women included: 40 PE w OD; 33 PE w/o OD, 51 normotensives	2020 to 2023	PE w OD, PE w/o OD	ARI

ARI, autoregulation index; CPP, cerebral prefusion pressure; HA, hyaluronic acid; OD, organ dysfunction; PE, preeclampsia; SDC-1, syndecan-1; TM, thrombomodulin; w, with; w/o, without.

Study V was a prospective, observational cohort study of women with preeclampsia, along with a normotensive control group. Women who were enrolled in the UPMOST and GoPROVE biobanks and underwent TCD examination were eligible for participation. Participants were divided into the following groups: normotensive pregnancies, preeclampsia without organ dysfunction, and preeclampsia with organ dysfunction. Table 2 presents an overview of the studies' designs.

POPULATIONS

Biobanks

The women included in Studies I and II were enrolled in the PROVE biobank at Tygerberg Hospital, Cape Town, South Africa, during 2018–2020. Tygerberg Hospital is a large referral hospital with approximately 8000 deliveries per year and approximately 30 000 deliveries in the referral area. Women were enrolled after a diagnosis of preeclampsia or after admission for birth (normotensive controls), which could be pre- or postpartum (Figure 7).

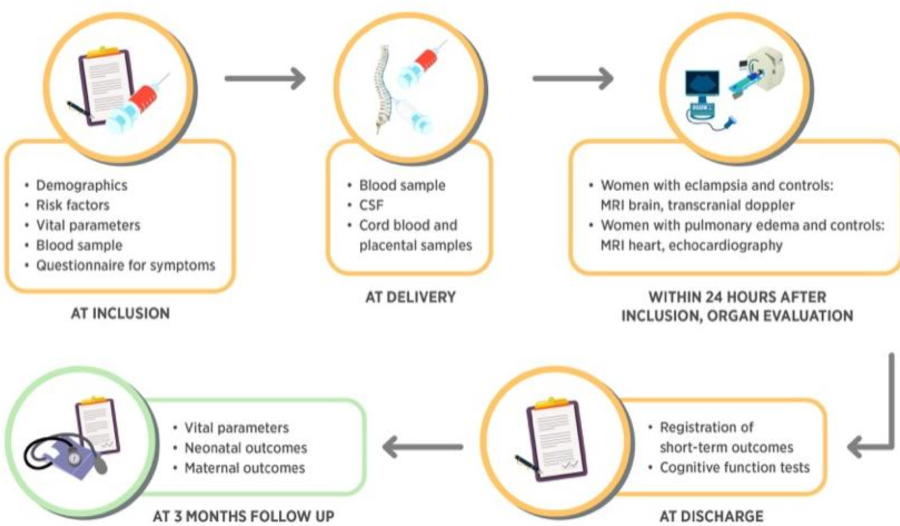


Figure 7. Diagram of study activities for participants enrolled in the PROVE biobank in Cape Town, South Africa.

The women included in Studies III and IV were enrolled in the GoPROVE biobank at Sahlgrenska University Hospital Östra, Västra Götaland, Sweden, from May 2019 to May 2024. The GoPROVE biobank protocol greatly resembles the PROVE protocol, with questionnaires, blood sampling, and various examinations for the participants. There was a planned revisit 1 year postpartum. The Sahlgrenska University Hospital Östra is a tertiary referral center with approximately 10 000 deliveries per year.

The women participating in Study V were enrolled in either the GoPROVE biobank or the UPMOST biobank at Akademiska Sjukhuset, Uppsala, Sweden, from September 2020 to October 2023. The UPMOST biobank greatly resembles PROVE and GoPROVE. Akademiska Sjukhuset is a tertiary referral center with approximately 4000 deliveries per year.

Study populations

In Study I, the population consisted of women in the PROVE biobank that had had a TCD measurement done. Women were included up to 5 days postpartum, but most were examined within 48 h. In Study II, the population consisted of women enrolled in the PROVE biobank during 2018–2020 with singleton pregnancies and plasma samples taken before birth. In Studies III and IV, the population consisted of women in the GoPROVE biobank with a diagnosis of preeclampsia but no organ dysfunction at the time of blood sampling. Women were enrolled from May 2019 to May 2024 (Study III) or May 2023 (Study IV). In Study V, the population consisted of women from either the GoPROVE or the UPMOST biobanks who underwent a TCD measurement between September 2020 and October 2023.

EXPOSURES

In Study I, the exposures were eclampsia, preeclampsia with organ dysfunction, preeclampsia without organ dysfunction, and normotensive pregnant controls. Preeclampsia, HELLP syndrome, and preeclampsia without organ dysfunction were defined according to the ACOG 2019 Practice Bulletin, with the additional requirement of proteinuria. (115) Eclampsia was defined as preeclampsia complicated by witnessed generalized tonic-clonic seizures in the absence of another etiology. Pulmonary edema was defined as worsening dyspnea, bilateral inspiratory crackles on auscultation, and features of pulmonary edema on X-ray. Normotensive pregnant controls never had a documented systolic blood pressure > 140 mmHg or a documented diastolic blood pressure > 90 mmHg during their pregnancies.

In Study II, the exposures were preeclampsia with multiple organ dysfunctions, with single organ dysfunction, or without any organ dysfunction. Preeclampsia, HELLP syndrome, eclampsia, pulmonary edema, preeclampsia without severe features, and normotensive pregnant controls were defined as in Study I. Renal impairment was defined as creatinine over 120 mmol/L; aspartate aminotransferase was recorded as the highest values and platelets and hemoglobin (Hb) were recorded as the lowest values retrieved from the medical charts before birth. Thrombocytopenia was defined as platelets $< 100 \times 10^9$/L. Multiple neurological complications were assessed as one organ dysfunction.

In Study III, the exposures were serum concentrations of sFlt-1 (pg/mL), PlGF (pg/mL), and the sFlt-1/PlGF ratio; in Study IV, the exposures were plasma concentrations of the GDPs syndecan-1 (ng/mL), hyaluronic acid (ng/mL), and thrombomodulin (ng/mL).

In Study V, the exposures were preeclampsia with or without severe features. Severe features were defined according to Duffy et al., similar to the composite outcome in Studies III and IV (see Outcomes section) (10). Women were assigned to the preeclampsia with organ dysfunction group if they had any severe feature at any time during their pregnancy and the postpartum period.

OUTCOMES

In Studies I and V, the outcomes were the autoregulation index; in Study I, the cerebral perfusion pressure index (mmHg) was also an outcome. All examinations in Study I were performed postpartum; in Study V, all examinations at inclusion were performed before birth. Follow-up examinations were performed 1 year postpartum.

In Study II, the outcomes were circulating concentrations of the GDPs syndecan-1 (ng/mL), hyaluronic acid (ng/mL), and thrombomodulin (ng/mL). In Studies III and IV, the primary outcome was a composite of any one of the 14 defined core outcomes included in a core set of outcomes for preeclampsia research published by Duffy et al. in 2020 (hereafter the “composite outcome”) (10). These outcomes were maternal mortality, eclampsia, stroke, cortical blindness, retinal detachment, pulmonary edema, acute kidney injury, liver capsule hematoma or rupture, placental abruption, postpartum hemorrhage, raised liver enzymes, low platelets, admission to ICU required, and intubation and mechanical ventilation (not for childbirth). Definitions are listed in Table 1. Secondary outcomes were all the single organ complications being part of the composite outcome with more than 10 events, as reported in each study (hereafter “single outcomes”).

TRANSCRANIAL DOPPLER

In Study I, TCD examinations were performed using equipment from Spencer Technologies (Seattle, USA), and non-invasive, continuous blood pressure was measured using Finometer Pro (Finapres Medical Systems, Netherlands). In Study V, TCD examinations were performed with equipment from Delica (Shenzhen Delica Medical Equipment Co., China), and non-invasive, continuous blood pressure was measured using Finapres Nova (FMS Medical, Netherlands). Blood pressure was measured in the middle finger. In Study I, data were recorded at 50 Hz; in Study V, data were recorded at 125 Hz. In both studies, the middle cerebral artery was identified using M-mode and reasonable blood flow velocities at an insonation depth of 45–65 mm. Bilateral readings during 7 minutes were obtained if possible. The participants were instructed to relax in a semi-recumbent position, and end-tidal carbon dioxide ($ETCO_2$) was measured with a nasal cannula.

Calculations of the autoregulation index were performed using custom-made software. Data were interpolated to 200 Hz, and the cerebral blood velocity signal was visually inspected to remove noise and large spikes. The signal was filtered with a median and a Butterworth filter. Heartbeat by heartbeat, heart rate, mean arterial pressure, cerebral blood velocity, and $ETCO_2$ was calculated before resampling all signals at 5 Hz. Transfer function analysis with the Welch method was applied to obtain coherence, gain, and phase in the low- and very-low-frequency range (<0.2 Hz). To estimate impulse and step response curves, an inverse fast Fourier transform was performed; the estimated step response curve was then compared to the 10 template curves from Tiecks et al. to find the best fit (61). The autoregulation index is continuous and can take on any value within 0–9. If bilateral readings were obtained, the autoregulation index was considered to be the average of these readings.

BIOMARKERS

Sample collection

In the PROVE population, venipuncture was performed by research personnel, and plasma samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes at inclusion. Samples were centrifuged, aliquoted, and frozen at –80 °C by research personnel and were then shipped frozen to Gothenburg University for analysis.

In the GoPROVE population, venipuncture was performed by midwives or research personnel at inclusion and at postpartum follow-up. Blood was collected in EDTA tubes and serum tubes without gel.

Samples were centrifuged at 2000 g within 24 h before being aliquoted and stored at −80 °C in the hospital's integrated biobank, Biobank Väst.

Biomarker analysis

In Study II, plasma concentrations of syndecan-1, hyaluronic acid, and thrombomodulin were analyzed with commercial enzyme-linked immunosorbent assay (ELISA) kits. All standard curves, samples, and controls were run in duplicates to ensure reliable results. In Study IV, hyaluronic acid was measured using the same protocol.

In Study III, serum concentrations of sFlt-1 and PlGF were analyzed using assays and the automatized platform DELFIA Xpress 1-2-3 (Revvity Inc, Wallac Oy, Turku, Finland) at iLab Medical AB, Gothenburg, Sweden. Samples were stored at and retrieved from Biobank Väst. Laboratory personnel were blinded to the study groups.

In Study IV, analyses of syndecan-1 and thrombomodulin were performed with ELLA (Biotechne, Minneapolis, USA), an automatized ELISA platform, using open cartridges. Samples were stored at and retrieved from Biobank Väst. All samples, standards, and controls were run in duplicates.

STATISTICS

Studies I and II

In Studies I and 2, differences between groups were assessed with a Kruskal–Wallis global test. In Study II, syndecan-1 concentrations were log-transformed to account for right-skewed distribution of data. Mann–Whitney U-tests with the Bonferroni correction were used for comparations of medians between groups.

Studies III and IV

In Studies III and IV, all biomarkers were log-transformed and then adjusted for gestational age using linear (sFlt-1) or quadratic (PlGF, the sFlt-1/PlGF ratio, and syndecan-1) regression models. This allowed the result for each individual in relation to the whole population to be expressed as the residuals from the regression models, also called the "multiples of the median." In Study III, Kaplan–Meier survival curves of the time to first event were presented for women below or above the gestational age-adjusted median of each biomarker, and differences in the time to event were assessed using the log-rank test.

Predictive accuracy was assessed using receiver operating characteristic (ROC) curves, with the area under the curve (AUC) and 95% CIs. Analyses were performed for the composite outcome and for single outcomes with ≥10 events in the study population. In Study III, if the AUC with 95% CI was entirely over 0.5, optimal cut-offs were determined using Youden's J-index and the minimal distance to (0, 1), and the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio were calculated. These calculations were also made for cut-offs given by the manufacturer of Delphia Xpress, which was originally intended to predict preeclampsia with severe features within a week in women with suspected preeclampsia. In Study III, subgroup analyses, unadjusted for gestational age, were performed for women with early-onset (<34+0 gestational weeks), late-onset (≥34+0 gestational weeks), preterm (<37+0 gestational weeks), and term (≥37+0 gestational weeks) preeclampsia.

Study V

To account for repeated measures and missing data at the one-year postpartum follow-up, analyses of autoregulation index in study 5 were performed with a regression model for repeated measures, assuming data were missing at random. This model accounted for intra-individual correlations between the paired observations. The same modelling framework was applied for both between-group comparisons and within-group changes. ETCO2 and magnesium therapy were included as covariates in sensitivity analyses. All tests were two-sided and conducted at the 5% significance level.

