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CONGRÉS CATALÀ
d'Obstetrícia i Ginecologia

9, 10 i 11 de novembre, 2016
Auditori AXA, Barcelona

SCOG
Societat Catalana
d'Obstetrícia i
Ginecologia

MANEIG CLÍNIC DE LA PREECLAMPSIA



Elisa Llurba

RD12/0072 Maternal, Child Health and Development Network VI
Plan Nacional I+D (2012-2016)



Red
SAMID



Preeclampsia

Endothelial dysfunction

#Sensitivity to
angiotensin II and
norepinephrine

Vasoconstriction

Arterial
hypertension

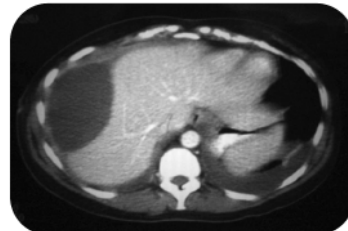
CEREBRAL
Headaches Blurred
vision
Eclampsia



• PGI₂/TXA₂
• NO

Coagulation
activation

Thrombocytopenia
Hemolysis



Platelet
aggregation

LIVER
Abnormal liver
enzymes
Epigastric pain

#Endothelial cell
permeability

Intravascular
hypovolemia

KIDNEY
Proteinuria

FETAL
Growth restriction
Hypoxia



NO, nitric oxide; PGI₂, prostacyclin; TXA₂, Thromboxane A₂

American College of Obstetricians and Gynecologists Task Force on
Hypertension in Pregnancy: Hypertension in Pregnancy 2013



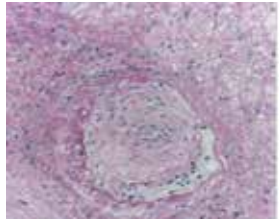
Arterial
hypertension



KIDNEY
Proteinuria



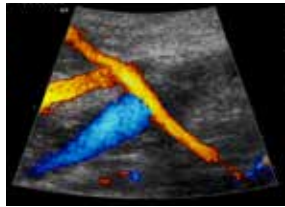
Clinical and pathophysiological features



Stage 1
DECIDUA

Deficient pro-angiogenic factor
expression (VEGF, PIGF)
Low HO1 activity

Abnormal remodelling spiral arteries and
trophoblast invasion
IMPARED PLACENTAL PERFUSION



Stage 2
PLACENTA

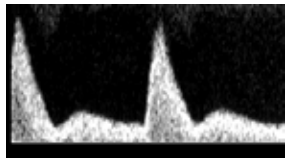
Hypoxia-reoxygenation

Oxidative damage

•Apoptosis

•sFlt-1
•sEng

•Cytokines



Endothelial dysfunction



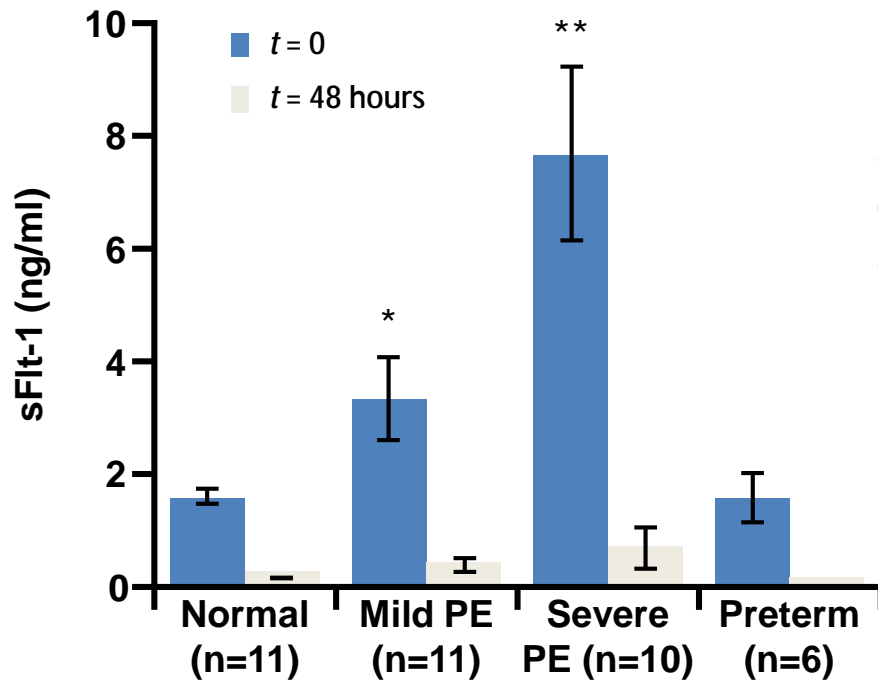
Stage 3
PERIPHERAL
VASCULATURE

Preeclampsia

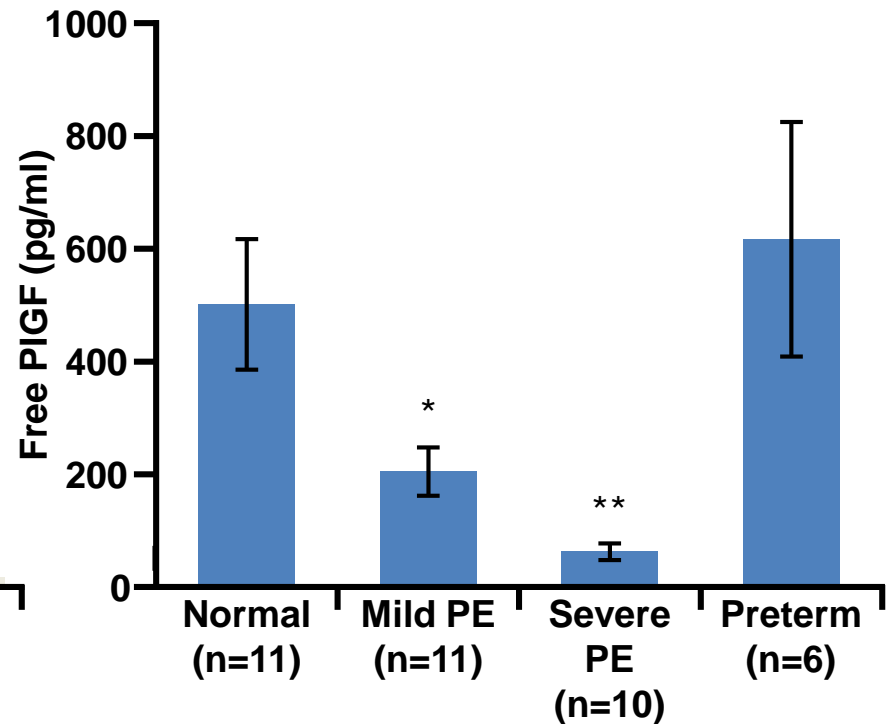
HO1, heme oxygenase-1; PIGF, placental growth factor; sEng, soluble endoglin;
sFlt-1, soluble fms-like tyrosine kinase 1; VEGF, vascular endothelial growth factor

Excess placental sFlt-1 may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia

Placental sFlt-1 Expression



Circulating PIGF



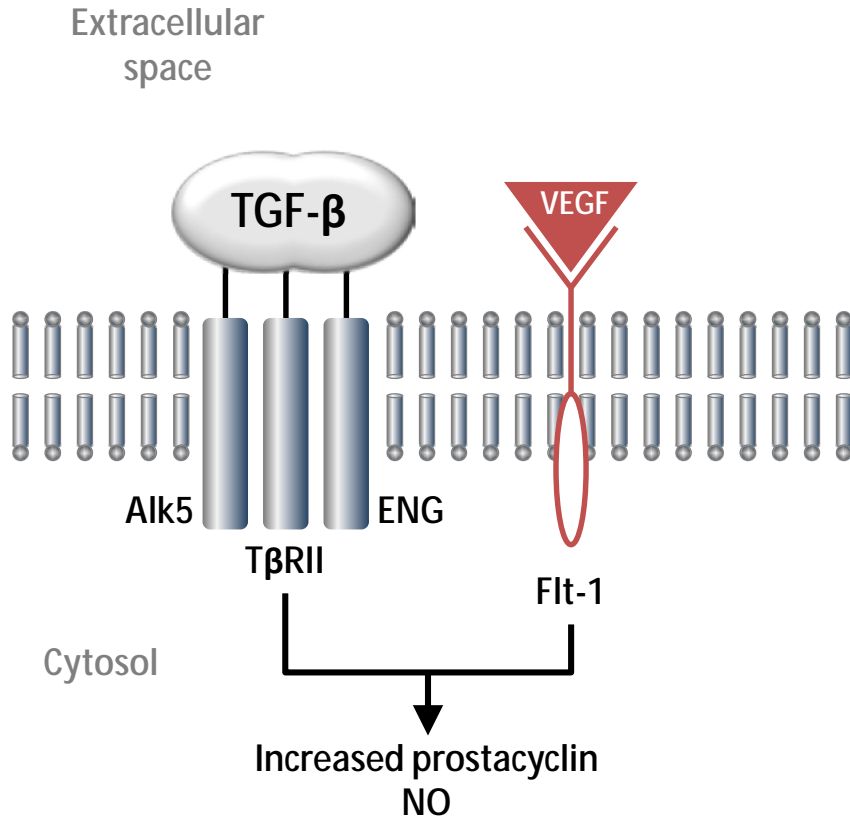
*P < 0.05 and **P < 0.01 as compared with normotensive controls. PE, preeclampsia

