UNIVERSITY OF GOTHENBURG

Dynamisk cerebral autoreglering och endoteldysfunktion vid preeklampsi

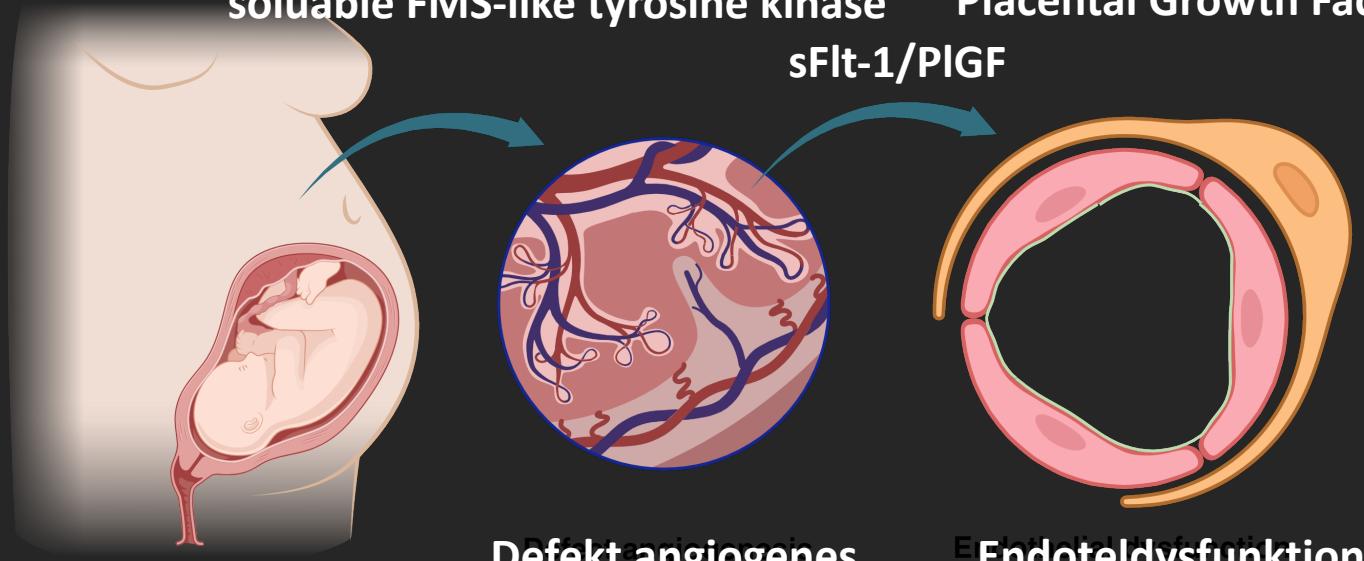
Niclas Carlberg
Doktorand
Göteborgs universitet