RESULTS

STUDY I

Study I comprised 87 women, of which 21 had normotensive pregnancies, 32 had preeclampsia without organ dysfunction, 18 had preeclampsia with organ dysfunction, and 16 had eclampsia. The women with eclampsia were found to have depressed cerebral autoregulation (autoregulation index 3.9, interquartile range 3.1–5.2) compared with women with preeclampsia with organ dysfunction (autoregulation index 5.6, interquartile range 4.4–6.8), women with preeclampsia without organ dysfunction (autoregulation index 6.8, interquartile range 5.1–7.4) and the normotensive controls (autoregulation index 7.1, interquartile range 6.1–7.9). Pairwise comparisons between eclampsia and the other groups are presented in Figure 8.

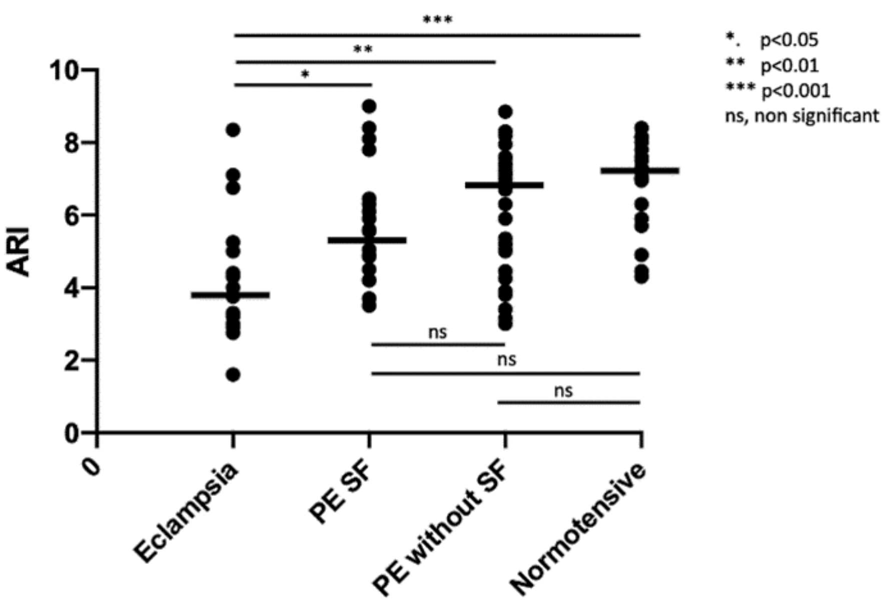


Figure 8. The autoregulation index in preeclampsia and normotensive pregnancies. ARI, autoregulation index; PE, preeclampsia; SF, severe features. Severe features refer to organ dysfunction, as termed in the text. (Source: Bergman et al. (Study I); reproduced with permission under the terms of the Creative Commons CC-BY license.)

STUDY II

Study II comprised 57 women, of which 10 had normotensive pregnancies, 10 had preeclampsia without any organ dysfunction, 24 had a single organ dysfunction, and 13 had multiple organ dysfunctions. There was no difference in the median concentrations of syndecan-1 between women with preeclampsia (461 ng/mL, interquartile range 321–750) and women with normotensive pregnancies (381 ng/mL, interquartile range 127–541, $p = 0.12$). Women with preeclampsia were found to have a median plasma concentration of hyaluronic acid three times as high as that of women with normotensive pregnancies (100.3 ng/mL, interquartile range 54.2–204 vs. 27.0 ng/mL, interquartile range 13.5–66.6, $p < 0.001$). Median plasma concentrations of thrombomodulin were 1.2-fold higher in women with preeclampsia (4.22 ng/mL, interquartile range 3.55–5.17) compared with women with normotensive pregnancies (3.49 ng/mL, interquartile range 3.01–3.68, $p = 0.007$). (Figure 9).

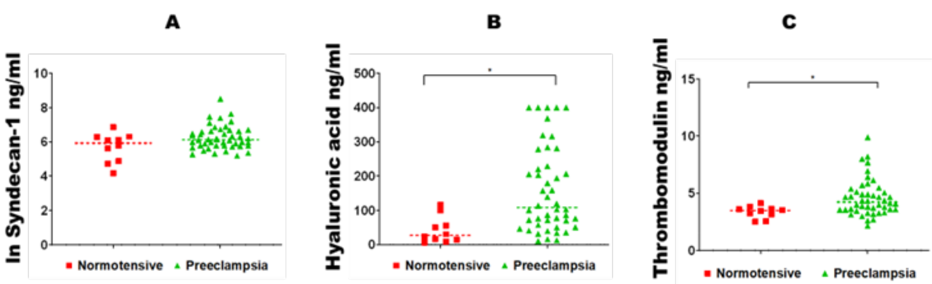


Figure 9. Scatter dots showing plasma concentrations and dotted line showing median plasma concentration for (A) ln syndecan-1, (B) hyaluronic acid, and (C) thrombomodulin. Squares represent normotensive pregnancies, triangles represent preeclampsia. (Source: Carlberg et al. (Study II); reproduced with permission under the terms of the Creative Commons CC-BY license.)

Among women compared according to disease severity, the median plasma concentrations did not differ for any of the markers when comparing preeclampsia without organ dysfunction with preeclampsia with a single organ dysfunction. A comparison between uncomplicated preeclampsia and preeclampsia with multiple organ dysfunctions showed no difference in the median plasma concentrations of syndecan-1 (433 ng/mL, interquartile range 296–760 vs. 635 ng/mL, interquartile range 376–881, $p = 0.40$) and hyaluronic acid (76.6 ng/mL, interquartile range 41.1–310 vs. 229 ng/mL, interquartile range 148–360, $p = 0.17$), but that of thrombomodulin was 1.2-fold higher (4.66 ng/mL, interquartile range 3.45–4.88 vs. 5.46 ng/mL, interquartile range 4.85–7.83, $p = 0.042$) (Figure 10).

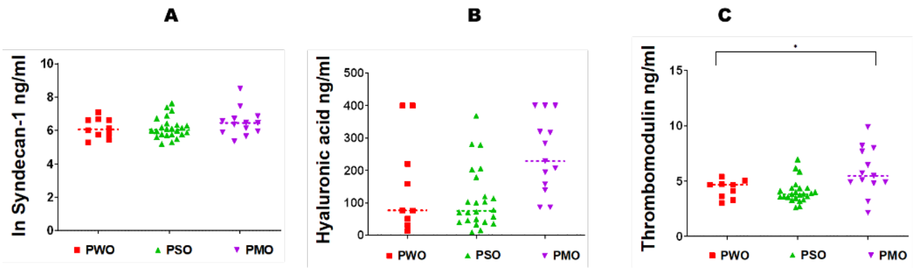
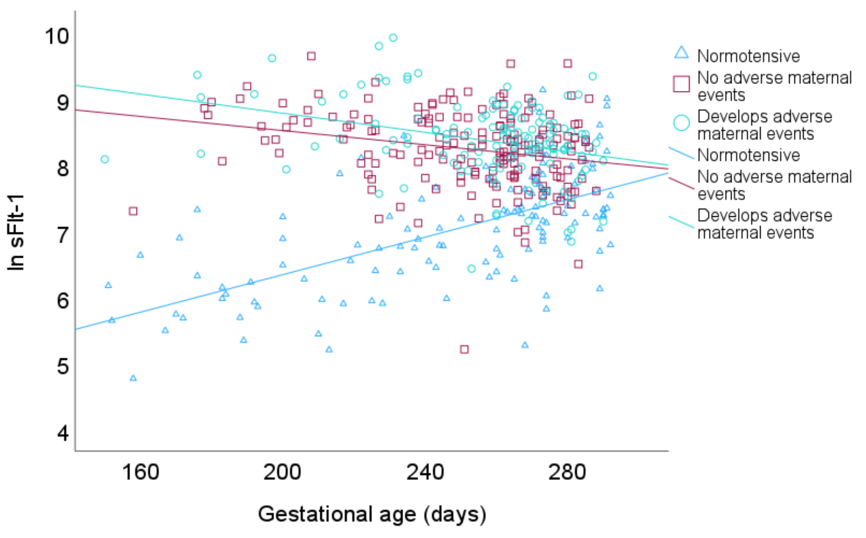


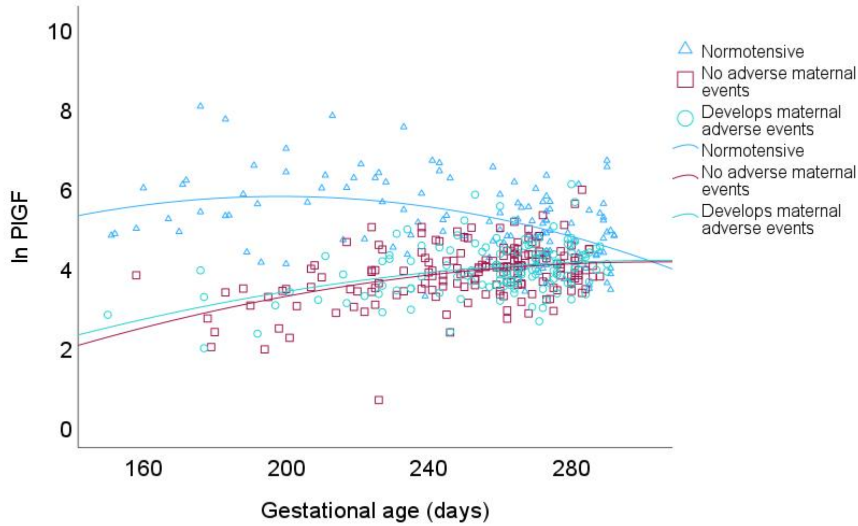
Figure 10. Scatter dots showing plasma concentrations and dotted line showing median plasma concentration for (A) ln syndecan-1, (B) hyaluronic acid, and (C) thrombomodulin. Squares represent preeclampsia without organ dysfunction, triangles pointing upwards represent preeclampsia with a single organ dysfunction, and triangles pointing downwards represent preeclampsia with multiple organ dysfunctions. (PWO, preeclampsia without organ dysfunction; PSO, preeclampsia with a single organ dysfunction; PMO, preeclampsia with multiple organ dysfunctions. Source: Carlberg et al. (Study II); reproduced with permission under the terms of the Creative Commons CC-BY license.).

STUDY III

Study III comprised 307 women, of whom 129 experienced a total of 166 organ complications. The median plasma concentration of sFlt-1 was 4092 pg/mL (interquartile range 2802–5947), that of PlGF was 49.6 pg/mL (interquartile range 32.6–74.3), and the median sFlt-1/PlGF ratio was 80 (interquartile range 49–146). There was no difference in the median plasma concentrations of sFlt-1 or PlGF between groups at baseline.

In earlier gestation, women with normotensive pregnancies had lower concentrations of sFlt-1, higher concentrations of PlGF, and a lower sFlt-1/PlGF ratio than women with preeclampsia. There were no apparent differences over different gestational weeks in the concentrations of angiogenic markers in women with preeclampsia who developed the composite outcome, compared with those who did not (Figure 11).





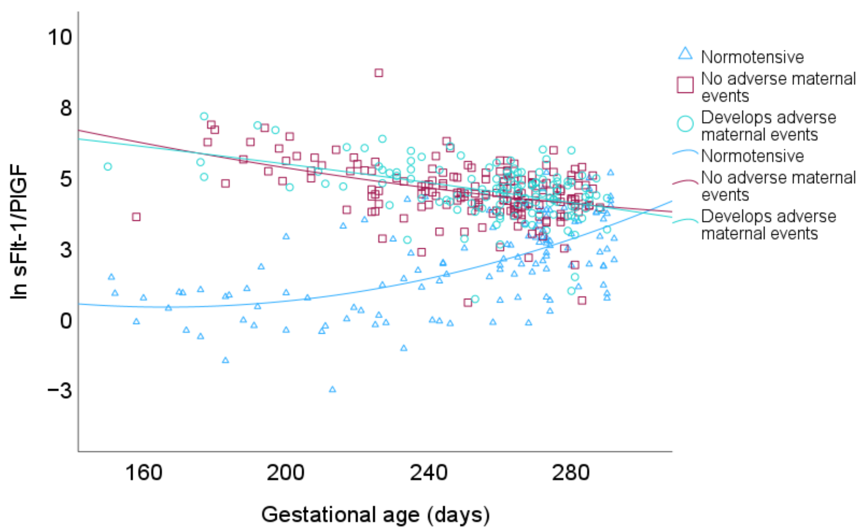


Figure 11. Scatter plots of sFlt-1, PlGF, and the sFlt-1/PlGF ratio over gestational age in women with normotensive pregnancies (triangles), preeclampsia without adverse maternal events (squares), and preeclampsia with subsequent adverse maternal events (circles). (PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase. Previously unpublished results.)

ROC-curve analyses showed that the AUC for sFlt-1 predicting the composite outcome was 0.59 (95% CI: 0.52–0.65). The optimal cut-off according to Youden's J-index was 2% lower than the gestational age specific median, translating into a sensitivity of 67% at a specificity of 50%. According to the minimal distance method, the optimal cut-off was instead 8% over the gestational age specific median, translating into a sensitivity of 59% with a specificity of 66%. For PlGF, the AUC was 0.48 (95% CI: 0.42–0.55) and for the sFlt-1/PlGF ratio, the AUC was 0.54 (95% CI: 0.48–0.61); as there were no statistical differences from 0.5, no optimal cut-offs were calculated (Table 3, page 44).