Maynard SE, et al. J Clin Invest 2003;111: 649-658

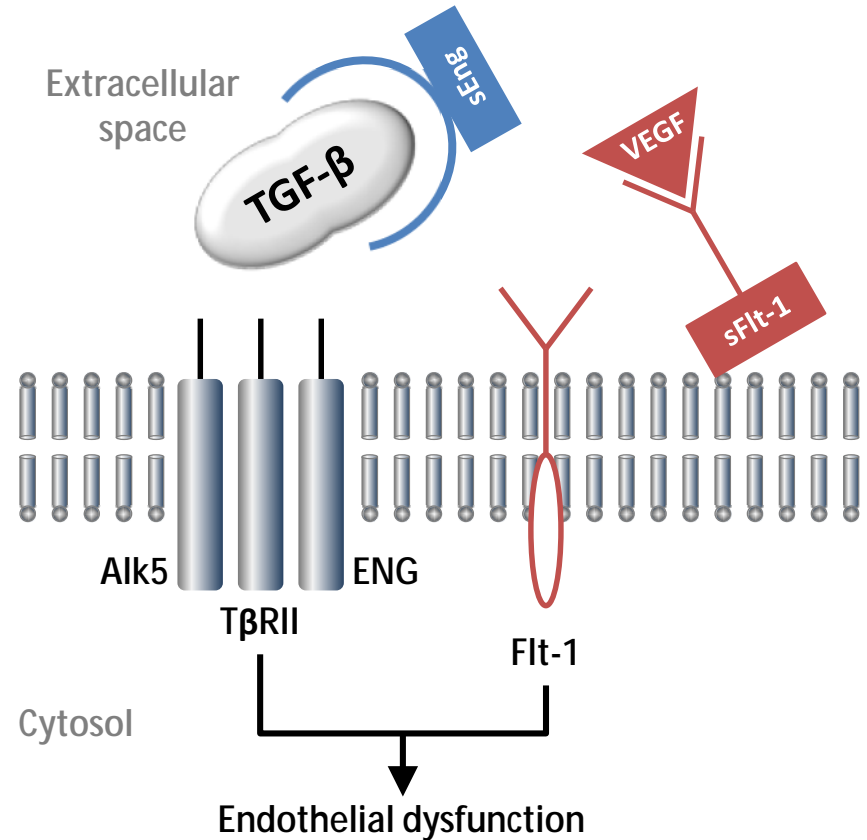
Preeclampsia

Endothelial dysfunction

Normal pregnancy



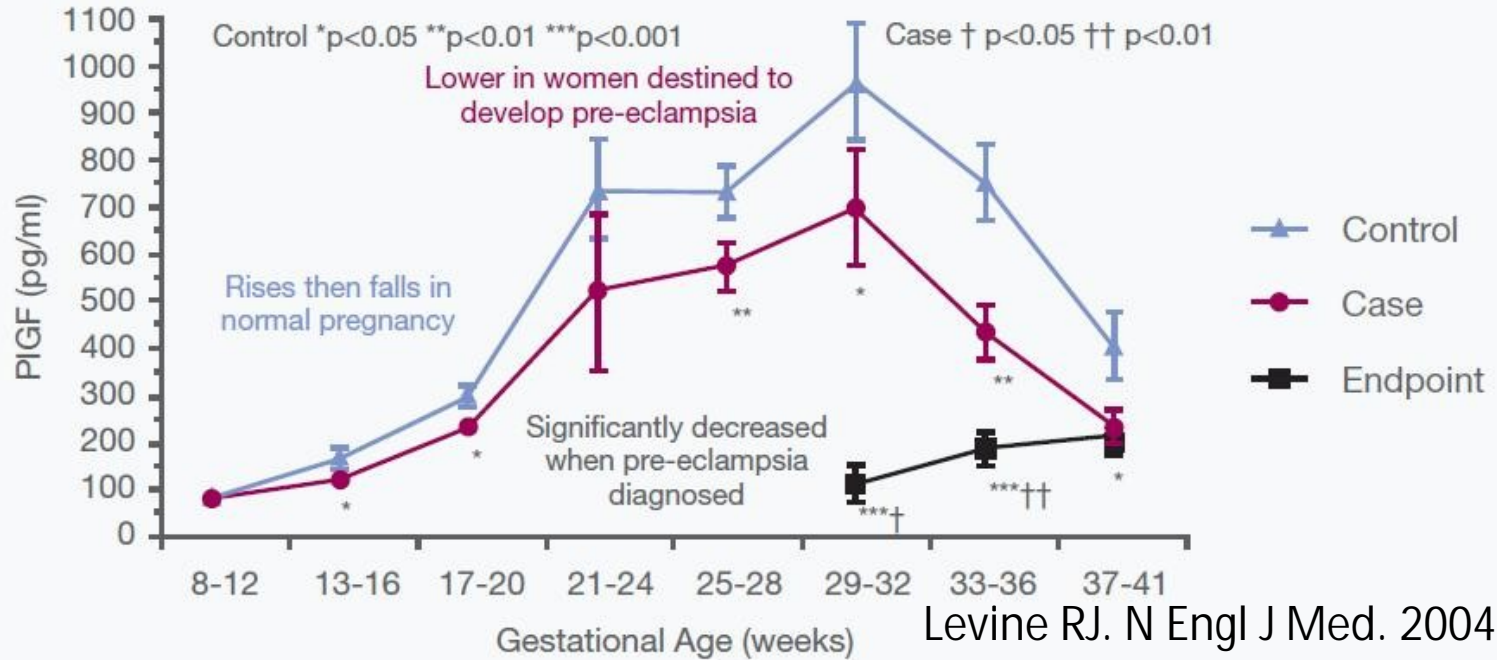
Preeclampsia



ENG, endoglin; Flt-1, fms-like tyrosine kinase 1;
TGF- β , tumor growth factor beta;
T β RII, TGF- β 2 binding receptor

Adapted from Karumanchi SA, Epstein FH. *Kidney Int* 2007;71:959–961

PREECLAMPSIA



sFlt1/PIGF ratio



1 TRIMESTER
PREDICTION



DIAGNOSIS
AND
MANAGEMENT

Preeclampsia

2nd cause maternal deaths

1

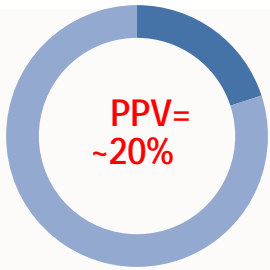
Selection of cases than
need surveillance

2

Prediction of adverse
outcome

PREECLAMPSIA: CLINICAL SCENARIOS

Suspicion of PE



BP/proteinuria/platelets/AST/uric acid
to predict preeclampsia

PROGNOSIS
STUDY

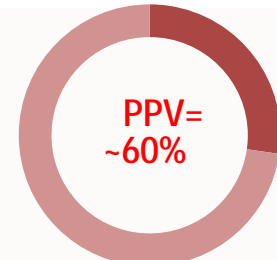
Established PE



BP plus proteinuria to predict
preeclampsia-related adverse
outcomes

DIAGNOSIS

Severe early-onset PE



PIERS to predict SEVERE
preeclampsia-related adverse
outcomes (48H)

MANAGEMENT

Verlohren S, et al. Hypertension, 2014

Rana S, et al. Circulation, 2012

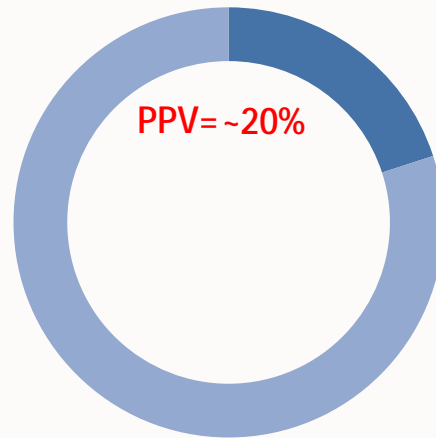
Schnettler WT, et al. BJOG, 2013

Menzies, J, 2007

VonDadelszen P, 2011

*Zhang J, et al.
Obstet Gynecol 2001*

Suspicion of PE



BP/proteinuria/platelets/AST/uric acid to predict preeclampsia

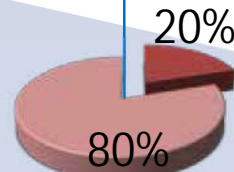
PROGNOSIS STUDY

PROGNOSIS *Prediction of short-term outcome in pregnant women*

SUSPICION OF PE
sFlt1/PIGF ratio?

- New onset HTA
- Aggravation HTA
- New onset PROT
- PE-related symptoms
- PE-related findings

Visits/week
4mL serum



No-PE or adverse
outcome within one week



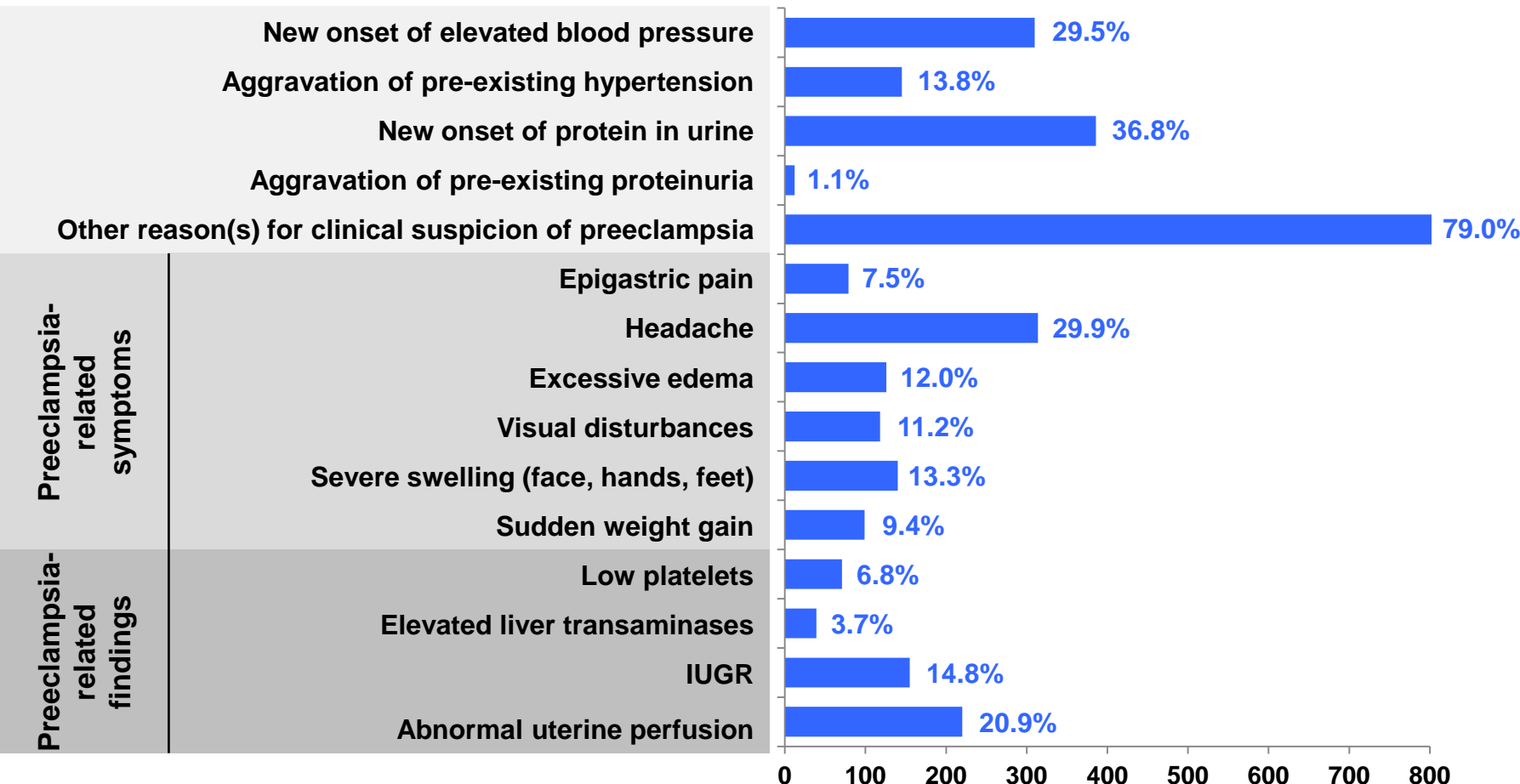
sFlt1/PIGF
ratio

PE/adverse outcome
within 4 weeks



• Study samples (4 ml serum/5 ml urine) for biomarker testing were collected, frozen and shipped to an independent laboratory for sFlt-1/PIGF testing

