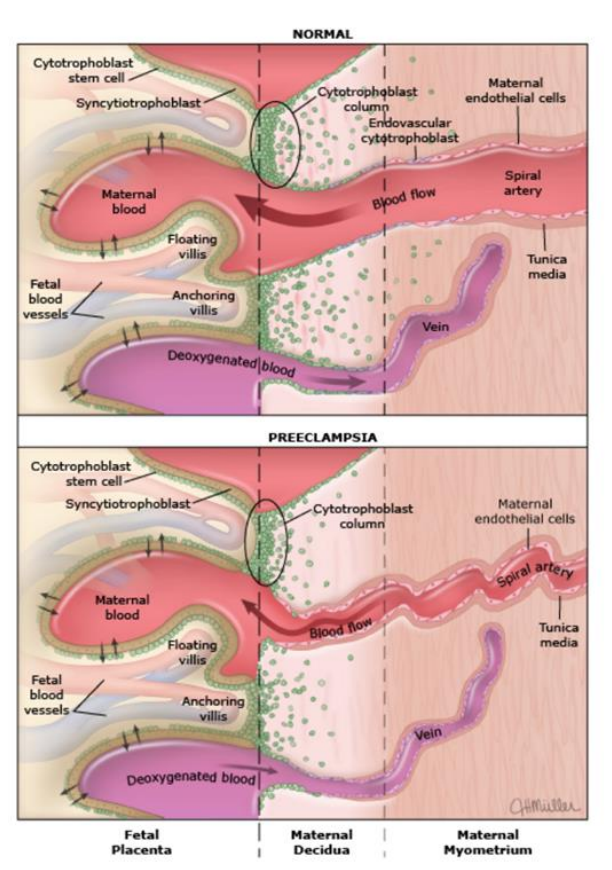
LaboCita
ANALYSES MÉDICALES

SCREENING OF PREECLAMPSIA
A good indicator or false hope?

Jérôme de Marchin

Service de Biologie Clinique – CHR de la Citadelle

Table of Content



LaboCita
ANALYSES MÉDICALES

Introduction to preeclampsia

- **Definitions and physiopathology**
- Risk factors
- Different clinical forms

LaboCita
ANALYSES MÉDICALES

Definition

Preeclampsia: Clinical features and diagnosis

Authors
Phyllis August, MD, MPH
Baha M Sibai, MD

Section Editor
Charles J Lockwood, MD, MHCM

Contributor disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Apr 2016. | **This topic last updated:** Jan 18, 2016.

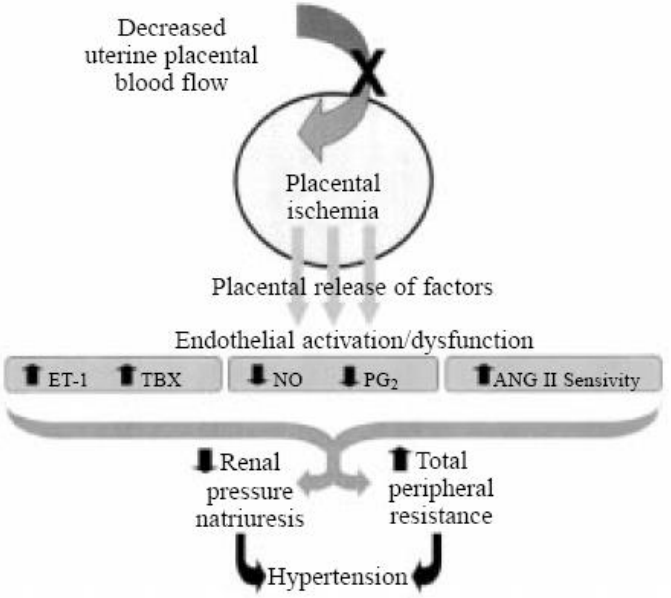
Criteria for the diagnosis of preeclampsia

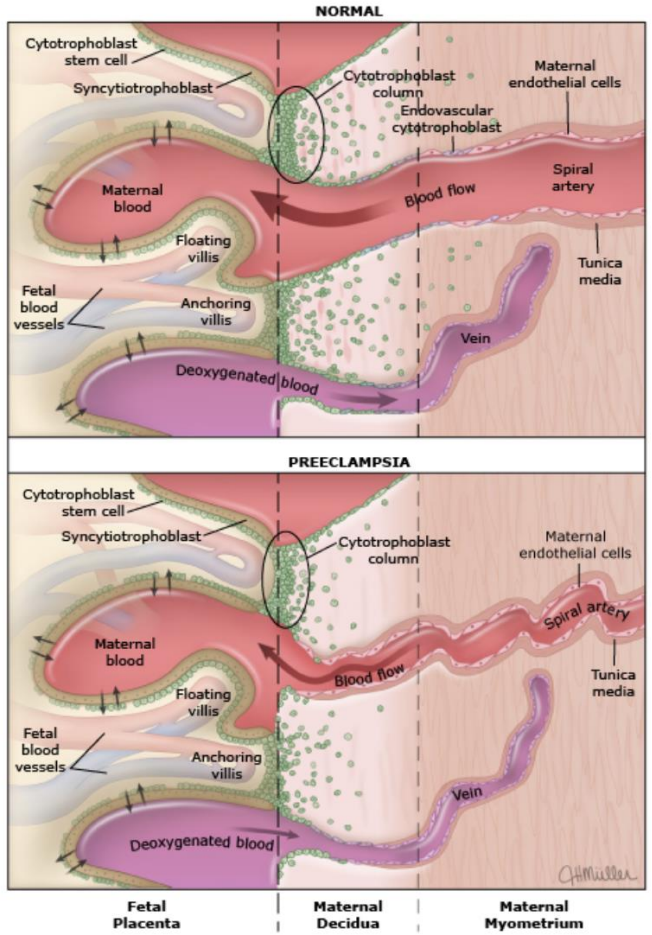
Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on two occasions at least four hours apart after 20 weeks of gestation in a previously normotensive patient
If systolic blood pressure is ≥160 mmHg or diastolic blood pressure is ≥110 mmHg, confirmation within minutes is sufficient
and
Proteinuria ≥0.3 grams in a 24-hour urine specimen or protein (mg/dL)/creatinine (mg/dL) ratio ≥0.3
Dipstick ≥1+ if a quantitative measurement is unavailable
In patients with new-onset hypertension without proteinuria, the new onset of any of the following is diagnostic of preeclampsia:
Platelet count <100,000/microliter
Serum creatinine >1.1 mg/dL or doubling of serum creatinine in the absence of other renal disease
Liver transaminases at least twice the normal concentrations
Pulmonary edema
Cerebral or visual symptoms

Adapted from: Hypertension in pregnancy: Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013; 122:1122.

Physiopathology

UpToDate®





Hypothesis for the role of sFlt1 in preeclampsia

Remodeling of maternal spiral arteries does not occur

↓

(?) Placental hypoperfusion

↓

(?) Placental ischemia

↓

sFlt1 increases

↓

Free VEGF and PlGF decrease

↓

Systemic maternal endothelial dysfunction

↓

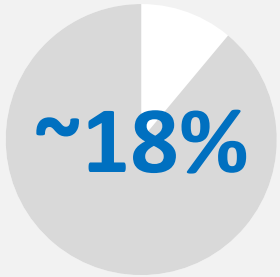
Thrombosis of arterioles
Hypertension
Dysfunction of multiple organs, especially kidney, liver, and brain

Karumanchi et al, *UpToDate, 2022*

LaboCita ANALYSES MÉDICALES

Importance of preeclampsia diagnosis

Consequences of PE to mother

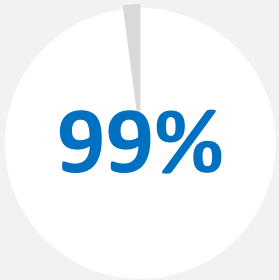


~18%

of maternal deaths

1 in 4

leading cause of maternal death in U.S.



99%

of deaths occur in low-income countries

6.4 deaths per **10,000** cases PE

Failure
Disseminated intravascular coagulation (DIC)

Stroke (36% of pregnancy-related stroke)
Seizure 1/400 women with PE)
Eclampsia (new onset seizure or coma)
Hypertensive encephalopathy
Retinal detachment
Cortical blindness
Complete blindness

Failure

Hemorrhage
DIC
Hysterectomy

August P. UpToDate 2019. Preeclampsia: Clinical features and diagnosis.
Duley L. Semin Perinatol 2009;33:130-7.
Ross M, et al. Eclampsia. Medscape 2019.

Abalos E, et al. Eur J Obstet Gynecol Reprod Biol 2013;170:1-7.
Norwitz ER. UpToDate 2019. Preeclampsia: Management and prognosis.

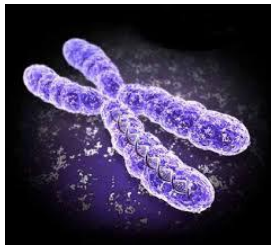
LaboCita
ANALYSES MÉDICALES

Introduction to preeclampsia

- Definitions and physiopathology
- **Risk factors**
- Different clinical forms

LaboCita
ANALYSES MÉDICALES

Risk factors



- Factors associated with family history
  - Family history in PE
  - Disease of polygenic, polymorphic inheritance with variable penetrance (no genetic map: no gene, no loci)
  - Anomaly of genomic parental imprinting, permissives genes, disease of mitochondrial DNA, discordant phenotype

- Physiological Factors
  - Age
  - Ethnicity (African)
  - Body mass index (BMI)
  - Weight at birth
  - Gestational age at birth

LaboCita
ANALYSES MÉDICALES

Risk factors

- Environmental Factors
  - Tabac
  - Alcohol, drugs, coffee
  - Nutritional factors
  - Living conditions (altitude, stress, socio-economic)
  - Seasonal variations
  - Physical Activity

- Immunological Factors
  - Nulliparity
  - « primipaternity »
  - Time between 2 pregnancies
  - Exposure to semen
  - Medical history of early miscarriage

- Factors associated with the pregnancy
  - Multiple pregnancies
  - Fetal malformation
  - Urinary tract infection
  - Gestational diabetes

LaboCita
ANALYSES MÉDICALES

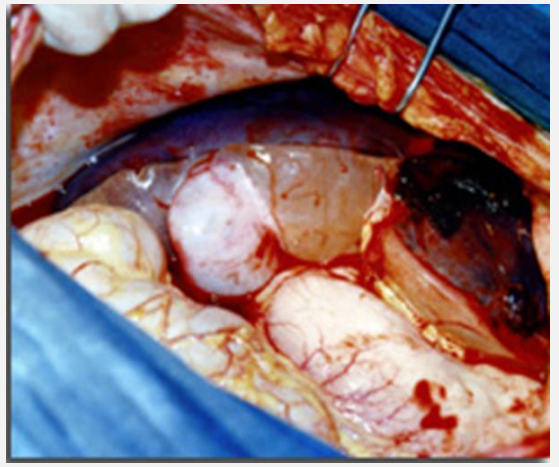
Introduction to preeclampsia

- Definitions and physiopathology
- Risk factors
- **Different clinical forms**

LaboCita
ANALYSES MÉDICALES

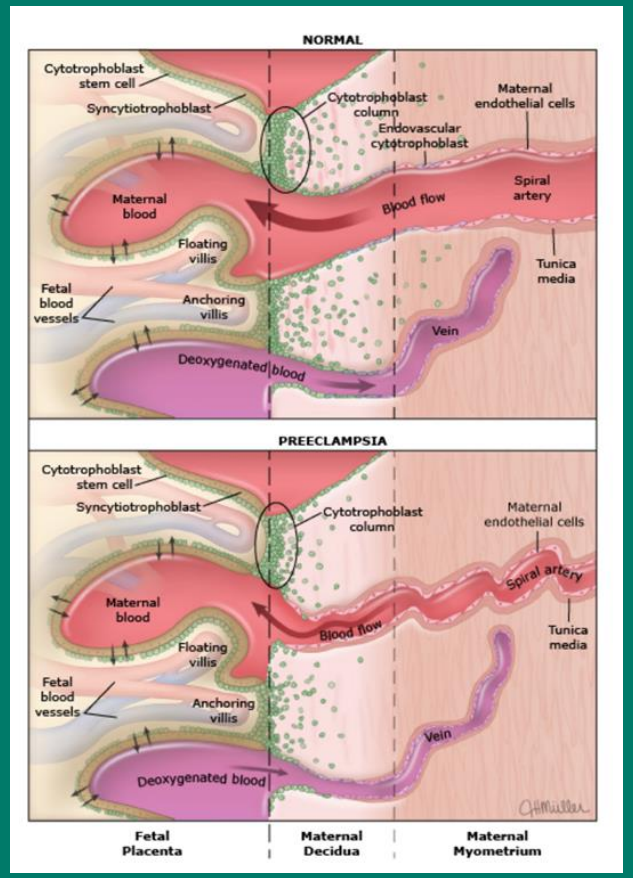
Different clinical forms

- Eclampsia
- HELLP Syndrome
- Placental abruption
- Intrauterine growth restriction
- Intrauterine fetal death
- Late miscarriage (no clear reason)



LaboCita
ANALYSES MÉDICALES

Table of Content



LaboCita
ANALYSES MÉDICALES

Inversed Pyramid

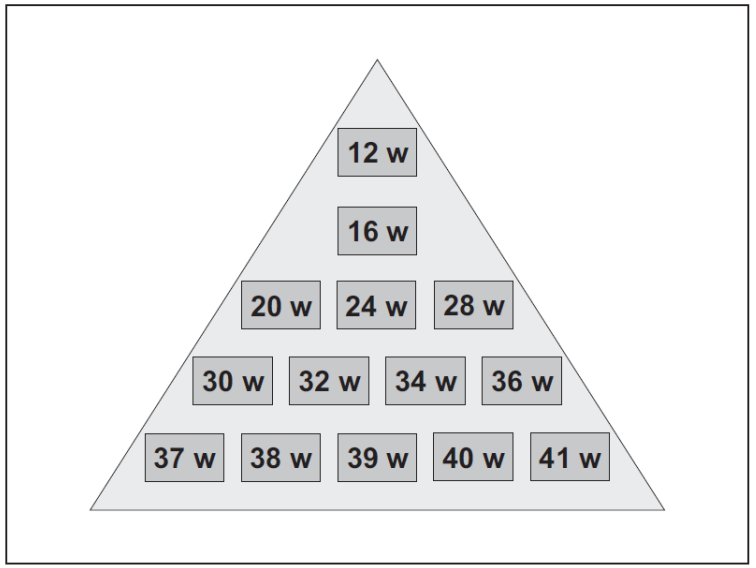


Fig. 1. Pyramid of traditional prenatal care established in 1929. w = Weeks.

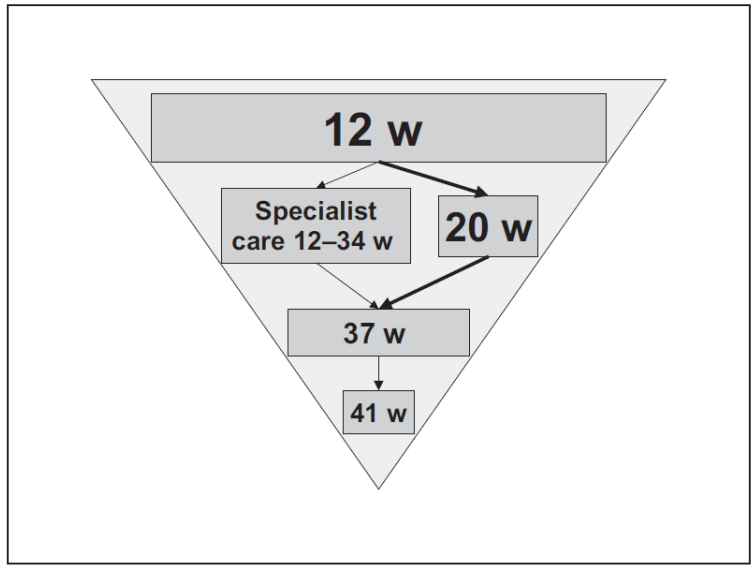


Fig. 2. Proposed new pyramid of prenatal care. w = Weeks.