Across all predictive tests based on Delfia Xpress cut-offs, the 95% Cis for the positive likelihood ratios did not consistently exceed 2, nor did those for the negative likelihood ratios fall consistently below 0.5.

sFlt-1 was predictive of the single outcomes thrombocytopenia (AUC 0.68, 95% CI: 0.56–0.81), elevated liver enzymes (AUC 0.68, 95% CI: 0.59–0.78), and acute kidney injury (AUC 0.72, 95% CI: 0.60–0.83). sFlt-1 was not predictive of postpartum hemorrhage. Low plasma concentrations of PlGF showed an inverse association with elevated liver enzymes (AUC 0.34, 95% CI: 0.24–0.44), indicating that high PlGF concentrations were associated with increased risk. Apart from elevated liver enzymes, PlGF was not predictive of any single outcome. The sFlt-1/PlGF ratio was also not predictive of any single outcome (Table 3, page 44).

When dividing women into groups of early- and late-onset preeclampsia, 63 women were categorized as having early-onset and 244 as having late-onset preeclampsia. In early-onset preeclampsia, sFlt-1 predicted the composite outcome (AUC 0.65, 95% CI: 0.50–0.79), whereas PlGF and the sFlt-1/PlGF ratio did not predict the composite outcome. sFlt-1 and the sFlt-1/PlGF ratio predicted the single outcome acute kidney injury (AUC 0.75, 95% CI: 0.54–0.97 and AUC 0.76, 95% CI: 0.61–0.91, respectively). For late-onset preeclampsia, none of sFlt-1, PlGF, or the sFlt-1/PlGF ratio predicted the composite outcome. sFlt-1 predicted thrombocytopenia (AUC 0.69, 95% CI: 0.57–0.81), elevated liver enzymes (AUC 0.70, 95% CI: 0.60–0.79), and acute kidney injury (AUC 0.71, 95% CI: 0.59–0.83). Lower PlGF plasma concentrations showed an inverse association with elevated liver enzymes (Table 3, page 44).

When dividing women into preterm and term preeclampsia, 128 women were categorized as having preterm and 179 as having term preeclampsia. None of sFlt-1, PlGF, or the sFlt-1/PlGF ratio predicted the composite outcome in the preterm or the term group. Among women with preterm preeclampsia, sFlt-1 and the sFlt-1/PlGF ratio predicted the single outcomes thrombocytopenia (AUC 0.75, 95% CI: 0.54–0.96 and 0.72, 95% CI: 0.57–0.87, respectively) and acute kidney injury (AUC 0.70, 95% CI: 0.55–0.86 and AUC 0.69, 95% CI: 0.55–0.83, respectively). In women with term preeclampsia, sFlt-1 was predictive for the single outcomes thrombocytopenia (AUC 0.66, 95% CI: 0.53–0.78), elevated liver enzymes (AUC 0.76, 95% CI: 0.64–0.87), and acute kidney injury (AUC 0.71, 95% CI: 0.55–0.87) (Table 3, page 45).

Table 3. Area under the ROC-curve for the composite outcome and for single outcomes with ≥10 events, presented for all women, early-onset preeclampsia, late-onset preeclampsia, preterm preeclampsia and term preeclampsia.

	sFlt-1	PlGF	sFlt-1/PlGF
All women			
The Composite Outcome	0,587 (0,522–0,652)	0,481 (0,415–0,547)	0,542 (0,476–0,608)
Thrombocytopenia	0,684 (0,557–0,811)	0,499 (0,342–0,656)	0,607 (0,466–0,748)
Elevated liver enzymes	0,683 (0,589–0,777)	0,337 (0,235–0,439)	0,498 (0,387–0,608)
Acute kidney injury	0,716 (0,604–0,828)	0,466 (0,332–0,601)	0,608 (0,466–0,750)
Postpartum hemorrhage	0,49 (0,427–0,568)	0,536 (0,464–0,607)	0,526 (0,454–0,598)
Early-onset preeclampsia			
The Composite Outcome	0,648 (0,503–0,793)	0,435 (0,289–0,580)	0,477 (0,333–0,622)
Thrombocytopenia	0,673 (0,414–0,933)	0,585 (0,348–0,823)	0,628 (0,430–0,825)
Elevated liver enzymes	0,681 (0,476–0,887)	0,358 (0,180–0,537)	0,479 (0,306–0,652)
Acute kidney injury	0,753 (0,538–0,967)	0,612 (0,396–0,828)	0,755 (0,605–0,906)
Postpartum hemorrhage	0,483 (0,227–0,739)	0,377 (0,173–0,581)	0,373 (0,223–0,522)
Late-onset preeclampsia			
The Composite Outcome	0,554 (0,481–0,627)	0,476 (0,402–0,550)	0,514 (0,440–0,588)
Thrombocytopenia	0,687 (0,567–0,808)	0,483 (0,299–0,668)	0,604 (0,421–0,787)
Elevated liver enzymes	0,698 (0,601–0,794)	0,357 (0,230–0,484)	0,526 (0,398–0,654)
Acute kidney injury	0,706 (0,585–0,828)	0,434 (0,263–0,606)	0,559 (0,389–0,730)
Postpartum hemorrhage	0,477 (0,401–0,553)	0,522 (0,445–0,599)	0,499 (0,420–0,577)

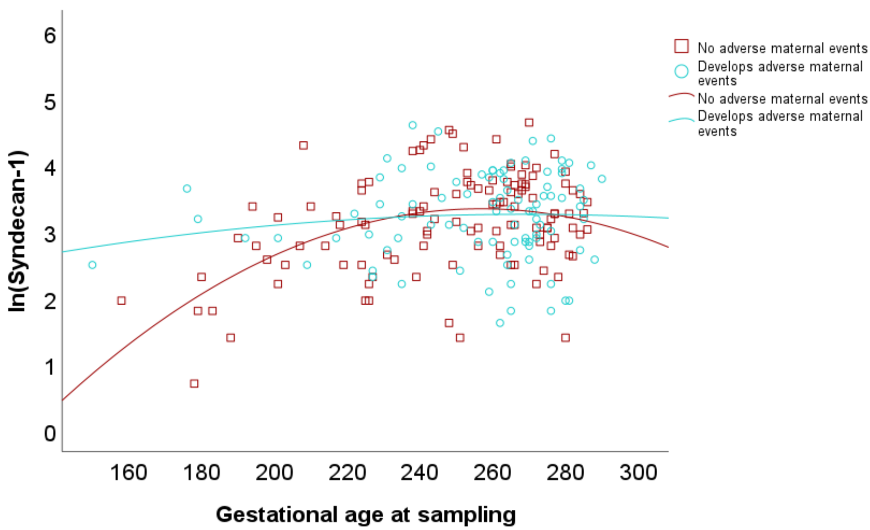
Table 3 (continued). Area under the ROC-curve for the composite outcome and for single outcomes with ≥10 events, presented for all women, early-onset preeclampsia, late-onset preeclampsia, preterm preeclampsia and term preeclampsia.

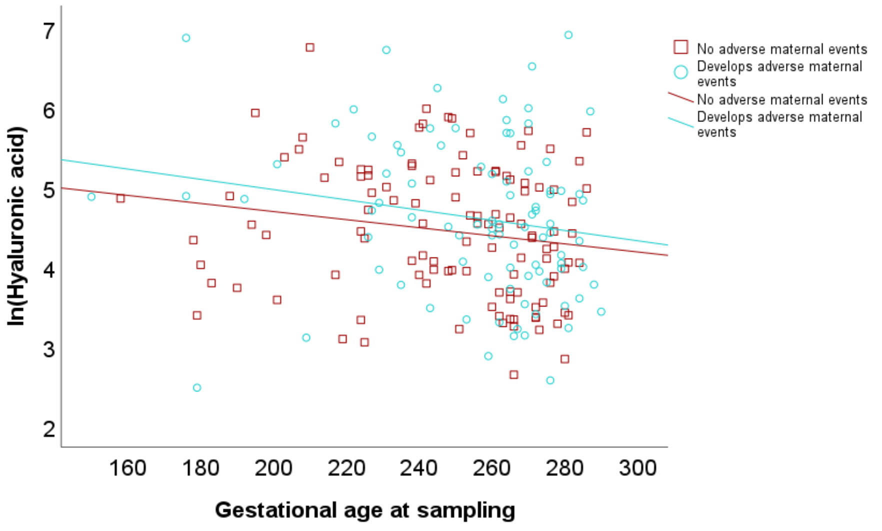
	sFlt-1	PlGF	sFlt-1/PlGF
Preterm preeclampsia			
The Composite Outcome	0,596 (0,492–0,700)	0,479 (0,372–0,586)	0,555 (0,451–0,659)
Thrombocytopenia	0,751 (0,543–0,958)	0,598 (0,383–0,812)	0,720 (0,570–0,869)
Elevated liver enzymes	0,620 (0,480–0,759)	0,368 (0,221–0,514)	0,483 (0,335–0,630)
Acute kidney injury	0,706 (0,547–0,855)	0,605 (0,454–0,756)	0,694 (0,553–0,834)
Postpartum hemorrhage	0,406 (0,257–0,555)	0,441 (0,272–0,609)	0,445 (0,283–0,606)
Term preeclampsia			
The Composite Outcome	0,571 (0,486–0,655)	0,490 (0,405–0,575)	0,532 (0,447–0,618)
Thrombocytopenia	0,657 (0,530–0,784)	0,504 (0,289–0,719)	0,595 (0,388–0,801)
Elevated liver enzymes	0,758 (0,644–0,872)	0,389 (0,228–0,550)	0,597 (0,444–0,750)
Acute kidney injury	0,708 (0,550–0,866)	0,312 (0,089–0,536)	0,471 (0,225–0,717)
Postpartum hemorrhage	0,506 (0,420–0,593)	0,534 (0,448–0,621)	0,517 (0,430–0,604)

PlGF, placental growth factor; ROC, receiver operator characteristics; sFlt-1, soluble fms-like tyrosine kinase.

STUDY IV

Study IV comprised 212 women with preeclampsia, of whom 92 developed a total of 121 organ complications. The median plasma concentration of syndecan-1 was 25 ng/mL (interquartile range 16–40), that of hyaluronic acid was 92.0 ng/mL (interquartile range 47.8–176.0), and that of thrombomodulin was 4.08 ng/mL (interquartile range 3.17–5.22). No difference was observed between women who developed the composite outcome and those who did not. (Figure 12)





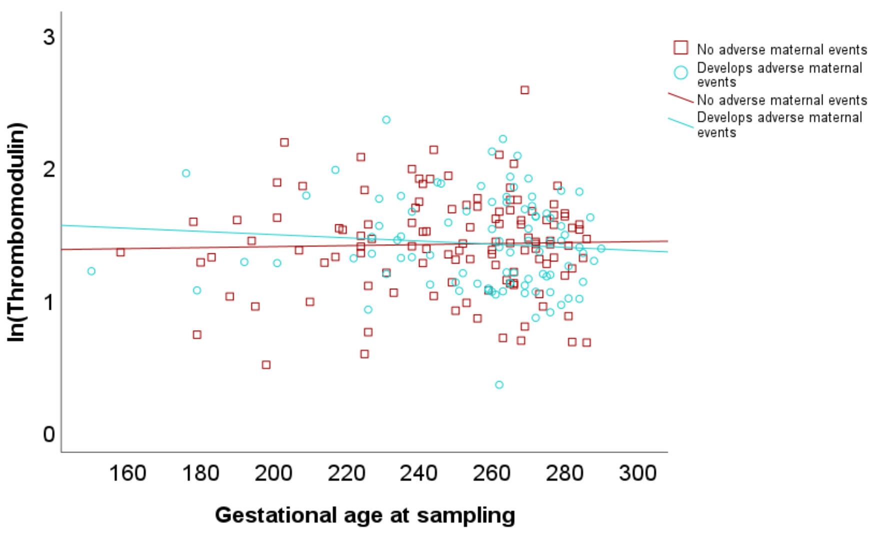


Figure 12. Scatterplots of ln syndecan-1, ln hyaluronic acid and ln thrombomodulin over gestational age in preeclampsia without adverse maternal events (squares) and preeclampsia with subsequent adverse maternal events (circles). (PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase. Previously unpublished results.)

None of syndecan-1, hyaluronic acid, or thrombomodulin predicted the composite outcome. The AUC for syndecan-1 was 0.52 (95% CI: 0.44–0.60), that of hyaluronic acid was 0.54 (95% CI: 0.46–0.62), and that of thrombomodulin was 0.49 (95% CI: 0.41–0.57) (Table 4)

Table 4. Predictive performance of syndecan-1, hyaluronic acid, and thrombomodulin for the composite outcome and single outcomes with ≥10 events, expressed as area under the receiver operator characteristics curve with 95% confidence intervals.