Reasons for suspicion of preeclampsia*



*More than one may apply for any individual subject
 IUGR, intrauterine growth restriction

Subjects, n

PROGNOSIS

Prediction of short-term outcome in pregnant women



PROGNOSIS SITES



1273 subjects enrolled

223 exclusion

- 48 inclusion/exclusion criteria
- 11 withdrew IC
- 78 multiple pregnancy
- 52 were lost to follow up
- 34 no sample Visit 1

1050 pooled subjects
4394 serum sample

199 PE
(19%)
126
Fetal adverse outcome
(12%)



726 no PE/adverse fetal outcome
(69.1%)

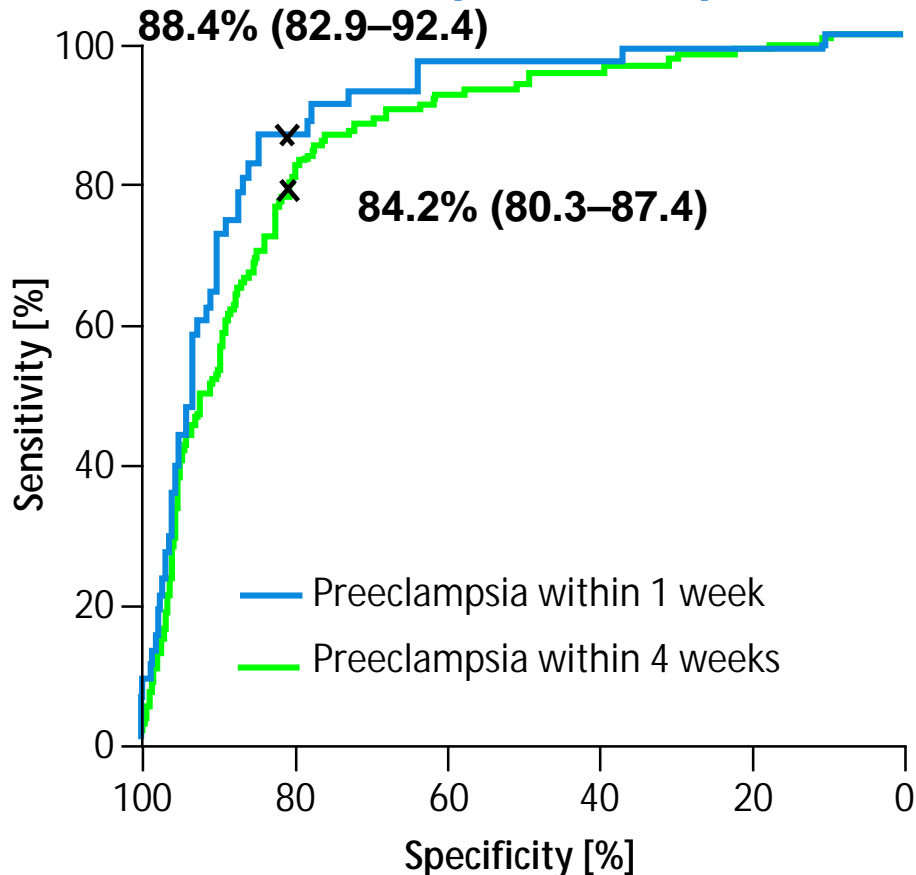


PROGNOSIS feasibility study

- The single cutoff model was selected for both rule-out and rule-in
- Feasibility testing showed no superiority for other models
 - Global sFlt-1/PIGF cutoff = 38
 - For all gestational ages
 - For both prediction claims (1-week rule out and 4-week rule in)

PROGNOSIS: Prediction of preeclampsia

sFlt-1/PIGF ratio cut-off of 38
(rule-out and rule-in)
(n=1,050)



Preeclampsia within 1 week:

	Estimate
NPV	99.1% (98.2–99.6)
Sensitivity	85.7% (72.8–94.1)
Specificity	79.1% (76.5–81.6)

Preeclampsia within 4 weeks:

	Estimate
PPV	38.6% (32.6–45.0)
Sensitivity	70.3% (61.9–77.8)
Specificity	83.1% (80.5–85.5)

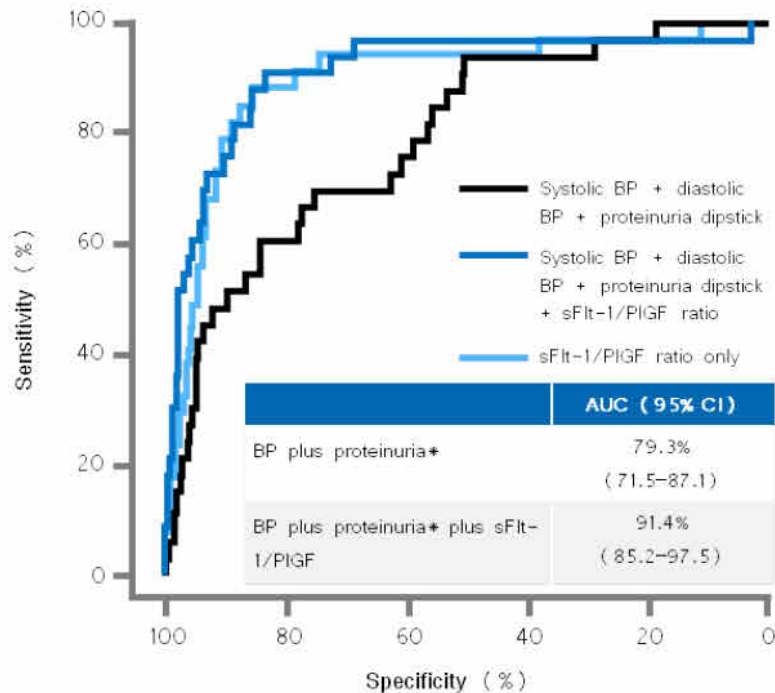
PROGNOSIS: Prediction of preeclampsia

sFlt-1/PIGF ratio cut-off of 38 (rule-out)

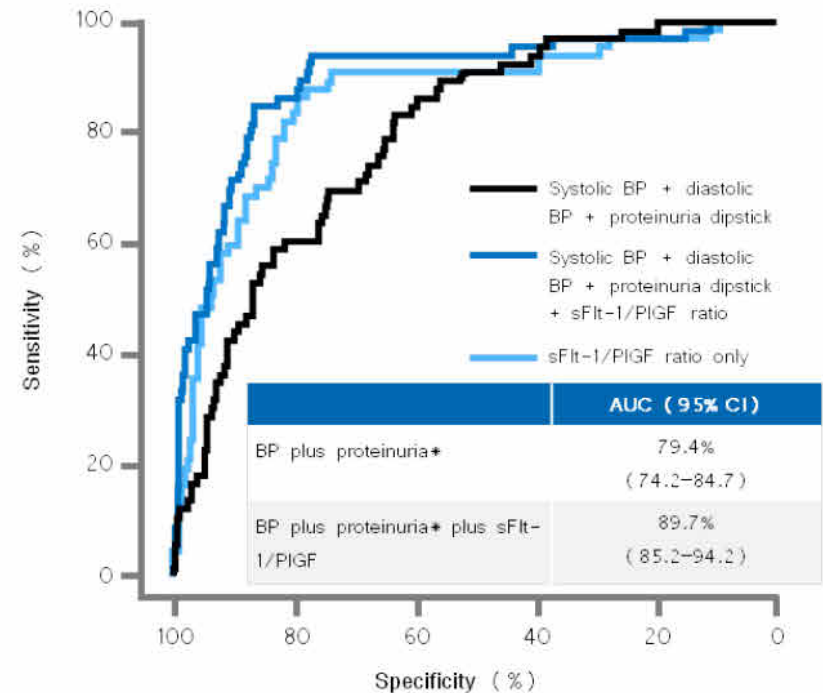
Estimate	Within 1 week	Within 2 weeks	Within 3 weeks	Within 4 weeks
% (95% CI)	99.3 (97.9–99.9)	97.9 (96.0–99.0)	95.7 (93.3–97.5)	94.3 (91.7–96.3)
NPV	80.0 (51.9–95.7)	78.0 (62.4–89.4)	70.0 (56.8–81.2)	66.2 (54.0–77.0)
Sensitivity	78.3 (74.6–81.7)	81.1 (77.5–84.4)	82.4 (78.8–85.7)	83.1 (79.4–86.3)

The sFlt-1/PlGF ratio enabled better prediction of preeclampsia than clinical data alone

Rule out preeclampsia within
1 week



Rule in preeclampsia within
4 weeks

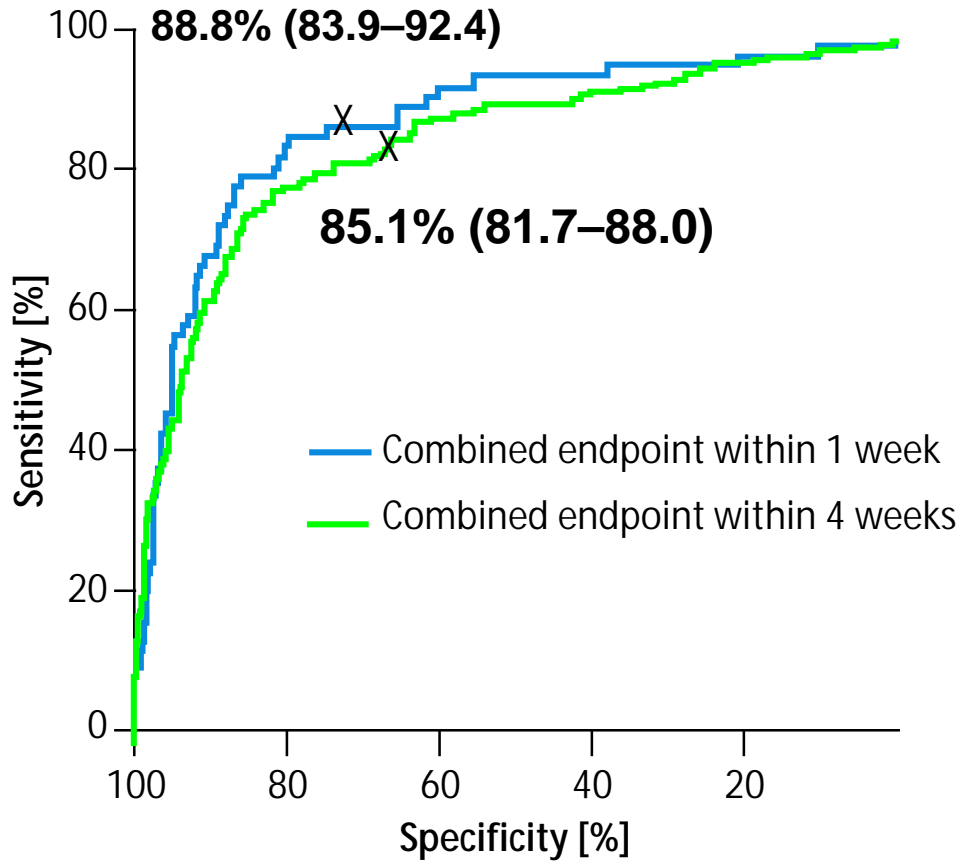


*Systolic BP plus diastolic BP plus proteinuria dipstick

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

Prediction maternal/fetal adverse outcomes

sFlt-1/PIGF ratio cut-off of 38
(rule-out and rule-in)