Two stage model

soluable FMS-like tyrosine kinase

Placental Growth Factor

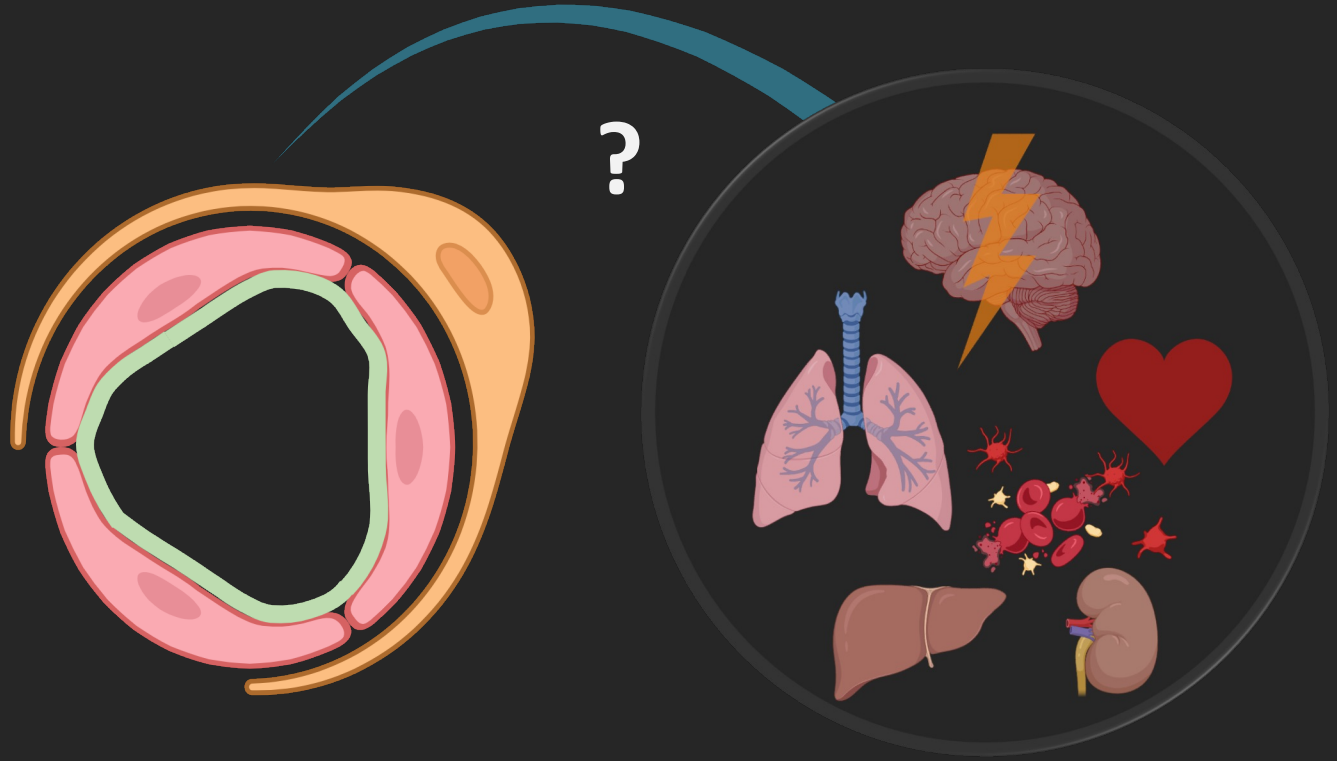
sFlt-1/PlGF



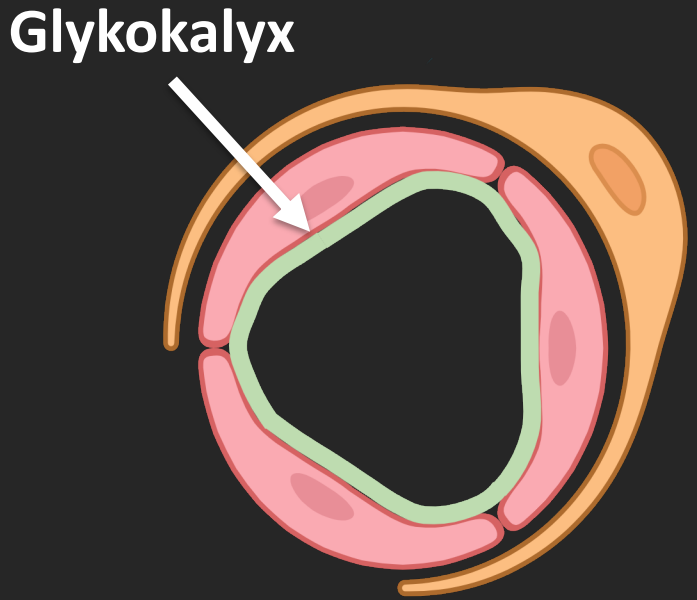
Defekt angiogenes

Endoteldysfunktion

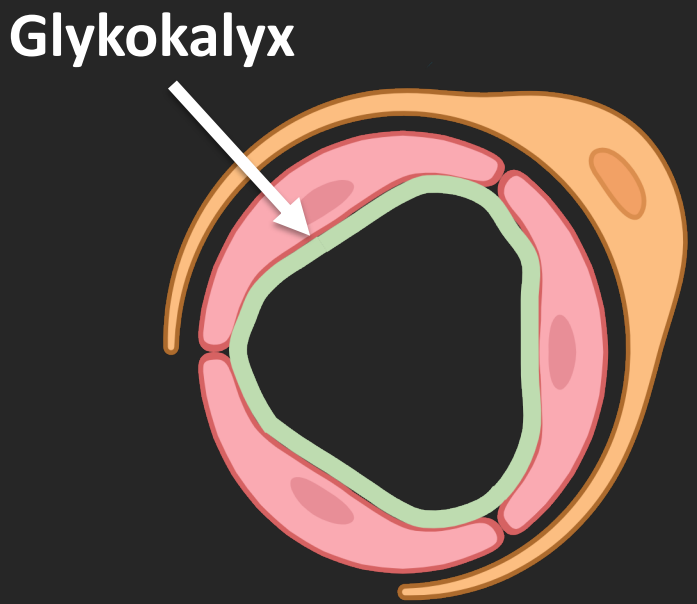
Endoteldysfunktion



Endoteldysfunktion



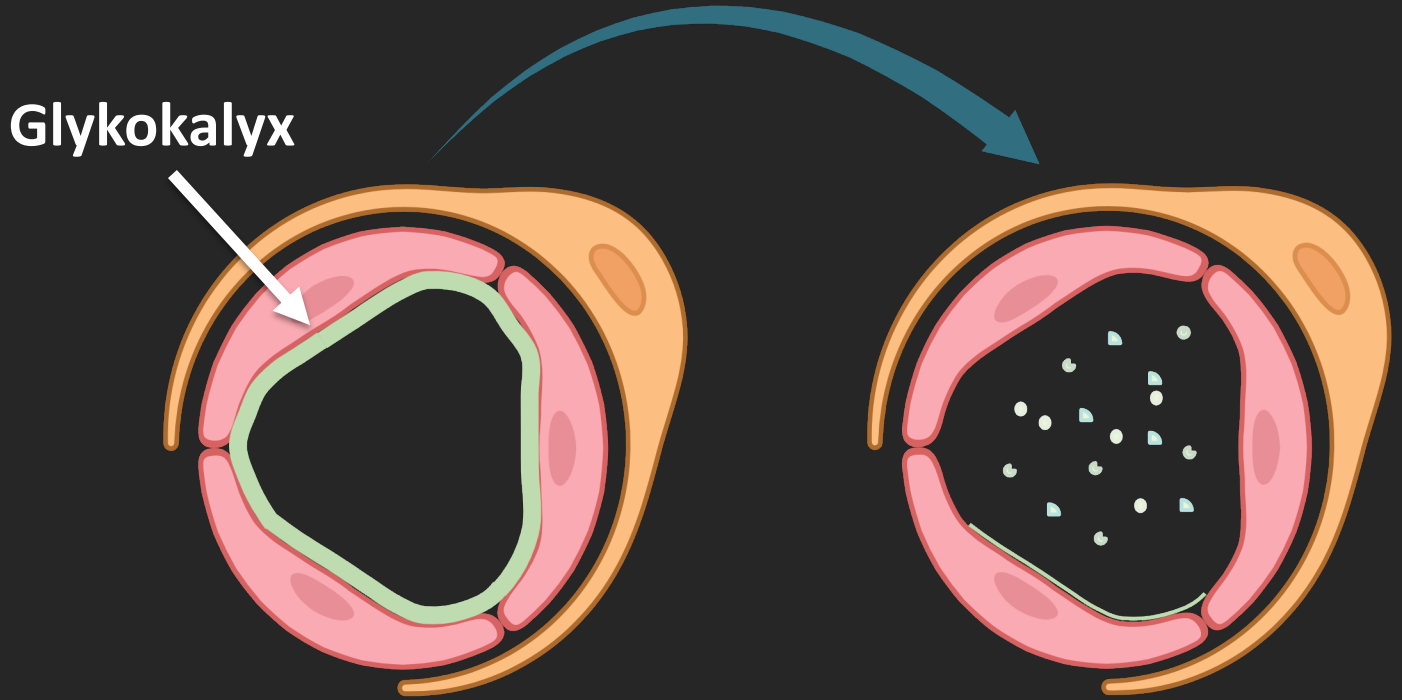
Endoteldysfunktion



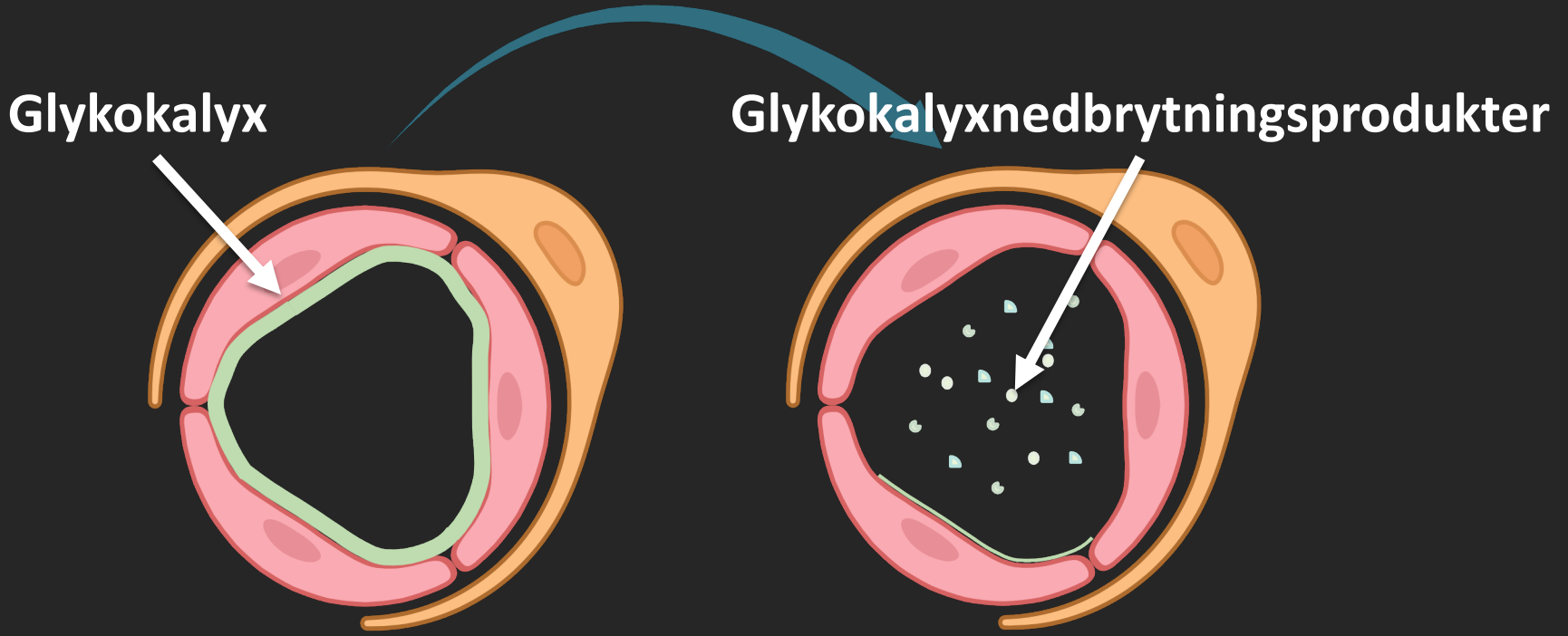
Glykokalyx funktioner

- Kärlpermeabilitet
- Kärltonus
- Koagulation
- Inflammation

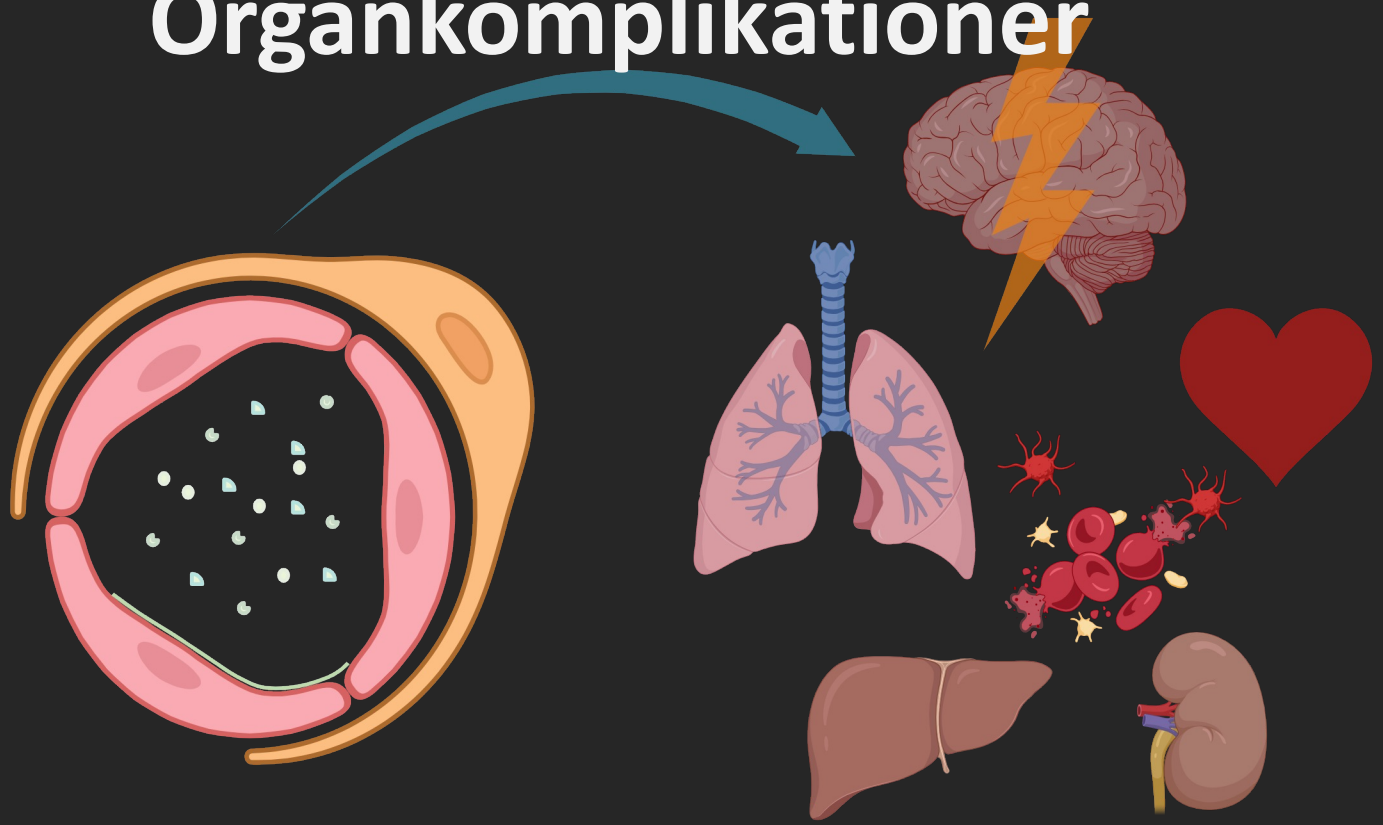
Endoteldysfunktion



Endoteldysfunktion



Organkomplikationer



Transkraniell Doppler

Doppler recording of cerebral arterial flow

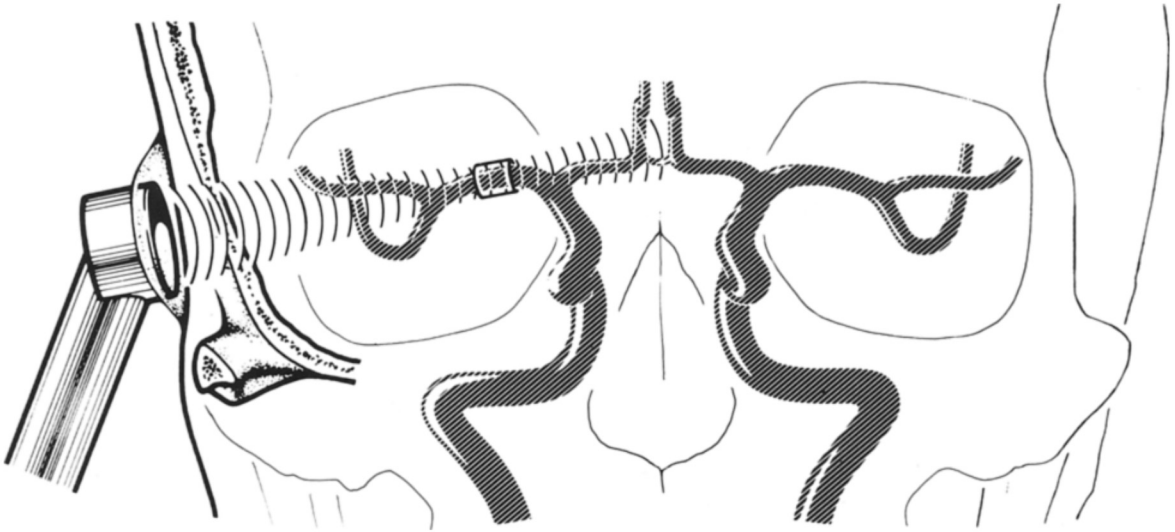
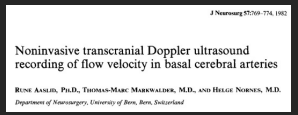


FIG. 3. Frontal view of the ultrasound probe directed toward the middle cerebral artery (MCA). The cylinder around the MCA indicates the observation region (sampling volume) for the Doppler recording. The distance from the middle of the cylinder to the probe corresponds to the depth setting.



J Neurosurg 57:769–774, 1982

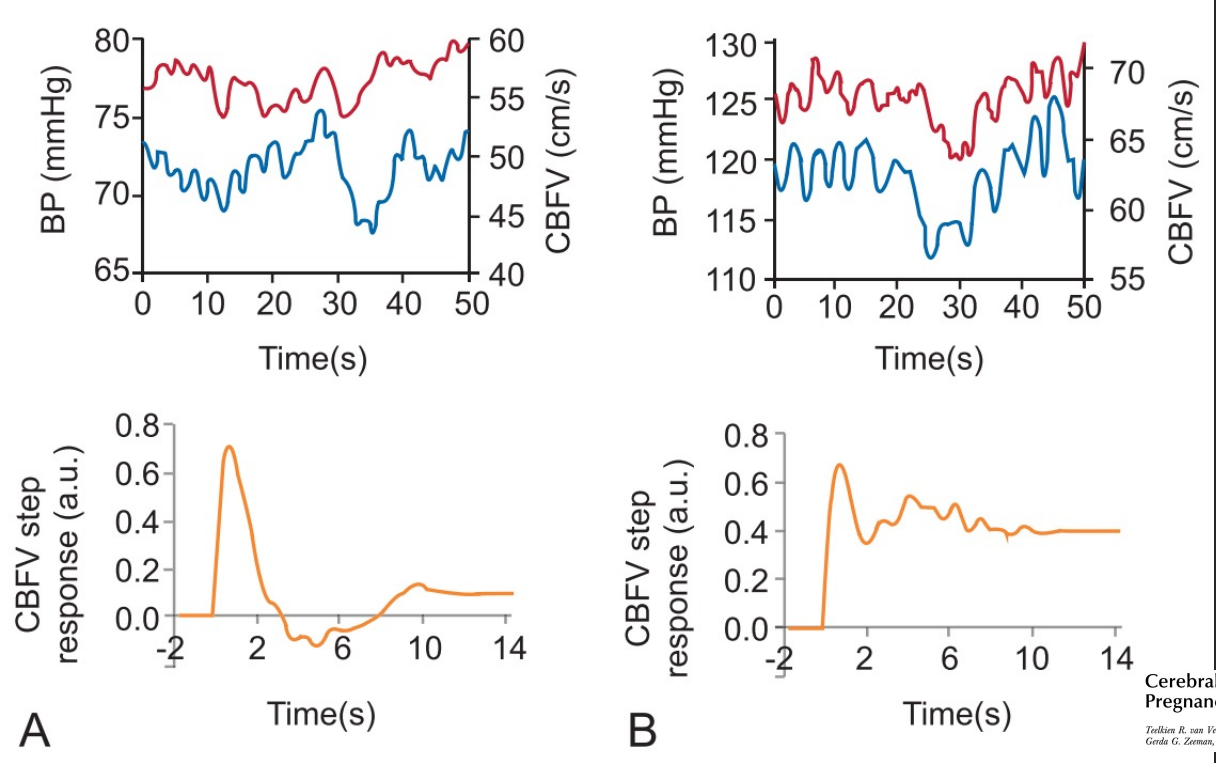
Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries

RUNE AASLID, PH.D., THOMAS-MARC MARKWALDER, M.D., AND HELGE NORNES, M.D.