Univariable	Syndecan-1	Hyaluronic acid	Thrombomodulin
The Composite Outcome	0,526 (0,446–0,606)	0,540 (0,459–0,620)	0,492 (0,412–0,572)
Thrombocytopenia	0,618 (0,445–0,792)	0,672 (0,517–0,827)	0,540 (0,368–0,712)
Elevated liver enzymes	0,643 (0,523–0,764)	0,692 (0,568–0,815)	0,603 (0,473–0,733)
Acute kidney injury	0,599 (0,451–0,747)	0,604 (0,487–0,72)	0,571 (0,448–0,694)
Postpartum hemorrhage	0,470 (0,381–0,560)	0,426 (0,338–0,514)	0,434 (0,345–0,523)

Syndecan-1 predicted the single outcome of elevated liver enzymes with an AUC of 0.64 (95% CI: 0.52–0.76). Hyaluronic acid predicted thrombocytopenia and elevated liver enzymes with AUCs of 0.67 (95% CI: 0.52–0.83) and 0.69 (95% CI: 0.57–0.82), respectively (Table 4).

Multivariable analyses were conducted, combining syndecan-1, hyaluronic acid, and thrombomodulin pairwise, and no combination was found to predict the composite outcome. The combination of syndecan-1 and hyaluronic acid predicted the single outcomes thrombocytopenia (AUC 0.67, 95% CI: 0.51–0.84) and elevated liver enzymes (AUC 0.70, 95% CI: 0.58–0.82). The combination of syndecan-1 and thrombomodulin predicted elevated liver enzymes with an AUC of 0.66 (95% CI: 0.54–0.78). The combination of hyaluronic acid and thrombomodulin predicted thrombocytopenia (AUC 0.67, 95% CI: 0.50–0.84) and elevated liver enzymes (AUC 0.71, 95% CI: 0.59–0.82). (Table 5)

Table 5. Predictive performance of pairwise combinations of syndecan-1, hyaluronic acid, and thrombomodulin for the composite outcome and single outcomes with ≥10 events, expressed as area under the receiver operator characteristics curve with 95% confidence intervals.

Multivariable	Syndecan-1 and Hyaluronic acid	Syndecan-1 and Thrombomodulin	Hyaluronic acid and Thrombomodulin
The Composite Outcome	0,542 (0,461–0,623)	0,528 (0,448–0,607)	0,546 (0,465–0,627)
Thrombocytopenia	0,674 (0,507–0,840)	0,621 (0,453–0,789)	0,673 (0,504–0,843)
Elevated liver enzymes	0,700 (0,581–0,820)	0,660 (0,536–0,784)	0,706 (0,591–0,822)
Acute kidney injury	0,617 (0,486–0,749	0,613 (0,468–0,758)	0,616 (0,491–0,742)
Postpartum hemorrhage	0,568 (0,482–0,655)	0,586 (0,497–0,675)	0,473 (0,389–0,558)

Multivariable analyses combining syndecan-1 with sFlt-1, hyaluronic acid with sFlt-1, and thrombomodulin with sFlt-1 were performed. None of the GDPs improved the predictive performance of sFlt-1 alone on the composite outcome or any single outcome.

STUDY V

Study V comprised 150 women from the UPMOST and GoPROVE biobanks participating in TCD examinations at both/either inclusion and/or 1 year postpartum. Due to the exclusion criteria or insufficient measurement quality, 26 women were excluded, leaving 124 women in the final analysis. During pregnancy, the mean autoregulation index was found to be higher in normotensive women compared with women with preeclampsia (6.90 (SD 0.77) vs. 6.12 (SD 1.45), mean difference 0.78 (95% CI 0.37–1.19)), but it did not differ between women with preeclampsia with or without severe features (6.24 (SD 1.49) vs. 5.98 (SD 1.40), mean difference 0.27 (95% CI −0.43–0.96)). At 1 year postpartum, there were no differences in the autoregulation index between any of the groups. Normotensive women had a higher autoregulation index during pregnancy than they did at 1 year postpartum (6.90 − 6.11 = 0.79 (95% CI 0.33–1.25)); women with preeclampsia had a similar autoregulation index during pregnancy as they did at 1 year postpartum (Table 6 and 7).

When adjusting for $ETCO_2$ and magnesium results remained similar.

Table 6. Cerebral autoregulation in normotensive pregnancies and preeclampsia during pregnancy and at one-year postpartum.

	Normotensive pregnancies	Preeclampsia	Mean difference (95% CI)
During pregnancy	n=69	n=47	
ARI	6.90 (0.77)	6.12 (1.45)	−0.78 (−1.19, −0.37)
One-year pp	n=54	n=31	
ARI	6.11 (1.14)	6.15 (1.10)	0.03 (−0.47, 0.54)
Change in ARI	−0.79 (−1.26, −0.32)	0.03 (−0.42, 0.49)	0.82 (0.17, 1.47)

Table 7. Cerebral autoregulation in normotensive pregnancies and preeclampsia with or without organ dysfunction.

	Preeclampsia with organ dysfunction	Preeclampsia without organ dysfunction	Mean difference
During pregnancy	n=37	n=32	
ARI	6.24 (1.49)	5.98 (1.40)	0.27 (−0.43, 0.96)
One year pp	n=31	n=23	
ARI	6.13 (1.23)	6.18 (0.94)	0.05 (−0.64, 0.54)
Change in ARI	−0.11 (−0.77, 0.55)	0.20 (−0.43, 0.83)	−0.31 (−1.22, 0.59)

Descriptive data is presented as mean (SD) or mean difference (95% CI). All observations were included in the analyses, even for individuals with single measurements. Linear mixed models were used to estimate changes over time within group and differences between groups at each time point, accounting for repeated measurements within individuals. Different variances for the two groups were assumed. ARI, autoregulation index; CI, confidence interval; pp, postpartum.

DISCUSSION

The studies in this thesis focus on preeclampsia and organ dysfunction and were conducted at three centers. All studies are clinical and use the autoregulation index, measured with TCD, GDPs, and angiogenic markers for the assessment or prediction of disease severity.

MAIN FINDINGS

Cerebral autoregulation is enhanced during pregnancy, depressed in preeclampsia, and even further depressed in eclampsia. At 1 year postpartum, all participants with normotensive pregnancies and preeclampsia showed similar cerebral autoregulation, irrespective of preeclampsia and organ dysfunction.

In preeclampsia, the endothelial glycocalyx appears to be degraded, as indicated by the increased circulating levels of its degradation products. However, plasma concentrations of these products generally did not predict subsequent organ dysfunction in preeclampsia, except for hyaluronic acid, which was associated with elevated liver enzymes.

Circulating concentrations of the angiogenic marker sFlt-1 showed moderate performance at best for the prediction of organ dysfunction in women with preeclampsia, also in preterm preeclampsia. PlGF was not predictive of organ dysfunction, and the sFlt-1/PlGF ratio generally showed poor performance.

RESULTS IN CONTEXT

Cerebral autoregulation

In Study V, cerebral autoregulation was enhanced in pregnancy, similar to findings in other studies (63, 64, 67). We found that the autoregulation index was lower in preeclampsia compared with normotensive pregnancies but similar compared with 1 year postpartum. Two previous studies reported a lower autoregulation index in preeclampsia compared with normotensive pregnancies, similar to our findings, and one small study with only five women with preeclampsia and five with normotensive pregnancies reported contradicting results, with enhanced autoregulation in preeclampsia (67-69). Taken together, the findings suggest that cerebral autoregulation is depressed in women with preeclampsia.

In Study I and V, there were no statistically significant differences in the autoregulation index between preeclampsia with or without organ dysfunction, suggesting that cerebral autoregulation is not proportional to disease severity in general. However, two previous case reports have described depressed autoregulation in eclampsia and posterior reversible encephalopathy syndrome, and Study I demonstrated an association between eclampsia and depressed cerebral autoregulation, so depressed autoregulation seems to be associated with cerebral complications (158, 159). As the measurements were taken after seizures, no conclusion regarding causality can be drawn from the observed association. In Study V, at 1 year postpartum, cerebral autoregulation was similar across the groups, irrespective of preeclampsia history or prior organ dysfunction. This result suggests that the long-term consequences of preeclampsia are not caused by persistently altered cerebral autoregulation, in line with a previous study showing comparable cerebral autoregulation in women irrespective of prior preeclampsia (70). Another study by the same researcher, however, reported reduced transfer function analysis phase values in six pregnant women with a previous history of preeclampsia, even in the absence of current disease, when compared with women without such history (64). This inconsistency makes interpretation somewhat difficult; nevertheless, in conclusion, the evidence suggests that depressed cerebral autoregulation in preeclampsia could contribute to cerebral complications in acute disease, but depressed cerebral autoregulation is not a longstanding sequela.

Glycocalyx degradation products

Syndecan-1

At preeclampsia diagnosis, no difference in the mean plasma concentrations of syndecan-1 was seen between preeclampsia with or without subsequent organ dysfunction. It is therefore unsurprising that syndecan-1 showed poor performance as a predictor of organ dysfunction. As Study IV is the first study to investigate this specific research question, no prior data are available for direct comparison.

Hyaluronic acid

Mean plasma concentrations of hyaluronic acid were three-fold higher in preeclampsia compared with normotensive pregnancies; they were also three-fold higher—although not statistically different—in preeclampsia with multiple organ dysfunction compared with preeclampsia without organ dysfunction. This finding aligns with previous studies, and the absence of difference between multiple organ dysfunction and no organ dysfunction could be explained by a type-two error (90, 95, 116, 117). In Study IV, hyaluronic acid was found to have the best predictive value for elevated liver enzymes. There is a possible explanation for this finding, as hyaluronic acid is degraded in liver sinusoidal cells, which are injured in hepatic involvement in preeclampsia; therefore, the elevated plasma concentrations of hyaluronic acid in preeclampsia with hepatic involvement might be caused by both endothelial glycocalyx degradation and reduced hepatic clearance in conjunction (78, 118).

Thrombomodulin

In Study II, the mean plasma concentration of thrombomodulin was elevated in preeclampsia and even higher in preeclampsia with multiple organ complications. In Study IV, no outcome was predicted by the plasma concentrations of thrombomodulin. A recent systematic review and meta-analysis found that thrombomodulin holds potential as a biomarker for assessing disease severity in preeclampsia. The lack of predictive value in Study IV could potentially be explained by differences in disease severity, as the women in the South African population (Study II) had more severe organ dysfunction than women in the Swedish cohort. Hyaluronic acid is loosely anchored and diffusely distributed within the endothelial glycocalyx, while thrombomodulin is anchored to the endothelial cell membrane. This could imply that the plasma concentrations of hyaluronic acid will rise before those of thrombomodulin, potentially explaining the difference between Study II and Study IV.

Angiogenic markers

In Study III, the angiogenic markers showed poor predictive performance for the composite outcome—results inferior to those reported in some previous studies. Six previous studies have reported on adverse maternal outcomes in women with a diagnosis of preeclampsia, and three studies reported results similar to those of our study (119–121). One study using a sFlt-1/PlGF ratio ≥ 85 found good negative-likelihood ratios that ruled out HELLP syndrome, elevated liver enzymes, low platelets, and placenta abruptio (122). Two studies proposed two different potentially useful cut-offs (sFlt-1/PlGF ratio > 377 or sFlt-1 > 7439), yielding sensitivities of 0.75 and 0.77 and specificities of 0.92 and 0.76, respectively (123, 124). In summary, the sFlt-1/PlGF ratio does not seem to perform as well for the prediction of organ dysfunction in women with a diagnosis of preeclampsia as it does for the prediction of preeclampsia with severe features in women with suspected preeclampsia.

Interpreting an unexpected PlGF pattern

When constructing the ROC curves for Study III, we found that PlGF was a poor predictor for both the composite and any single outcome. For elevated liver enzymes, it even showed an inverted ROC-curve, suggesting that high serum concentrations of PlGF were associated with organ dysfunction. Our assumption, based on previous studies, was that low serum concentrations of PlGF would predict the outcome (109, 125). It could be noted that sFlt-1 and PlGF are heparin-binding proteins that may accumulate within the endothelial glycocalyx and form a releasable pool (126-128). In pregnant women treated with low-molecular-weight heparin, the plasma concentrations of PlGF were higher and the sFlt-1/PlGF ratio was lower in the third trimester compared with those in the controls (129). These results suggest that pregnant women have a considerable store of sFlt-1 and PlGF in the endothelial glycocalyx and the placenta. This releasable store may contribute to elevated plasma concentrations of both sFlt-1 and PlGF in preeclampsia with organ dysfunction, potentially making sFlt-1 a more reliable and PlGF a less reliable predictor of organ dysfunction.