Combined endpoint within 1 week

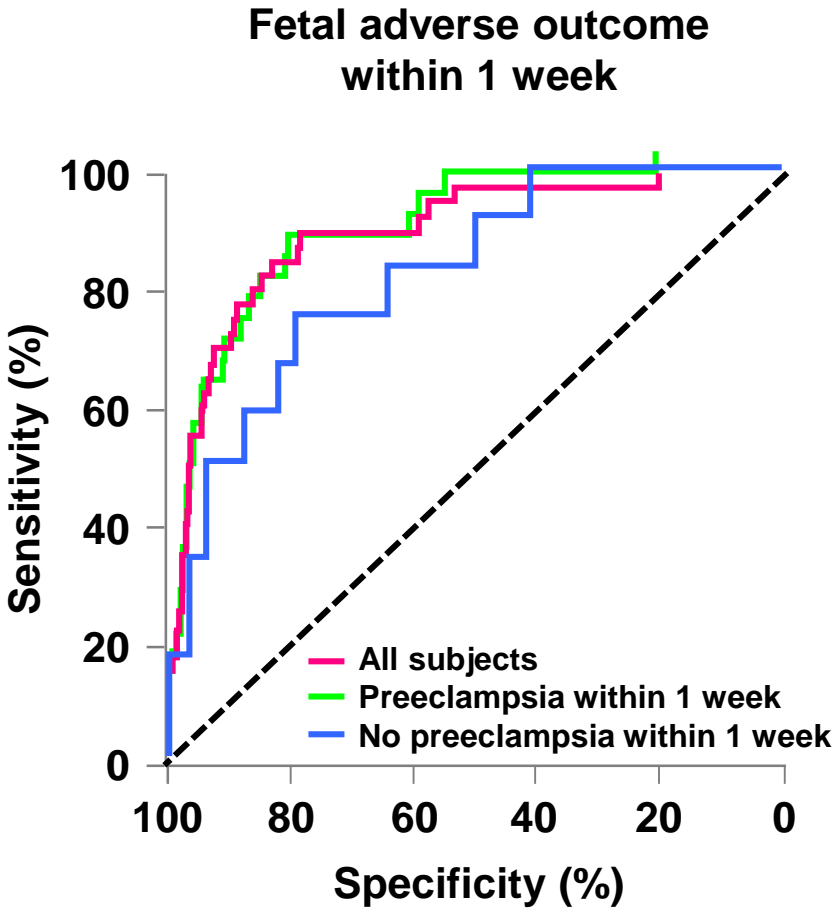
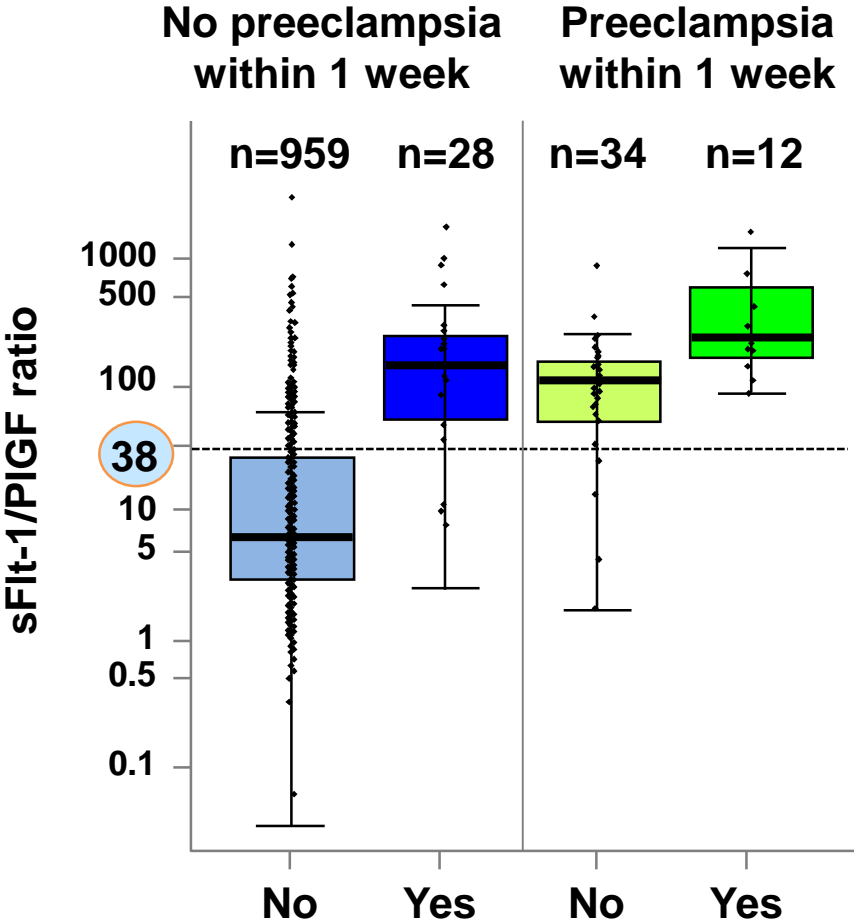
	Estimate
NPV	98.5% (97.4–99.2)
PPV	24.9% (19.5–30.9)
Sensitivity	83.1% (72.3–91.0)
Specificity	81.4% (78.7–83.8)

Combined endpoint within 4 weeks

	Estimate
PPV	61.6% (55.1–67.8)
NPV	90.5% (88.2–92.4)
Sensitivity	66.1% (59.4–72.3)
Specificity	88.7% (86.3–90.8)

Zeisler H, Llurba E, Chantraine F, Vatish M, Staff A, Sennström M, Olovsson M, Brennecke S, Stepan H, Allegranza D, Dilba P, Schoedl M, Hund M, Verloren S. Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia: The PROGNOSIS Study. NEJM. 2016

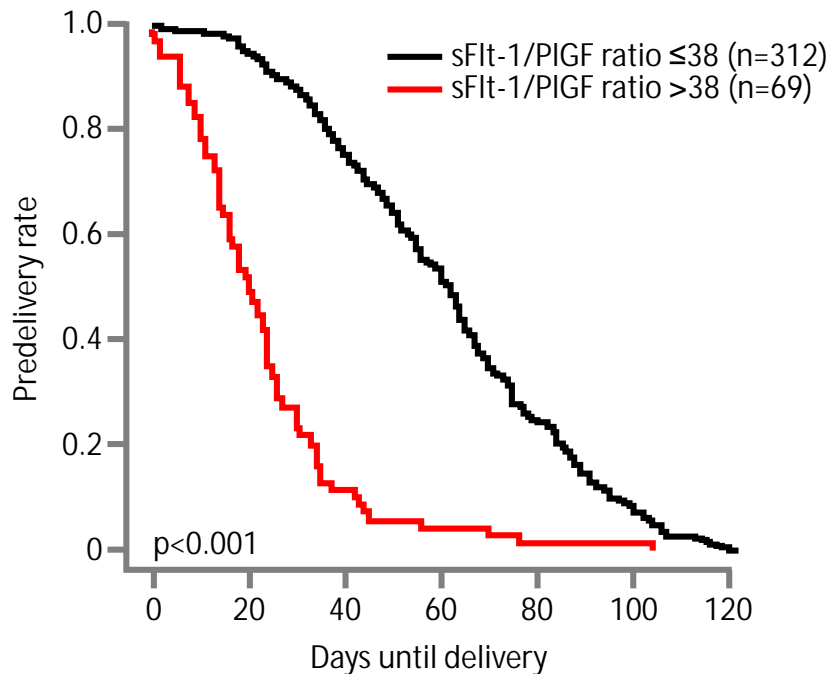
Fetal adverse outcomes within 1 week



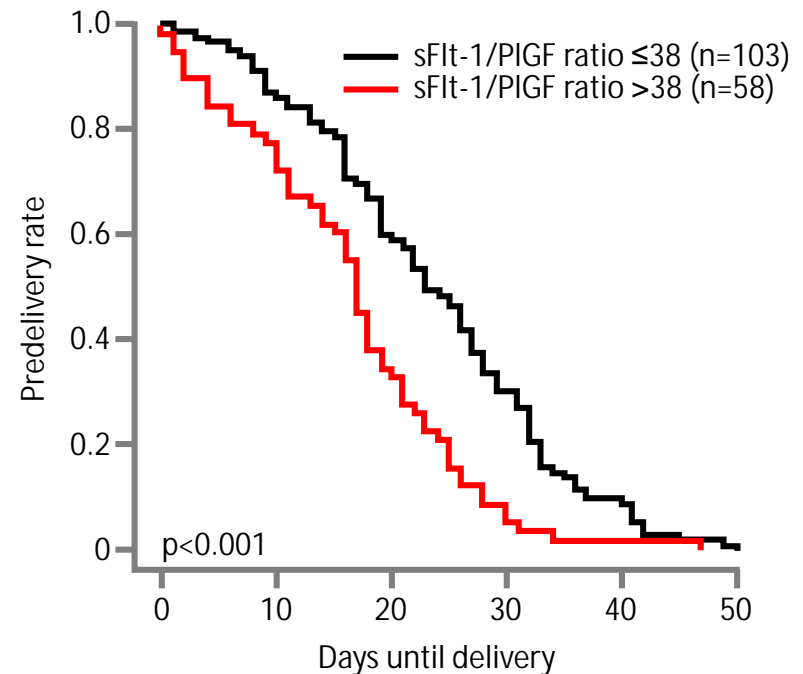
Zeisler H, Llurba E, Chantraine F, Vatis M, Staff A, Sennström M, Olovsson M, Brennecke S, Stepan H, Allegranza D, Dilba P, Schoedl M, Hund M, Verloren S. Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia: The PROGNOSIS Study. NEJM, 2016

Time to delivery for women with suspicion of preeclampsia (sFlt-1/PIGF ratio of >38)