Department of Neurosurgery, University of Bern, Bern, Switzerland

Transkraniell Doppler

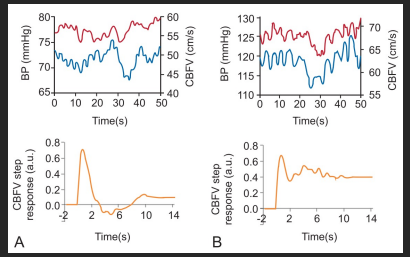
Dynamisk cerebral autoreglering



Cerebral Autoregulation in Normal Pregnancy and Preeclampsia

Trelkien R. van Veen, BS, Ronney B. Panerai, PhD, Sina Haeri, MD, MHSA, Annemiek C. Griffioen, BS, Gerda G. Zeeman, MD, PhD, and Michael A. Belfort, MD, PhD

Dynamisk cerebral autoreglering



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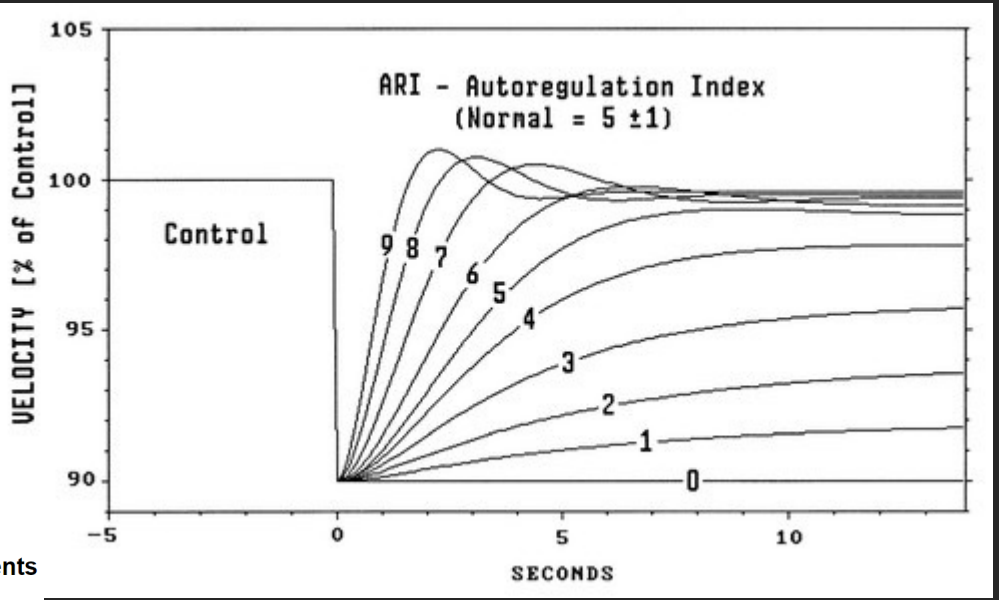


Comparison of Static and Dynamic Cerebral Autoregulation Measurements

Frank P. Tiecks, Arthur M. Lam, Rune Aaslid and David W. Newell

Originally published 1 Jun 1995 |
https://doi-org.ezproxy.ub.gu.se/10.1161/01.STR.26.6.1014 |
Stroke. 1995;26:1014–1019

estimated Cerebral Perfusion Pressure

$$eCPP = \frac{mCBFV\ x\ (MAP - DAP)}{mCBFV - dCBFV}$$

eCPP = estimated Cerebral Perfusion Pressure
mCBFV = mean Cerebral Blood Flow Velocity
dCBFV = diastolic Cerebral Blood Flow Velocity
MAP = Mean Arterial blood Pressure
DAP = Diastolic Arterial blood Pressure

Syfte

Att undersöka om dynamisk cerebral autoreglering, angiogena markörer och glykokalyxnedbrytningsprodukter korrellerar till och kan förutsäga organkomplikationer hos kvinnor med preeklampsi

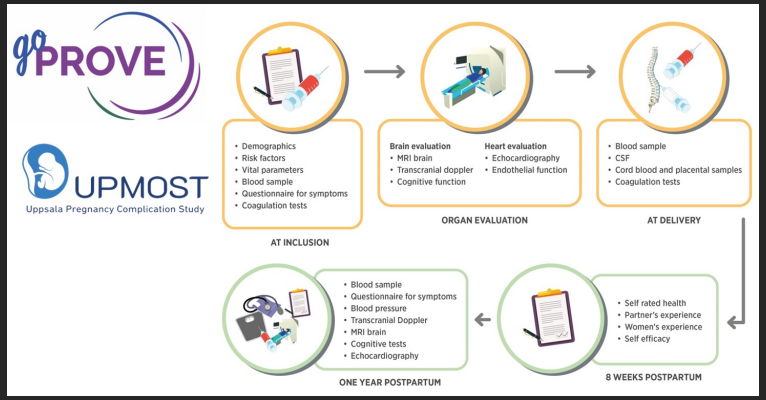
Studie 1 Studie 2 Studie 3 Studie 4

PROVE TCD

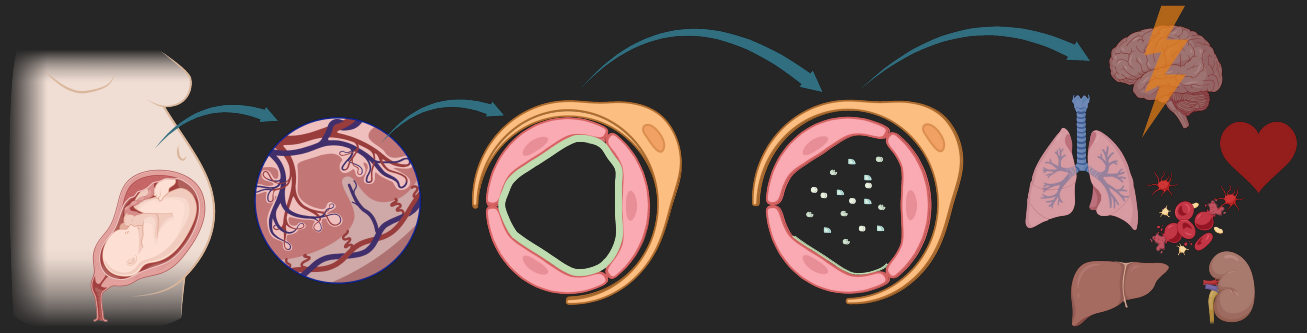
PROVE GDP

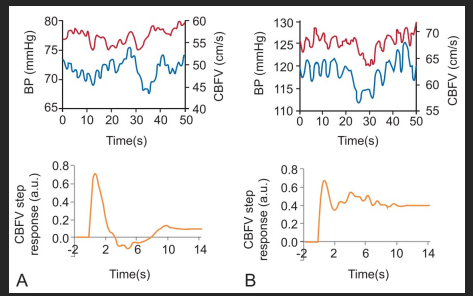
goPROVE AM GDP

goPROVE UPMOST Uppsala Pregnancy Complication Study TCD



Sammanfattning





$$eCPP = \frac{mCBFV\ x\ (MAP - DAP)}{mCBFV - dCBFV}$$

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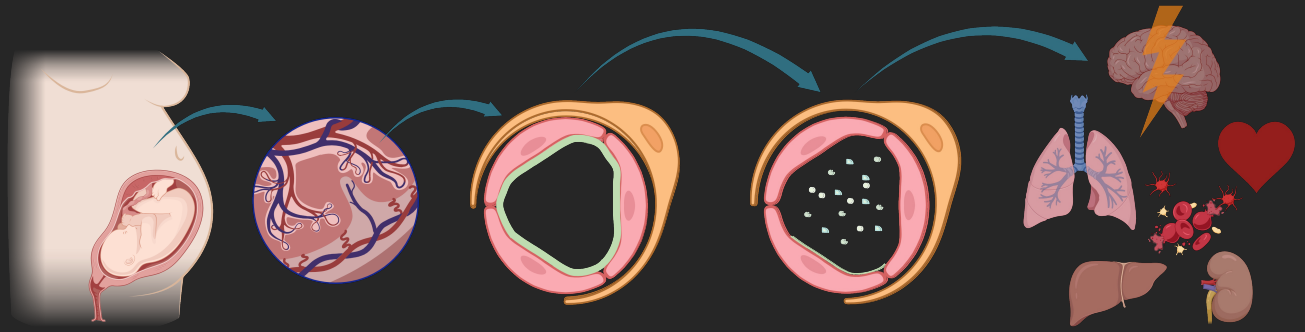
Tack för att ni lyssnade!