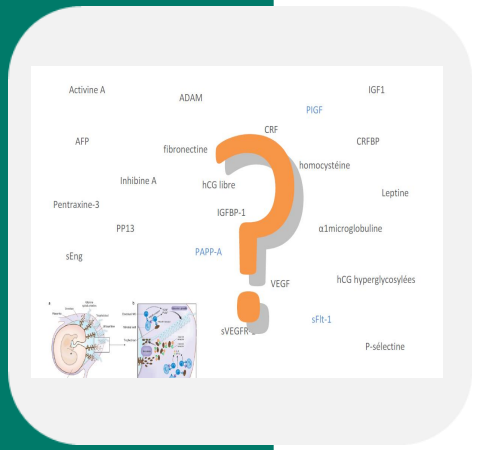
Goal

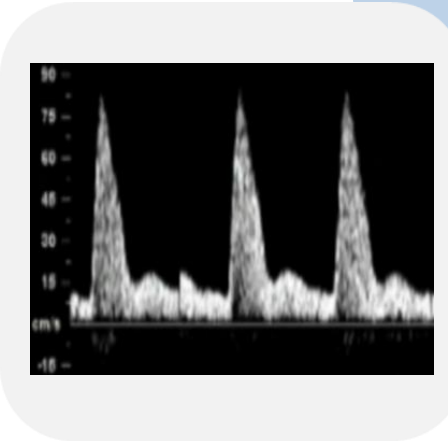
- Prepare the parents for childbirth
- Optimal follow up of the pregnancy
- Support the decision for childbirth
- Transfer parents to a center MIC/NIC
- Consider in utero treatment

LaboCita
ANALYSES MÉDICALES

Principle of risk estimation

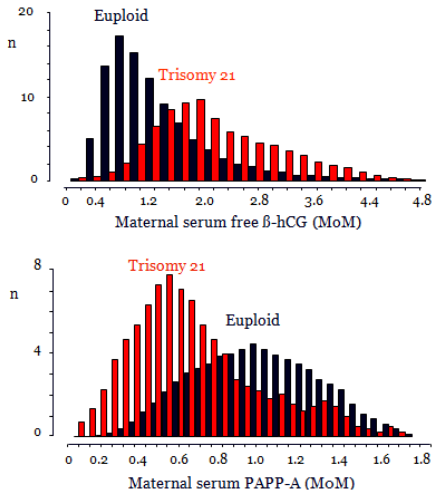
- Caracteristics and maternal « risk factors»
- Biomarkers
- Mean arterial pressure (MAP)
- Uterine artery Doppler

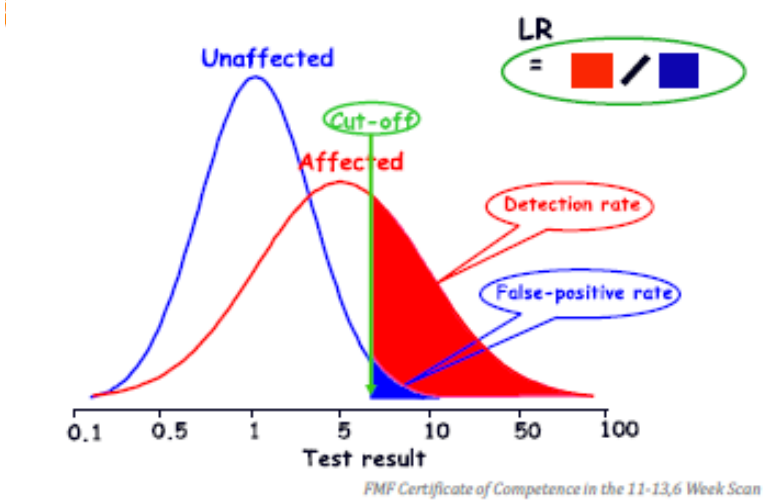


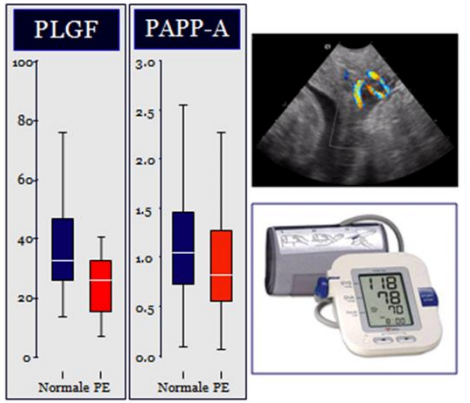


Principle of risk estimation

- Prenatal screening for aneuploidy is routine bioclinical practice performed worldwide.
- The same statistical methodology, developed and perfected over more than three decades, has been adapted for screening for pre-eclampsia.
  - Each parameter is first converted into a pregnancy-specific MoM (multiple of the median) for the same gestational age, smoking status, maternal weight, ethnicity and method of conception.

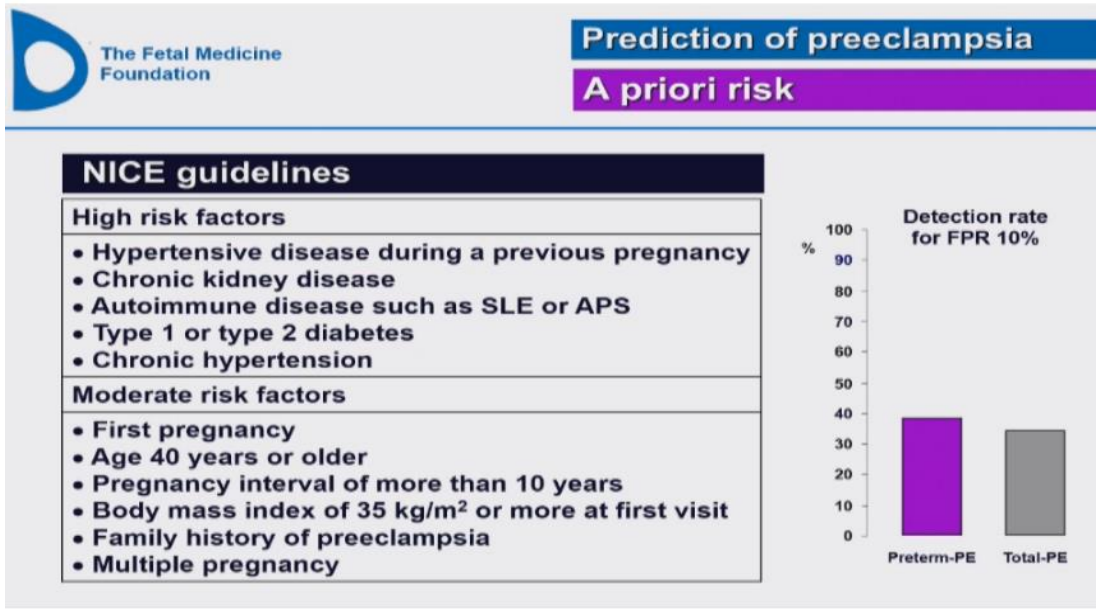


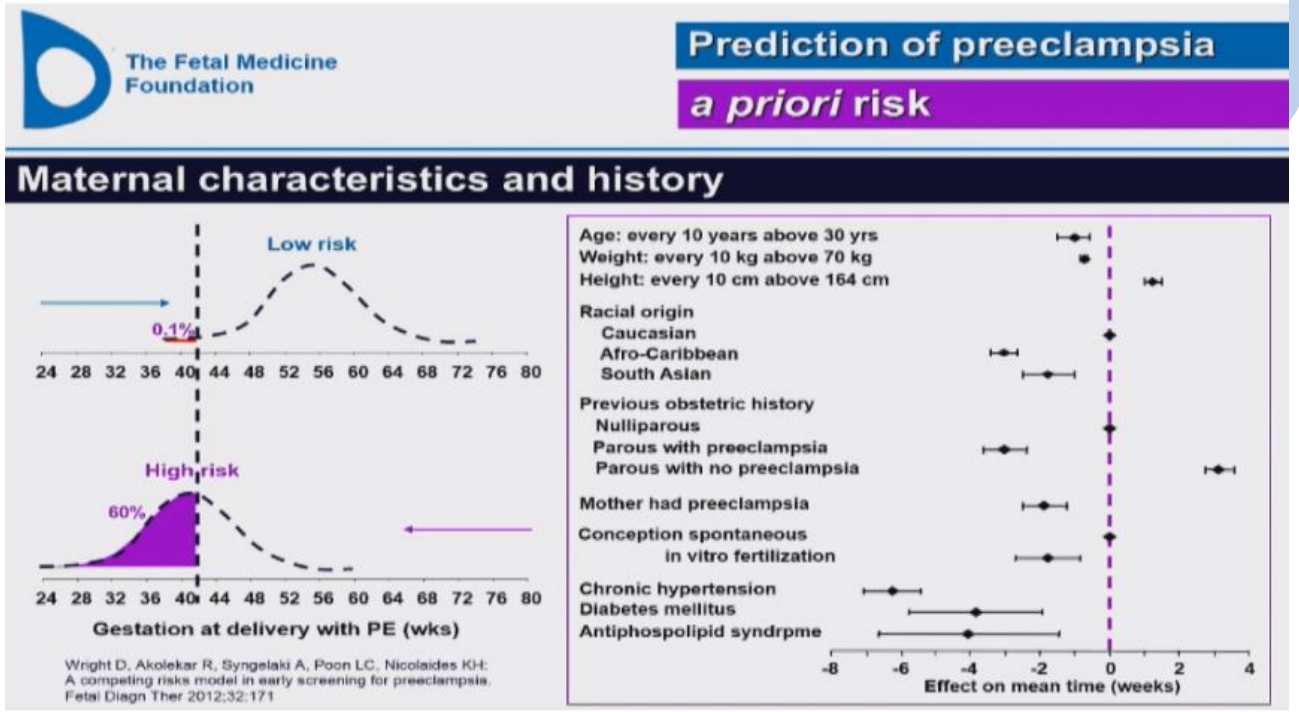




LaboCita
ANALYSES MÉDICALES

Caracteristics and maternal « risk factors»





LaboCita
ANALYSES MÉDICALES

Biomarkers

Activine A

ADAM

IGF1

PIGF

CRF

AFP

CRFBP

fibronectine

homocystéine

Inhibine A

hCG libre

Leptine

Pentraxine-3

IGFBP-1

PP13

α1microglobuline

PAPP-A

sEng

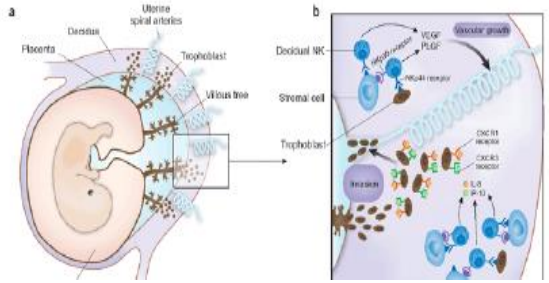
VEGF

hCG hyperglycosylées

sFlt-1

sVEGFR-1

P-sélectine



LaboCita
ANALYSES MÉDICALES

Biomarkers

- **PIGF**: Placental Growth Factor
- **sFlt-1**: Soluble fms-like tyrosine kinase 1
- **PAPP-A**: Pregnancy Associated Plasma Protein A

LaboCita
ANALYSES MÉDICALES

PAPP-A

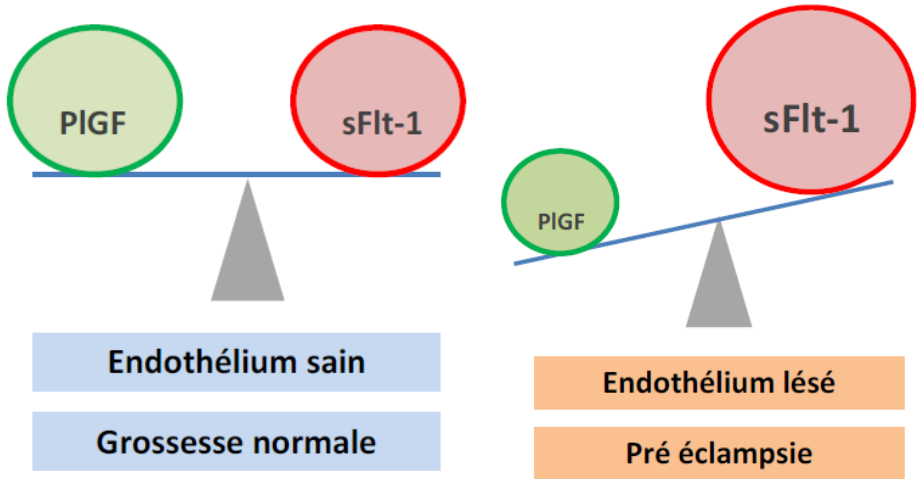
- Pregnancy Associated Plasma Protein-A
  - Macromolecular glycoprotein
  - Produced by the trophoblast
- Regularly ↑ during pregnancy

The concentration is significantly lower for pregnancies at risk of preeclampsia

LaboCita
ANALYSES MÉDICALES

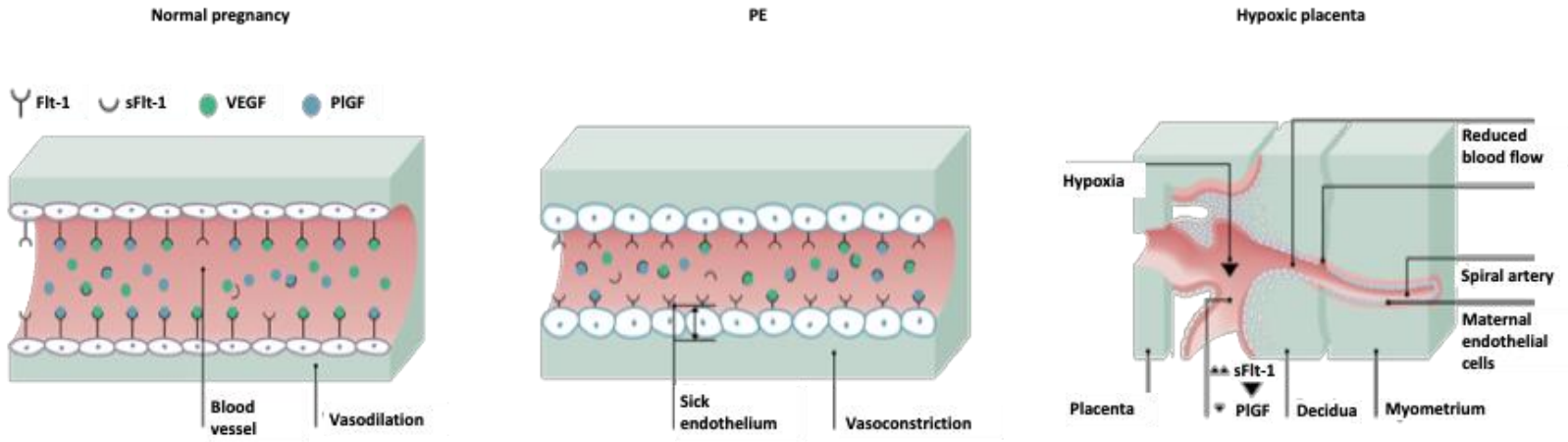
PlGF and sFlt1

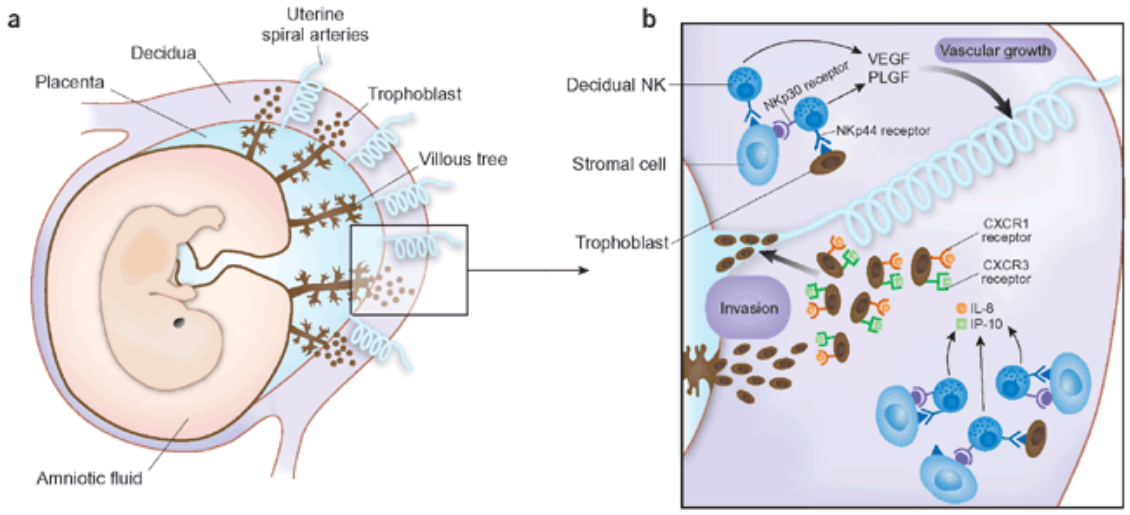
- **PlGF:** Placental Growth Factor
  - Factor pro-angiogenic
  - Participates in the normal functioning of the endothelial cell
- **sFlt-1:** Soluble fms-like tyrosine kinase 1
  - Factor anti-angiogenic