METHODOLOGICAL CONSIDERATIONS

Factors influencing the autoregulation index

Calculation of the autoregulation index for the estimation of cerebral autoregulation with TCD and non-invasive continuous blood pressure measurements is a well-established method, and we found a low inter-examiner variability. Yet, many factors influence the results of these examinations.

End-tidal CO_2

Hypoventilation, with subsequent increased partial pressure of carbon dioxide in arterial blood, is known to elicit vasodilation with increased cerebral blood flow and cerebral blood velocities but a depressed cerebral autoregulation (130, 131). Hyperventilation, with subsequent decreased partial pressure of carbon dioxide in arterial blood, is known to elicit vasoconstriction with decreased cerebral blood flow and cerebral blood velocities but an enhanced cerebral autoregulation (130, 131). In a study with 45 healthy volunteers breathing 5% and 8% inspired fraction carbon dioxide, a distinct sigmoid dose-response relationship between $ETCO_2$ and the autoregulation index or cerebral blood flow was found (132). In contrast to these experimental studies, a study on cerebrovascular reactivity in chronic obstructive pulmonary disease showed similar autoregulation index in patients and controls, despite a difference in $ETCO_2$ (133). When adjusting for $ETCO_2$ in our study, the results remained similar. This may be explained by the fact that experimental interventions induce acute effects, whereas the reduction in $ETCO_2$ in pregnancy represents a gradual, long-term change.

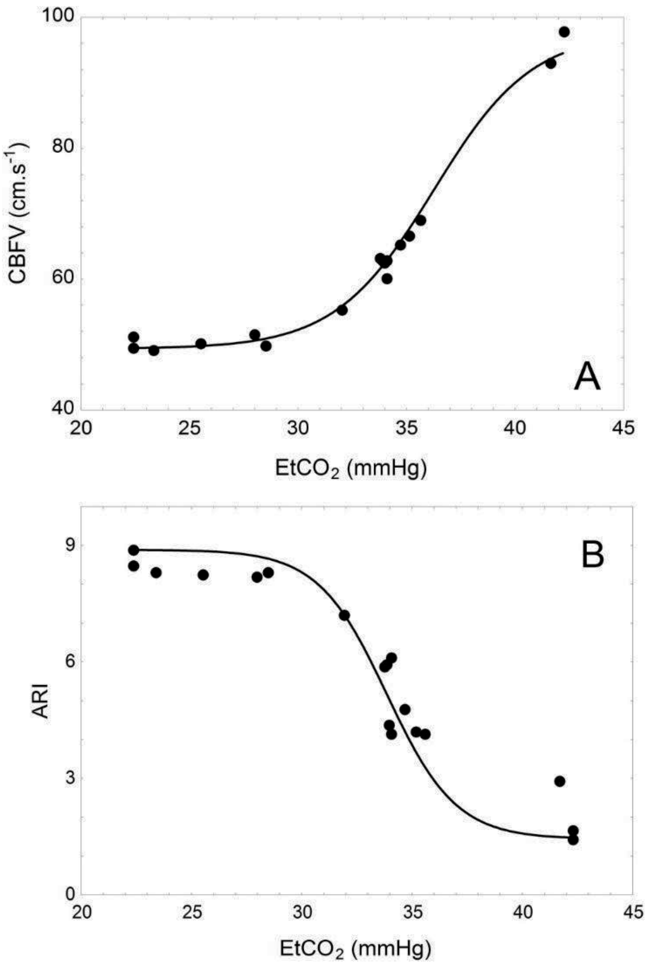


Figure 13. Autoregulation index is proportional to $ETCO_2$. This curve shows measurements from one individual breathing air, and inspired carbon dioxide 5% and 8%. (Source: Minhas et al. (132) p 4. Reproduced with permission from Physiologic Measurements, IOP Publishing.)

Hematocrit

The rheological properties of the blood, especially the hematocrit, are known to alter autoregulation index due to their influence on cerebral blood velocity. Hypervolemic hemodilution, seen in pregnancy, has been shown to depress cerebral autoregulation, whereas preeclampsia is associated with hemoconcentration relative to normotensive pregnancies (134, 135). Given that normotensive pregnant women in study V exhibit enhanced cerebral autoregulation, adjusting for hemoglobin (as a proxy for hematocrit) would likely accentuate rather than diminish the observed difference in autoregulation index between normotensive pregnancy and preeclampsia.

Other factors

Sympathetic/parasympathetic activity, neuronal activity, body temperature, and intracranial and intrathoracic pressure are also known to alter cerebral autoregulation (136). The procedural conditions were kept as constant as possible, and we consider it unlikely that variations in any of these variables except intracranial pressure were substantial enough to influence the results. If intracranial pressure varied, it likely covaried with disease severity rather than fluctuating randomly, thus potentiating the effect of preeclampsia. Many diseases are known to alter cerebral autoregulation, at least regionally, such as traumatic brain injury, stroke, carotid stenosis, and malignant hypertension (137–140). Chronic hypertension, however, does not seem to alter either static or dynamic cerebral autoregulation (141). A recent systematic review on TCD examinations in patients with type-2 diabetes concluded that cerebral autoregulation is often impaired in these patients (142). Nevertheless, in a study of pregnant women with diabetes, including gestational diabetes and type-2 diabetes mellitus, as well as overweight (pre-pregnancy body mass index >25 kg/m^2) and healthy controls, the autoregulation index was similar in all groups (diabetes 6.6 (SD 1.1), overweight 6.7 (SD 0.6), and controls 6.6 (SD 0.8)) (63). In summary, none of the above-mentioned variables were considered to substantially influence the results in our studies.

The anterior and the posterior circulation

The brain receives its arterial blood supply via the internal carotid and vertebral arteries, which anastomose to form the circle of Willis. From here, the anterior and the middle cerebral arteries forms the anterior circulation, and the posterior cerebral artery forms the posterior circulation (160). Sympathetic innervation is more pronounced in the anterior cerebral vasculature than in the posterior territories, reflecting regional differences in cerebral autoregulation (161, 162). In posterior reversible encephalopathy syndrome, eclampsia and preeclampsia, lesions seen on computer tomography scans and magnetic resonance imaging are predominantly occipital (163, 164). This may support the theory that the posterior circulation is more vulnerable to high blood pressure and hyperperfusion because of less sympathetic innervation and depressed cerebral autoregulation compared with the anterior circulation (162).

Constancy of the middle cerebral artery cross-sectional area

An important prerequisite for the interpretation of studies regarding cerebral autoregulation measured by TCD, and a potential source of confounding, is that changes in cerebral blood flow velocities reflect changes in cerebral blood flow. This is true only if the sectional area of the vessel at the place where the measurement takes place is constant (54). The sectional areas of the middle and posterior cerebral arteries have been investigated by magnetic resonance imaging and were found to be constant during pregnancy and unchanged by preeclampsia (143, 144). In anesthetized cats, on the other hand, the diameter of vessels the size of the middle cerebral artery was found to constrict by 8% when the blood pressure changed from 120 mmHg to 160 mmHg (145). The inner diameter of the internal carotid artery has been found to increase in pregnancy and continuously increase during the course of pregnancy (146). In summary, changes in diameter in the middle cerebral artery during measurements are unlikely to have influenced the results.

Factors influencing plasma concentrations of glycocalyx degradation products

There are numerous factors influencing the plasma concentrations of GDPs and their association with endothelial dysfunction, and a systematic review and critical appraisal on this subject has been published (147). First, it is uncertain whether GDPs truly originate from the endothelium. Several alternative sources are possible, such as the placenta, plasma cells, or ingested meals (75, 148). In one study, an infusion of 1000 mL Ringers lactate more than doubled the mean plasma concentrations of hyaluronic acid (from 12 (SD 5.8) ng/mL to 27 (SD 13.9) ng/mL), probably due to wash out via lymphatic flow from interstitial tissue (149). Secondly, kinetics are complex, and a study has reported that differences in the renal excretion of syndecan-1 may result in five-fold differences in plasma concentrations (76). As renal clearance of syndecan-1 is closely correlated to renal clearance of creatinine, syndecan-1 would be expected to be a good marker for acute kidney injury, but this was not observed in our population. Syndecan-1 plasma levels appear to be influenced by factors beyond renal excretion. A third important aspect concerns the temporal dynamics of endothelial glycocalyx degradation. The kinetics of the plasma concentrations of GDPs remain poorly characterized, and the point at which the clinical symptoms of endothelial dysfunction emerge during the pathophysiological process of organ complications in preeclampsia is not well characterized.

Alternative methods for assessing glycocalyx degradation

Glycocalyx degradation have been investigated in preeclampsia using side stream darkfield imaging, showing larger perfused boundary regions as a sign of glycocalyx degradation in early-onset preeclampsia (117). Degradation has also been assessed with transmission electron microscopy, showing reduced thickness of endothelial glycocalyx in preeclampsia compared with healthy pregnant controls and non-pregnant women (165).

Challenges in defining optimal cut-offs for sFlt-1 and PlGF

Numerous studies have investigated the predictive values of angiogenic markers in identifying women at risk for maternal adverse outcomes. Some of these studies have proposed novel optimal cut-offs and reported numerical cut-off values, while others have used numerical cut-offs already proposed in previous studies. As the distribution of serum concentrations of both sFlt-1 and PlGF vary across gestational age, the predictive value of a numerical cut-off will inevitably vary with gestational age (119, 150). To overcome this problem, many studies have tested their cut-off (or cut-offs) in subpopulations, dividing women into, for example, early- or late-onset preeclampsia, or a gestational age of <34 weeks, 34–37 weeks, or >37 weeks. Unfortunately, there are numerous ways of dividing populations and very few studies harmonize, making comparations difficult. A few studies have expressed biomarkers as multiples of the median or have defined a cut-off at specific percentiles of the gestational-age-adjusted sFlt-1 or PlGF serum concentration to deal with this problem (120, 151-154).

Adjusting for gestational age

In Study III, we chose to recalculate every serum concentration of sFlt-1, PlGF, and the sFlt-1/PlGF ratio to multiples of the median. This is a way of expressing how high or low a value is in relation to the median at that specific gestational age and a way of adjusting for differences in gestational age between individuals and groups. While this approach was an attempt to address the issue of gestational-age-related variability, some inherent limitations must be acknowledged. The median must be defined and calculated. In Study III, the population consisted of women with a diagnosis of preeclampsia. When a normotensive reference population is used to calculate the median, the differences between the plasma concentrations of PlGF in normotensive pregnancies and those in preeclampsia are much greater in early gestation, resulting in a dilution of the differences between preeclampsia with and without the composite outcome at term. We therefore chose to use the study population—that is, only women with preeclampsia—as the reference, thereby limiting the generalizability of our findings to women with a diagnosis of preeclampsia but allowing unbiased comparisons within this group. To aid comparison with prior studies, using subgroups at different gestational age, we also chose to divide our population into both early and late onset, and preterm and term preeclampsia, and repeated the analyses on unadjusted data. The results remained similar.

The importance of different outcomes

In Studies III and IV, the use of a composite outcome based on a core outcome set for preeclampsia research has both benefits and drawbacks. (10) A composite outcome usually pools rare events, thus increasing the statistical power, and often reflects different but equally important aspects of a disease, thereby increasing the clinical relevance of a study. With a composite outcome, the risk of selective reporting bias diminishes, and this is especially true if a core set of outcomes are predefined and commonly used in a field. One important benefit then is the future possibility of pooling results in meta-analyses. Among drawbacks are that different components of the composite outcome are treated as equally important, and that some outcomes might be much more common than others and thus gain disproportionate influence. In Studies III and IV, postpartum hemorrhage was by far the most common component of the composite outcome but was only weakly associated with preeclampsia in our dataset. As a result, the predictive value of outcomes such as thrombocytopenia and elevated liver enzymes was diluted within the composite outcome. There are also challenges in clinical decision-making where the composite outcome is not helpful, but other outcomes could be relevant (155).

CLINICAL IMPLICATIONS

Cerebral autoregulation is depressed in preeclampsia, underscoring the importance of prompt treatment of high blood pressure and caution to avoid blood pressure elevations when inducing general anesthesia in women with preeclampsia.

Cerebral autoregulation is not depressed 1 year after preeclampsia, so our results suggest that persistently altered cerebral autoregulation is not the underlying cause of the long-term consequences of preeclampsia.

Plasma concentrations of syndecan-1, hyaluronic acid, thrombomodulin, sFlt-1, PlGF, and the sFlt-1/PlGF ratio should not be used to predict organ dysfunction in women with preeclampsia in a clinical context.

RESEARCH IMPLICATIONS

Cerebral autoregulation is not depressed one year after preeclampsia, so our results suggest that persistently altered cerebral autoregulation is not the underlying cause of long-term consequences of preeclampsia. As endothelial glycocalyx seems to be degraded in preeclampsia, and glycocalyx degradation have been associated with atherosclerosis, this may suggest a possible pathophysiological pathway (156). It would be of great interest to follow this cohort in the future and measure autoregulation index and glycocalyx degradation products in relation to clinical outcomes.