Niclas Carlberg
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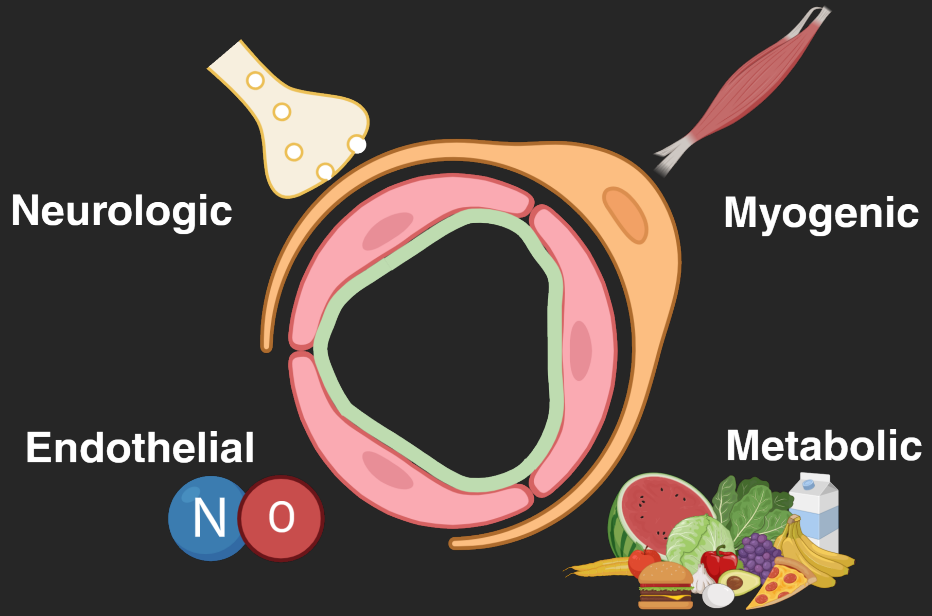
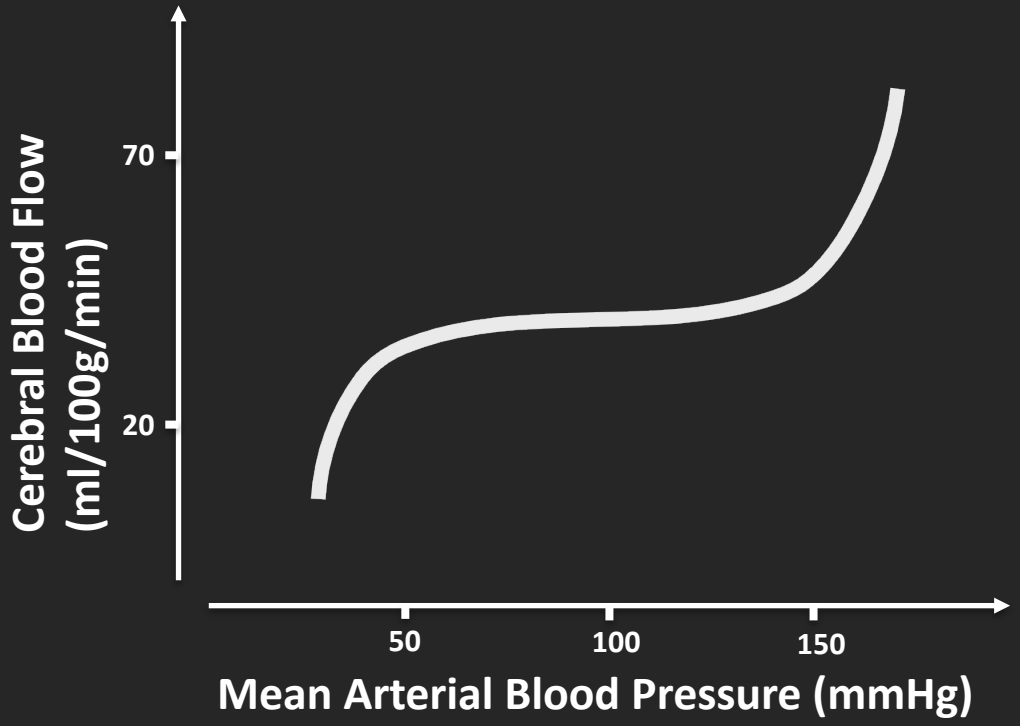
Alla illustrationer är gjorda med BioRender

Reglering av cerebralt blodflöde



Reglering av cerebralt blodflöde



Aim Study 1

To compare ARI and eCPP in women with eclampsia, preeclampsia with and without organ complications, and normotensive pregnancies

Eclampsia	Preeclampsia with organ complications	Preeclampsia without organ complications	Normotensive pregnancies

Method

Included in PROVE biobank
N=316

No TCD measurment or excluded
N=228

TCD measurments
N=87

Eclampsia
N=16

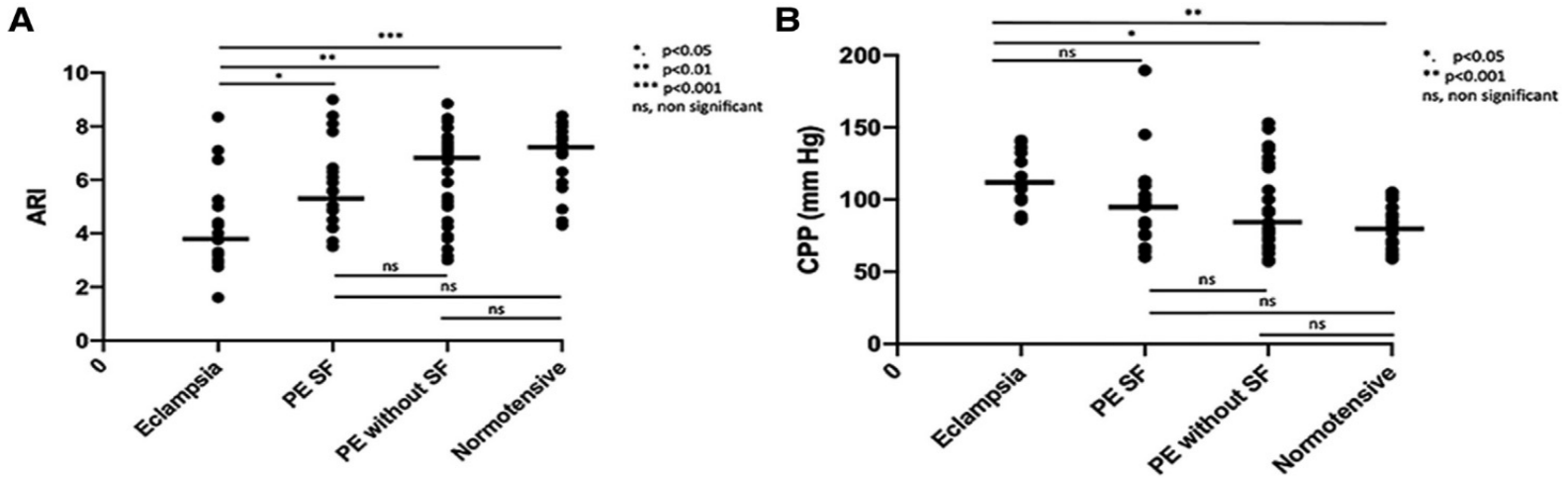
Preeclampsia with organ complications
N=18

Preeclampsia without organ complications
N=32

Normotensive pregnancies
N=21

Results

FIGURE 2
Dynamic cerebral autoregulation and cerebral perfusion pressure in preeclampsia and normotensive pregnancies



A, Dynamic cerebral ARI. **B,** CPP in, Eclampsia PE with SF, PE without SF, and pregnancies with normal blood pressure. Medians are marked in each group. Differences among groups are estimated by Mann-Whitney *U* test with Bonferroni correction.

ARI, autoregulatory index; *CPP*, cerebral perfusion pressure; *PE*, preeclampsia; *SF*, severe feature.

Conclusion

- Women with eclampsia have lower ARI than all other groups and higher eCPP compared with women with preeclampsia without severe features and normotensive pregnancies

Aim Study 2

- To compare concentrations of GDP in women with preeclampsia of different severity.

Preeclampsia with multiple organ complications	Preeclampsia with a single organ complication	Preeclampsia without organ complications	Normotensive pregnancies

Method

- Blood samples were taken, aliquoted and frozen to −80˚
- Shipped frozen to Gothenburg
- Analyzed with ELISA
- Syndecan-1, hyaluronic acid, thrombomodulin

Included in PROVE biobank
N=233

Postpartum or not analysed
N=176

Samples analysed
N=57

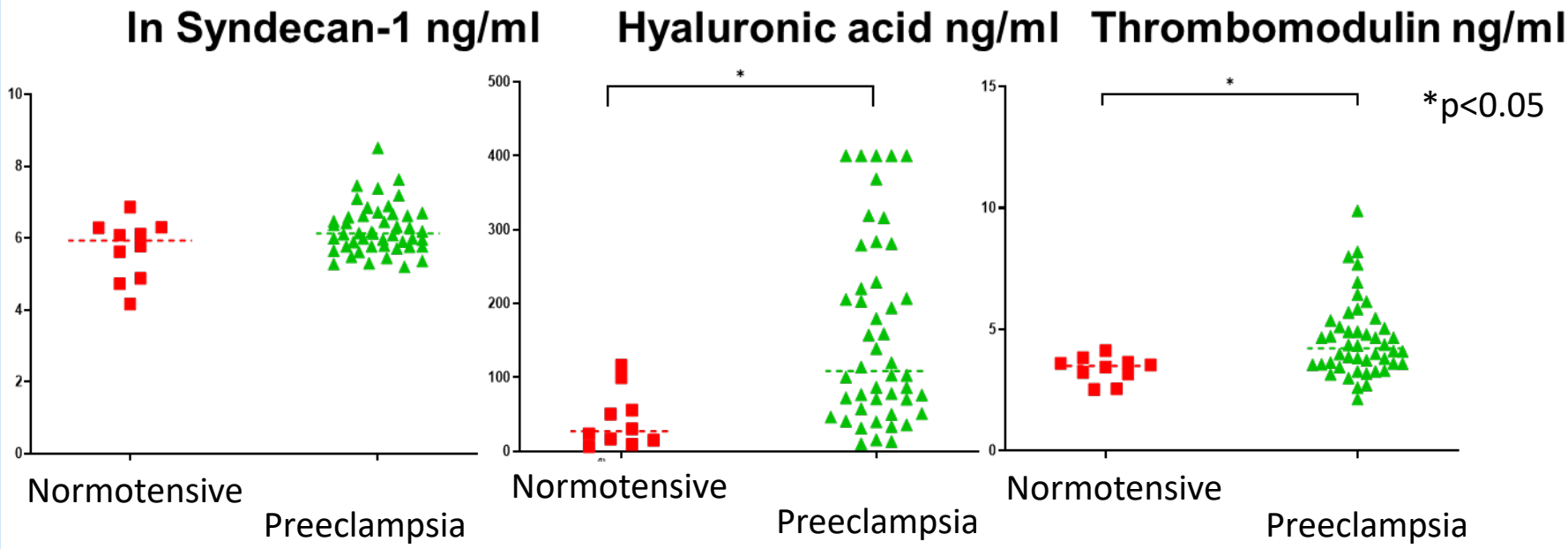
Preeclampsia with multiple organ complications
N=13

Preeclampsia with a single organ complication
N=24

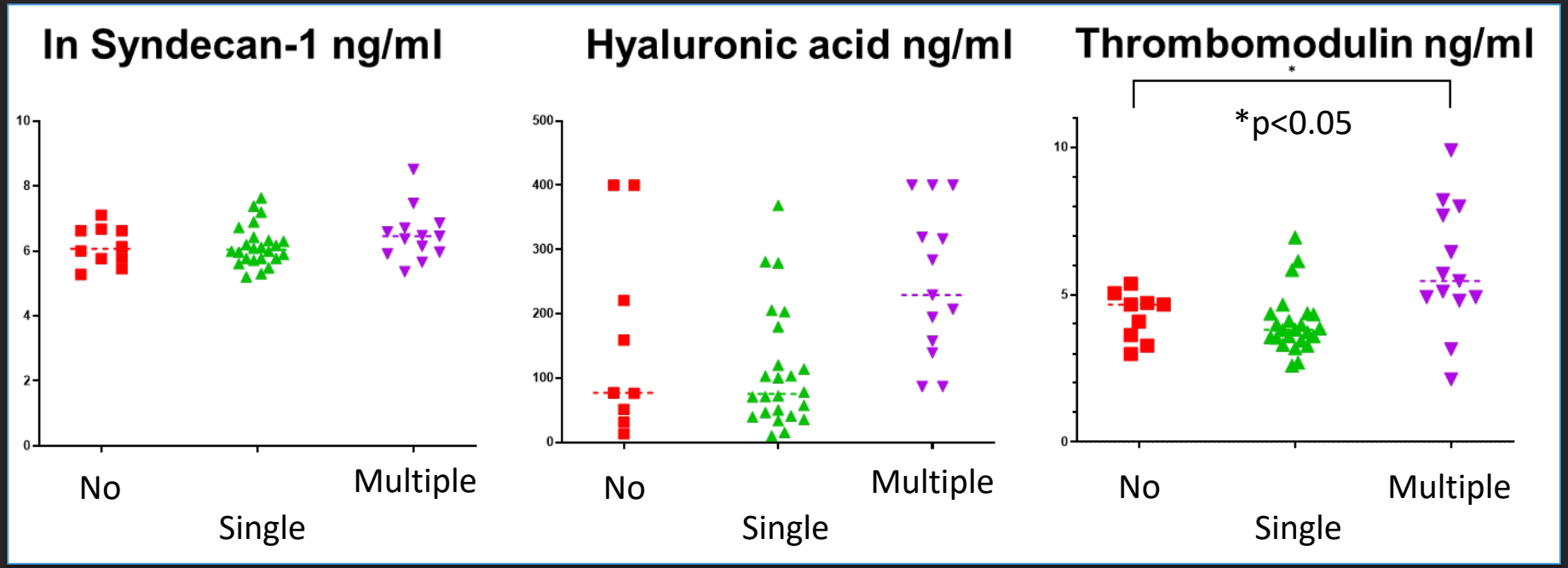
Preeclampsia without organ complications
N=10