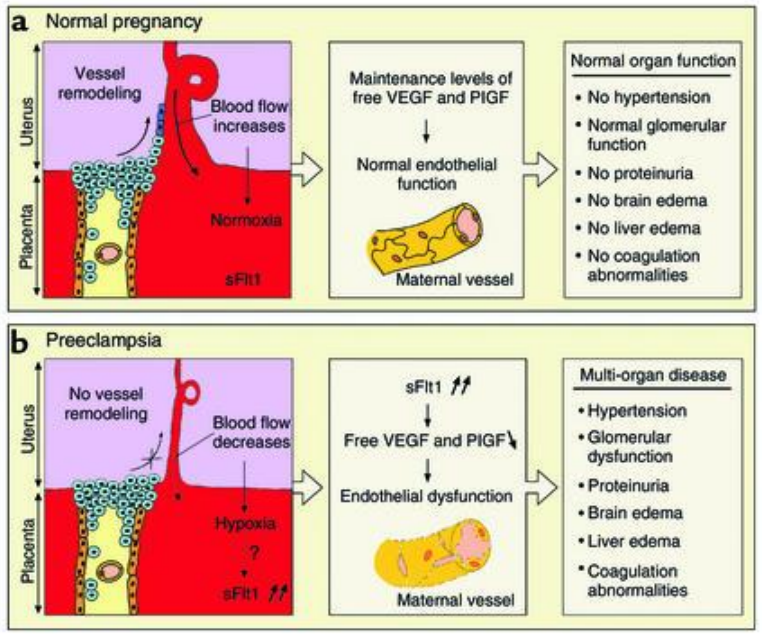


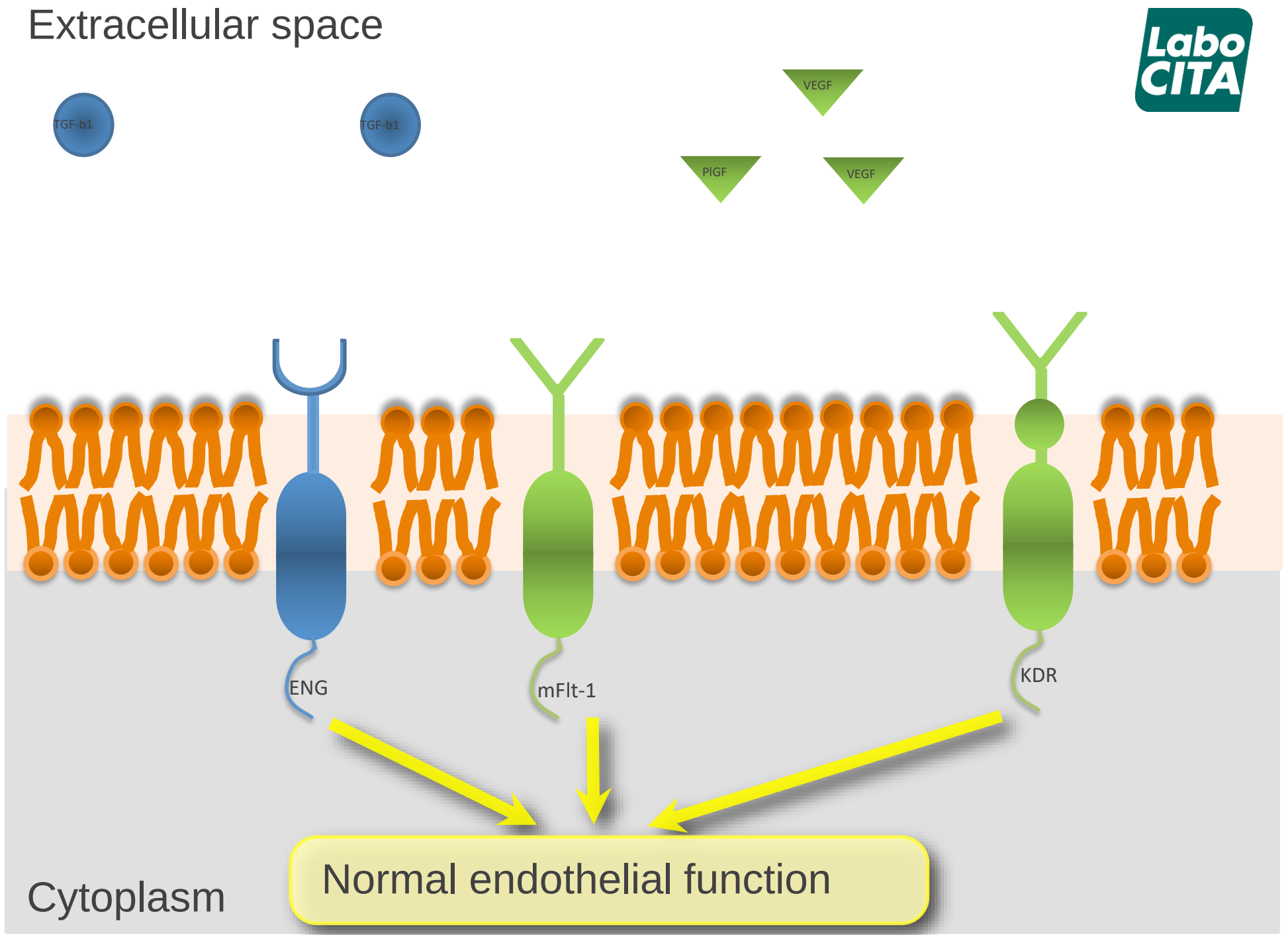
LaboCita
ANALYSES MÉDICALES

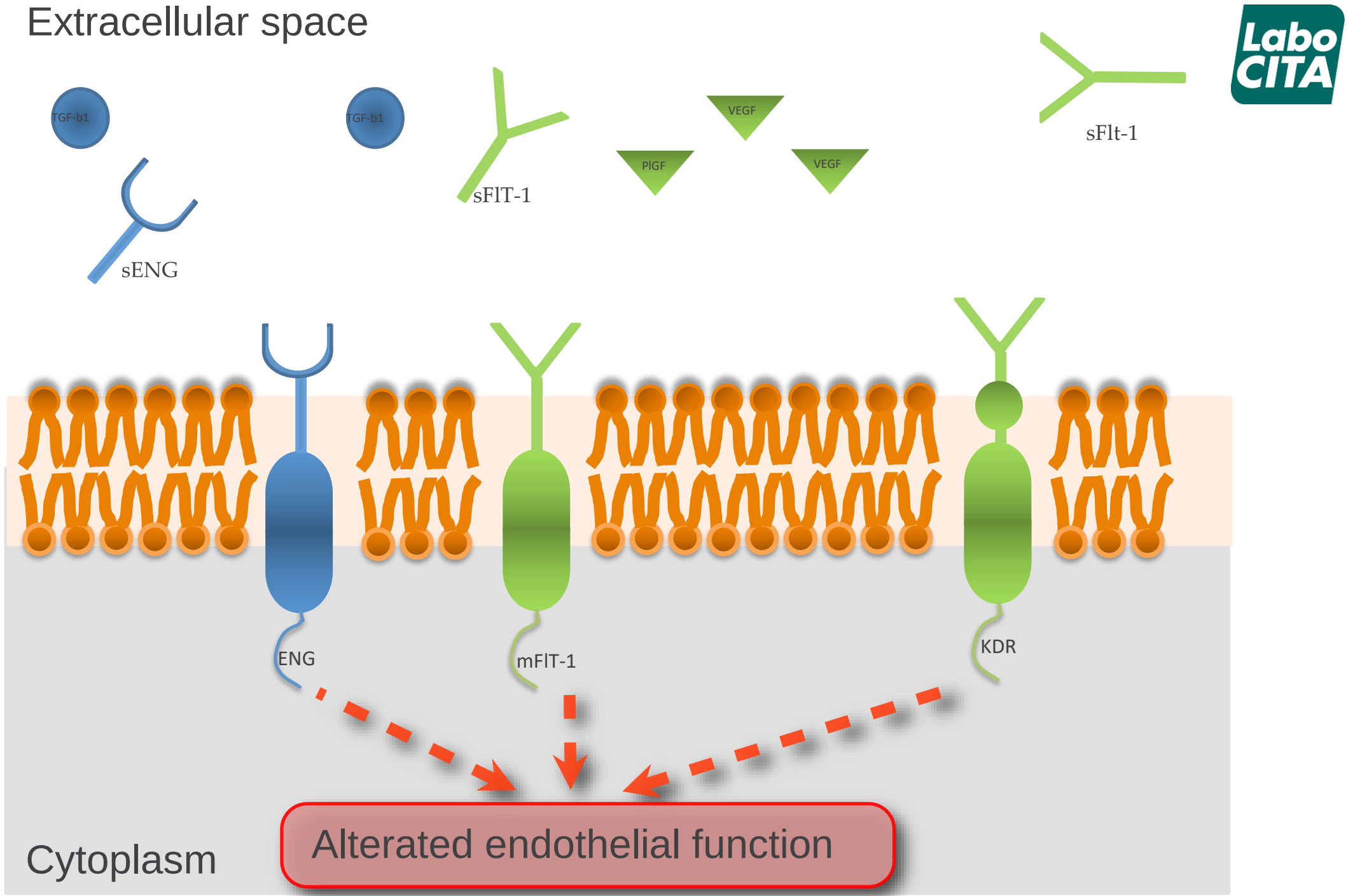
PlGF and sFlt1





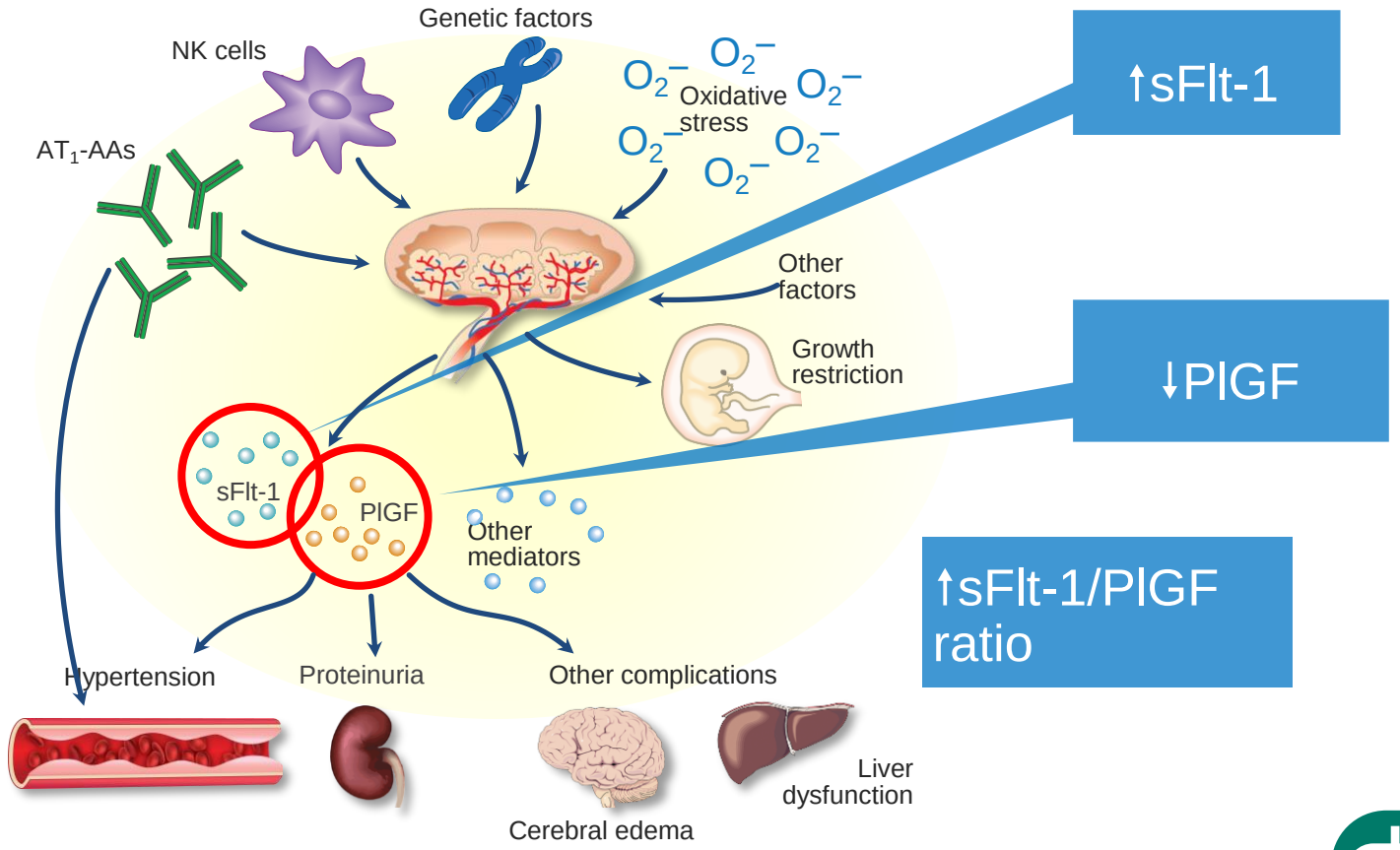



Extracellular space
TGF-b1
TGF-b1
VEGF
PIGF
VEGF
ENG
mFlt-1
KDR
Cytoplasm
Normal endothelial function


Extracellular space
TGF-b1
TGF-b1
sFlT-1
VEGF
PlGF
VEGF
sFlt-1
sENG
ENG
mFlT-1
KDR
Cytoplasm
Alterated endothelial function

Early marker and Multi-organ

- **The sFlt-1/PlGF ratio is elevated 4–5 weeks before clinical signs of preeclampsia**



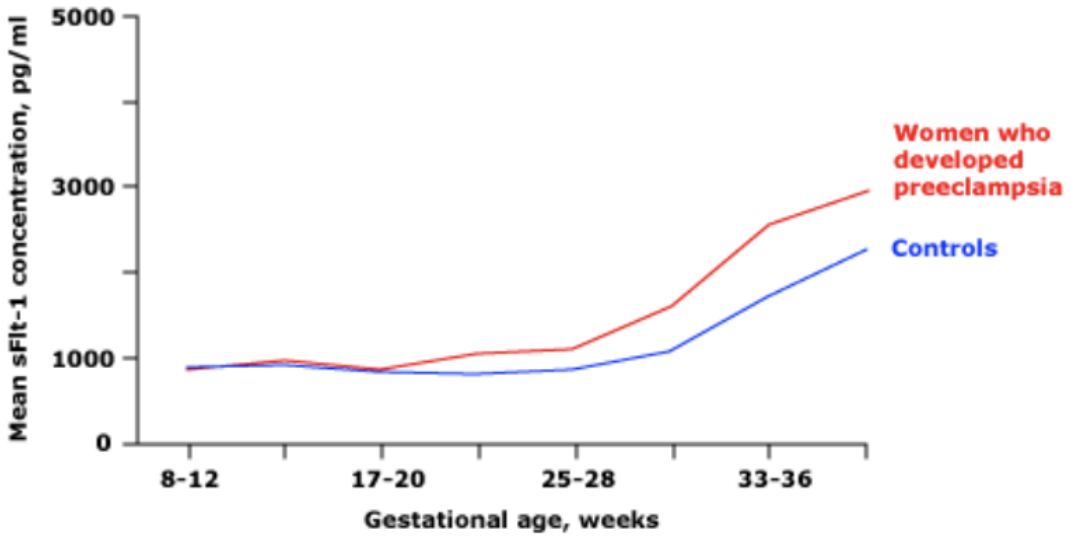
AT1-AAs = agonistic AT(1) receptor autoantibodies; NK = natural killer
PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1
VEGF = vascular endothelial growth factor