Visit 1 at early gestational phase



Visit 1 at late gestational phase

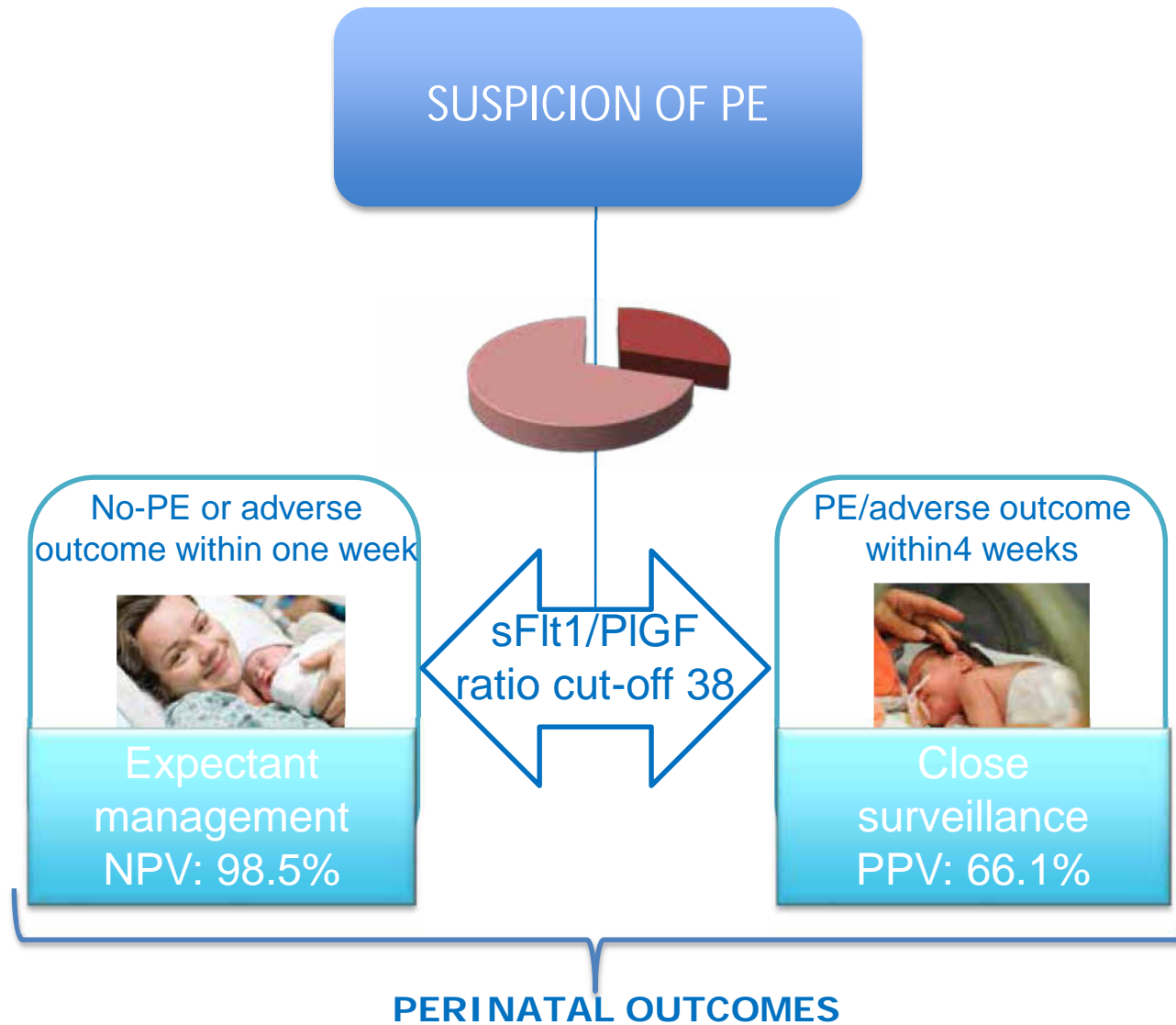


*P values were calculated using a log rank test

Early gestational phase = 24 weeks plus 0 days to 33 weeks plus 6 days; Late gestational phase = 34 weeks plus 0 days onwards

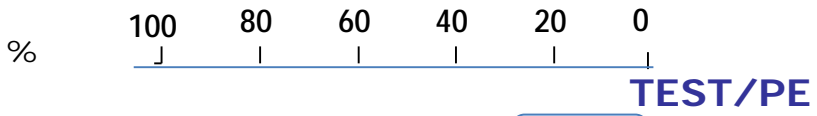
PIGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1

PROGNOSIS *Prediction of short-term outcome in pregnant women*



PROGNOSIS Prediction of short-term outcome in pregnant women

SUSPICION OF PREECLAMPSIA

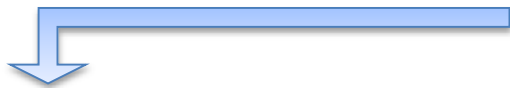


32.2% +/+

42.3% +/-

23.5% -/-

2% -/+



- 47% Admissions
- 72% test for fetal surveillance
- 48% maternal imaging
- 40% blood test



1215 \$

PreOS: Influence of sFlt-1 and PlGF on decision making of physicians in pregnant women with suspicion of preeclampsia

On behalf of the PreOS investigators

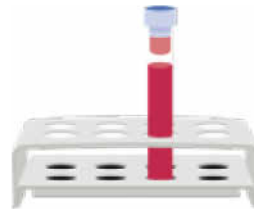
Primary objective

To assess the influence of the sFlt-1/PlGF ratio on the decision making of physicians to hospitalize pregnant women with suspicion of preeclampsia

PreOS study design

**Clinical decisions before
knowledge of sFlt-1/PIGF ratio**

**Clinical decisions guided by
knowledge of sFlt-1/PIGF ratio**



Medical data
(except sFlt-1/PIGF ratio)
available

Investigator decisions
recorded using iPad®

Collection of serum for
sFlt-1/PIGF measurement

Date/time of test result
recorded

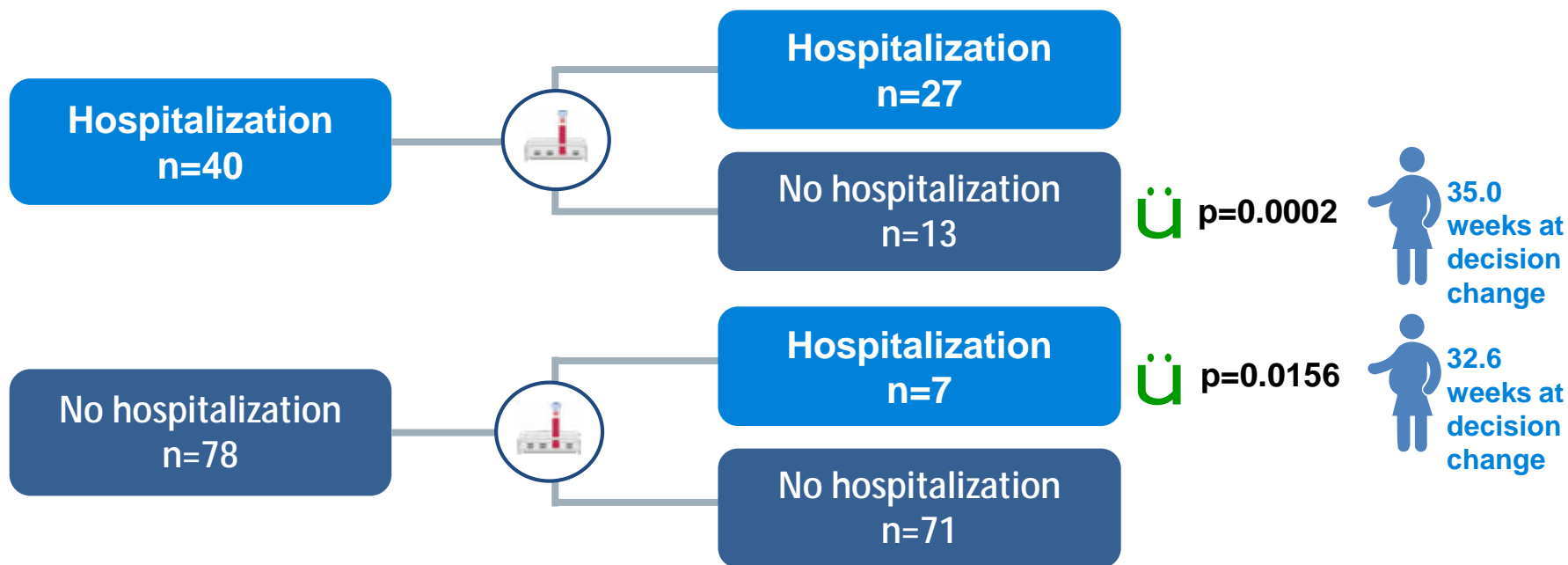
sFlt-1/PIGF ratio available
to investigator

Revised or confirmed
decisions recorded using
iPad®

Primary endpoint: Decision to hospitalize

Hospitalization decision before test result known

Hospitalization decision after test result known



ü All changed decisions were appropriate as assessed by adjudication committee
McNemar p value for any change was p<0.0001

Per-protocol population (n=118)