Normotensive pregnancies
N=10

Results


ln Syndecan-1 ng/ml
Hyaluronic acid ng/ml
Thrombomodulin ng/ml
*p<0.05
Normotensive
Preeclampsia
Normotensive
Preeclampsia
Normotensive
Preeclampsia

Results

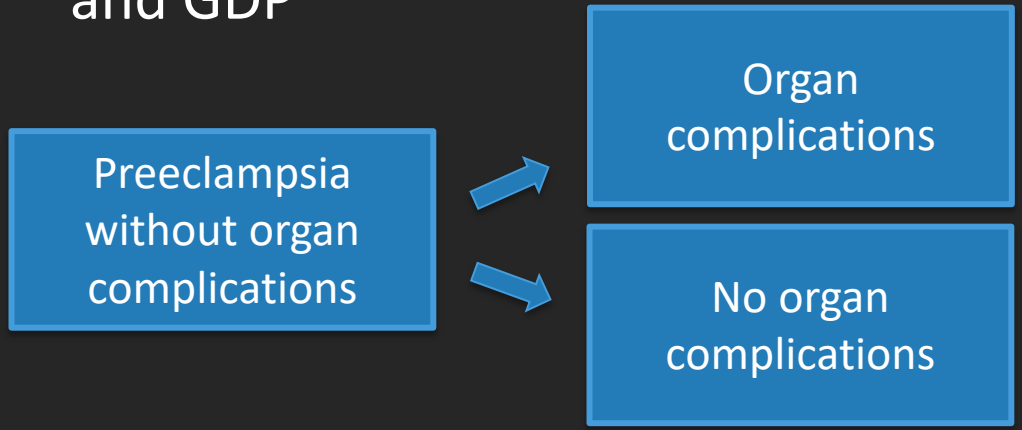

In Syndecan-1 ng/ml
10
8
6
4
2
0
No
Single
Multiple
Hyaluronic acid ng/ml
500
400
300
200
100
0
No
Single
Multiple
Thrombomodulin ng/ml
*
*p<0.05
10
5
0
No
Single
Multiple

Conclusion

- Hyaluronic acid and thrombomodulin are elevated in preeclampsia
- Thrombomodulin is associated with severity of disease

Aim Study 3

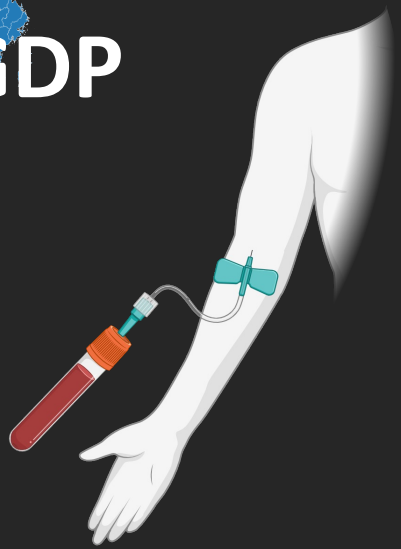
To predict organ complications in women with preeclampsia by AM and GDP



Method

goPROVE

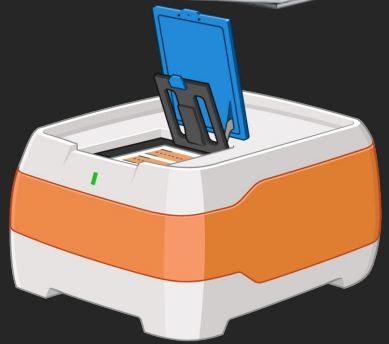
GDP



sFlt-1
PlGF

syndecan-1
hyaluronic acid
thrombomodulin

Delphia Xpress



ELLA (ELISA)

Statistics

- Cox proportional hazards regression
- Kaplain-Meier survival curves
- Incidence rates Poisson regression
- ROC curve analysis
- Sensitivity, Specificity, PPV, NPV

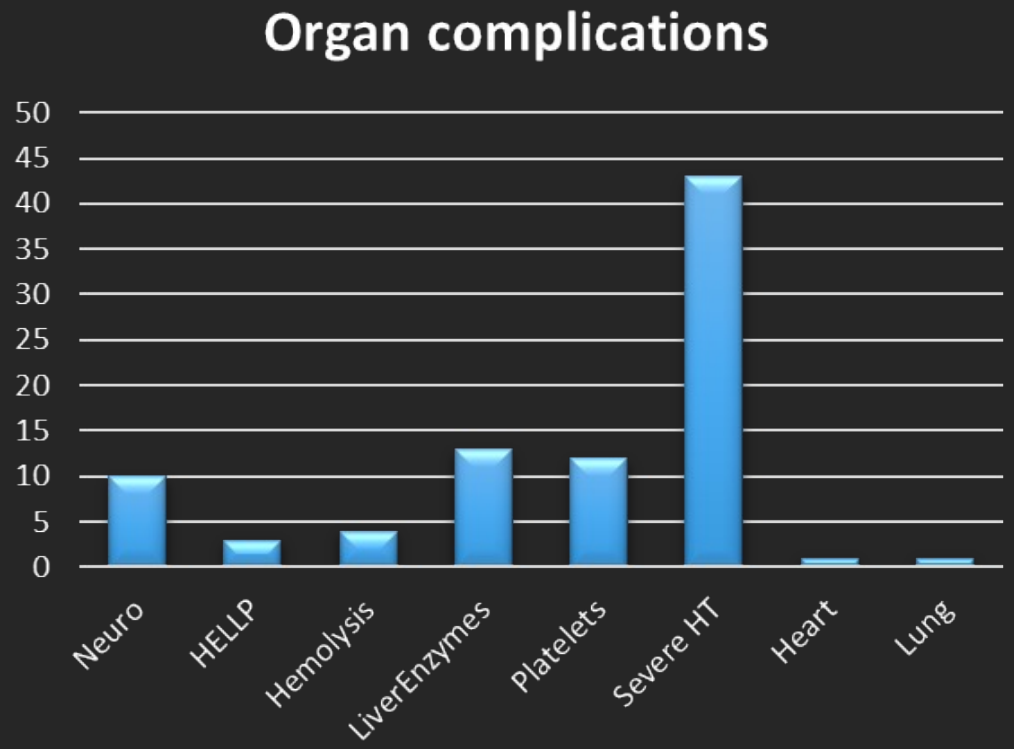
Results

Preeclampsia without organ complications N=140

Organ complications N=56

No organ complications N=84

Results


Organ complications
50
45
40
35
30
25
20
15
10
5
0
Neuro
HELLP
Hemolysis
LiverEnzymes
Platelets
Severe HT
Heart
Lung

Discussion

Strengths and limitations

- ☺ Simple study design
- ☺ Clinically useful setting
- ☹ Few organ complications

Possible conclusions

Positive and negative predictive values

AM – time for clinical studies in Sweden?

GDP – interesting to study in other populations?

Aim Study 4

To compare ARI and eCPP in preeclampsia with and without organ complications and normotensive pregnancies at diagnosis and one year postpartum.

Preeclampsia with organ complications	Preeclampsia without organ complications	Normotensive pregnancies

Statistics

- Dependent t-test within groups (between diagnosis and one-year follow-up)
- Welch's T-test between groups

Preeclampsia with organ complications	Preeclampsia without organ complications	Normotensive pregnancies

Statistics

- All analyzes both adjusted and unadjusted
- Hb, Mg, $ETCO_2$, blood pressure medication

Preeclampsia with organ complications	Preeclampsia without organ complications	Normotensive pregnancies

Possible conclusion

- ARI and eCPP differs with severity of disease?
- ARI and eCPP are normalized one year postpartum?
- ARI and eCPP still differs between groups one year postpartum?

Conclusion

- Preeclampsia
- Organ complications
- Transcranial Doppler
- Angiogenic markers
- Glycocalyx degradation products

Preeklampsi

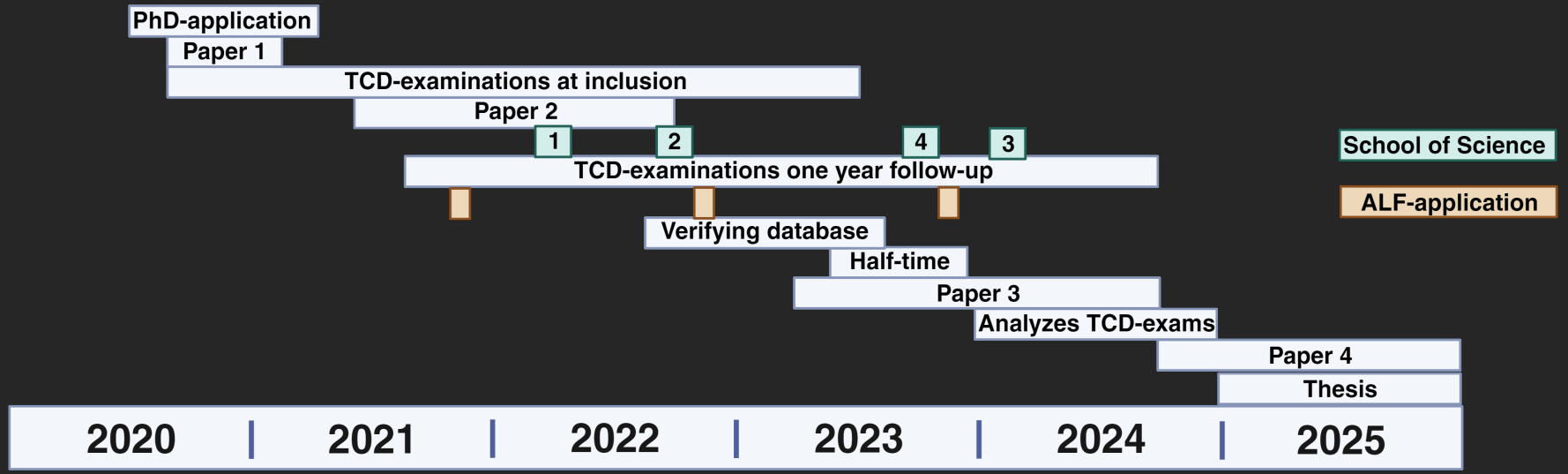
- 3–5% av alla graviditeter
- 40 000 döda globalt
- Både akut sjuklighet och långtidseffekter
- Neonatal sjuklighet och morbiditet