LaboCita ANALYSES MÉDICALES

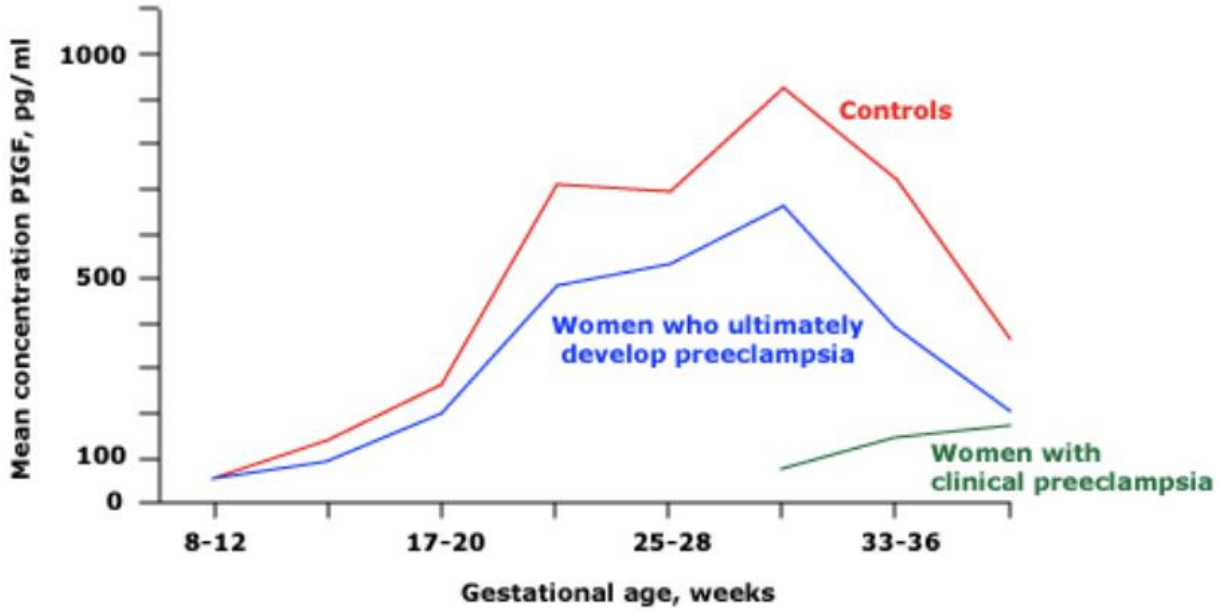
Concentrations of sFlt-1 and PlGF

Imbalances are detectable prior to the onset of PE

Concentration of sFlt-1 in women who developed preeclampsia and normal controls



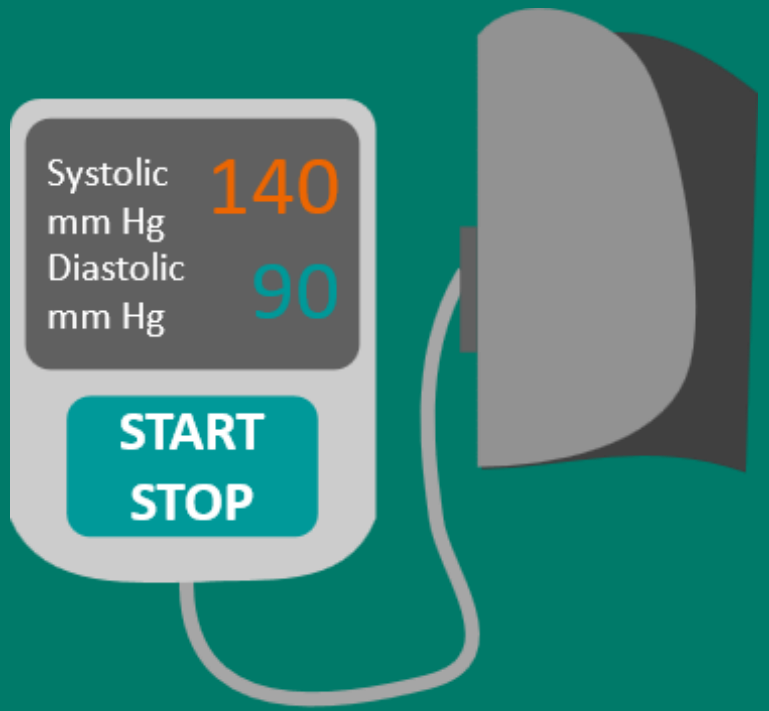
Concentration of PIGF in various groups

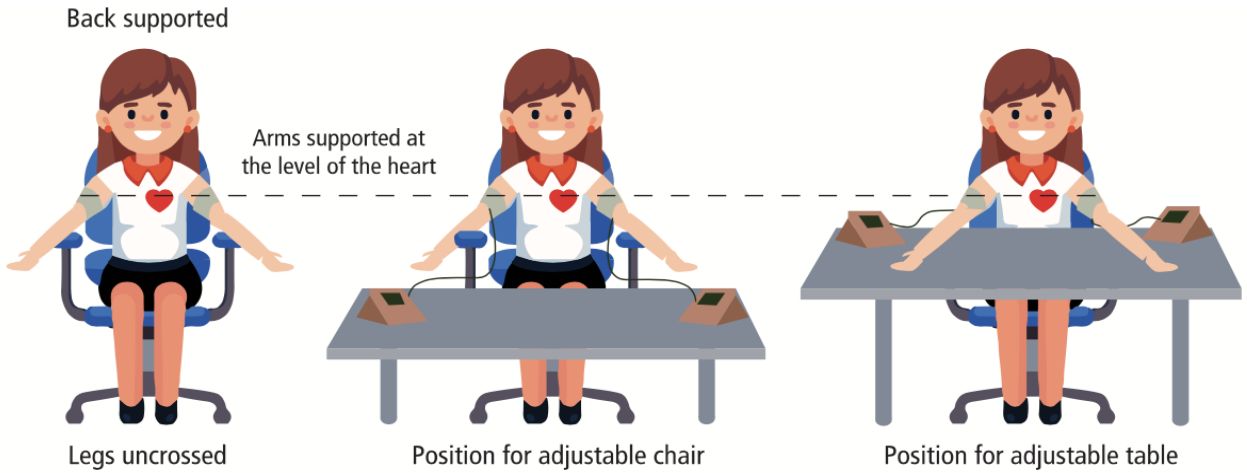


Karumanchi et al, *UpToDate, 2022*

LaboCita
ANALYSES MÉDICALES

Mean arterial pressure (MAP)





Correct positioning of a woman for blood pressure measurement. Courtesy of PerkinElmer Life and Analytical Sciences.

Poon et al, Int J Gynecol Obstet, 2019

LaboCita
ANALYSES MÉDICALES

Uterine artery Doppler

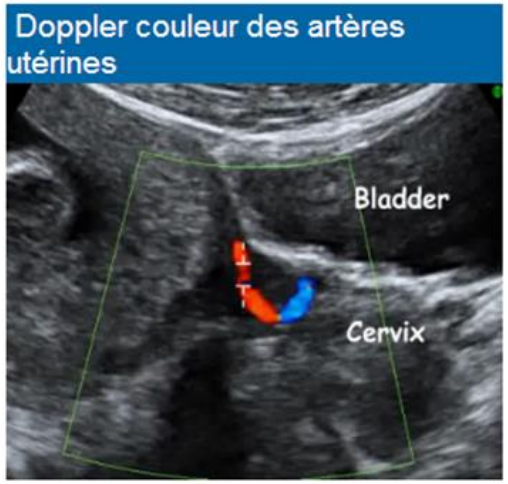
Dépistage de la pré-éclampsie

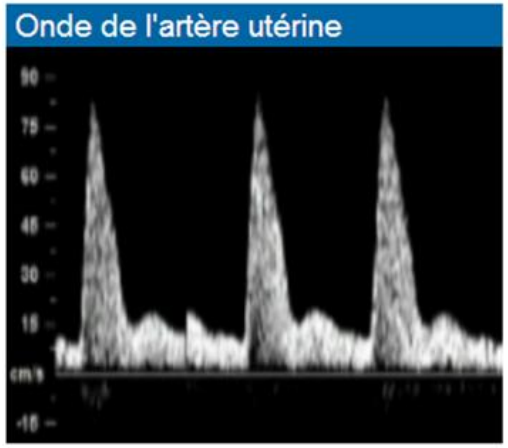
Doppler des artères utérines

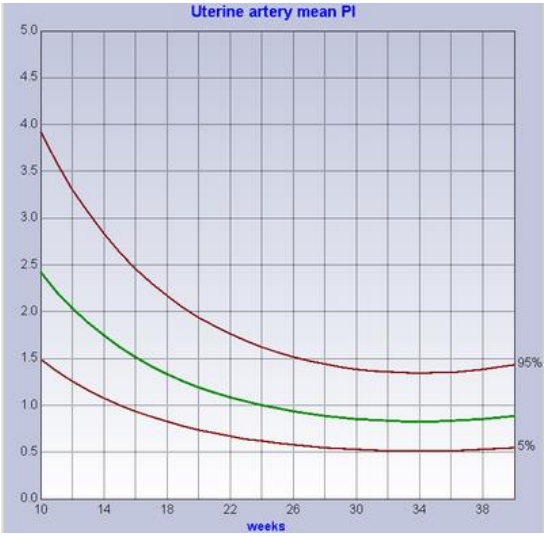
Lors de l'évaluation de l'index de pulsatilité (IP) des artères utérines, l'âge gestationnel doit être de 11^{+0}-13^{+6} semaines et la LCC de 45-84 mm

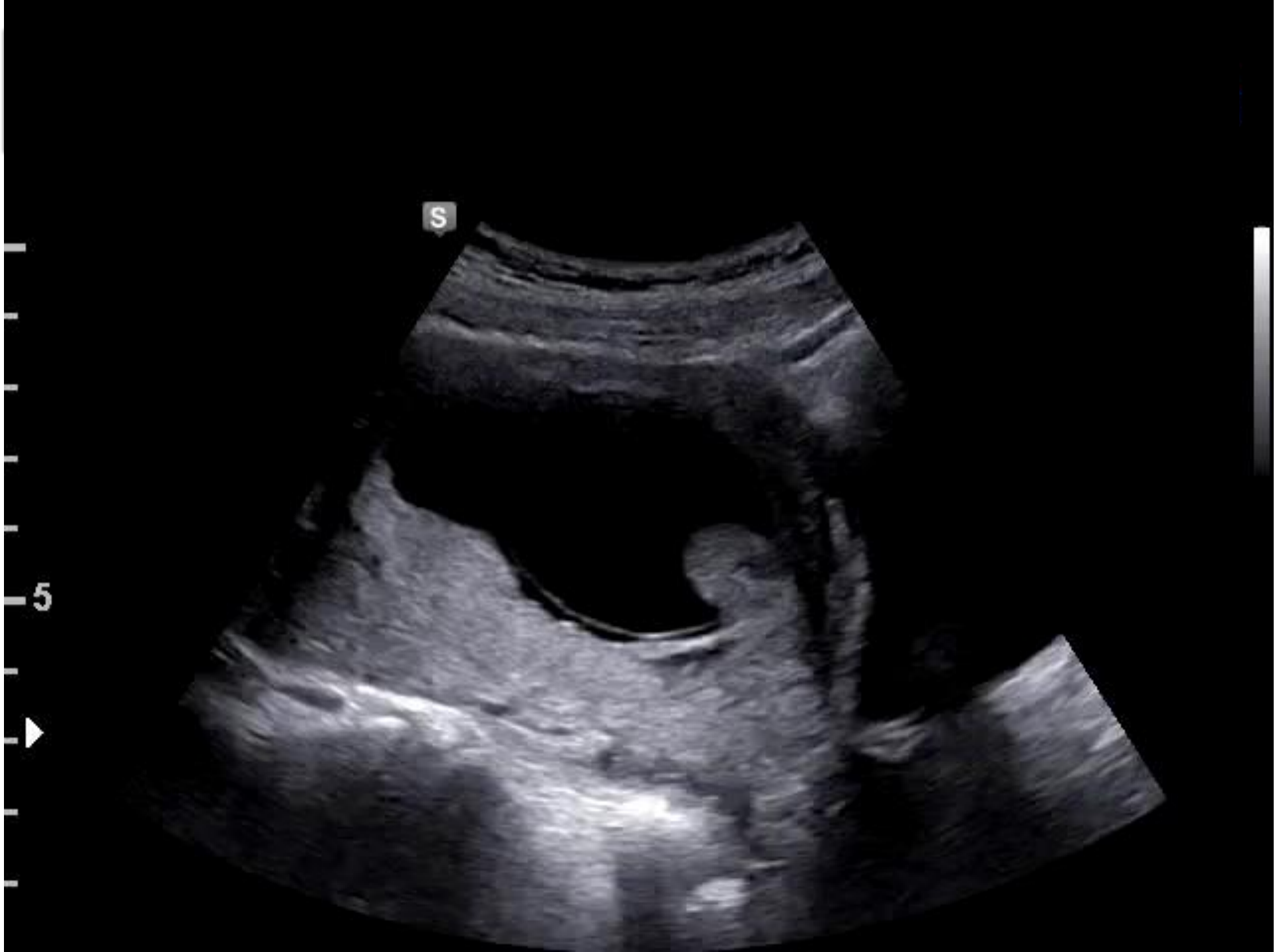
PRACTICAL POINTS

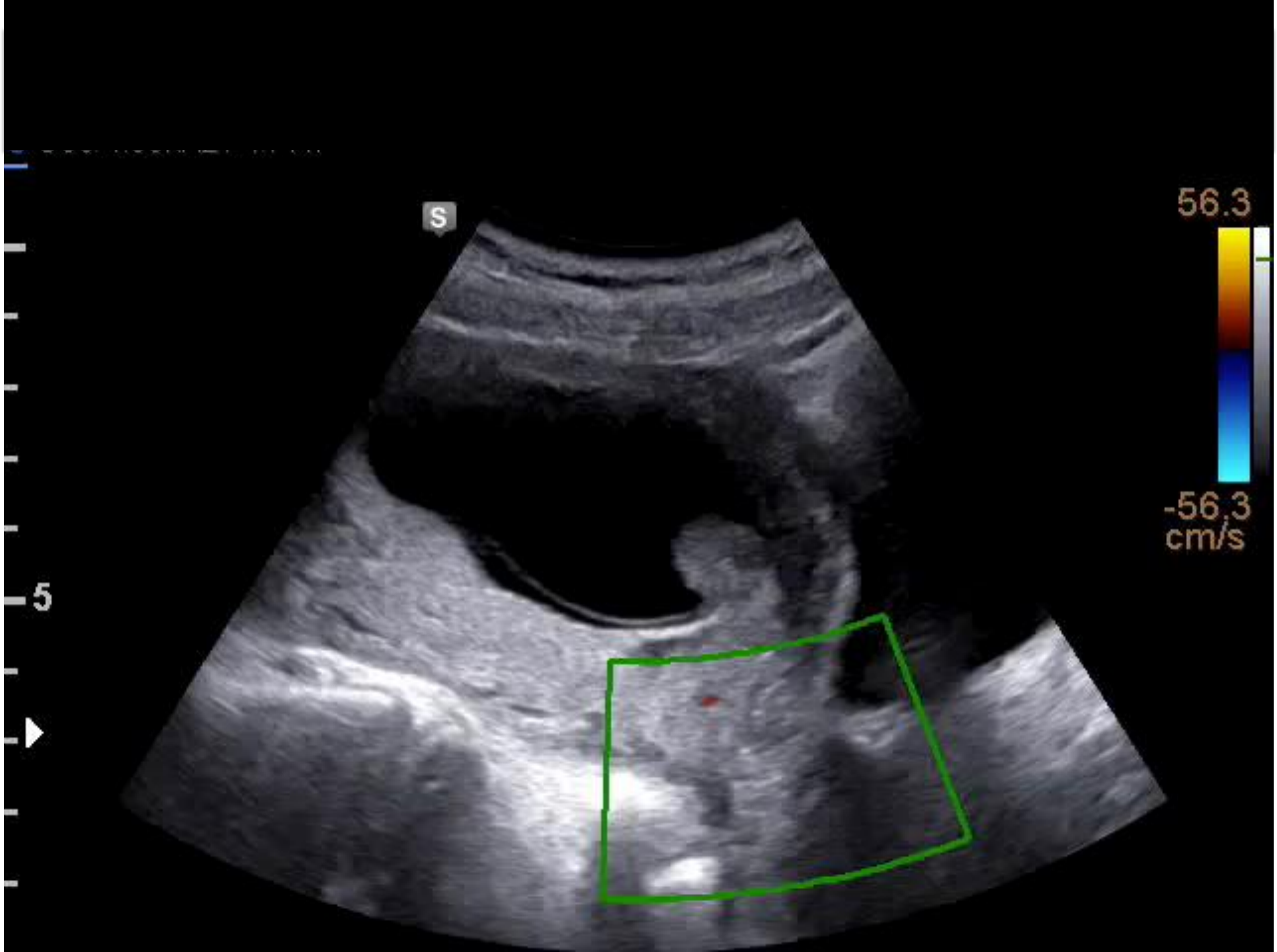
1. Obtain a sagittal section of the uterus and cervical canal. Zoom to the area of interest.
2. Identify the internal cervical os. Gently tilt the transducer from side to side using color flow mapping to identify the uterine arteries. When you apply color Doppler, narrow the color box and adjust the velocity scale and the filter.
3. Apply pulsed wave Doppler with the sampling gate set at 2 mm to cover the whole vessel. Ensure that the angle of insonation is < 30°.
4. Record at least three consecutive uniform waveforms.