PREECLAMPSIA: CLINICAL SCENARIOS

Established PE



PPV=
~30%

BP plus proteinuria to predict
preeclampsia-related adverse
outcomes

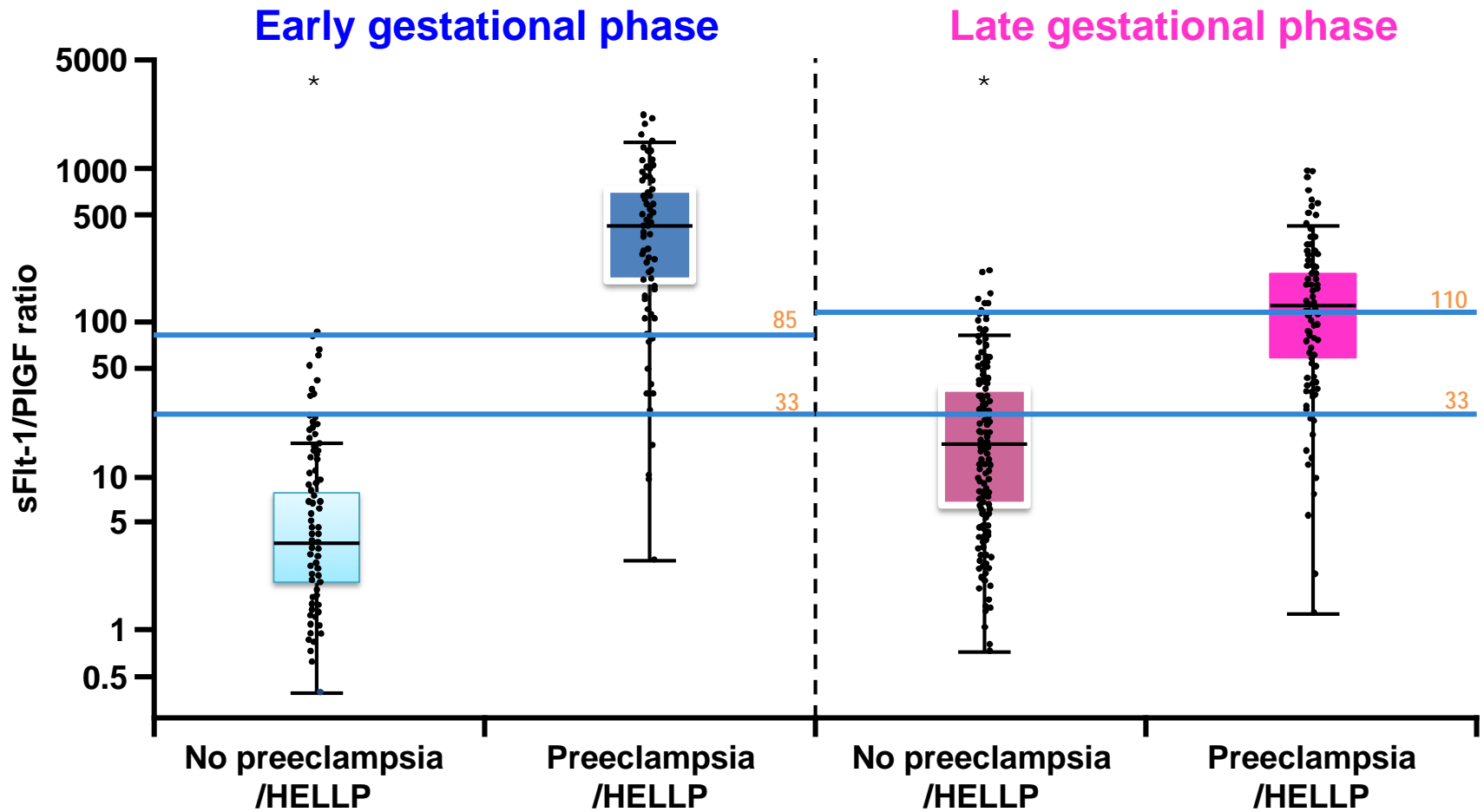
DIAGNOSIS

Verlohren S, et al. Hypertension, 2014

Rana S, et al. Circulation, 2012

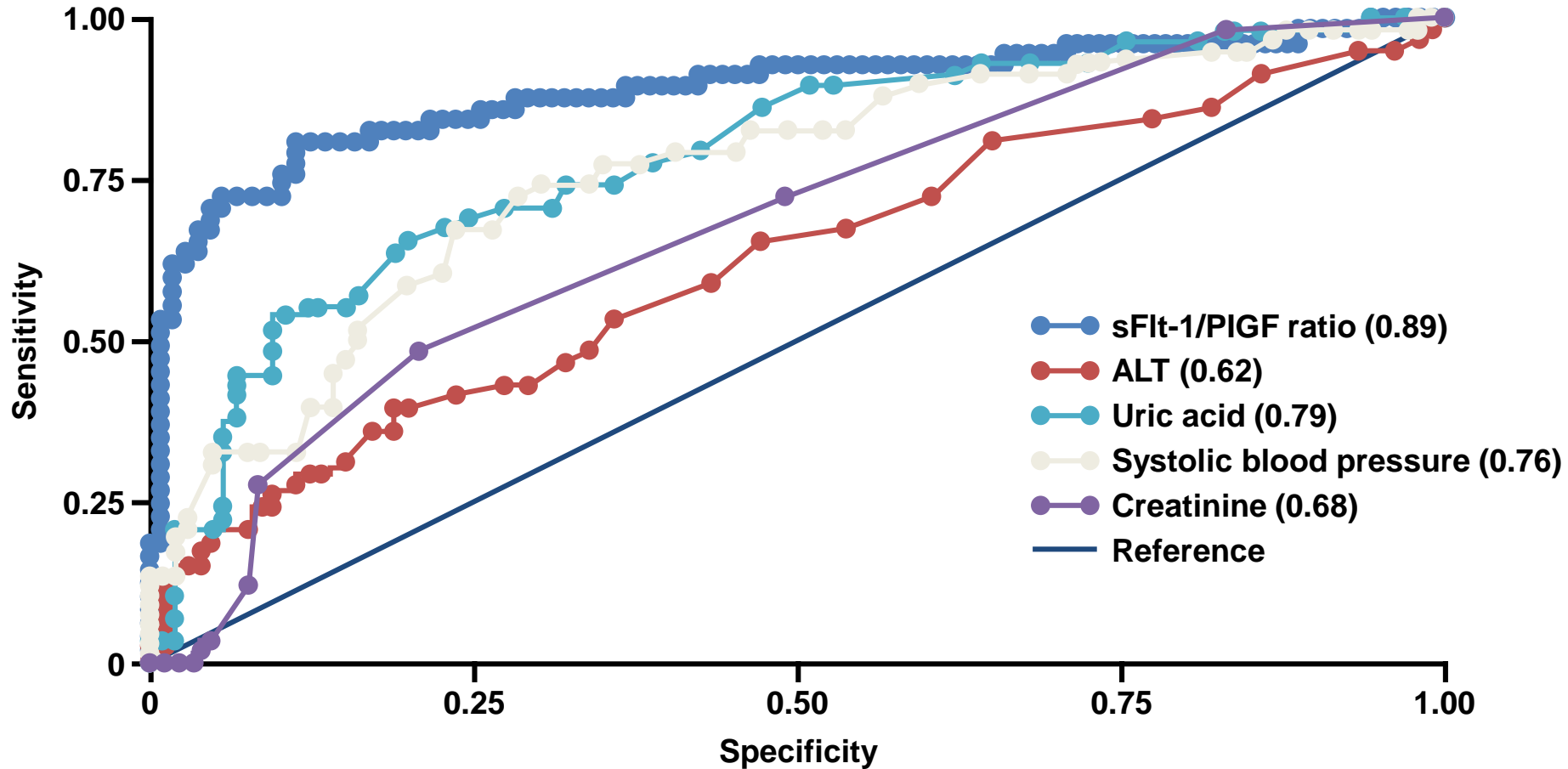
Schnettler WT, et al. BJOG, 2013

sFit-1/PIGF ratio for aid in diagnosis of preeclampsia

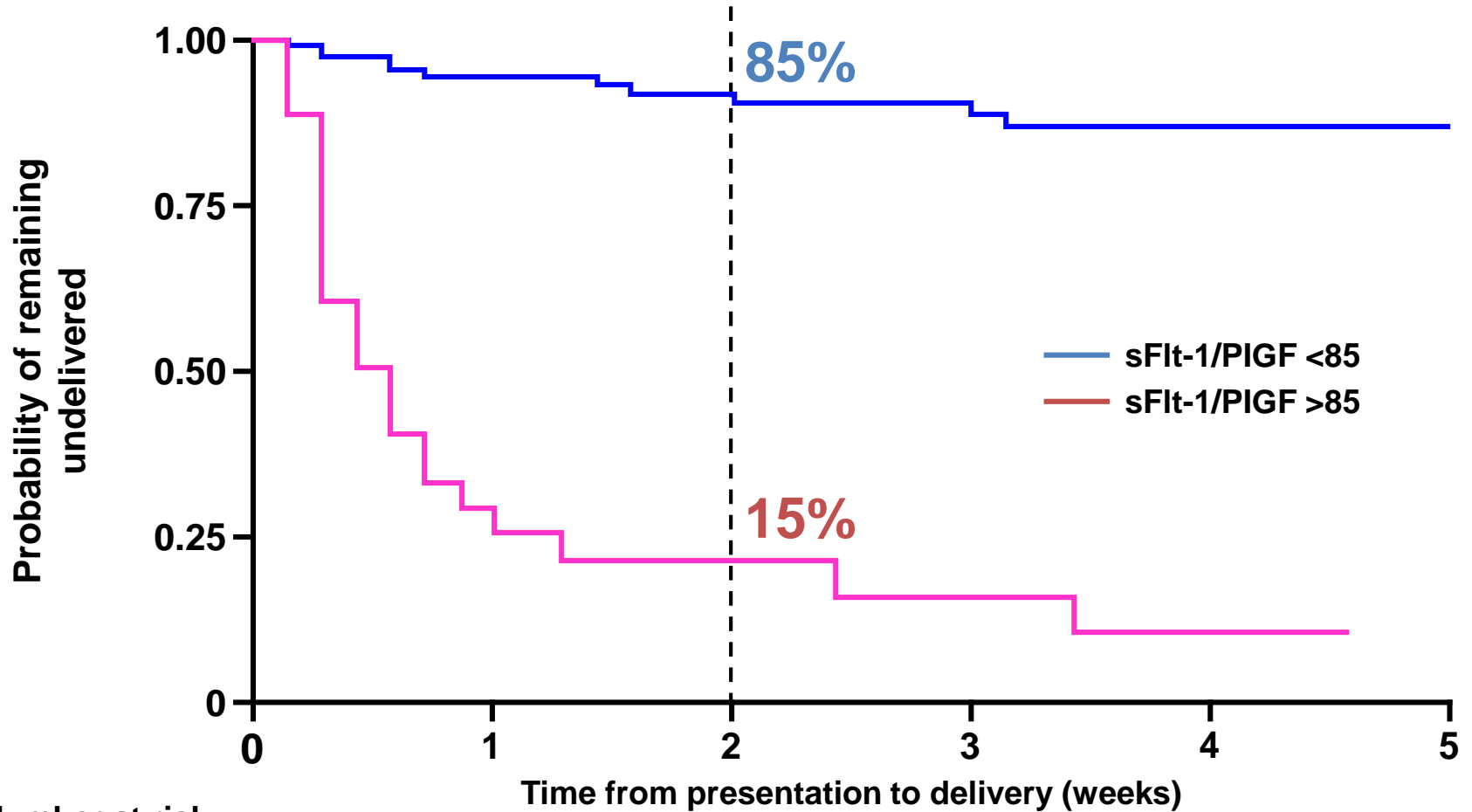


*p<0.001 for the comparison preeclampsia HELLP vs no preeclampsia/HELLP
HELLP, hemolysis, elevated liver enzymes, low platelets syndrome

sFlt-1/PIGF ratio for prognosis in patients with established preeclampsia



sFlt-1/PIGF ratio and remaining pregnancy duration



Number at risk

sFlt-1/PIGF <85 118

89

66

53

41

32

sFlt-1/PIGF >85 35

8

4

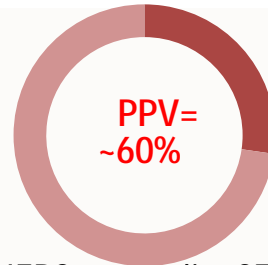
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PREECLAMPSIA: CLINICAL SCENARIOS

Severe early-onset PE



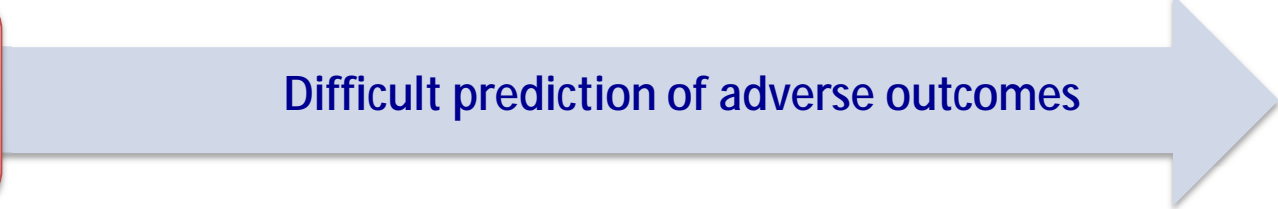
PIERS to predict SEVERE
preeclampsia-related adverse
outcomes (48H)

