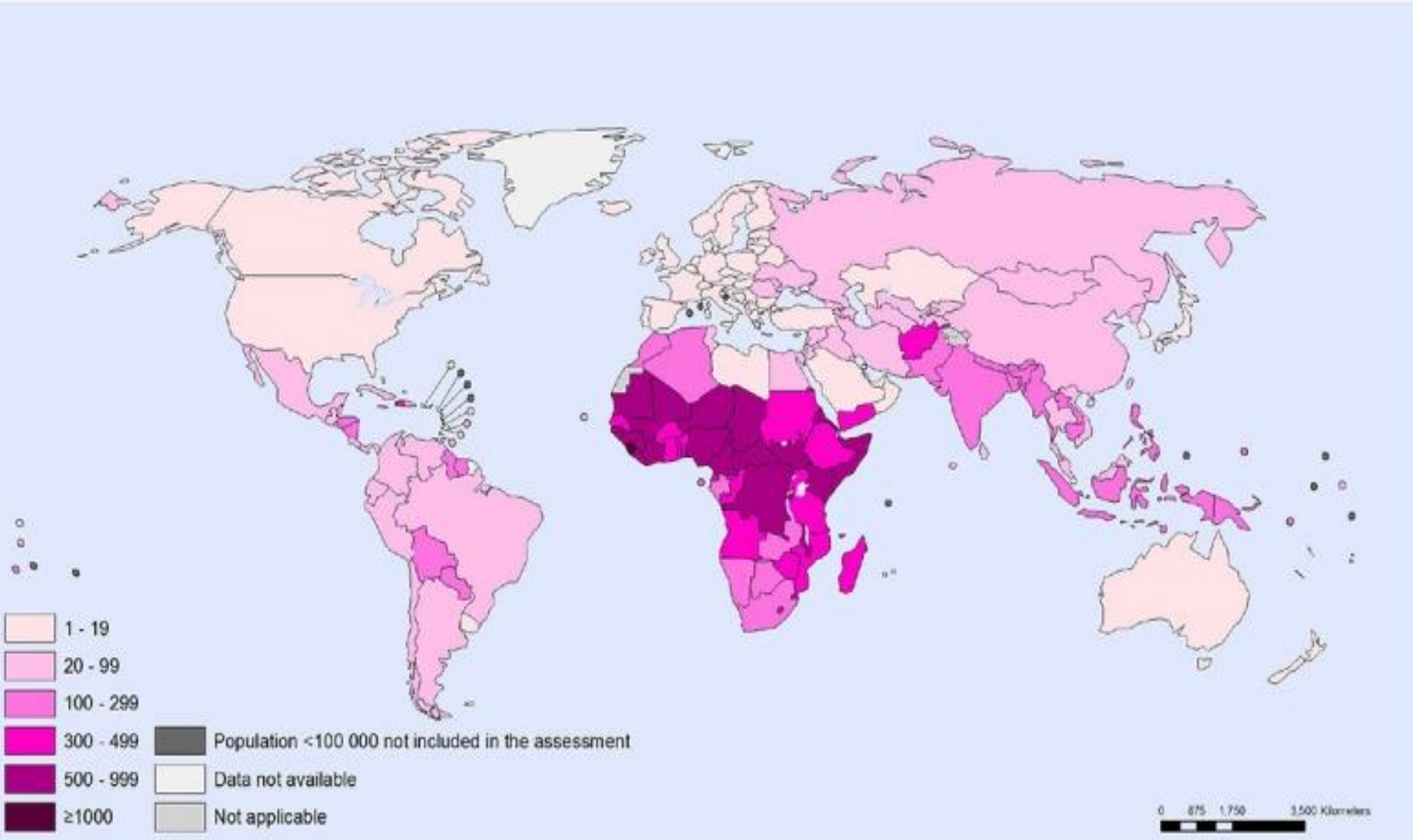
PREECLAMPSIA
CAN DIAGNOSIS– SHORT- TERM PREDICTION?