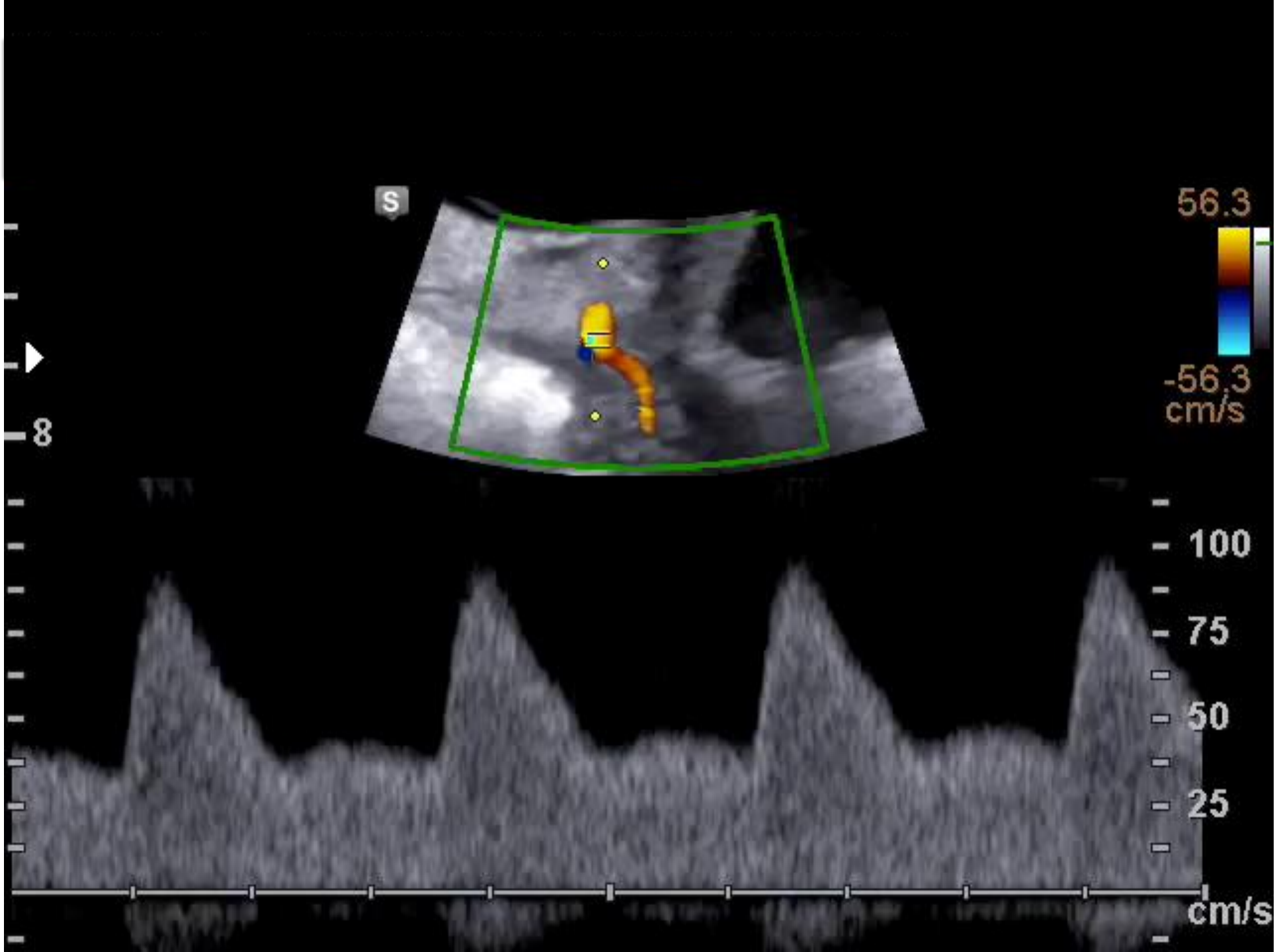






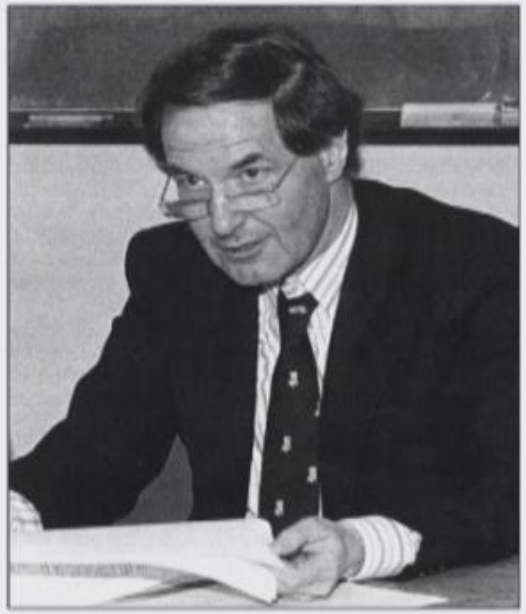

S
5


S
56.3
-56.3
cm/s
5


S
56.3
-56.3
cm/s
8
100
75
50
25
cm/s

Uterine artery Doppler

The Fetal Medicine Foundation



New Doppler technique for assessing uteroplacental blood flow

Stuart Campbell et al THE LANCET 1983;1:675-7.

Pulsed, Doppler ultrasound was used to study blood flow velocity profiles in the uterine vessels during the second and third trimesters of pregnancy.

In 30 normal pregnancies there was high diastolic velocity and low pulsatility.

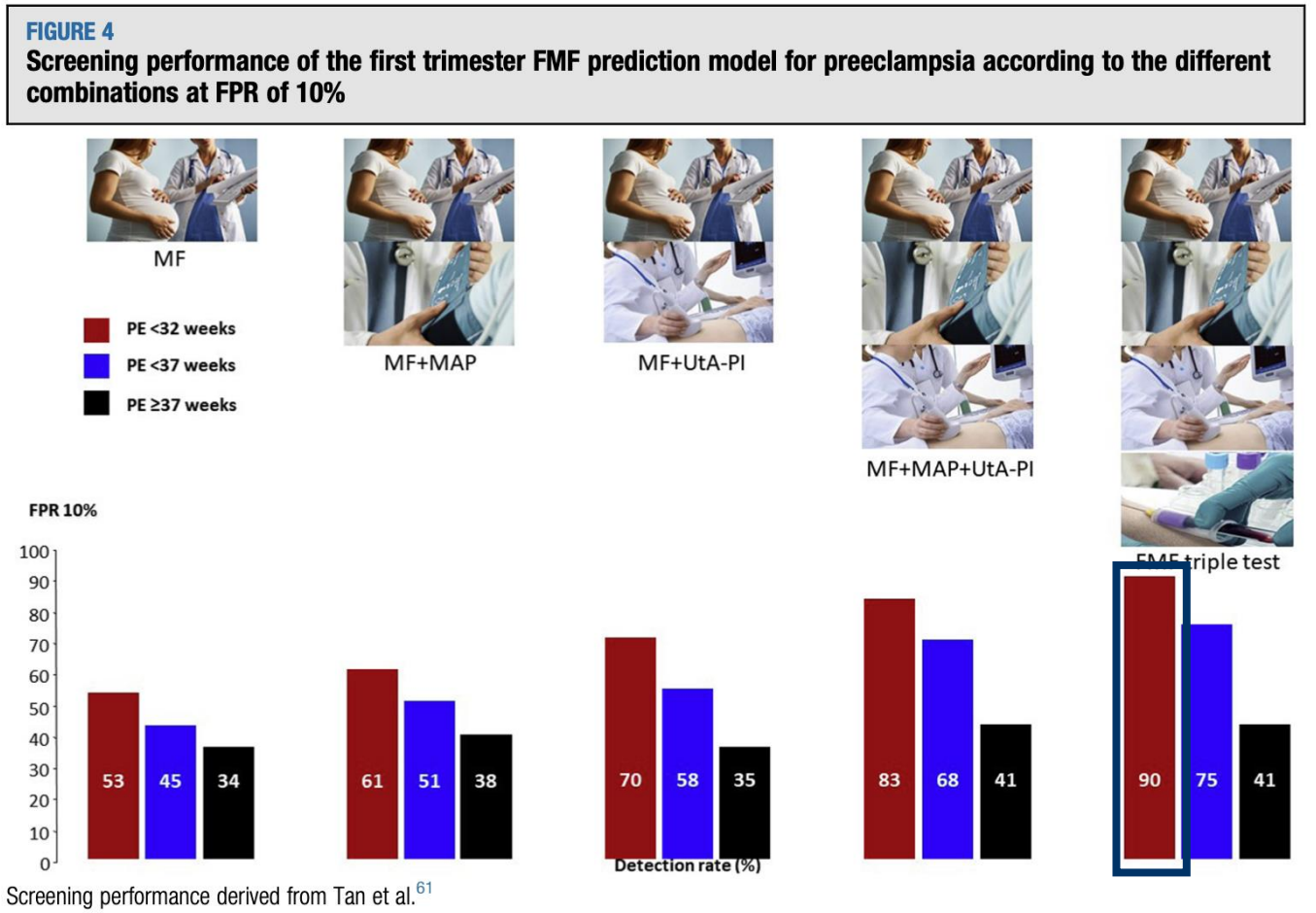
In 31 pregnancies complicated with proteinuric hypertension, poor fetal growth, and fetal hypoxia the waveforms were suggestive of raised vascular resistance.

This non-invasive technique may give early warning of impaired uteroplacental perfusion and can be used to evaluate methods of improving uterine blood flow.

LaboCita
ANALYSES MÉDICALES

Principle of risk estimation

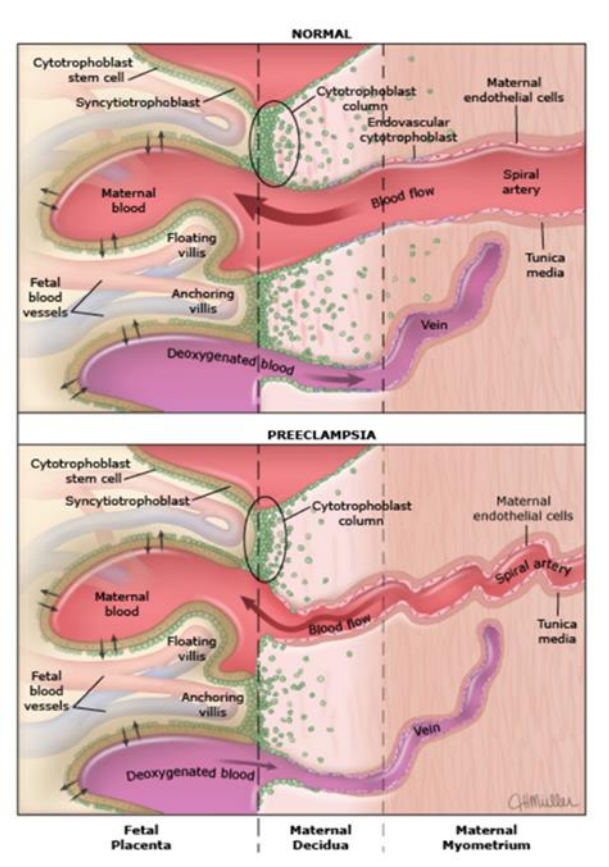
- Caracteristics and maternal « risk factors»
- Biomarkers
- Mean arterial pressure (MAP)
- Uterine artery Doppler



Screening performance derived from Tan et al.[61]

Chaemsaithong et al, AJOG, 2022

Table of Content



LaboCita
ANALYSES MÉDICALES

Prognosis

Correlation of sFlt-1/PlGF Ratio with Time to Delivery or Preterm Birth in PROGNOSIS (Prediction of Short-term Outcome in Pregnant Women with Suspected Preeclampsia Study)

H Zeisler,[1] E Llurba,[2] F Chantraine,[3] M Vatish,[4] AC Staff,[5] M Sennström,[6] M Olovsson,[7] SP Brennecke,[8] H Stepan,[9] D Allegranza,[10] C Dinkel,[11] M Schoedl,[11] M Hund,[10] and S Verlohren[12]

1Vienna, Austria; 2Barcelona, Spain; 3Liege, Belgium; 4Oxford, UK;

5Oslo, Norway; 6Stockholm, Sweden; 7Uppsala, Sweden; 8Melbourne, Australia; 9Leipzig, Germany;

10Rotkreuz, Switzerland;

11Penzberg, Germany; 12Berlin, Germany

LaboCita
ANALYSES MÉDICALES

Prognosis

The ‘gold standard’ for the diagnosis of preeclampsia

is based on proteinuria and blood pressure screening

but, pregnancies at risk for complications of preeclampsia are not correctly identified

Poor discrimination of high-risk pregnancies may cause unnecessary hospitalizations of patients who will not develop preeclampsia

Patients who develop preeclampsia may be underdiagnosed by screening of the blood pressure and proteinuria

A valid method to predict the development of preeclampsia is needed

LaboCita
ANALYSES MÉDICALES

Objectives of the study

1

- To demonstrate that low ratios of sFlt-1/PlGF predict absence of preeclampsia/eclampsia/HELLP syndrome within 1 week of baseline visit *(rule out)*
- To demonstrate that high ratios of sFlt-1/PlGF predict diagnosis of preeclampsia/eclampsia/HELLP syndrome within 4 weeks of baseline visit *(rule in)*

2

- Correlation of the sFlt-1/PlGF ratio with time to delivery and preterm birth were secondary exploratory objectives

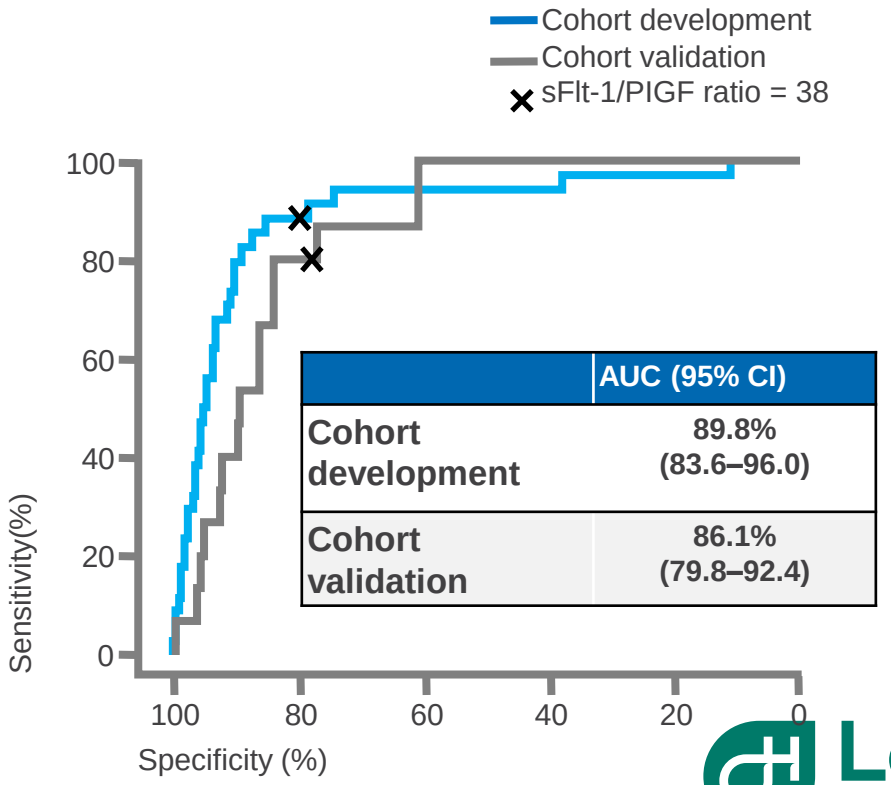
HELLP = hemolysis, elevated liver enzymes, low platelets
PIGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1

LaboCita
ANALYSES MÉDICALES

“Ruling out” preeclampsia

When using the sFlt-1/PlGF cut-off ratio of ≤38, preeclampsia can be ruled out within a week with a negative predictive value of 99.3% (NPV)

Rule out of preeclampsia within a week (95% CI)		
	Cohort development	Cohort validation
NPV	98.9% (97.3–99.7)	99.3% (97.9–99.9)
Sensitivity	88.2% (72.5–96.7)	80.0% (51.9–95.7)
Specificity	80.0% (76.1–83.6)	78.3% (74.6–81.7)