Preeklampsi

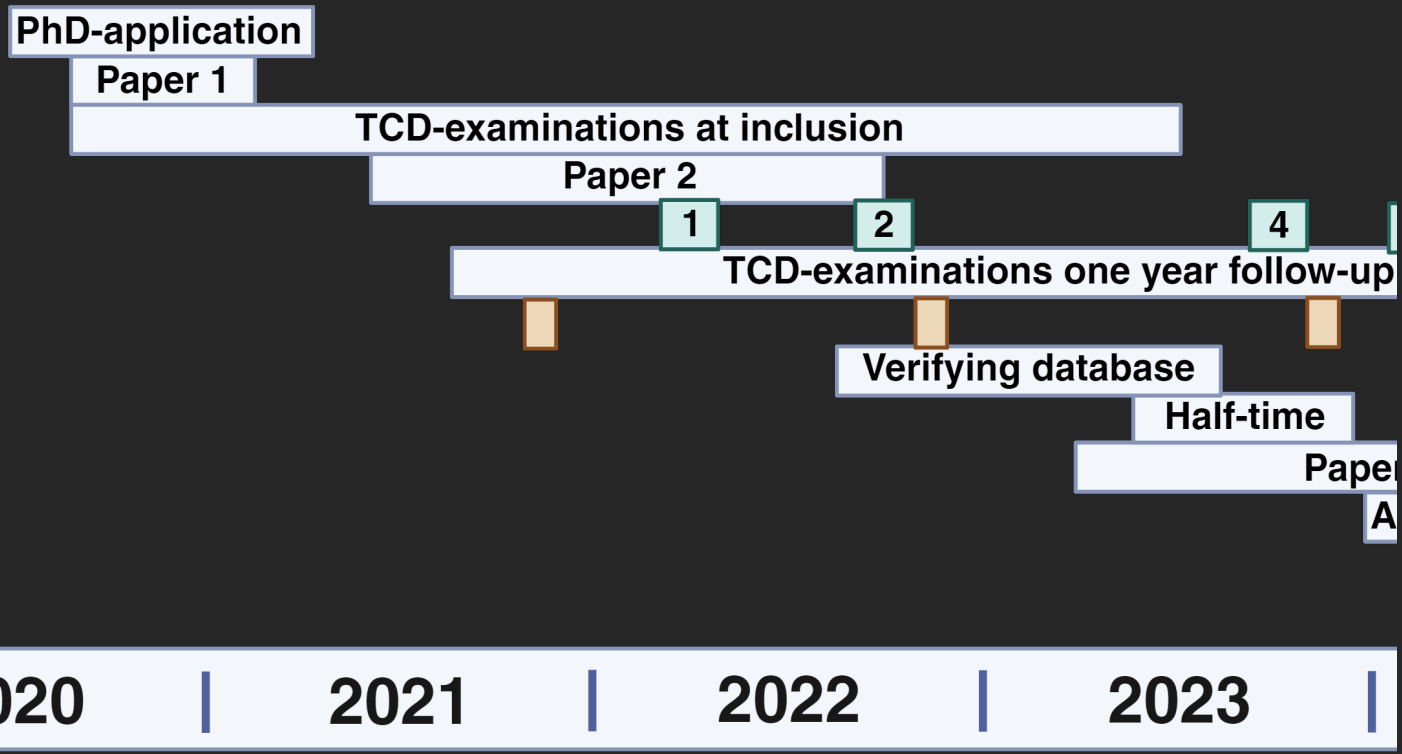
Hypertension efter 20:e graviditetsveckan + minst en organmanifestation

- Nervsystemet
- Hjärta
- Lungor
- Lever
- Njure
- Koagulation

Gannt


PhD-application
Paper 1
TCD-examinations at inclusion
Paper 2
1
2
4
3
TCD-examinations one year follow-up
Verifying database
Half-time
Paper 3
Analyzes TCD-exams
Paper 4
Thesis
School of Science
ALF-application
2020
2021
2022
2023
2024
2025

Gantt


PhD-application
Paper 1
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Half-time
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2020
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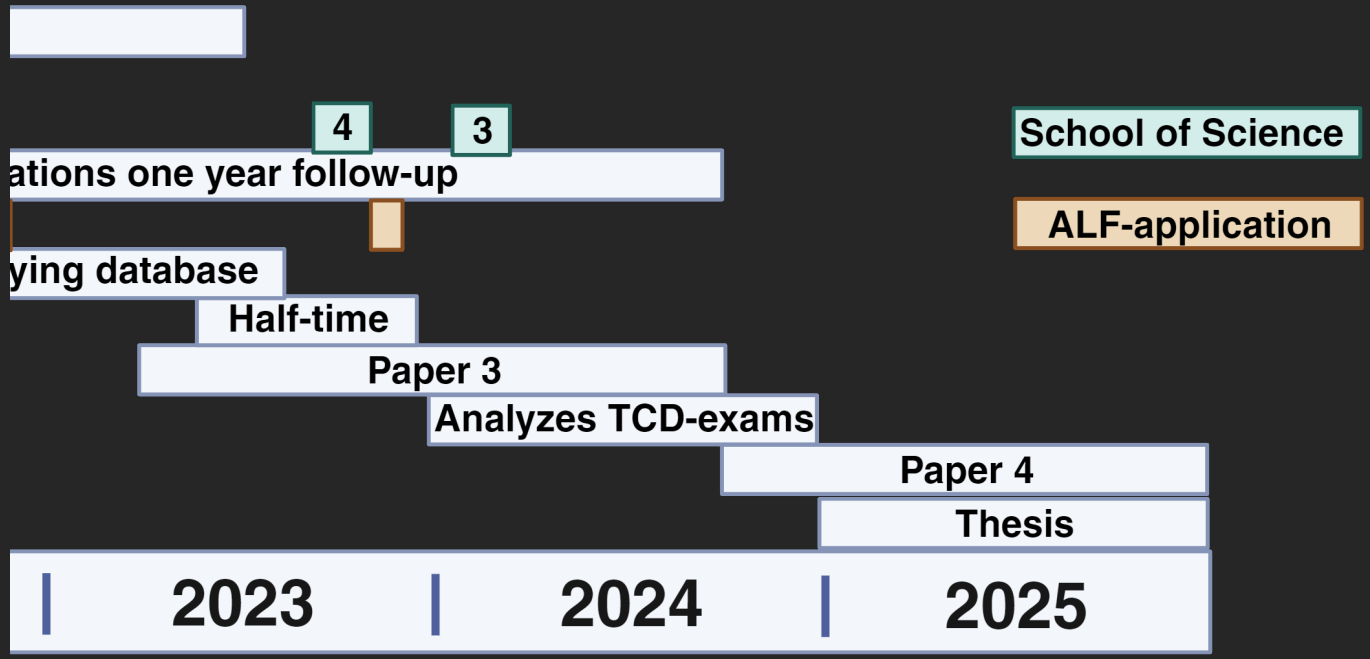
2022
2023

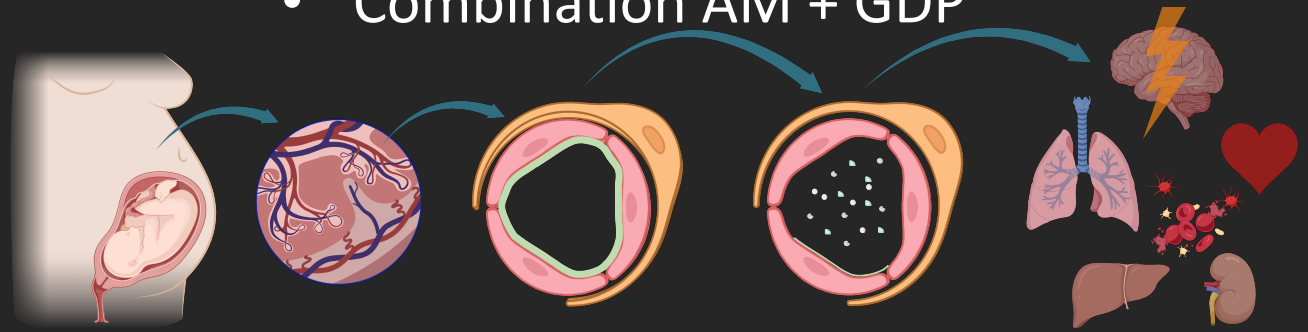
Gantt


4
3
ations one year follow-up
ying database
Half-time
Paper 3
Analyzes TCD-exams
Paper 4
Thesis
2023
2024
2025
School of Science
ALF-application

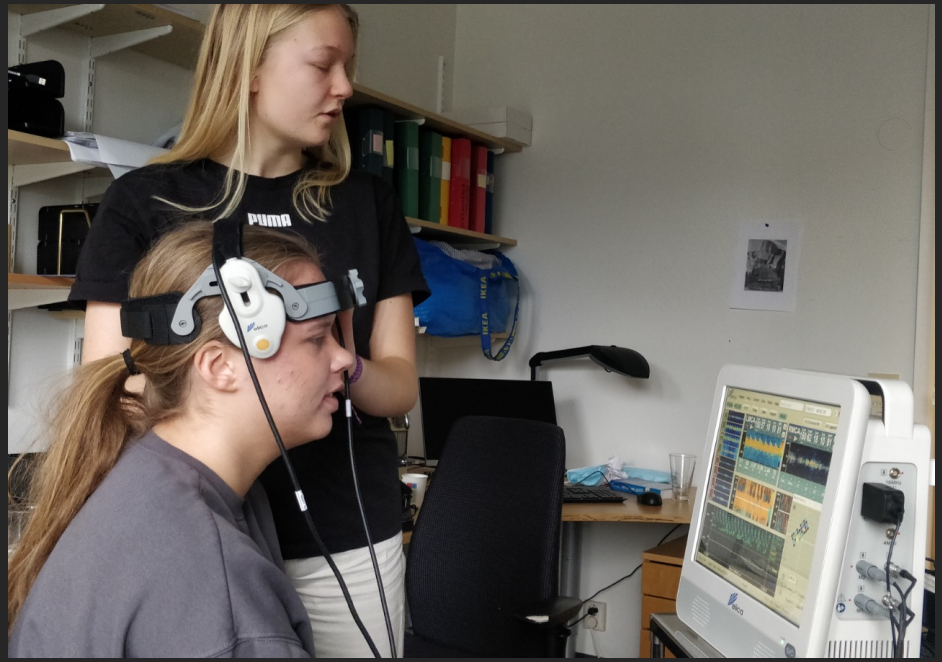
Discussion

Results in context

- Validation of AM in Sweden
- Exploration of GDP as predictors
- Combination AM + GDP

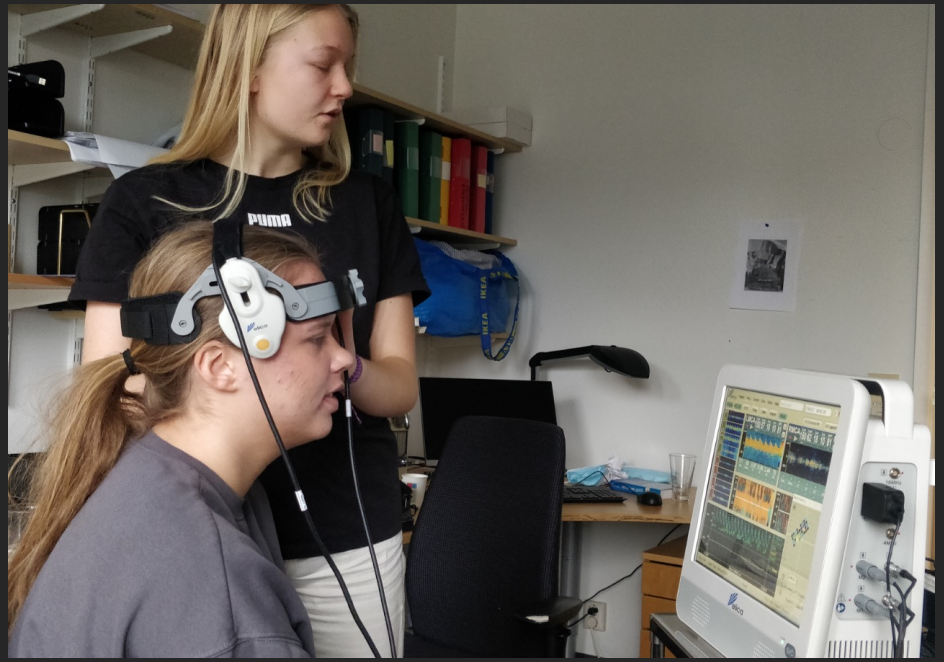


Transcranial Doppler – Autoregulation Index



Semirecumbent position
Finapres finger cuff
Nasal cannula
”Helmet” with probes
Calibration off
Arm cuff pressure
7 minutes recording
Original data in the machine
Data file on memory stick
Record registered manually