PGs. Huỳnh Nguyễn Khánh Trang

Maternal mortality ratio (per 100 000 live births), 2015



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization
Source - WHO Trends in Maternal Mortality 1990 to 2015

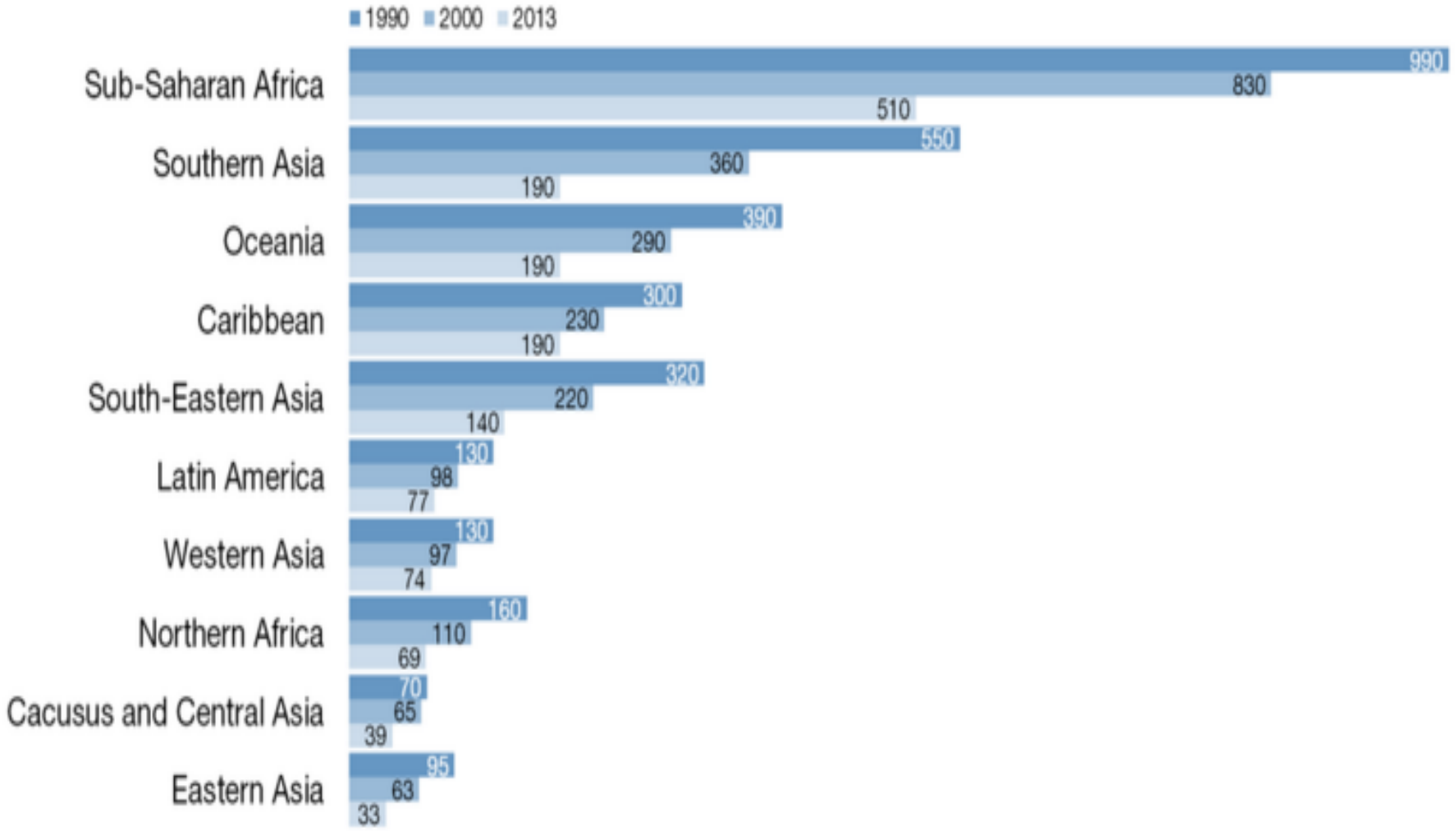
World Health Organization

Maternal deaths per 100,000 live births

Women aged 15-49 in 1990, 2000, and 2013

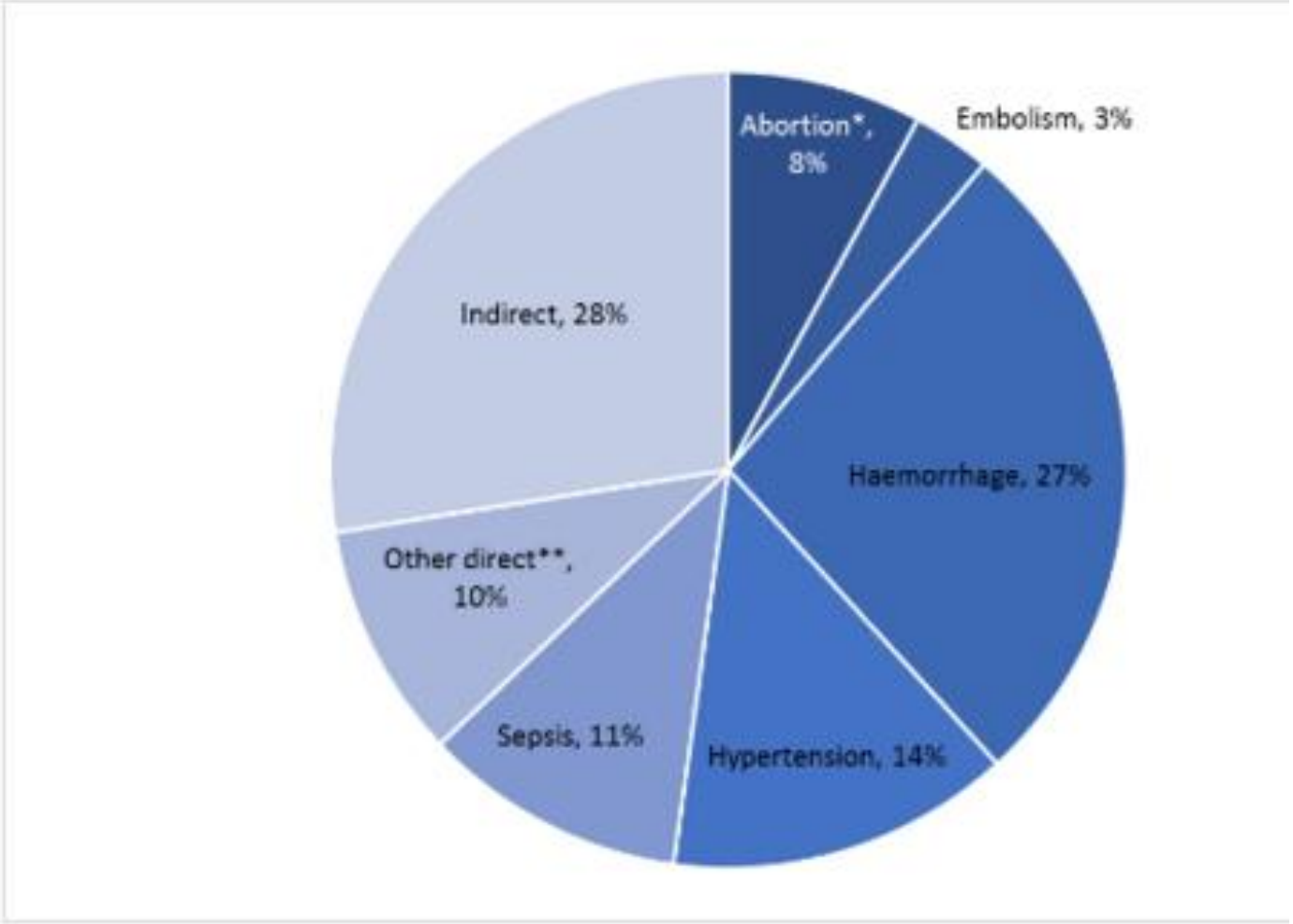