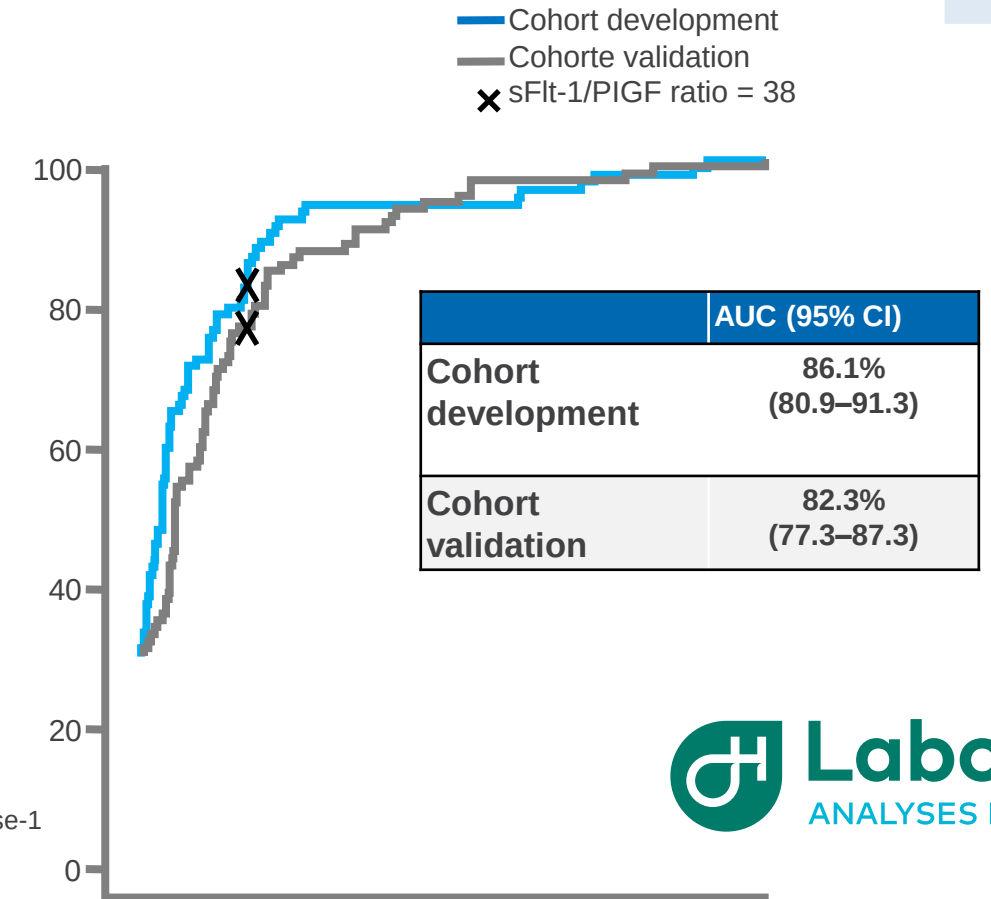
AUC = area under the curve; CI = confidence interval
PIGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1

LaboCita ANALYSES MÉDICALES

“Ruling in” preeclampsia

When using the sFlt-1/PlGF cut-off ratio of >38, preeclampsia can be found within 4 weeks with a positive predictive value of 36.7% (PPV)

Rule in preeclampsia within 4 weeks (95% CI)		
	Cohort development	Cohort validation
PPV	40.7% (31.9–49.9)	36.7% (28.4–45.7)
Sensitivity	74.6% (62.5–84.5)	66.2% (54.0–77.0)
Specificity	83.1% (79.3–86.5)	83.1% (79.4–86.3)



	AUC (95% CI)
Cohort development	86.1% (80.9–91.3)
Cohort validation	82.3% (77.3–87.3)

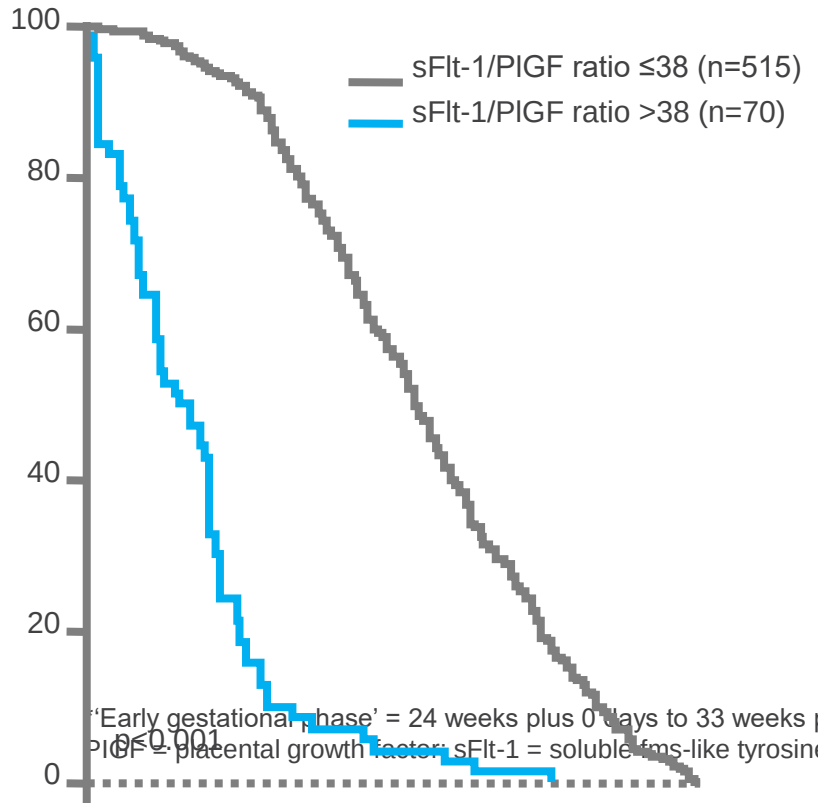
AUC = area under the curve; CI = confidence interval
PIGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1

LaboCita ANALYSES MÉDICALES

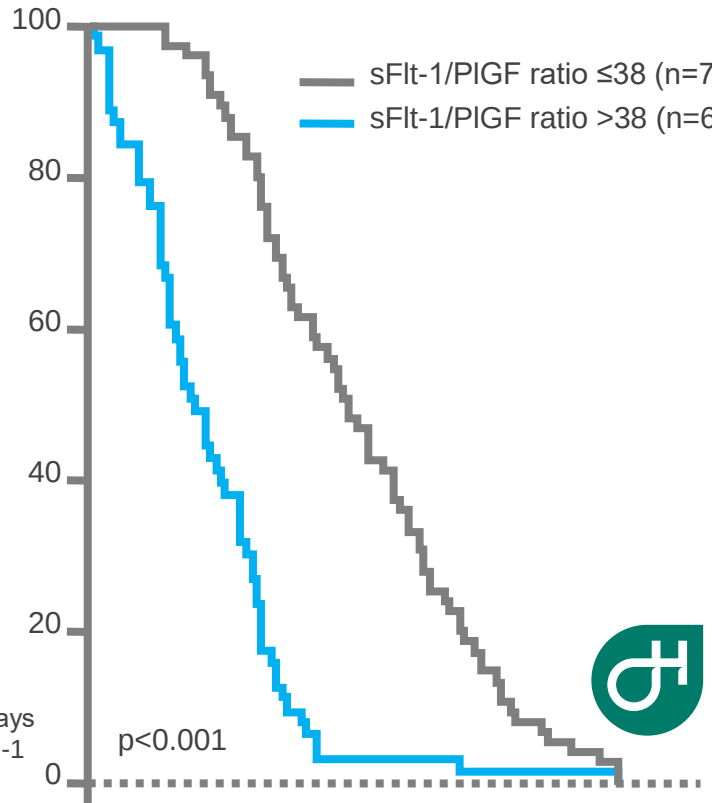
Time until delivery (<34 AS*)

All sFlt-1/PlGF ratio >38 were associated with shorter time to delivery

Women *without* preeclampsia



Women *with* preeclampsia



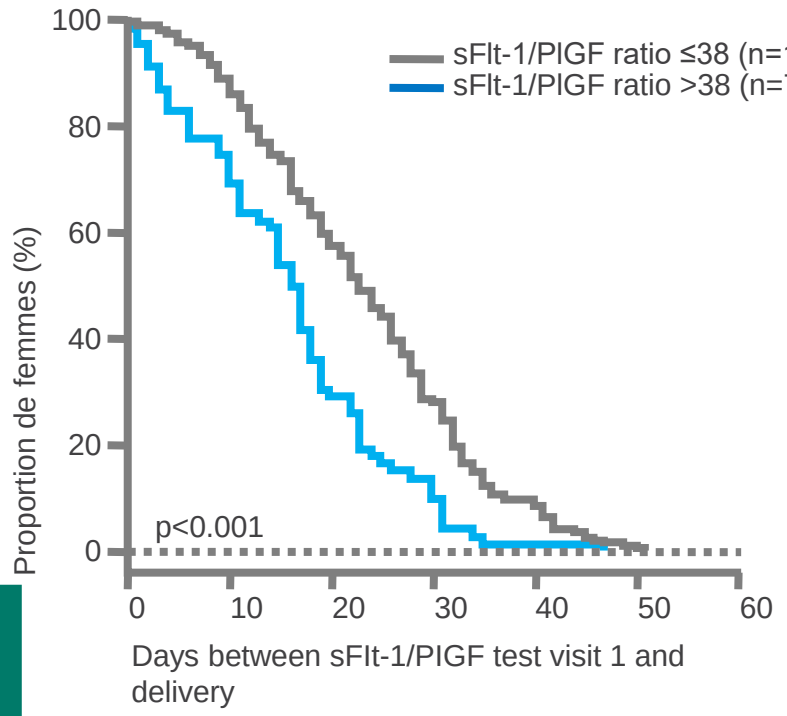
'Early gestational phase' = 24 weeks plus 0 days to 33 weeks plus 6 days
PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1

LaboCita
ANALYSES MÉDICALES

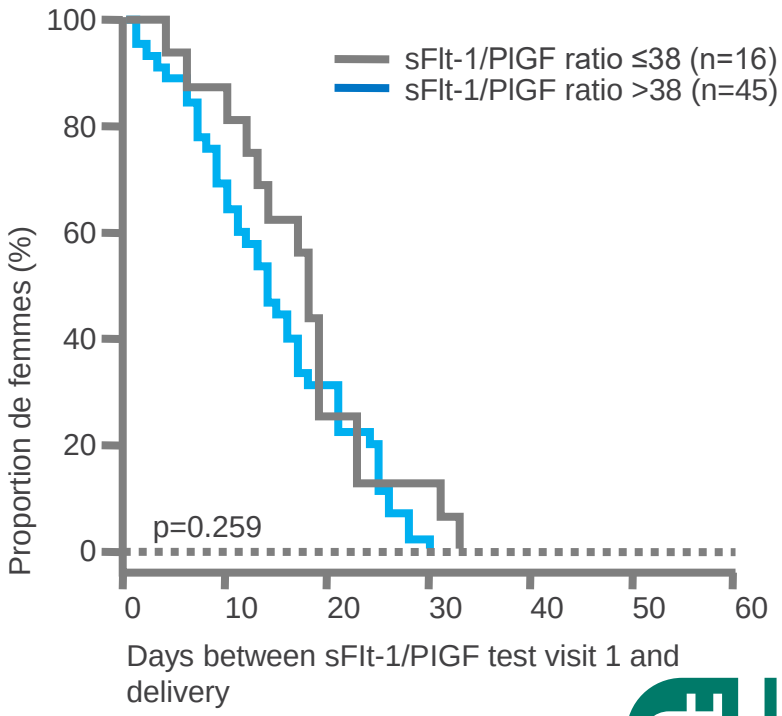
Time until delivery (≥34 AS*)

All sFlt-1/PlGF ratio >38 were associated with shorter time to delivery

Women without preeclampsia



Women with preeclampsia



*'Late gestational phase' = 34 weeks plus 0 days onwards
PIGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1

LaboCita
ANALYSES MÉDICALES

Conclusions Prognosis

- The sFlt-1/PlGF cut-off ratio of 38 is useful for the short-term prediction of the absence or presence of preeclampsia in women at risk
  - NPV (rule out) 99.3%
  - PPV (rule in) 36.7%
- The maternal sFlt-1/PlGF ratio provides information on the risk of preterm birth
  - An sFlt-1/PlGF ratio >38 was associated with a shorter time to delivery, especially before 34 weeks
- Women with an sFlt-1/PlGF ratio (>38) should be monitored more carefully, regardless of whether they develop preeclampsia

PIGF = placental growth factor; NPV = negative predictive value
PPV = positive predictive value; sFlt-1 = soluble fms-like tyrosine kinase-1

LaboCita
ANALYSES MÉDICALES

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 7, 2016 VOL. 374 NO. 1

Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia

Harald Zeisler, M.D., Elisa Llurba, M.D., Ph.D., Frederic Chantraine, M.D., Ph.D., Manu Vatish, M.B., Ch.B., D.Phil., Anne Cathrine Staff, M.D., Ph.D., Maria Sennström, M.D., Ph.D., Matts Olovsson, M.D., Ph.D., Shaun P. Brennecke, M.B., B.S., D.Phil., Holger Stepan, M.D., Deirdre Allegranza, B.A., Peter Dilba, M.Sc., Maria Schoedl, Ph.D., Martin Hund, Ph.D., and Stefan Verlohren, M.D., Ph.D.

ULTRASOUND in Obstetrics & Gynecology

isuog

Original Paper | Open Access

The sFlt-1/PlGF Ratio: ruling out pre-eclampsia for up to 4 weeks and the value of retesting

H. Zeisler, E. Llurba, F. J. Chantraine, M. Vatish, A. C. Staff, M. Sennström, M. Olovsson, S. P. Brennecke, H. Stepan, D. Allegranza, M. Schoedl, S. Grill, M. Hund, S. Verlohren

First published: 16 July 2018 | https://doi.org/10.1002/uog.19178

Hypertension: *Original Research* VOL. 128, NO. 2, AUGUST 2016

Soluble fms-Like Tyrosine Kinase-1-to-Placental Growth Factor Ratio and Time to Delivery in Women With Suspected Preeclampsia

Harald Zeisler, MD, Elisa Llurba, MD, PhD, Frédéric Chantraine, MD, PhD, Manu Vatish, MD, DPhil, MRCOG, Anne Cathrine Staff, MD, PhD, Maria Sennström, MD, PhD, Matts Olovsson, MD, PhD, Shaun P. Brennecke, MBBS, DPhil (Oxon), Holger Stepan, MD, Deirdre Allegranza, BA (Hons), Carina Dinkel, MSc, Maria Schoedl, PhD, Peter Dilba, MSc, Martin Hund, PhD, and Stefan Verlohren, MD, PhD

Recommendations for the use of sFlt-1/PlGF ratio in women with signs and symptoms of PE

sFlt-1/PlGF results (EP/LP)	Interpretation	Time to delivery	What should be done?
Low: <38	Rule out PE: 1 week: NPV 99% 4 weeks: NPV 95%	Unmodified	Reassuring the patient No further determination are needed unless new suspicion arises
Intermediate: 38-85/38-110	Rule in PE: 4 weeks: PPV 40%	20% remain pregnant after 1 month	Follow-up visit and retest in 1-2 weeks Maternal education about signs and symptoms of PE
High: >85/>110	Diagnosis of PE (or PD-related disorder) is highly likely	15% remain pregnant after 2 weeks	Follow-up visit and retest in 2-4 days EP: consider referral to high-level center LP: consider lowering the threshold for labor induction
Very high: >655/>201	Short-term complications and need to deliver are highly likely	30% remain pregnant after 2 days	Close surveillance EP: corticoids to the mother for fetal maturation

LaboCita ANALYSES MÉDICALES

I Herraiz, E Llubra, S Verlohren, A Galindo, *Fetal Diagn Ther, 2018*

Implementation of the sFlt-1/PlGF ratio can save money

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 26 (2021) 31–37

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

Enhancing the value of the sFlt-1/PlGF ratio for the prediction of preeclampsia: Cost analysis from the Belgian healthcare payers' perspective

Frederic Chantraine [a], Kristel Van Calsteren [b], Roland Devlieger [b], Damien Gruson [c], Joachim Van Keirsbilck [d], Ana Dubon Garcia [e], Katleen Vandeweyer [e], Leonardo Gucciardo [f,*]

› J Matern Fetal Neonatal Med. 2017 Sep;30(18):2166-2173. doi: 10.1080/14767058.2016.1242122. Epub 2017 Feb 2.

Budget impact analysis of sFlt-1/PlGF ratio as prediction test in Italian women with suspected preeclampsia

Tiziana Frusca [1], Maria-Teresa Gervasi [2], Davide Paolini [3], Matteo Dionisi [3], Francesca Ferre [4 5], Irene Cetin [6]

› Dis Markers. 2019 Aug 14;2019:4096847. doi: 10.1155/2019/4096847. eCollection 2019.

sFlt-1/PlGF Ratio as a Predictive Marker in Women with Suspected Preeclampsia: An Economic Evaluation from a Swiss Perspective

Markus Hodel [1], Patricia R Blank [2], Petra Marty [2], Olav Lapaire [3]

› BMC Health Serv Res. 2018 Aug 6;18(1):603. doi: 10.1186/s12913-018-3406-1.

Economic assessment of the use of the sFlt-1/PlGF ratio test to predict preeclampsia in Germany

Dietmar Schlembach [1], Martin Hund [2], Annabel Schroer [3], Cyrill Wolf [2]

Multicenter Study › Pregnancy Hypertens. 2018 Jul;13:30-36. doi: 10.1016/j.preghy.2018.04.014. Epub 2018 Apr 17.