Future studies could focus on the effects of magnesium and common antihypertensive drugs such as labetalol and nifedipine on cerebral autoregulation in women with preeclampsia and to explore associations with cognitive dysfunction, neurological symptoms and biomarkers of neuronal injury, blood-brain barrier disruption and endothelial dysfunction.

Our results do not encourage future studies on syndecan-1 or thrombomodulin as predictors of organ dysfunction in preeclampsia. Hyaluronic acid is unlikely to have a role as a marker of thrombocytopenia or hepatic involvement in preeclampsia, but validation of these findings in other populations is warranted. Future studies could identify other markers of glycocalyx degradation that may be more suited for the prediction of organ dysfunction in preeclampsia

The finding that PlGF failed to predict organ dysfunction in women diagnosed with preeclampsia highlights the need to validate diagnostic tests within the specific population and for the intended clinical purpose. Further studies validating sFlt-1 and PlGF as predictors for organ dysfunction in preeclampsia in different populations, such as low- and middle-income settings, are warranted. Studies are needed to determine whether plasma concentrations of sFlt-1 and PlGF correlate with glycocalyx degradation. An investigation into whether the sFlt-1/PlGF ratio has value as a predictor of neonatal outcomes is also warranted.

CONCLUSION

Cerebral autoregulation is enhanced in healthy pregnancy and depressed in eclampsia and preeclampsia. By 1 year postpartum, cerebral autoregulation has normalized, and long-term consequences of preeclampsia are not the result of persistently depressed cerebral autoregulation.

Women with preeclampsia have higher circulating levels of the GDPs hyaluronic acid and thrombomodulin, especially in cases with multiple organ complications, indicating a link to endothelial dysfunction and glycocalyx loss. Syndecan-1 levels did not differ between preeclampsia and normotensive pregnancies or by disease severity. The predictive value of GDPs for organ dysfunction in preeclampsia is poor. Future studies should investigate new biomarkers predicting organ dysfunction in preeclampsia.

In a Swedish population, circulating concentrations of the angiogenic markers sFlt-1, PlGF, and the sFlt-1/PlGF ratio generally exhibited poor predictive value for organ dysfunction in preeclampsia. However, sFlt-1 demonstrated moderate predictive performance for some individual outcomes such as thrombocytopenia, elevated liver enzymes, and acute kidney injury. Multivariable analyses with GDPs did not improve the predictive performance of sFlt-1 alone.

FUTURE PERSPECTIVES

There is a need for clinical tools predicting organ dysfunction in preeclampsia. Assessment of cerebral autoregulation in preeclampsia may facilitate risk stratification and guide targeted treatment in these women. To achieve this, reliable point-of-care devices are required, and should be developed. With improved equipment and increased knowledge on cerebral autoregulation, measurements with transcranial Doppler may influence clinical practice and contribute to reduced morbidity and mortality.

Emerging evidence suggest that the integrity of the endothelial glycocalyx may play a role in vascular tone and microcirculatory regulation (157). Investigating its potential involvement in impaired autoregulation could offer new insights into the pathophysiology of eclampsia and stroke. Interventions aimed at preserving endothelial function and glycocalyx integrity may hold promise not only for mitigating cerebral complications, but potentially also for reducing the risk of systemic manifestations such as HELLP syndrome, acute kidney injury, and pulmonary edema. Insights into endothelial and glycocalyx integrity may also have implications beyond preeclampsia.

Angiogenic markers may be implemented in clinical practice as an aid for diagnosis and risk stratification in suspected preeclampsia, but further studies are needed to find biomarkers for organ dysfunction in preeclampsia.

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REFERENCES

1. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2018;13:291-310.
2. Skogsdal Y och Conner P och Elvander L, Storck Lindholm E, Kloow M, Algovik M, Petersson K, Svanvik T, Granfors M på uppdrag av Graviditetsregistret. Graviditetsregistrets Årsrapport 2022. 2023-09-24. graviditetsregistret.se
3. Gemechu KS, Assefa N, Mengistie B. Prevalence of hypertensive disorders of pregnancy and pregnancy outcomes in Sub-Saharan Africa: A systematic review and meta-analysis. Womens Health (Lond). 2020;16:1745506520973105.
4. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: An endothelial cell disorder. Am J Obstet Gynecol. 1989;161(5):1200-4.
5. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol. 2011;204(3):193-201.
6. Aplin JD, Myers JE, Timms K, Westwood M. Tracking placental development in health and disease. Nat Rev Endocrinol. 2020;16(9):479-94.
7. Melchiorre K, Giorgione V, Thilaganathan B. The placenta and preeclampsia: Villain or victim? Am J Obstet Gynecol. 2022;226(2s):S954-s62.
8. Bergman K, Svanvik T, Basic C, Rosengren A, Zverkova Sandström T, Celind J, et al. Heart disease in pregnancy and risk of pre-eclampsia: A Swedish register-based study. Open Heart. 2024;11(1).
9. Redman CWG, Staff AC, Roberts JM. Syncytiotrophoblast stress in preeclampsia: The convergence point for multiple pathways. Am J Obstet Gynecol. 2022;226(2s):s907-s27.
10. Duffy J, Cairns AE, Richards-Doran D, van't Hooft J, Gale C, Brown M, et al. A core outcome set for pre-eclampsia research: An international consensus development study. BJOG. 2020;127(12):1516-26.
11. Cresswell JA, Alexander M, Chong MYC, Link HM, Pejchinovska M, Gazeley U, et al. Global and regional causes of maternal deaths 2009-

20: A WHO systematic analysis. Lancet Glob Health. 2025;13(4):e626-e34.

12. Nathan HL, Seed PT, Hezelgrave NL, De Greeff A, Lawley E, Conti-Ramsden F, et al. Maternal and perinatal adverse outcomes in women with pre-eclampsia cared for at facility-level in South Africa: A prospective cohort study. J Glob Health. 2018;8(2):020401.
13. Moodley J, Ngene NC. Maternal deaths due to eclampsia in teenagers: Lessons from assessment of maternal deaths in South Africa. Afr J Prim Health Care Fam Med. 2020;12(1):e1-e6.
14. Felker A, Patel R, Kotnis R, Kenyon S, Knight M (Eds.) on behalf of MBRRACE-UK. Maternal, newborn and infant clinical outcome review programme. Saving lives, improving mothers' care. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2023.
15. Malhamé I, Nerenberg K, McLaughlin K, Grandi SM, Daskalopoulou SS, Metcalfe A. Hypertensive disorders and cardiovascular severe maternal morbidity in the US, 2015–2019. JAMA Network Open. 2024;7(10):e2436478-e.
16. Heitkamp A, Sandberg E, Moodley A, Burke J, van Roosmalen J, Gebhardt S, et al. Pulmonary oedema in the course of severe maternal outcome in South Africa: A cohort study combined with clinical audit. Trop Med Int Health. 2023;28(8):677-87.
17. Yagani S, Jain K, Bhatia N, Singla K, Bagga R, Bahl A. Incidence of interstitial alveolar syndrome on point-of-care lung ultrasonography in pre-eclamptic women with severe features: A prospective observational study. Anesth Analg. 2023;137(6):1158-66.
18. Stanhewicz AE, Nuckols VR, Pierce GL. Maternal microvascular dysfunction during preeclamptic pregnancy. Clin Sci (Lond). 2021;135(9):1083-101.
19. Taber-Hight E, Shah S. Acute kidney injury in pregnancy. Adv Chronic Kidney Dis. 2020;27(6):455-60.
20. Wang Y, Gu Y, Gu X, Cooper DB, Lewis DF. Evidence of kidney injury in preeclampsia: Increased maternal and urinary levels of NGAL and KIM-1 and their enhanced expression in proximal tubule epithelial cells. Front Med. 2023;10:1130112.
21. Shalaby AS, Shemies RS. Pregnancy-related acute kidney injury in the African continent: Where do we stand? A systematic review. J Nephrol. 2022;35(9):2175-89.

22. Noubiap JJ, Bigna JJ, Nyaga UF, Jingi AM, Kaze AD, Nansseu JR, et al. The burden of hypertensive disorders of pregnancy in Africa: A systematic review and meta-analysis. J Clin Hypertens (Greenwich). 2019;21(4):479-88.

23. Brito M, Gamito M, Neves AR, Caeiro F, Martins A, Dias E, et al. Conservative management of a pregnancy complicated by preeclampsia and postpartum spontaneous hepatic rupture: A case report and review of the literature. Eur J Obstet Gynecol Reprod Biol. 2021;267:79-89.

24. Tsokos M, Longauer F, Kardosová V, Gavel A, Anders S, Schulz F. Maternal death in pregnancy from HELLP syndrome. A report of three medico-legal autopsy cases with special reference to distinctive histopathological alterations. Int J Legal Med. 2002;116(1):50-3.

25. Parker SE, Werler MM. Epidemiology of ischemic placental disease: A focus on preterm gestations. Semin Perinatol. 2014;38(3):133-8.

26. Ødegård RA, Vatten LJ, Nilsen ST, Salvesen KÅ, Austgulen R. Preeclampsia and fetal growth. Obstet Gynecol. 2000;96(6):950-5.

27. Davies EL, Bell JS, Bhattacharya S. Preeclampsia and preterm delivery: A population-based case-control study. Hypertens Pregnancy. 2016;35(4):510-9.

28. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel J, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: A secondary analysis of the World Health Organisation Multicountry Survey on Maternal and Newborn Health. BJOG. 2014;121(s1):14-24.

29. Tikkanen M. Placental abruption: Epidemiology, risk factors and consequences. Acta Obstet Gynecol Scand. 2011;90(2):140-9.

30. Cutland CL, Sawry S, Fairlie L, Barnabas S, Frajzyngier V, Roux JL, et al. Obstetric and neonatal outcomes in South Africa. Vaccine. 2024;42(6):1352-62.

31. Duley L, Gulmezoglu AM, Henderson-Smart DJ. Anticonvulsants for women with pre-eclampsia. Cochrane Database Syst Rev. 2000(2):Cd000025.

32. Yunas I, Islam MA, Sindhu KN, Devall AJ, Podesek M, Alam SS, et al. Causes of and risk factors for postpartum haemorrhage: A systematic review and meta-analysis. Lancet. 2025;405(10488):1468-80.

33. von Schmidt auf Altenstadt JF, Hukkelhoven CW, van Roosmalen J, Bloemenkamp KW. Pre-eclampsia increases the risk of postpartum haemorrhage: A nationwide cohort study in the Netherlands. PLoS One. 2013;8(12):e81959.

34. Erez O, Othman M, Rabinovich A, Leron E, Gotsch F, Thachil J. DIC in pregnancy—Pathophysiology, clinical characteristics, diagnostic scores, and treatments. J Blood Med. 2022;13:21-44.

35. Pergialiotis V, Bellos I, Constantinou T, Voskos A, Papapanagiotou A, Loutradis D, et al. Magnesium sulfate and risk of postpartum uterine atony and hemorrhage: A meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2021;256:158-64.

36. Wetta LA, Szychowski JM, Seals S, Mancuso MS, Biggio JR, Tita AT. Risk factors for uterine atony/postpartum hemorrhage requiring treatment after vaginal delivery. Am J Obstet Gynecol. 2013;209(1):51.e1-6.

37. Mei JY, Afshar Y. Hypertensive complications of pregnancy: Hepatic consequences of preeclampsia through HELLP syndrome. Clin Liver Dis. 2023;22(6):195-9.

38. ACOG practice bulletin no. 207: Thrombocytopenia in pregnancy. Obstet Gynecol. 2019;133(3):e181-e93.

39. Patel PB, Patel N, Hedges MA, Benson AE, Tomer A, Lo JO, et al. Hematologic complications of pregnancy. Eur J Haematol. 2025;114(4):596-614.

40. Einav S, Leone M. Epidemiology of obstetric critical illness. Int J Obstet Anesth. 2019;40:128-39.

41. Gogarten W. Preeclampsia and anaesthesia. Curr Opin Anaesthesiol. 2009;22(3):347-51.

42. Bergman L, Thorgeirsdottir L, Elden H, Hesselman S, Schell S, Ahlm E, et al. Cognitive impairment in preeclampsia complicated by eclampsia and pulmonary edema after delivery. Acta Obstet Gynecol Scand. 2021;100(7):1280-7.

43. Hastie R, Brownfoot FC, Cluver CA, Walker SP, Hesselman S, Tong S, et al. Predictive value of the signs and symptoms preceding eclampsia: A systematic review. Obstet Gynecol. 2019;134(4):677-84.

44. ARG-Preeklampsi. Riktlinjer för hypertonisjukdomar under graviditet [Guidelines for hypertensive disorders during pregnancy]; 2019. Available from: https://www.sfog.se/media/338533/pe-riktlinje-230214.pdf

45. Ban L, Abdul Sultan A, Stephansson O, Tata LJ, Sprigg N, Nelson-Piercy C, et al. The incidence of first stroke in and around pregnancy: A population-based cohort study from Sweden. Eur Stroke J. 2017;2(3):250-6.