Transcranial Doppler – Autoregulation Index



TRANSKRANIELL DOPPLER-UNDERSÖKNING: PROTOKOLL

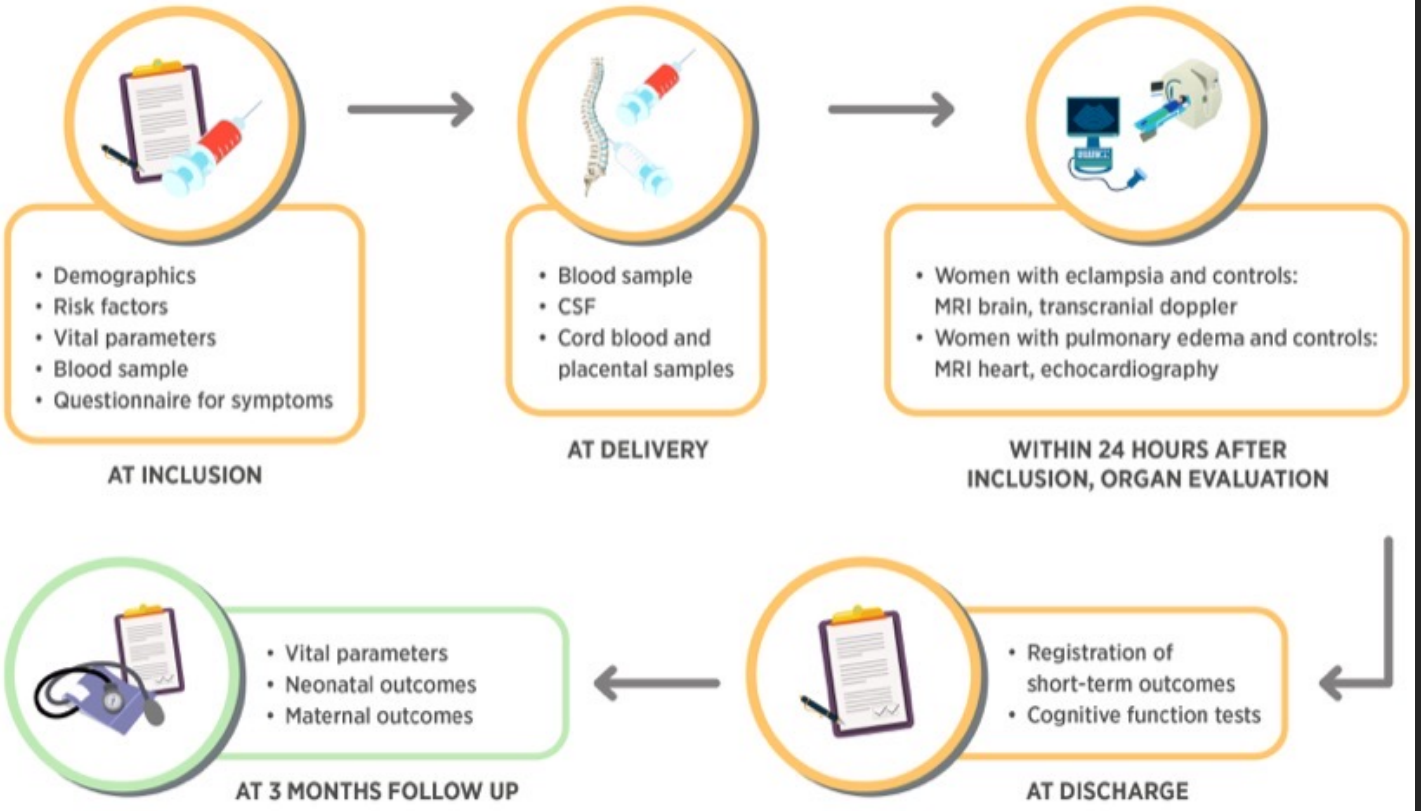
Datum:
Tid för undersökning:
Initialer patient:
Studiepatientnummer:
Filnamn:
Nr i ~~Delcap~~:

PROVE

	Vänster	Höger
~~Mätdag~~:		
Dominant hand:		
Blodtryck:		
~~Endtidal~~ CO_2		
POX vid mätstart:		
Puls vid mätstart:		
Syrgasbehandling vid mätstart:	Ingen / Grimma / Mask / CPAP	
GCS vid mätstart:		
Neurologiska symtom:		
Tidigare magnesium:	Ja / Nej	
Pågående magnesium:	Ja / Nej	
~~Antihypertensiv~~ medicinering:		
Lägsta hemoglobin innan mätstart:		
Kommentarer:		

	Vänster	Höger
Systolisk hastighet:		
Diastolisk hastighet:		
Medelhastighet:		
ARI:		
CPP:		

PROVE

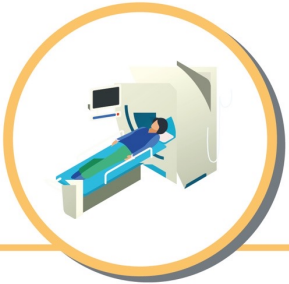

• Demographics
• Risk factors
• Vital parameters
• Blood sample
• Questionnaire for symptoms
AT INCLUSION
• Blood sample
• CSF
• Cord blood and placental samples
AT DELIVERY
• Women with eclampsia and controls: MRI brain, transcranial doppler
• Women with pulmonary edema and controls: MRI heart, echocardiography
WITHIN 24 HOURS AFTER INCLUSION, ORGAN EVALUATION
• Registration of short-term outcomes
• Cognitive function tests
AT DISCHARGE
• Vital parameters
• Neonatal outcomes
• Maternal outcomes
AT 3 MONTHS FOLLOW UP

goPROVE

UPMOST
Uppsala Pregnancy Complication Study

- Demographics
- Risk factors
- Vital parameters
- Blood sample
- Questionnaire for symptoms
- Coagulation tests

AT INCLUSION



Brain evaluation
- MRI brain
- Transcranial doppler
- Cognitive function

Heart evaluation
- Echocardiography
- Endothelial function

ORGAN EVALUATION

- Blood sample
- CSF
- Cord blood and placental samples
- Coagulation tests

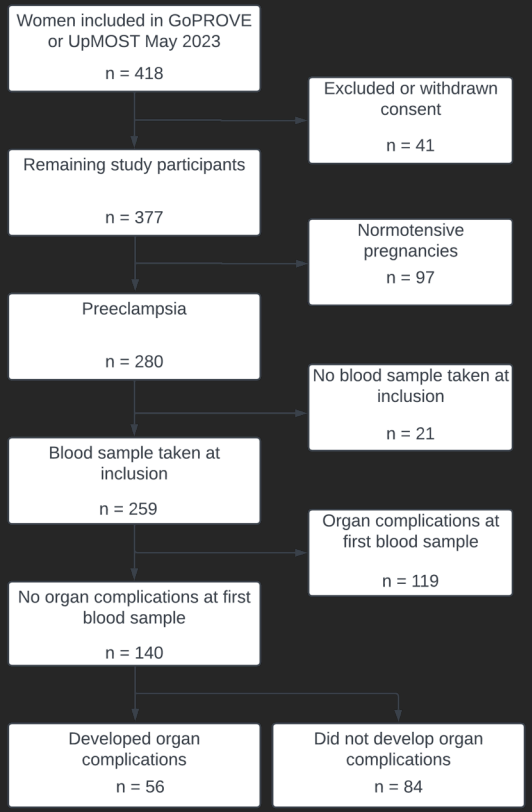
AT DELIVERY

- Self rated health
- Partner's experience
- Women's experience
- Self efficacy

8 WEEKS POSTPARTUM

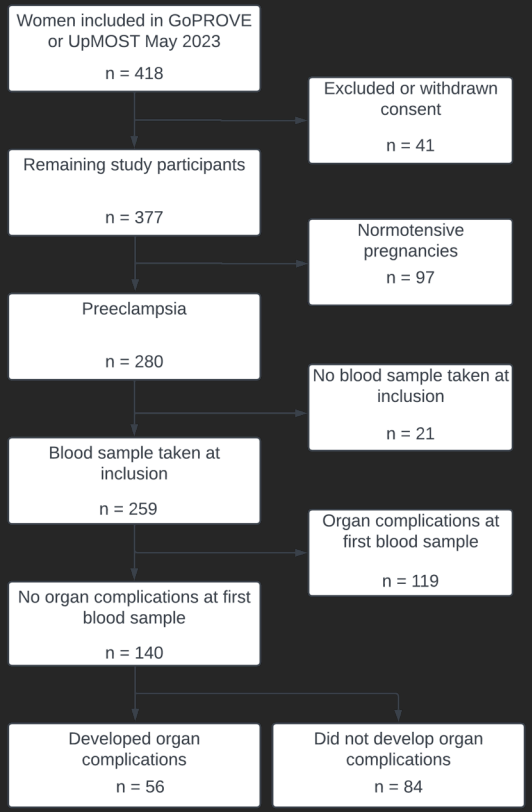
- Blood sample
- Questionnaire for symptoms
- Blood pressure
- Transcranial Doppler
- MRI brain
- Cognitive tests
- Echocardiography

ONE YEAR POSTPARTUM



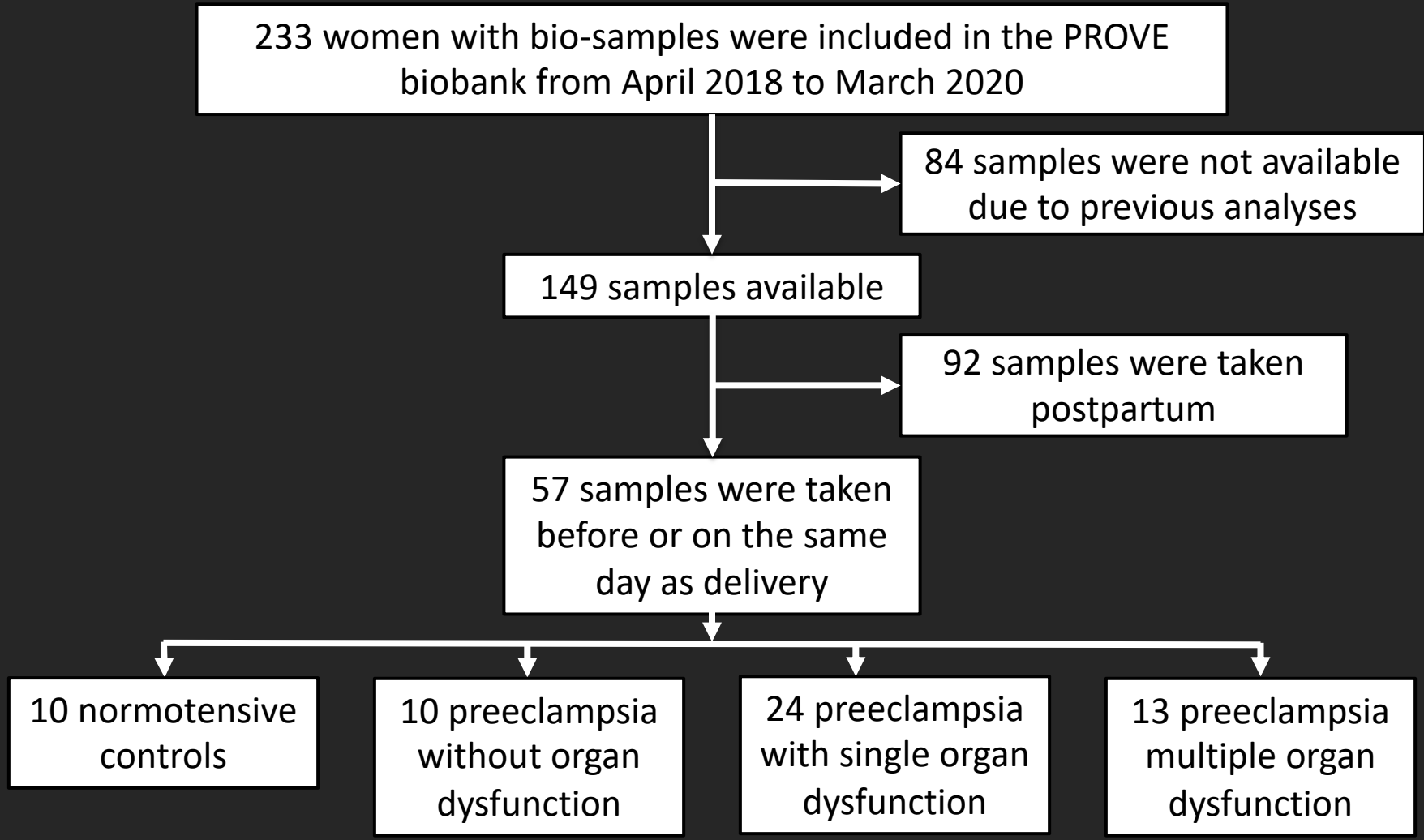
Results

- 140 women
- 56 developed complications
- 84 did not develop complications
- 97 complications (events)
- Severe hypertension despite treatment