Economic evaluation of sFlt-1/PlGF ratio test in pre-eclampsia prediction and diagnosis in two Brazilian hospitals

Sarah Franco Figueira [1], Cyrill Wolf [2], Marisa D'Innocenzo [3], João Paulo Venezian de Carvalho [1], Mariana Granado Barbosa [4], Eduardo Zlotnik [5], Eduardo Cordioli [5]

Acta Obstet. Ginecol. Port. • Volume 13, Pages 82 - 90

sFlt-1/PlGF ratio for the predictive diagnosis of preeclampsia: budget impact analysis from the public healthcare perspective in Portugal

Campos A., Machado A., Martins H., Sao Jose Pais M., Ersek K., Lopes N.

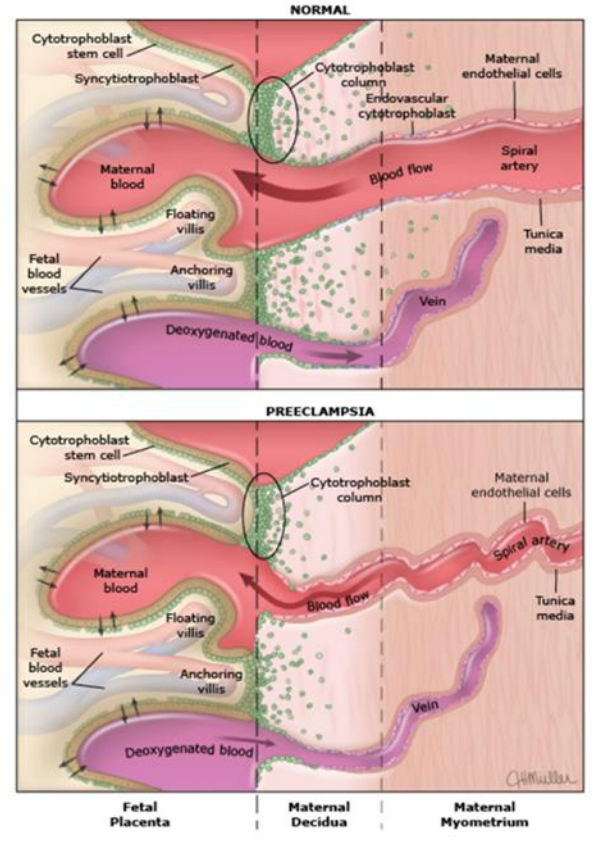
› Ultrasound Obstet Gynecol. 2016 Dec;48(6):765-771. doi: 10.1002/uog.15997. Epub 2016 Nov 8.

sFlt-1/PlGF ratio test for pre-eclampsia: an economic assessment for the UK

M Vatish [1], T Strunz-McKendry [2], M Hund [3], D Allegranza [3], C Wolf [3], C Smare [4]

LaboCita ANALYSES MÉDICALES

Table of Content

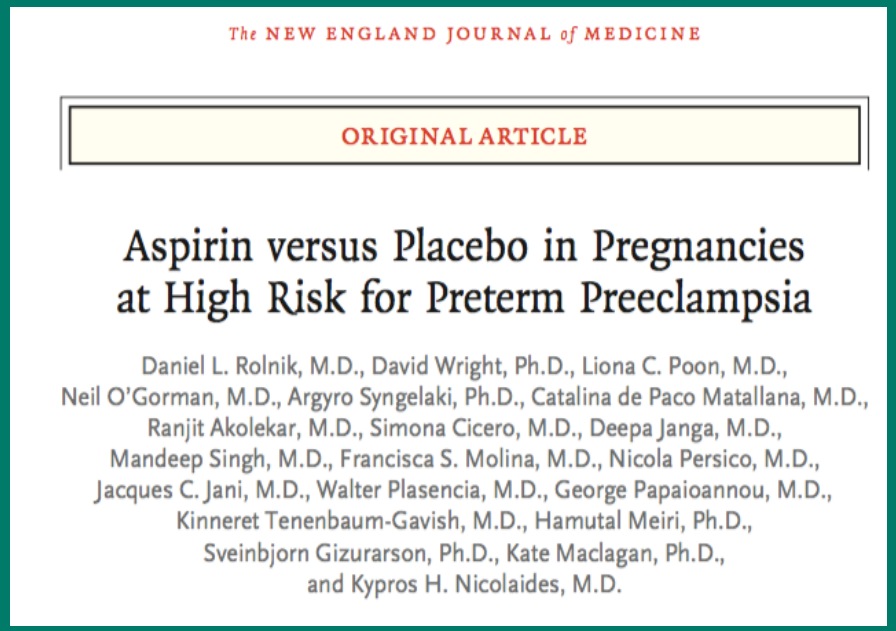


LaboCita
ANALYSES MÉDICALES

Prevention of PE

ASPRE

2017



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia

Daniel L. Rolnik, M.D., David Wright, Ph.D., Liona C. Poon, M.D., Neil O'Gorman, M.D., Argyro Syngelaki, Ph.D., Catalina de Paco Matallana, M.D., Ranjit Akolekar, M.D., Simona Cicero, M.D., Deepa Janga, M.D., Mandeep Singh, M.D., Francisca S. Molina, M.D., Nicola Persico, M.D., Jacques C. Jani, M.D., Walter Plasencia, M.D., George Papaioannou, M.D., Kinneret Tenenbaum-Gavish, M.D., Hamutal Meiri, Ph.D., Sveinbjorn Gizurarson, Ph.D., Kate Maclagan, Ph.D., and Kypros H. Nicolaides, M.D.

- multicenter, double-blind, placebo-controlled trial
- randomly assigned 1776 women with singleton pregnancies
- at high risk for preterm pre- eclampsia
- to receive aspirin (150 mg per day), or placebo
- from 11 to 14 weeks of gestation until 36 weeks
- primary outcome was delivery with preeclampsia before 37 weeks of gestation

LaboCita
ANALYSES MÉDICALES

ASPRE

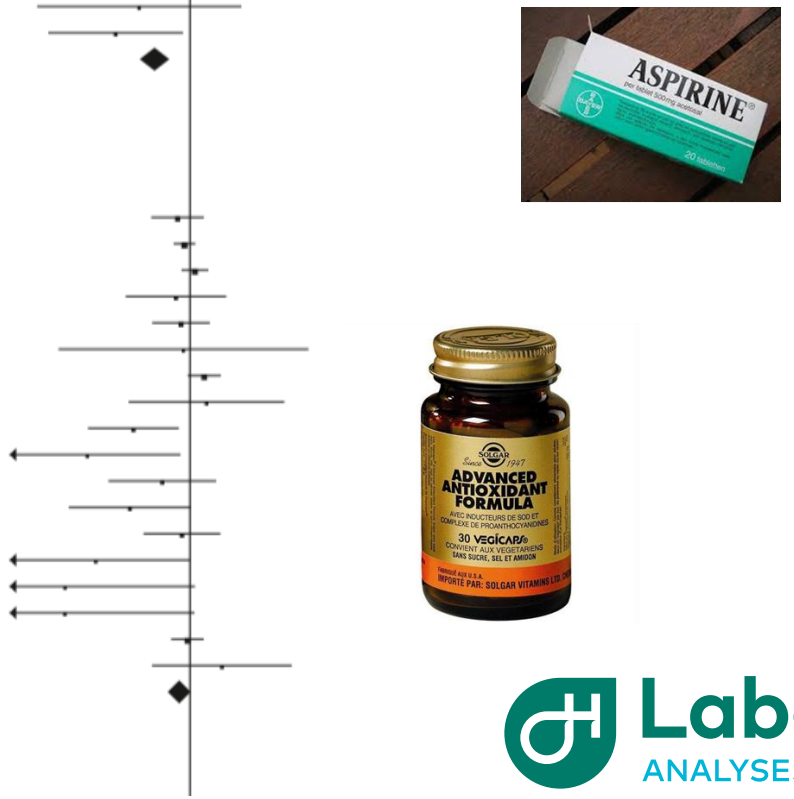
- 798 Aspirin-Group
- 822 Placebo-Group
- Preeclampsia
  - 13/789 (1,6%) Aspirin-Group
  - 35/822 (4,3%) Placebo-Group
- Aspirin use was associated with a 62% reduction in the incidence of preterm PE and an 82% reduction in the incidence of PE at <34 weeks gestation.
- Treatment with low-dose aspirin in women at high risk for preterm preeclampsia resulted in a lower incidence of this diagnosis than placebo.

Project "ASPRE": Combined Multi-Marker Screening and Randomised Patient Treatment with Aspirin for Evidence-Based Pre-eclampsia Prevention. This is a multicentre collaboration on the prediction and prevention of preeclampsia sponsored by the Seventh Framework Programme of the European Union.

LaboCita
ANALYSES MÉDICALES

Preeclampsia

Study or subgroup	Treatment Events	Total	Control Events	Total	Weight (%)	Risk ratio M-H, random (95% CI)
1.1 16 or fewer weeks						
August 1994	3	24	5	25	2.5	0.63 (0.17–2.33)
Azar 1990	1	46	4	45	1.1	0.24 (0.03–2.10)
Beaufils 1985	0	48	6	45	0.6	0.07 (0.00–1.25)
Benigni 1989	0	17	0	16		Not estimable
Ebrashy 2005	25	73	40	63	9.3	0.54 (0.37–0.78
Hermida 1997	3	50	7	50	2.6	0.43 (0.12–1.56)
Michael 1992	1	55	5	55	1.1	0.20 (0.02–1.66)
Tulppala 1997	1	33	3	33	1.0	0.33 (0.04–3.04)
Vainio 2002	2	43	10	43	2.2	0.20 (0.05–0.86)
Subtotal (95% CI)		**389**		**375**	**20.5**	**0.47 (0.34–0.65)**
Total events	36		80			
Heterogeneity: Tau^2=0.00; Chi^2=5.45; df=7 (*P*=.61); I^2=0%						
Test for overall effect: Z=4.57 (*P*<.001)						
1.2 More than 16 weeks						
Byaruhanga 1998	17	113	23	117	7.1	0.77 (0.43–1.35)
Caritis 1998	111	663	118	626	10.8	0.89 (0.70–1.12)
CLASP 1994	91	1,259	80	1,233	10.2	1.11 (0.83–1.49)
Davies 1995	5	58	7	60	3.4	0.74 (0.25–2.20)
ECPPA 1996	16	284	22	322	6.6	0.82 (0.44–1.54)
Ferrier 1996	1	23	1	20	0.7	0.87 (0.06–13.02)
Golding 1998	66	1,253	50	1,294	9.4	1.36 (0.95–1.95)
Grab 2000	3	22	2	21	1.7	1.43 (0.27–7.73)
Hauth 1993	5	302	17	302	3.9	0.29 (0.11–0.79)
McParland 1990	1	48	10	52	1.2	0.11 (0.01–0.81)
Morris 1996	4	52	7	50	3.1	0.55 (0.17–1.76)
Rogers 1999	3	118	7	75	2.5	0.27 (0.07–1.02)
Rotchell 1998	10	739	12	746	4.8	0.84 (0.37–1.94)
Schiff 1989	1	34	7	31	1.2	0.13 (0.02–1.00)
Schrocksnadel 1992	0	22	6	19	0.7	0.07 (0.00–1.11)
Wallenburg 1986	0	23	7	23	0.7	0.07 (0.00–1.10)
Yu 2003	49	276	52	278	9.5	0.95 (0.67–1.35)
Zimmerman 1997	4	13	2	13	2	2.00 (0.44–9.08)
Subtotal (95% CI)		**5,302**		**5,282**	**79.5**	**0.81 (0.63–1.03)**
Total events	387		430			
Heterogeneity: Tau^2=0.09; Chi^2=32.49; df =17 (*P*=.01); I^2=48%						
Test for overall effect: Z=1.75 (*P*=.08)						

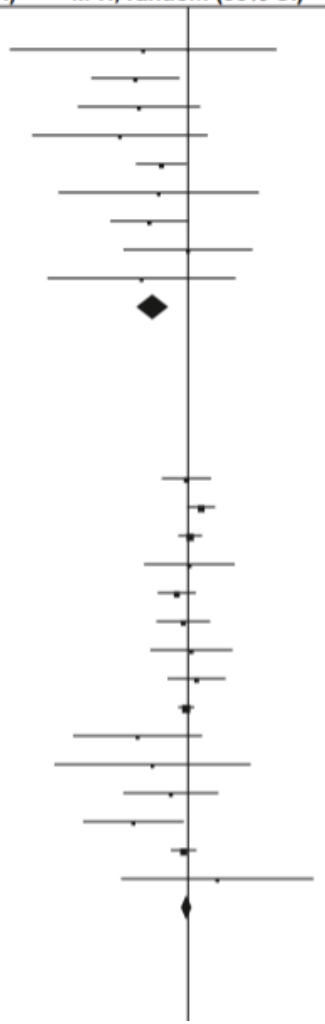


Bujold et al, 2010

LaboCita
ANALYSES MÉDICALES

RCIU

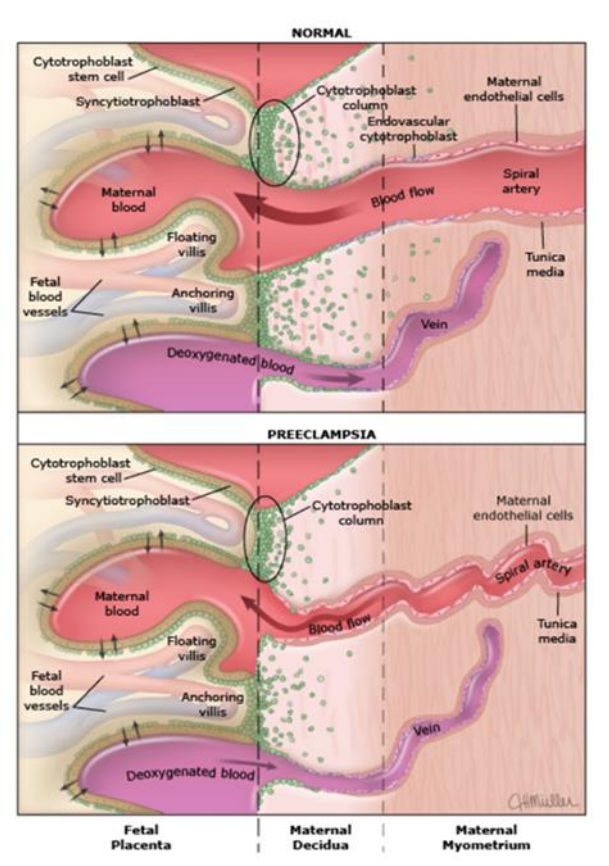
Study or subgroup	Favors experimental Events	Total	Control Events	Total	Weight (%)	Risk ratio M-H, random (95% CI)
2.1 16 or fewer weeks						
August 1994	0	24	1	25	0.3	0.35 (0.01–8.12)
Beaufils 1985	4	48	13	45	2.2	0.29 (0.10–0.82)
Benigni 1989	2	17	6	16	1.2	0.31 (0.07–1.33)
Dasari 1998	1	25	5	25	0.6	0.20 (0.03–1.59)
Ebrashy 2005	13	73	21	63	5.4	0.53 (0.29–0.98)
Hermida 1997	1	50	2	50	0.5	0.50 (0.05–5.34)
Hermida 1999	6	124	14	116	2.7	0.40 (0.16–1.01)
Tulppala 1997	3	33	3	33	1.1	1.00 (0.22-4.60)
Vainio 2002	1	43	3	43	0.5	0.33 (0.04–3.08)
Subtotal (95% CI)		**437**		**416**	**14.5**	**0.44 (0.30–0.65)**
Total events	31		68			
Heterogeneity: Tau^2=0.00; Chi^2=3.06; df=8 (*P*=.93); I^2=0%						
Test for overall effect: Z=4.10 (*P*<.001)						
2.2 More than 16 weeks						
Byaruhanga 1998	18	114	20	122	5.7	0.96 (0.54–1.73)
Caritis 1998	81	910	55	845	11.2	1.37 (0.98–1.90)
CLASP 1994	93	1,321	87	1,301	12.7	1.05 (0.79–1.40)
Davies 1995	6	58	6	60	2.1	1.03 (0.35–3.02)
ECPPA 1996	28	286	42	329	8.0	0.77 (0.49–1.20)
Hauth 1993	17	302	19	302	5.0	0.89 (0.47–1.69)
McParland 1990	7	48	7	52	2.5	1.08 (0.41–2.86)
Morris 1996	14	52	11	50	4.4	1.22 (0.62–2.43)
Newnham 1995	25	29	27	30	16.1	0.96 (0.79–1.16)
Schiff 1989	2	34	6	31	1.1	0.30 (0.07–1.40)
Schrocksnadel 1992	1	22	2	19	0.5	0.43 (0.04–4.40)
Wallenburg 1986	4	23	6	23	1.9	0.67 (0.22–2.05)
Wang 1996	3	40	12	44	1.7	0.28 (0.08–0.90)
Yu 2003	61	276	68	278	12.0	0.90 (0.67–1.22)
Zimmerman 1997	2	13	1	13	0.5	2.00 (0.21–19.44)
Subtotal (95% CI)		**3,528**		**3,499**	**85.5**	**0.98 (0.87–1.10)**
Total events	362		369			
Heterogeneity: Tau^2=0.00; Chi^2=14.14; df=14 (*P*=.44); I^2=1%						
Test for overall effect: Z=0.38 (*P*=.071)						