46. Miller EC. Preeclampsia and cerebrovascular disease: The maternal brain at risk. Hypertension. 2019;74(1):5-13.

47. Leffert LR, Clancy CR, Bateman BT, Bryant AS, Kuklina EV. Hypertensive disorders and pregnancy-related stroke: Frequency, trends, risk factors, and outcomes. Obstet Gynecol. 2015;125(1):124-31.

48. Tawati DA, Chan WS. A systematic review of posterior reversible encephalopathy syndrome in pregnant women with severe preeclampsia and eclampsia. Obstet Med. 2023;16(4):236-41.

49. Roos NM, Wiegman MJ, Jansonius NM, Zeeman GG. Visual disturbances in (pre)eclampsia. Obstet Gynecol Surv. 2012;67(4):242-50.

50. Khoromi S. Secondary headaches in pregnancy and the puerperium. Front Neurol. 2023;14:1239078.

51. Adekomi AD, Moodley J, Naicker T. Neuropathological complications associated with hypertensive disorders of pregnancy. Hypertens Pregnancy. 2019;38(3):171-5.

52. Bushnell C, Chireau M. Preeclampsia and stroke: Risks during and after pregnancy. Stroke Res Treat. 2011;2011:858134.

53. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie trial: A randomised placebo-controlled trial. Lancet. 2002;359(9321):1877-90.

54. Claassen J, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: Physiology and clinical implications of autoregulation. Physiol Rev. 2021;101(4):1487-559.

55. Lassen NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev. 1959;39(2):183-238.

56. McHenry LC, West JW, Cooper ES, Goldberg HI, Jaffe ME. Cerebral autoregulation in man. Stroke. 1974;5(6):695-706.

57. Johnson AC, Cipolla MJ. The cerebral circulation during pregnancy: Adapting to preserve normalcy. Physiology (Bethesda). 2015;30(2):139-47.

58. Chapman AC, Cipolla MJ, Chan SL. Effect of pregnancy and nitric oxide on the myogenic vasodilation of posterior cerebral arteries and the lower limit of cerebral blood flow autoregulation. Reprod Sci. 2013;20(9):1046-54.

59. Cipolla MJ, Bishop N, Chan SL. Effect of pregnancy on autoregulation of cerebral blood flow in anterior versus posterior cerebrum. Hypertension. 2012;60(3):705-11.

60. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg. 1982;57(6):769-74.

61. Tiecks FP, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. Stroke. 1995;26(6):1014-9.

62. Brodie FG, Atkins ER, Robinson TG, Panerai RB. Reliability of dynamic cerebral auto regulation measurement using spontaneous fluctuations in blood pressure. Clin Sci. 2009;116(6):513-20.

63. Veen Tv. Cerebral hemodynamics in normal and complicated pregnancy. Rijksuniversiteit Groningen; 2016.

64. Janzarik WG, Ehlers E, Ehmann R, Gerds TA, Schork J, Mayer S, et al. Dynamic cerebral autoregulation in pregnancy and the risk of preeclampsia. Hypertension. 2014;63(1):161-6.

65. Miller EC, Katsidoniotaki MI, Haghighi N, Dos Santos KRM, Booker WA, Petersen N, et al. Dynamic cerebral autoregulation in postpartum individuals with and without preeclampsia. Pregnancy Hypertens. 2023;33:39-45.

66. Janzarik WG, Jacob J, Katagis E, Markfeld-Erol F, Sommerlade L, Wuttke M, et al. Preeclampsia postpartum: Impairment of cerebral autoregulation and reversible cerebral hyperperfusion. Pregnancy Hypertens. 2019;17:121-6.

67. van Veen TR, Panerai RB, Haeri S, Griffioen AC, Zeeman GG, Belfort MA. Cerebral autoregulation in normal pregnancy and preeclampsia. Obstet Gynecol. 2013;122(5):1064-9.

68. van Veen TR, Panerai RB, Haeri S, Singh J, Adusumalli JA, Zeeman GG, et al. Cerebral autoregulation in different hypertensive disorders of pregnancy. Am J Obstet Gynecol. 2015;212(4):513 e1-7.

69. Williams KP, Galerneau F, Small M. Transfer function analysis of dynamic cerebral autoregulation in preeclampsia. Pregnancy Hypertens. 2015;5(4):322-4.

70. Janzarik WG, Gerber AK, Markfeld-Erol F, Sommerlade L, Allignol A, Reinhard M. No long-term impairment of cerebral autoregulation after preeclampsia. Pregnancy Hypertens. 2018;13:171-3.

71. Moore KH, Murphy HA, George EM. The glycocalyx: A central regulator of vascular function. Am J Physiol Regul Integr Comp Physiol. 2021;320(4):r508-r18.

72. Lepedda AJ, Nieddu G, Piperigkou Z, Kyriakopoulou K, Karamanos N, Formato M. Circulating heparan sulfate proteoglycans as biomarkers in health and disease. Semin Thromb Hemost. 2021;47(3):295-307.

73. Rapraeger AC. Syndecan-regulated receptor signaling. J Cell Biol. 2000;149(5):995-8.

74. Teng YH, Aquino RS, Park PW. Molecular functions of syndecan-1 in disease. Matrix Biol. 2012;31(1):3-16.

75. Human protein atlas. Available from: www.proteinatlas.org

76. Hahn RG, Zdolsek M, Zdolsek J. Plasma concentrations of syndecan-1 are dependent on kidney function. Acta Anaesthesiol Scand. 2021;65(6):809-15.

77. Alberts B. The cell. Garland; 1989. p. 804.

78. Fraser JRE, Laurent TC, Engström-Laurent A, Laurent UGB. Elimination of hyaluronic acid from the blood stream in the human. Clin Exp Pharmacol Physiol. 1984;11(1):17-25.

79. Smedsrød B, Pertoft H, Eriksson S, Fraser JR, Laurent TC. Studies in vitro on the uptake and degradation of sodium hyaluronate in rat liver endothelial cells. Biochem J. 1984;223(3):617-26.

80. Parnigoni A, Viola M, Karousou E, Rovera S, Giaroni C, Passi A, et al. Hyaluronan in pathophysiology of vascular diseases: Specific roles in smooth muscle cells, endothelial cells, and macrophages. Am J Physiol Cell Physiol. 2022;323(2):c505-c19.

81. Hassani Lahsinoui H, Amraoui F, Spijkers LJA, Veenboer GJM, Peters SLM, van Vlies N, et al. Soluble syndecan-1 and glycosaminoglycans in preeclamptic and normotensive pregnancies. Sci Rep. 2021;11(1):4387.

82. Liao YE, Liu J, Arnold K. Heparan sulfates and heparan sulfate binding proteins in sepsis. Front Mol Biosci. 2023;10:1146685.

83. Martin FA, Murphy RP, Cummins PM. Thrombomodulin and the vascular endothelium: Insights into functional, regulatory, and therapeutic aspects. Am J Physiol Heart Circ Physiol. 2013;304(12):H1585-97.

84. Califano F, Giovanniello T, Pantone P, Campana E, Parlapiano C, Alegiani F, et al. Clinical importance of thrombomodulin serum levels. Eur Rev Med Pharmacol Sci. 2000;4(3):59-66.

85. Kataoka H, Ushiyama A, Akimoto Y, Matsubara S, Kawakami H, Iijima T. Structural behavior of the endothelial glycocalyx is associated with pathophysiologic status in septic mice: An integrated approach to analyzing the behavior and function of the glycocalyx using both electron and fluorescence intravital microscopy. Anesth Analg. 2017;125(3):874-83.

86. Nelson A, Berkestedt I, Schmidtchen A, Ljunggren L, Bodelsson M. Increased levels of glycosaminoglycans during septic shock: Relation to mortality and the antibacterial actions of plasma. Shock. 2008;30(6):623-7.

87. Schott U, Solomon C, Fries D, Bentzer P. The endothelial glycocalyx and its disruption, protection and regeneration: A narrative review. Scand J Trauma Resusc Emerg Med. 2016;24:48.

88. Becker BF, Jacob M, Leipert S, Salmon AH, Chappell D. Degradation of the endothelial glycocalyx in clinical settings: Searching for the sheddases. Br J Clin Pharmacol. 2015;80(3):389-402.

89. de Jesus Fernandes Martins Lima JF, Moreira da Silva TE, dos Santos Lopes AC, Ferreira Freire VA, Barros-Pinheiro M, Alpoim PN. Soluble thrombomodulin in preeclampsia: Systematic review and meta-analysis. Clinica Chimica Acta. 2025;574:120323.

90. Berg S, Engman A, Holmgren S, Lundahl T, Laurent TC. Increased plasma hyaluronan in severe pre-eclampsia and eclampsia. Scand J Clin Lab Invest. 2001;61(2):131-7.

91. Jokimaa V, Inki P, Kujari H, Hirvonen O, Ekholm E, Anttila L. Expression of syndecan-1 in human placenta and decidua. Placenta. 1998;19(2):157-63.

92. Gandley RE, Althouse A, Jeyabalan A, Bregand-White JM, McGonigal S, Myerski AC, et al. Low soluble syndecan-1 precedes preeclampsia. PLoS One. 2016;11(6):e0157608.

93. Hofmann-Kiefer KF, Knabl J, Martinoff N, Schiessl B, Conzen P, Rehm M, et al. Increased serum concentrations of circulating glycocalyx components in HELLP syndrome compared to healthy pregnancy: An observational study. Reprod Sci. 2013;20(3):318-25.

94. Jokimaa VI, Kujari HP, Ekholm EM, Inki PL, Anttila L. Placental expression of syndecan 1 is diminished in preeclampsia. Am J Obstet Gynecol. 2000;183(6):1495-8.

95. Osmers RG, Schutz E, Diedrich F, Wehry B, Krauss T, Oellerich M, et al. Increased serum levels of hyaluronic acid in pregnancies complicated by preeclampsia or hemolysis, elevated liver enzymes, and low platelets syndrome. Am J Obstet Gynecol. 1998;178(2):341-5.

96. Sun Q, Lu Y, Zhong J, Yang X, Zhong L, Zhang W, et al. A retrospective case-control study on the diagnostic values of hemostatic markers in hypertensive disorder of pregnancy. Lab Med. 2023;54(4):392-9.

97. Shaarawy M, Didy HE. Thrombomodulin, plasminogen activator inhibitor type 1 (PAI-1) and fibronectin as biomarkers of endothelial damage in preeclampsia and eclampsia. Int J Gynaecol Obstet. 1996;55(2):135-9.

98. Hsu CD, Iriye B, Johnson TR, Witter FR, Hong SF, Chan DW. Elevated circulating thrombomodulin in severe preeclampsia. Am J Obstet Gynecol. 1993;169(1):148-9.

99. Edvinsson C, Piani F, Matthes F, Vanherle L, Erlandsson L, Meissner A, et al. Sphingosine-1-phosphate, a marker of endothelial injury and disease severity in preeclampsia. Hypertension. 2025;82(5):914-25.

100. Liao L, Zhao X, Zhou M, Deng Y, Li Y, Peng C. sFlt-1: A double regulator in angiogenesis-related diseases. Curr Pharm Des. 2021;27(40):4160-70.

101. Kamba T, McDonald DM. Mechanisms of adverse effects of anti-VEGF therapy for cancer. Br J Cancer. 2007;96(12):1788-95.

102. Müller-Deile J, Schiffer M. Renal involvement in preeclampsia: Similarities to VEGF ablation therapy. J Pregnancy. 2011;176973.

103. Abdel-Rahman O, El Halawani H. Risk of cardiovascular adverse events in patients with solid tumors treated with ramucirumab: A meta analysis and summary of other VEGF targeted agents. Crit Rev Oncol Hematol. 2016;102:89-100.

104. Cross SN, Ratner E, Rutherford TJ, Schwartz PE, Norwitz ER. Bevacizumab-mediated interference with VEGF signaling is sufficient to induce a preeclampsia-like syndrome in nonpregnant women. Rev Obstet Gynecol. 2012;5(1):2-8.

105. Chau K, Hennessy A, Makris A. Placental growth factor and pre-eclampsia. J Hum Hypertens. 2017;31(12):782-6.

106. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest. 2003;111(5):649-58.

107. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004;350(7):672-83.

108. Chappell LC, Cluver CA, Kingdom J, Tong S. Pre-eclampsia. Lancet. 2021;398(10297):341-54.

109. Duhig KE, Myers J, Seed PT, Sparkes J, Lowe J, Hunter RM, et al. Placental growth factor testing to assess women with suspected pre-eclampsia: A multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. Lancet. 2019;393(10183):1807-18.