Results

- 30 years old (range 22–44 years)
- Nulliparous (81,4%)
- BMI 27,1 kg/m^2 (SD 6,2 kg/m^2)
- Normal lab-tests

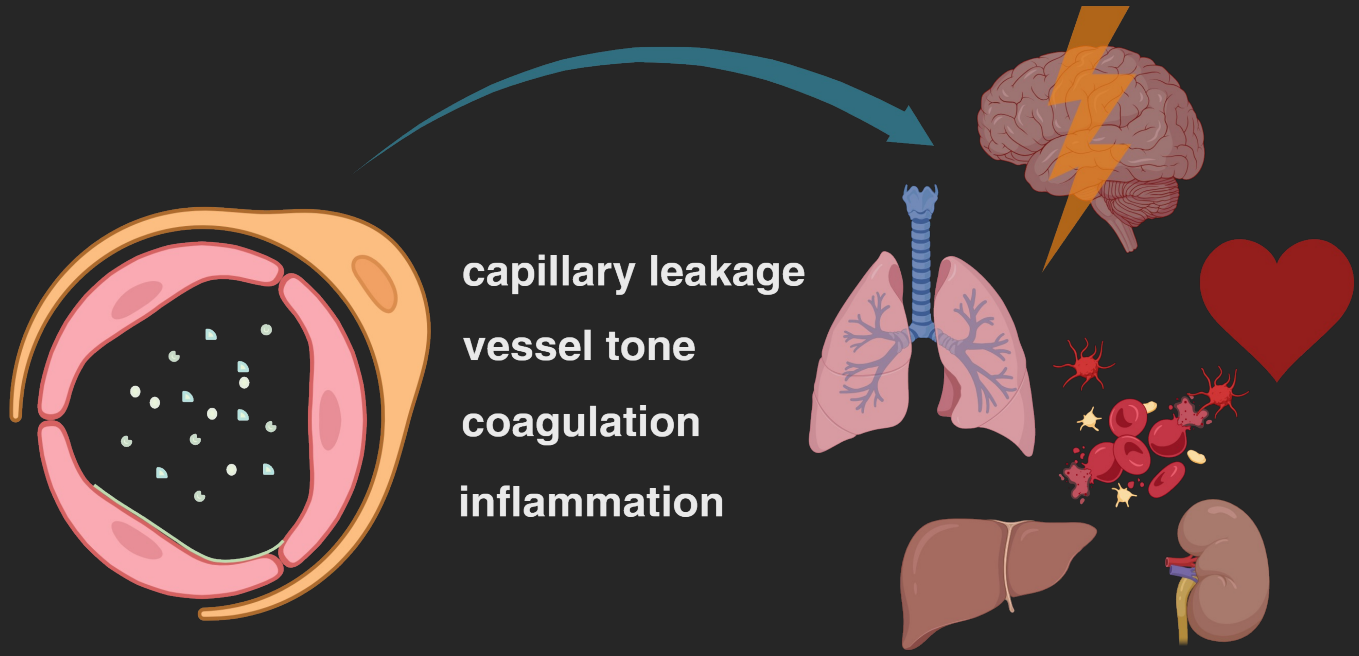

233 women with bio-samples were included in the PROVE biobank from April 2018 to March 2020
84 samples were not available due to previous analyses
149 samples available
92 samples were taken postpartum
57 samples were taken before or on the same day as delivery
10 normotensive controls
10 preeclampsia without organ dysfunction
24 preeclampsia with single organ dysfunction
13 preeclampsia multiple organ dysfunction

Discussion

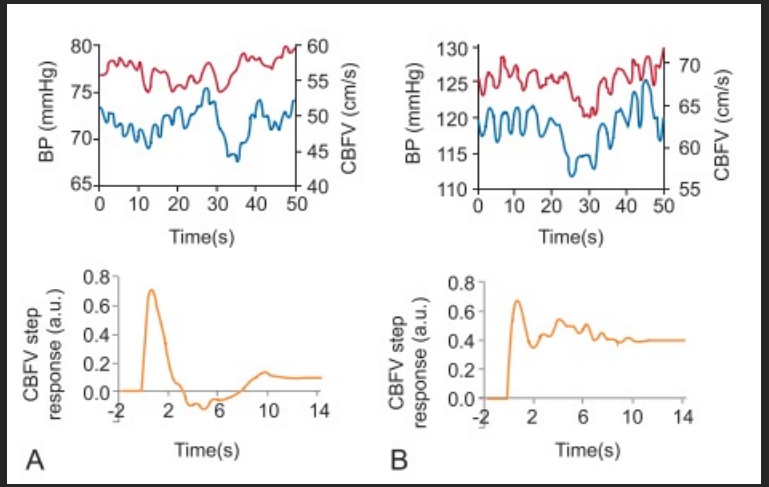
Clinical and research implications

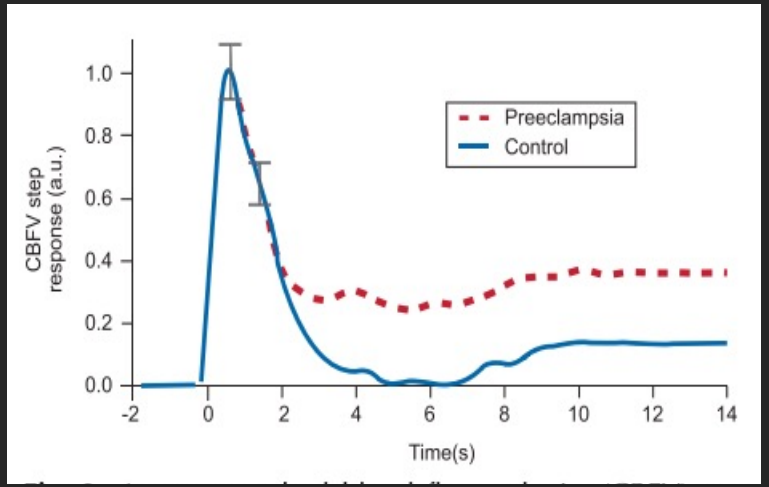
- PPV and NPV of AM – ready for clinical trials in Sweden?
- PPV and NPV of GDP – need for further validation or useless?

Organ complications



Dynamic cerebral autoregulation





Cerebral Autoregulation in Normal Pregnancy and Preeclampsia

Teelkien R. van Veen, BS, Ronney B. Panerai, PhD, Sina Haeri, MD, MHSA, Annemiek C. Griffioen, BS, Gerda G. Zeeman, MD, PhD, and Michael A. Belfort, MD, PhD

Definition of organ complications study 1

Eclampsia was confirmed when PE was complicated by witnessed generalized tonic-clonic seizures in the absence of another etiology. Pulmonary edema was diagnosed when there was worsening dyspnea, bibasilar inspiratory crackles on auscultation, and features of pulmonary edema on chest x-ray. Hemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome) and PE without SFs were diagnosed in accordance with the ACOG Practice Bulletin.

Definition of organ complications study 2

Eclampsia, neurological deficits, pulmonary edema, renal impairment, hemolysis and elevated liver enzymes and low platelet syndrome (HELLP), elevated liver enzymes, liver rupture and platelets below 100×10^9 were considered as endorgan complications. Eclampsia was defined as generalized tonic clonic seizures in a woman diagnosed with preeclampsia in the absence of another etiology. Multiple neurological complications were assessed as one end-organ complication. HELLP was defined as a platelet count less than 100×10^9/L, aspartate aminotransferase (AST) greaterthan 70 U/L and lactate dehydrogenase (LD) > 600 U/L or hemolysis on a peripheral blood smear. Pulmonary edema was diagnosed when there was worsening dyspnea, bilateral fine inspiratory crackles on auscultation and features of pulmonary edema on chest x-ray. Serum creatinine above 120 µmol/L was considered as renal impairment. Severe hypertension, defined as a systolic blood pressure ≥ 160 mm Hg systolic and/or a diastolic blood pressure ≥ 110 mm Hg, was not considered an end-organ complication.

Definition of organ complications study 3

Acute Severe Hypertension	**BP > 160/110 mmHg at any time**
Severe Hypertension despite treatment	Blood pressure at two times higher than 160/110 mmHg despite adequate treatment OR need for intravenous treatment
Haemolysis	Haptoglobin <0,25g/L or LD >10 µkat/l.
Thrombocytopenia	Platelet particle concentration <100 x 10^9/L
Transaminase elevation (Abnormal LFT, due to PE)	ALT or AST ≥2 times highest normal value (ALT >1.5 µkat/L and AST <1.2 µkat/L)
HELLP-syndrome	Haptoglobin <0,25g/L or LD >10 µkat/l AND ALT or AST ≥2 times highest normal value AND Platelet particle concentration <100 x 10^9/L
Epigastric pain	Epigastric pain, persistent >one day
Jaundice	Bilirubin >25 µmol/L
Acute renal injury (insufficiency)	Creatinine ≥90 µmol/L or oliguria <500 ml/day
Small for gestational age	Newborn weight <−2 standard deviations adjusted for length of pregnancy.
Eclampsia	Generalised tonic-clonic seizures in a woman with preeclampsia. ICD code O15

Neurological symptoms	**Persistent headache despite analgesia (other than morphine or equipotent analgesia), OR clonus (≥3) OR persistent visual impairment**
Coma	Glasgow coma scale ≤8 (Reaction level scale >3)
Cortical blindness	PRES diagnosed in medical charts OR radiological evidence of PRES OR diagnose I67.83
CVA	ICD code I60, I61, I63 and I64
DIC	ICD code D65. DIC-score according to Erez, 26 p = DIC
Heart (cardiac) failure (due to PE)	Ejection fraction ≤40% OR ICD code I50 OR ICD code O90.3
Respiratory failure	Intubation
Pulmonary oedema	Pulse oximetry ≤90 AND auscultatory crackles OR x-ray signs of pulmonary edema OR ultrasound signs of pulmonary edema
Dialysis	Renal replacement therapy
Postpartum haemorrhage	More than 500 ml bleeding if vaginal delivery OR more than 1000 ml if caesarean section

Statistics

- Kruskal-Wallis global test
- Mann-Whitney U-test
- Bonferroni correction

Statistics

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Overall Aim

To evaluate the role of dynamic cerebral autoregulation, angiogenic markers, and endothelial biomarkers as determinants of presence and degree of organ complications in general and cerebral complications in particular, in preeclampsia at diagnosis and one year postpartum.