MANAGEMENT

Menzies, J, 2007

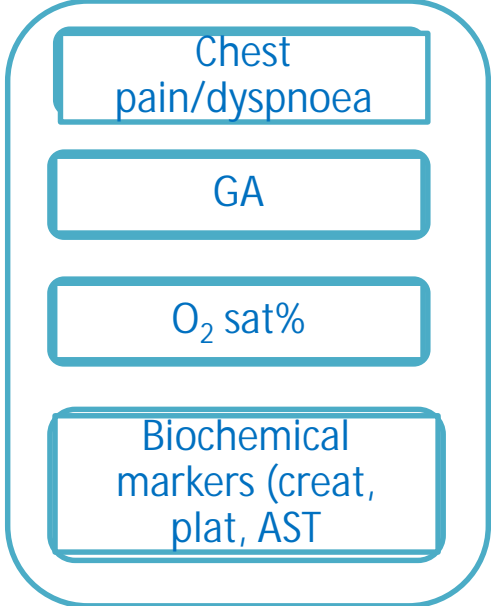
VonDadelszen P, 2011

Severe early-onset PE/IUGR < 34w



PROPOSED APPROACHES

Pre-eclampsia Integrated Estimate of RiSk (PIERS)



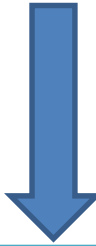
Menzies, J, 2007

VonDadelszen P, 2011

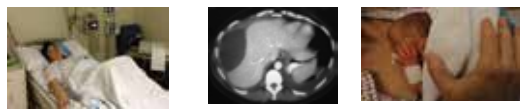


PIGF

sFit1

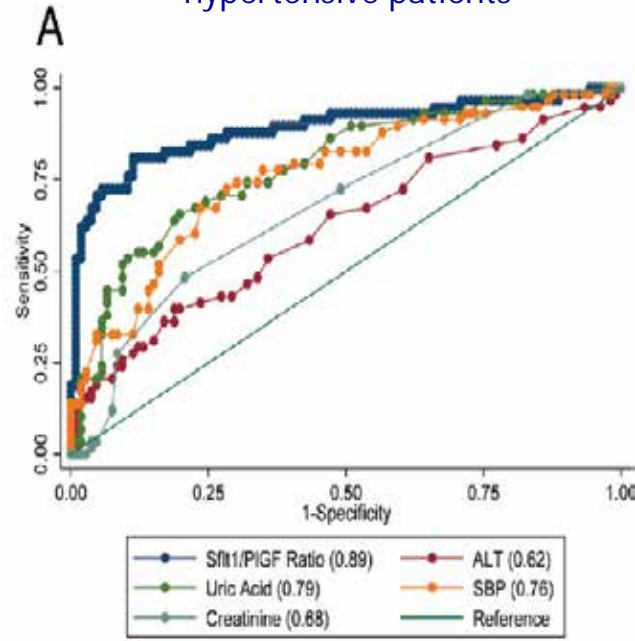


PE/IUGR



Levine RJ. N Engl J Med. 2004

Mixed population of hypertensive patients



Rana S, Circulation, 2012

Aim: evaluate the predictive value of angiogenic factors in severe early-onset preeclampsia

OBJECTIVE 1:

Association of sFlt1/PlGF ratio at admission

OBJECTIVE 2:

Association Ratio progression from admission to delivery

OBJECTIVE 3:

Predictive performance of sFlt1/PlGF ratio

with adverse maternal or fetal outcome

Study design:

n= 46

severe early-onset PE +/-IUGR at 24.0-32.6 w
sFlt-1/plGF at admission and delivery

Admission to delivery interval: 6 d [5.8]

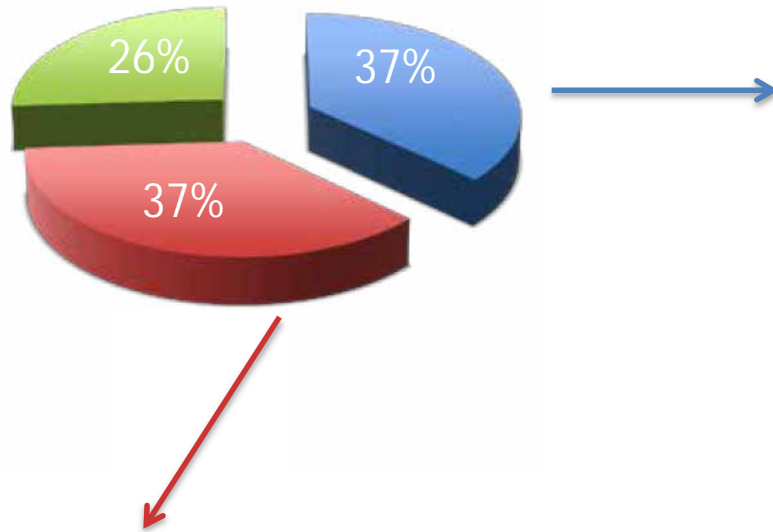


GA admission (w)	29 (2.8)
GA delivery (w)	30.5 (3)
PIERS >5%	7 (15%)
Birth weight (gr)	1194 (472)
Apgar 1'	6.4 (1.9)
Apgar 5'	8.5 (1.2)
Arterial Ph	7.21 (0.1)

RESULTS

ADVERSE OUTCOME

■ Maternal ■ Fetal ■ No complications

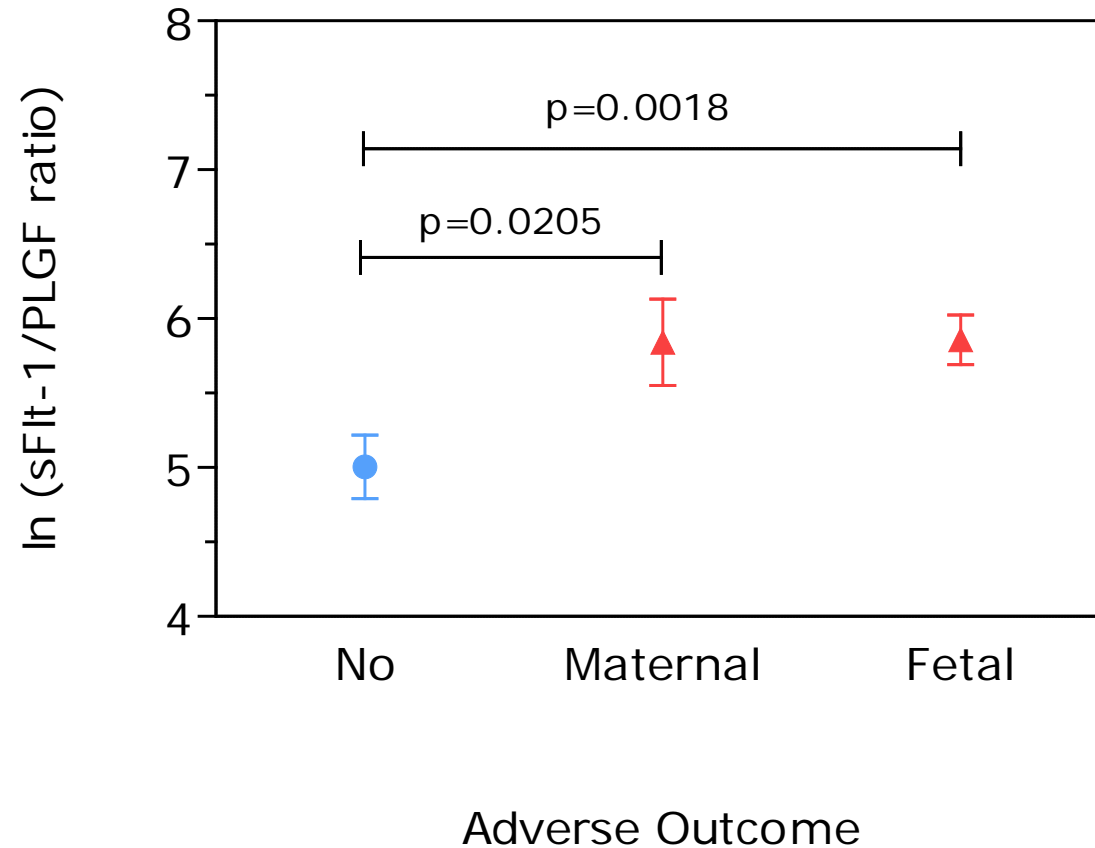


• Abruptio placentae	5 (10.8%)
• Severe HELLP	3 (6.5%)
• Pulmonary embolism	1 (2.1%)
• Cerebral haemorrhage	1 (2.1%)
• Severe headache or/and visual disturbances/severe hypertension	7 (15.2%)

• Non-reassuring fetal CTG	8 (17.3%)
• Reverse AU or absent/rev DV Doppler	9 (19.5%)

RESULTS:

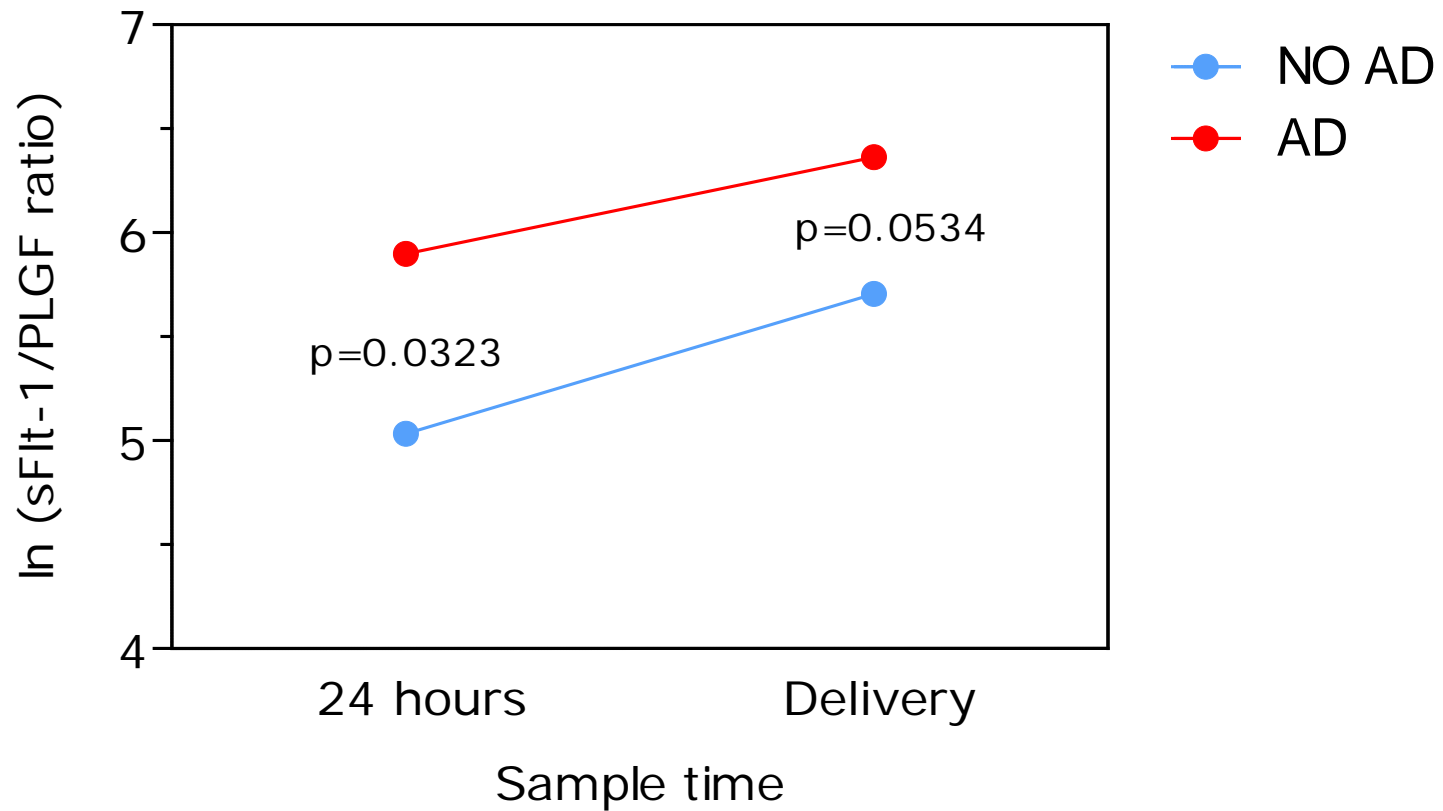
sFlt1/PLGF ratio at admission according to the presence or absence of adverse outcome



- ü Circulating sFlt1/PLGF ratio was higher in those women with maternal or fetal adverse outcomes

RESULTS:

sFlt-1/PLGF Ratio progression and outcome

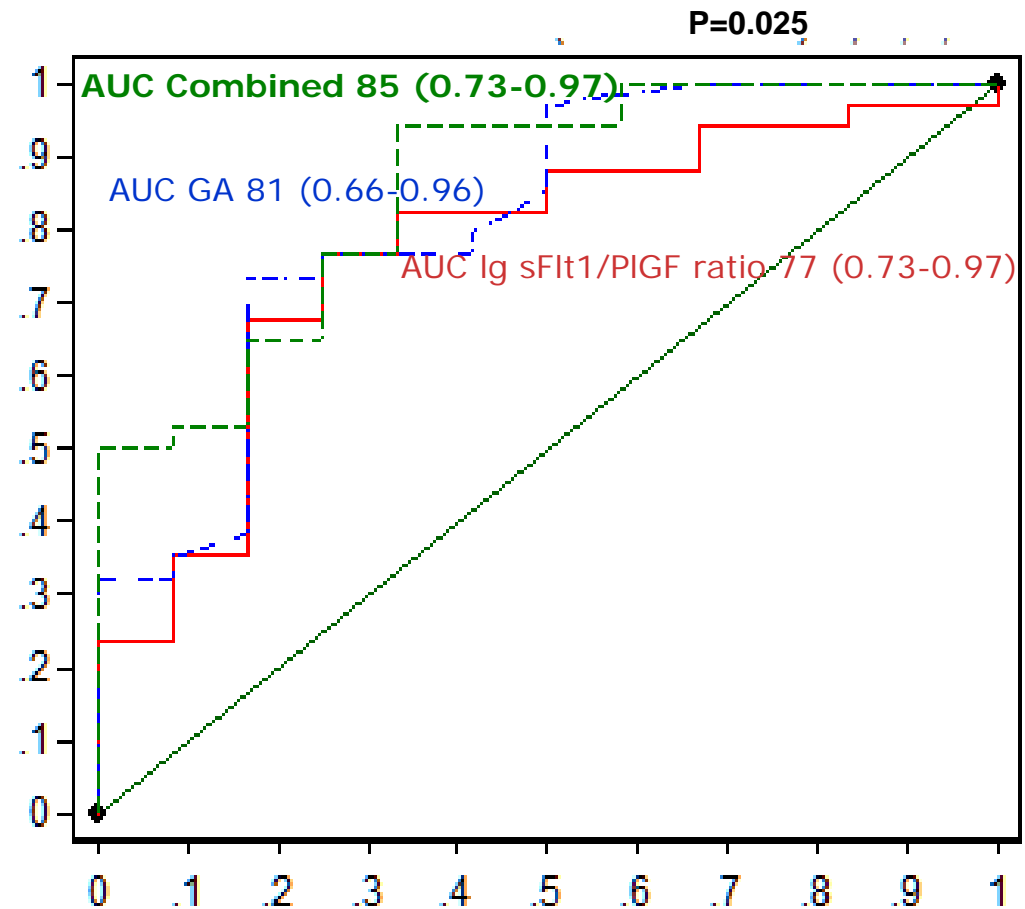


- ü No differences in the ratio progression were observed according to the outcome.

RESULTS:

Predictive performance of sFlt1/PIGF ratio – Logistic regression

Screening test	OR	(95% CI)	P-value
GA	0.56	(0.37; 0.83)	0.004
sFlt1/PIGF	3.04	(1.21; 7.62)	0.017
Blood pressure	1.01	0.97; 1.06)	0.62
Creat	2.16	0.10; 6.61	0.34
ALT	0.95	(0.98; 1.00)	0.34
LDH	1.01	(1.00; 1.01)	0.13



- ü sFlt-1/PIGF ratio in combination with gestational age may be useful for the prognostic assessment of maternal and fetal complications at the time of diagnosis of early-onset PE.

TAKE HOME MESSAGES

Se recomienda centrar esfuerzos en las pacientes con sospecha clínica de preeclampsia, donde existen más riesgo de acontecimientos adversos maternos y fetales.

El ratio sFlt1/PlGF ha demostrado su utilidad en discriminar aquellas pacientes con riesgo de desarrollar la enfermedad respecto a las pacientes que no van a desarrollar la enfermedad en las próximas 1 y 4 semanas.

El ratio sFlt1/PlGF es más eficaz que los signos y síntomas clásicos de la enfermedad para determinar aquellas pacientes con mayor riesgo de complicaciones maternas y/o fetales

En el futuro, los factores angiogénicos se incorporarán a la definición, pronóstico y monitorización de la PE

**PIGF-based testing to help diagnose
suspected pre-eclampsia (Triage PIGF
test, Elecsys immunoassay sFlt-1/PIGF
ratio, DELFIA Xpress PIGF 1-2-3 test, and
BRAHMS sFlt-1 Kryptor/BRAHMS PIGF
plus Kryptor PE ratio)**

Diagnostics guidance

Published: 11 May 2016

[nice.org.uk/guidance/dg23](https://www.nice.org.uk/guidance/dg23)

Recomendaciones

1.-The Triage PIGF test and the Elecsys immunoassay sFlt-1/PIGF ratio, used with standard clinical assessment and subsequent clinical follow-up, are recommended to help **rule-out** pre-eclampsia in women presenting with **suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation.**

2.-The Triage PIGF test and the Elecsys immunoassay sFlt-1/PIGF ratio, used with standard clinical assessment and subsequent clinical follow-up, show promise in helping to diagnose (**rule-in**) pre-eclampsia in women presenting **with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation.** However, there is currently **insufficient evidence** to recommend their routine adoption for diagnosing pre-eclampsia in the NHS



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Evaluación y Fomento de la
Investigación



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de Desarrollo Regional
"Una manera de hacer Europa"

2016

**CONVOCATORIA DE AYUDAS DE PROYECTOS DE INVESTIGACIÓN EN SALUD
MEMORIA DE SOLICITUD**

Expediente Nº
PI16/00375

TITULO: Incorporación del ratio sFlt1/PIGF en el diagnóstico y clasificación de preeclampsia: Ensayo clínico randomizado (EuroPE estudio)

INVESTIGADOR/A PRINCIPAL: ELISA LLURBA OLIVÉ

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Red
SAMID

Sospecha clínica
(criterios PROGNOSIS)

PE clínica
(gold standard: definición
ISSHP)

RANDOMIZACIÓN

Grupo Estudio (RATIO)

Grupo Control (No-RATIO)

<38

38-84

>85

TA >140/90 y
labstix 2+ / >
300mg/d
Prot.
+
>210

TA >140/90 y
labstix 2+ / >
300mg/d Prot.
+
>600

TA >140/90 Y
labstix 2+ / >
300mg/d Prot.

TA <140/90 Y
labstix ≤1+ /
<300mg/d Prot.

No PE –
reevaluar en 4
semanas

No PE –
reevaluar en 1
semana

Diagnóstico
de PE
(manejo según
protocolo)

Diagnóstico
de PE grave
(manejo según
protocolo)

Finalizar
gestación

Diagnóstico
de PE
(manejo según
protocolo)

Reevaluar según
protocolo

Objetivo 1ario: mejores resultados materno-fetales en grupo RATIO



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MULTIPLE PREGNANCIES

The Elecsys® immunoassay sFlt-1/PIGF ratio, sFlt-1, and PIGF reference ranges in normal multiple pregnancies

Median (5th–95th percentile)	Gestational age (w+d)					
	10+0–14+6	15+0–19+6	20+0–23+6	24+0–28+6	29+0–33+6	34+0–36+6
	Multiple					
	n=75	n=201	n=180	n=192	n=77	n=33
sFlt-1/PIGF ratio	30.73 (6.84–50.22)	6.35 (2.29–14.82)	3.82 (1.34–11.62)	4.31 (1.32–43.68)	41.56 (4.53–152.53)	72.97 (24.15–98.22)
sFlt-1	1993 (1009–4457)	2461 (1291–5090)	2560 (1287–4815)	2982 (1483–10135)	8909 (2483–25605)	11958 (6492–56670)
PIGF	71 (31–321)	400 (195–201)	637 (280–1637)	665 (167–1796)	255 (87–858)	213 (93–395)

Table. NPV using the sFlt-1/PIGF ratio cut-off value of 38 to rule out preeclampsia within one, two, three, and four weeks after testing

% (95% CI)	Within 1 week	Within 2 weeks	Within 3 weeks	Within 4 weeks
NPV	99.3 (97.9–99.9)	97.9 (96.0–99.0)	95.7 (93.3–97.5)	94.3 (91.7–96.3)
Sensitivity	80.0 (51.9–95.7)	78.0 (62.4–89.4)	70.0 (56.8–81.2)	66.2 (54.0–77.0)
Specificity	78.3 (74.6–81.7)	81.1 (77.5–84.4)	82.4 (78.8–85.7)	83.1 (79.4–86.3)