Bujold et al, 2010

LaboCita
ANALYSES MÉDICALES

Table of Content

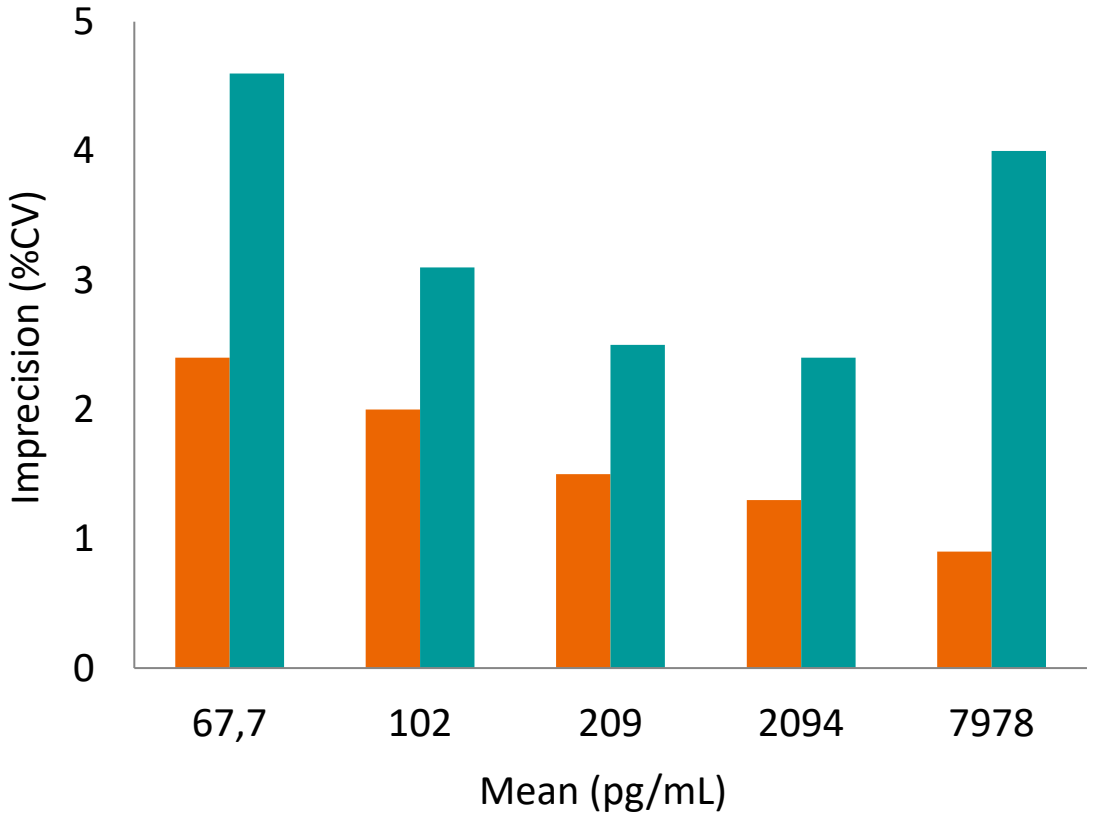


LaboCita
ANALYSES MÉDICALES

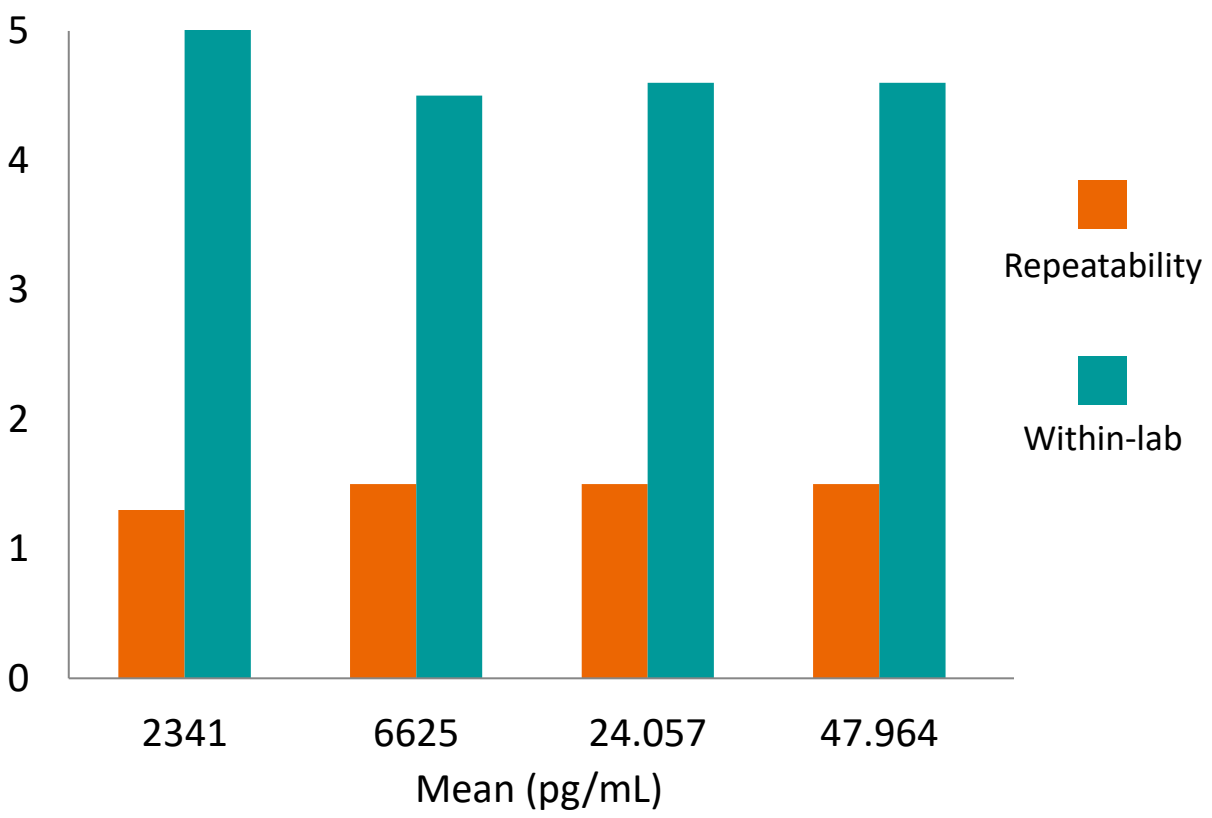
Atellica® IM PlGF and sFLT-1
Robust precision across the assay range

SIEMENS Healthineers

Atellica® IM PlGF assay



Atellica® IM sFlt-1 assay

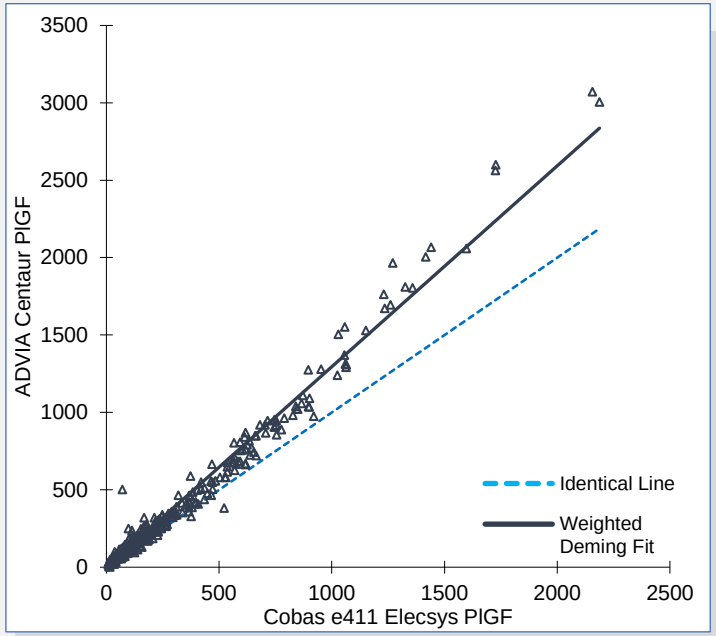


Atellica IM IFUs: 11205117_EN Rev. 01, 2021-012, 11205121_EN Rev. 01, 2021-12

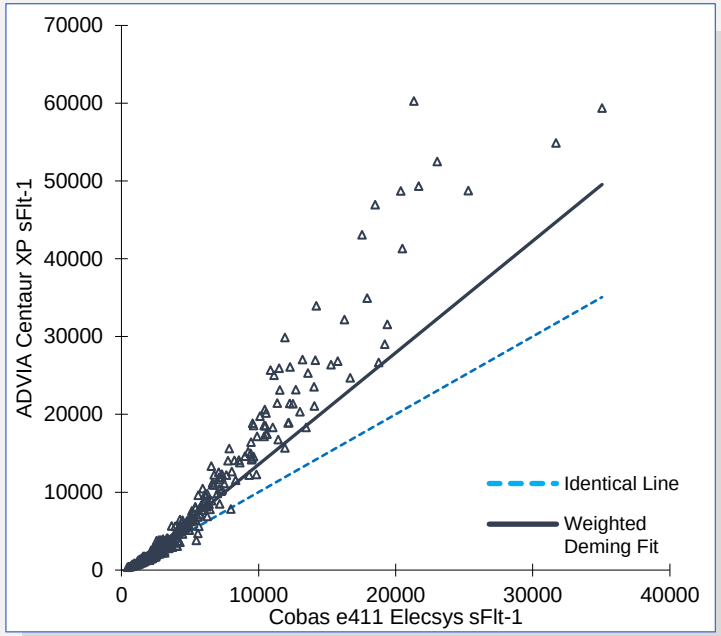
Method Comparisons:

Comparable Commercial Assays / Roche

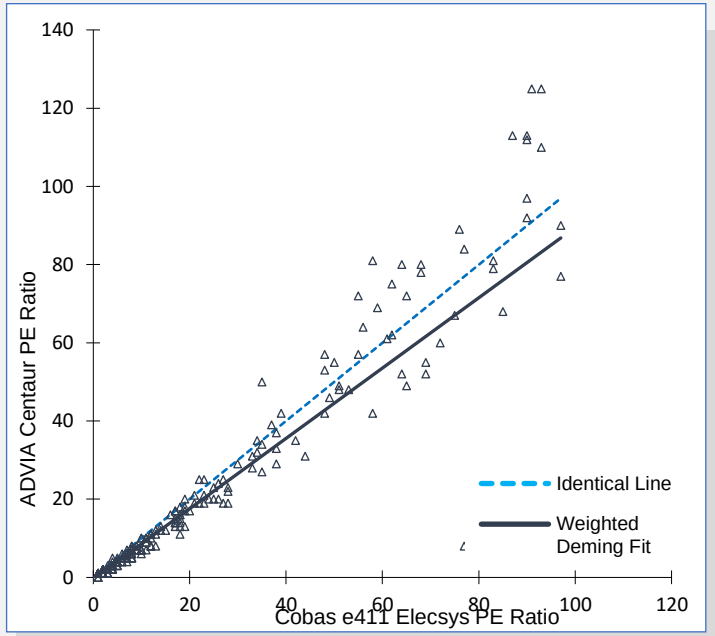
Centaur XP PlGF vs Cobas e411 Elecsys PlGF



Centaur XP sFlt-1 vs Cobas e411 Elecsys sFlt-1

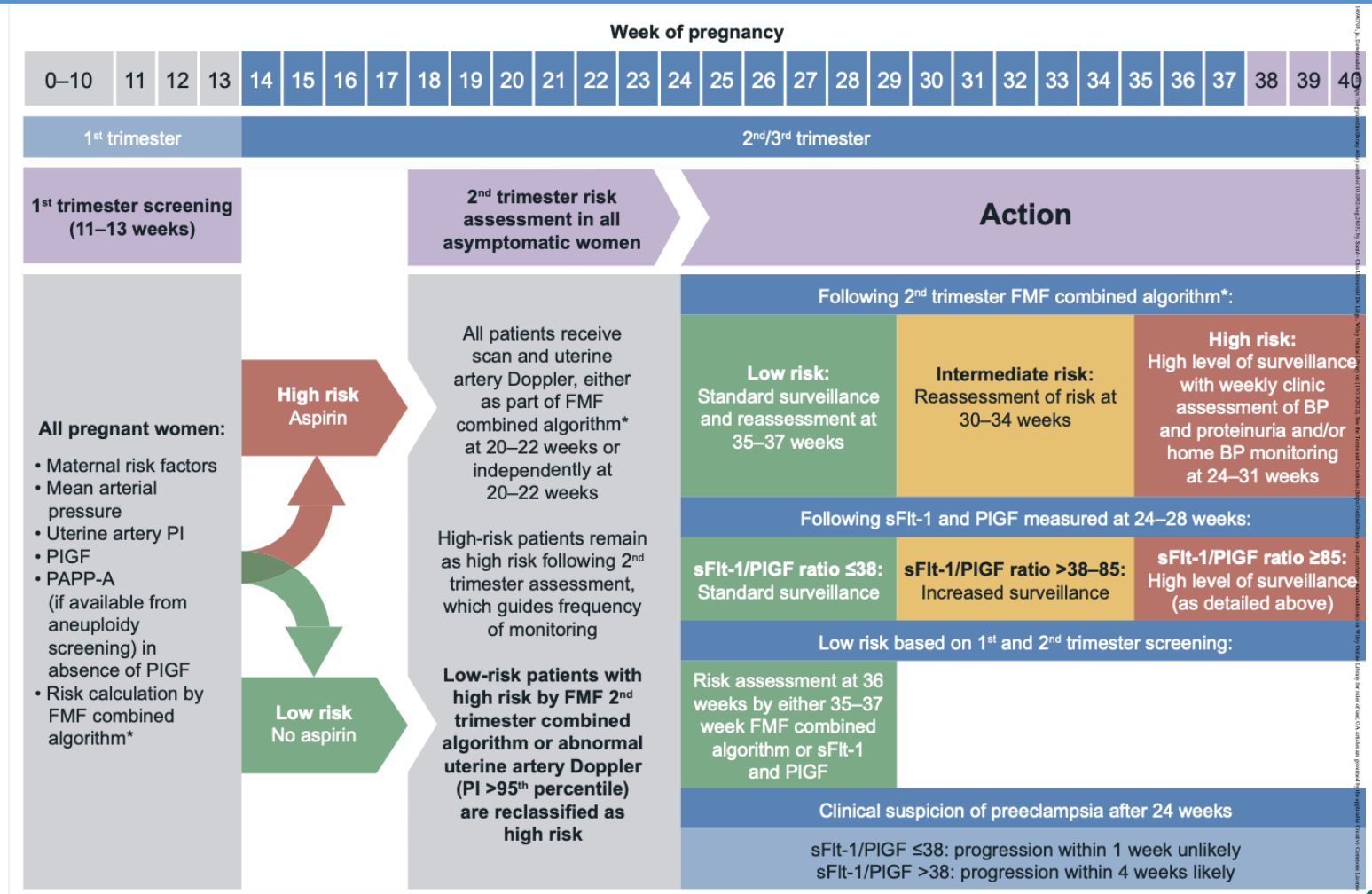


Centaur XP PE ratio vs Cobas e411 Elecsys PE ratio



Assay	Specimen	Comparative Assay (x)	Regression Equation	Sample Interval / Range	n	r
ADVIA Centaur XP PlGF Assay	Serum	Cobas e411 Elecsys PlGF Assay	y = 1.30 x – 2.7 pg/mL	8 – 2,187 pg/mL	338	0.980
ADVIA Centaur XP sFlt-1 Assay		Cobas e411 Elecsys sFlt-1 Assay	y = 1.44 x - 822 pg/mL	451 – 35,061 pg/mL	338	0.944
ADVIA Centaur XP PE ratio [Low End of the Range]		Cobas e411 Elecsys PE ratio [Low End of the Range]	Y = 0.90 x – 0.48	1 -- 97	225	0.924

FollowUp



Stepan et al *UOG, 2022*

LaboCita ANALYSES MÉDICALES

Take Home message

- T1 PE screening works
- sFlt-1/PlGF is a diagnostic aid for PE at T2/T3
- PE T2/T3 screening algorithms exist but require confirmation by prospective randomized studies

LaboCita
ANALYSES MÉDICALES

LaboCita

ANALYSES MÉDICALES