110. NICE. PLGF-based testing to help diagnose suspected preterm pre-eclampsia. Available from: https://www.nice.org.uk/guidance/dg492022

111. Rolnik DL, Wright D, Poon LCY, Syngelaki A, O'Gorman N, de Paco Matallana C, et al. ASPRE trial: Performance of screening for preterm pre-eclampsia. Ultrasound Obstet Gynecol. 2017;50(4):492-5.

112. Bucher V, Mitchell AR, Gudmundsson P, Atkinson J, Wallin N, Asp J, et al. Prediction of adverse maternal and perinatal outcomes associated with pre-eclampsia and hypertensive disorders of pregnancy: A systematic review and meta-analysis. EClinicalMedicine. 2024;76:102861.

113. Bergman L, Bergman K, Langenegger E, Moodley A, Griffith-Richards S, Wikström J, et al. PROVE pre-eclampsia obstetric adverse events: Establishment of a biobank and database for pre-eclampsia. Cells. 2021;10(4).

114. Thorgeirsdottir L, Andersson M, Karlsson O, Thorn SE, Oras J, Sengpiel V, et al. Study protocol: Establishment of a multicentre pre-eclampsia database and biobank in Sweden: GO PROVE and UPMOST, a prospective cohort study. BMJ Open. 2021;11(11):e049559.

115. ACOG practice bulletin no. 202: Gestational hypertension and preeclampsia. Obstet Gynecol. 2019;133(1):e1–25.

116. Kornacki J, Wirstlein P, Wender-Ozegowska E. Levels of syndecan-1 and hyaluronan in early- and late-onset preeclampsia. Pregnancy Hypertens. 2019;18:108-11.

117. Weissgerber TL, Garcia-Valencia O, Milic NM, Codsi E, Cubro H, Nath MC, et al. Early onset preeclampsia is associated with glycocalyx degradation and reduced microvascular perfusion. J Am Heart Assoc. 2019;8(4):e010647.

118. von Salmuth V, van der Heiden Y, Bekkers I, van Runnard Heimel P, Spaanderman MA, Peeters LL, et al. The role of hepatic sinusoidal obstruction in the pathogenesis of the hepatic involvement in HELLP syndrome: Exploring the literature. Pregnancy Hypertens. 2020;19:37-43.

119. Suresh S, Patel E, Mueller A, Morgan J, Lewandowski WL, Verlohren S, et al. The additive role of angiogenic markers for women with confirmed preeclampsia. Am J Obstet Gynecol. 2022.

120. Chaiworapongsa T, Romero R, Savasan ZA, Kusanovic JP, Ogge G, Soto E, et al. Maternal plasma concentrations of angiogenic/anti-angiogenic factors are of prognostic value in patients presenting to the obstetrical triage area with the suspicion of preeclampsia. J Matern Fetal Neonatal Med. 2011;24(10):1187-207.

121. Karge A, Desing L, Haller B, Ortiz JU, Lobmaier SM, Kuschel B, et al. Performance of sFlt-1/PIGF ratio for the prediction of perinatal outcome in obese pre-eclamptic women. J Clin Med. 2022;11(11).

122. Leaños-Miranda A, Graciela Nolasco-Leaños A, Ismael Carrillo-Juárez R, José Molina-Pérez C, Janet Sillas-Pardo L, Manuel Jiménez-Trejo L, et al. Usefulness of the sFlt-1/PlGF (soluble fms-like tyrosine kinase-1/placental growth factor) ratio in diagnosis or misdiagnosis in women with clinical diagnosis of preeclampsia. Hypertension. 2020;76(3):892-900.

123. Mirkovic L, Tulic I, Stankovic S, Soldatovic I. Prediction of adverse maternal outcomes of early severe preeclampsia. Pregnancy Hypertens. 2020;22:144-50.

124. Nóbrega L, Katz L, Lippo L, Amorim MM. Association of sFlt-1 and C-reactive protein with outcomes in severe preeclampsia: A cohort study. Med (Balt). 2022;101(11).

125. Bremner L, Gill C, Seed PT, Conti-Ramsden F, Webster L, Fleminger J, et al. Rule-in and rule-out of pre-eclampsia using DELFIA Xpress PlGF 1-2-3 and sFlt-1: PlGF ratio. Pregnancy Hypertens. 2022;27:96-102.

126. Weissgerber TL, Rajakumar A, Myerski AC, Edmunds LR, Powers RW, Roberts JM, et al. Vascular pool of releasable soluble VEGF receptor-1

(sFLT1) in women with previous preeclampsia and uncomplicated pregnancy. J Clin Endocrinol Metab. 2014;99(3):978-87.

127. Moore KH, Chapman H, George EM. Unfractionated heparin displaces sFlt-1 from the placental extracellular matrix. Biol Sex Differ. 2020;11(1):34.

128. Sela S, Natanson-Yaron S, Zcharia E, Vlodavsky I, Yagel S, Keshet E. Local retention versus systemic release of soluble VEGF receptor-1 are mediated by heparin-binding and regulated by heparanase. Circ Res. 2011;108(9):1063-70.

129. Yinon Y, Ben Meir E, Margolis L, Lipitz S, Schiff E, Mazaki-Tovi S, et al. Low molecular weight heparin therapy during pregnancy is associated with elevated circulatory levels of placental growth factor. Placenta. 2015;36(2):121-4.

130. Panerai RB, Deverson ST, Mahony P, Hayes P, Evans DH. Effects of CO_2 on dynamic cerebral autoregulation measurement. Physiol Meas. 1999;20(3):265-75.

131. Dineen NE, Brodie FG, Robinson TG, Panerai RB. Continuous estimates of dynamic cerebral autoregulation during transient hypocapnia and hypercapnia. J Appl Physiol. 2010;108(3):604-13.

132. Minhas JS, Panerai RB, Robinson TG. Modelling the cerebral haemodynamic response in the physiological range of PaCO(2). Physiol Meas. 2018;39(6):065001.

133. Corrêa DI, de-Lima-Oliveira M, Nogueira RC, Carvalho-Pinto RM, Bor-Seng-Shu E, Panerai RB, et al. Integrative assessment of cerebral blood regulation in COPD patients. Respir Physiol Neurobiol. 2024;319:104166.

134. Ogawa Y, Iwasaki K, Aoki K, Shibata S, Kato J, Ogawa S. Central hypervolemia with hemodilution impairs dynamic cerebral autoregulation. Anesth Analg. 2007;105(5):1389-96.

135. Heilmann L, Siekmann U, Schmid-Schönbein H, Ludwig H. Hemoconcentration and pre-eclampsia. Arch Gynecol. 1981;231(1):7-21.

136. Panerai RB. Nonstationarity of dynamic cerebral autoregulation. Med Eng Phys. 2014;36(5):576-84.

137. Panerai RB, Kerins V, Fan L, Yeoman PM, Hope T, Evans DH. Association between dynamic cerebral autoregulation and mortality in severe head injury. Br J Neurosurg. 2004;18(5):471-9.

138. Nogueira RC, Aries M, Minhas JS, N HP, Xiong L, Kainerstorfer JM, et al. Review of studies on dynamic cerebral autoregulation in the acute phase of stroke and the relationship with clinical outcome. J Cereb Blood Flow Metab. 2022;42(3):430-53.

139. White RP, Markus HS. Impaired dynamic cerebral autoregulation in carotid artery stenosis. Stroke. 1997;28(7):1340-4.

140. Immink RV, van den Born BJ, van Montfrans GA, Koopmans RP, Karemaker JM, van Lieshout JJ. Impaired cerebral autoregulation in patients with malignant hypertension. Circulation. 2004;110(15):2241-5.

141. Eames PJ, Blake MJ, Panerai RB, Potter JF. Cerebral autoregulation indices are unimpaired by hypertension in middle-aged and older people. Am J Hypertens. 2003;16(9 Pt 1):746-53.

142. Vidyashree M, Deepeshwar S, Nagarathna R, Manjunath NK, Kaligal C, Kanthi A, et al. Transcranial Doppler studies in Type 2 diabetes mellitus: A systematic review. Diabetes Res Clin Pract. 2022;186:109808.

143. Zeeman GG, Hatab M, Twickler DM. Maternal cerebral blood flow changes in pregnancy. Am J Obstet Gynecol. 2003;189(4):968-72.

144. Zeeman GG, Hatab MR, Twickler DM. Increased cerebral blood flow in preeclampsia with magnetic resonance imaging. Am J Obstet Gynecol. 2004;191(4):1425-9.

145. Kontos HA, Wei EP, Navari RM, Levasseur JE, Rosenblum WI, Patterson JL. Responses of cerebral arteries and arterioles to acute hypotension and hypertension. Am J Physiol Heart Circ Physiol. 1978;234(4):H371-H83.

146. Nevo O, Soustiel JF, Thaler I. Maternal cerebral blood flow during normal pregnancy: A cross-sectional study. Am J Obstet Gynecol. 2010;203(5):475.e1-e6.

147. Hahn RG, Patel V, Dull RO. Human glycocalyx shedding: Systematic review and critical appraisal. Acta Anaesthesiol Scand. 2021;65(5):590-606.

148. Fraser JR, Gibson PR. Mechanisms by which food intake elevates circulating levels of hyaluronan in humans. J Intern Med. 2005;258(5):460-6.

149. Berg S, Engman A, Hesselvik JF, Laurent TC. Crystalloid infusion increases plasma hyaluronan. Crit Care Med. 1994;22(10):1563-7.

150. Salahuddin S, Wenger JB, Zhang D, Thadhani R, Karumanchi SA, Rana S. KRYPTOR-automated angiogenic factor assays and risk of preeclampsia-related adverse outcomes. Hypertens Pregnancy. 2016;35(3):330-45.

151. Chaiworapongsa T, Romero R, Gotsch F, Suksai M, Gallo DM, Jung E, et al. Preeclampsia at term can be classified into 2 clusters with different clinical characteristics and outcomes based on angiogenic biomarkers in maternal blood. Am J Obstet Gynecol. 2023;228(5):569.e1-e24.

152. Chappell LC, Duckworth S, Seed PT, Griffin M, Myers J, Mackillop L, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: A prospective multicenter study. Circulation. 2013;128(19):2121-31.

153. Sibiude J, Guibourdenche J, Dionne MD, Le Ray C, Anselem O, Serreau R, et al. Placental growth factor for the prediction of adverse outcomes in patients with suspected preeclampsia or intrauterine growth restriction. PLoS One. 2012;7(11):e50208.

154. Villalain C, Herraiz I, Cantero B, Quezada S, Lopez A, Simón E, et al. Angiogenesis biomarkers for the prediction of severe adverse outcomes in late-preterm preeclampsia. Pregnancy Hypertens. 2020;19:74-80.

155. Bonnet MP, Garnier M, Keita H, Compere V, Arthuis C, Raia-Barjat T, et al. Guidelines for the management of women with severe pre-eclampsia. Anaesth Crit Care Pain Med. 2021;40(5):100901.

156. Mitra R, O'Neil GL, Harding IC, Cheng MJ, Mensah SA, Ebong EE. Glycocalyx in Atherosclerosis-Relevant Endothelium Function and as a Therapeutic Target. Curr Atheroscler Rep. 2017;19(12):63.

157. Chappell D, Westphal M, Jacob M. The impact of the glycocalyx on microcirculatory oxygen distribution in critical illness. Curr Opin Anaesthesiol. 2009;22(2):155-62.

158. Oehm E, Reinhard M, Keck C, Els T, Spreer J, Hetzel A. Impaired dynamic cerebral autoregulation in eclampsia. Ultrasound Obstet Gynecol. 2003;22(4):395-8.

159. Oehm E, Hetzel A, Els T, Berlis A, Keck C, Will HG, et al. Cerebral hemodynamics and autoregulation in reversible posterior leukoencephalopathy syndrome caused by pre-/eclampsia. Cerebrovasc Dis. 2006;22(2-3):204-8.

160. Willis T. Cerebri anatome. London: John Martyn och James Allestry; 1664.

161. Edvinsson L, Owman C, Sjöberg NO. Autonomic nerves, mast cells, and amine receptors in human brain vessels. A histochemical and pharmacological study. Brain Res. 1976;115(3):377-93.

162. Srichawla BS, Garcia-Dominguez MA. Regional dynamic cerebral autoregulation across anterior and posterior circulatory territories: A detailed exploration and its clinical implications. World J Crit Care Med. 2024;13(4):97149.

163. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med. 1996;334(8):494-500.

164. Demirtaş Ö, Gelal F, Vidinli BD, Demirtaş LO, Uluç E, Baloğlu A. Cranial MR imaging with clinical correlation in preeclampsia and eclampsia. Diagn Intervention Radiol. 2005;11(4):189-94.

165. Mugerli S, Zupančič D, Rok R, Lučovnik M. Transmission electron microscopy demonstration of reduced endothelial glycocalyx in severe preeclampsia. Placenta. 2022;126:64-9.

166. SIRUtdataportalen (https://portal.icuregswe.org/utdata/sv/report/prod_diagnoser-antal)