WORLD ECONOMIC FORUM

COMMITTED TO IMPROVING THE STATE OF THE WORLD



Source: The Millennium Development Goals Report 2015

The causes of maternal death are mostly preventable

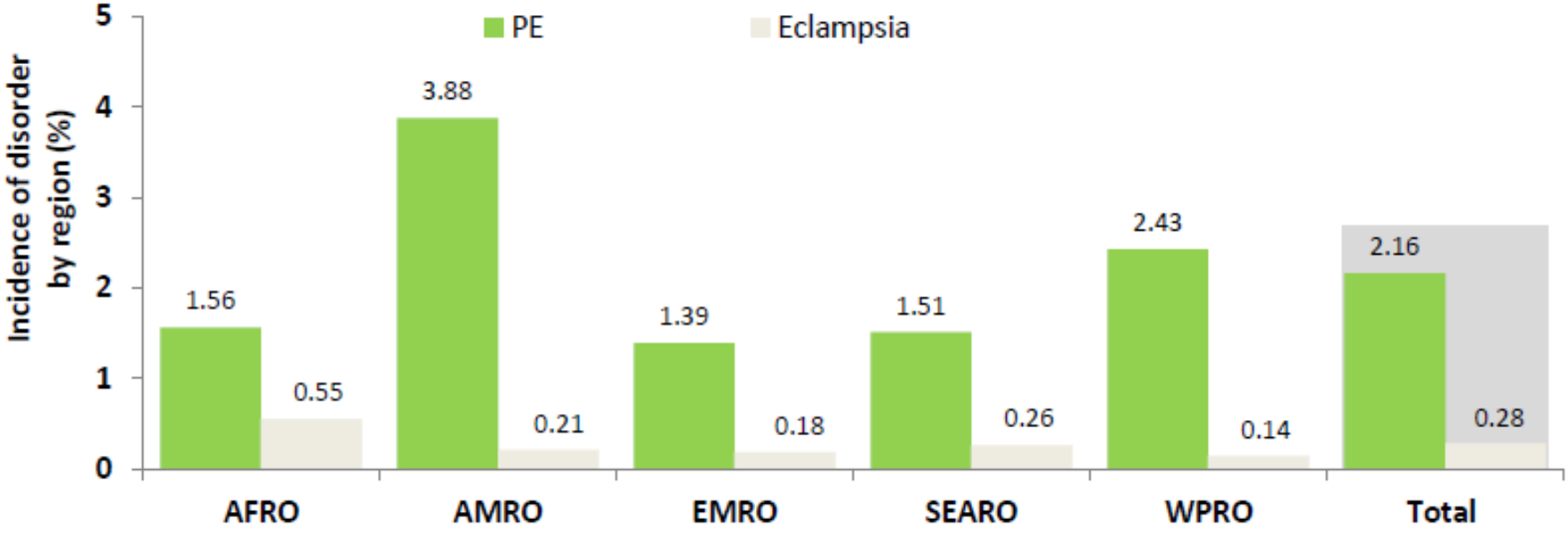


*Nearly all (99 per cent) of abortion deaths are due to unsafe abortions.

**This category includes deaths due to obstructed labour or anaemia.

Source: Source: Say L et al. 2014.

Incidence of PE and eclampsia by region



Across five WHO regions comprising 29 countries, the global incidence of PE and eclampsia was **2.16% and 0.28%**, respectively

Abalos et al (2014). *BJOG* 121 Suppl 1:14-24

AFRO: African region; AMRO: American region; EMRO: Eastern Mediterranean region; PE: Preeclampsia; SEARO: South-East Asia region; WHO: World health organisation; WPRO: Western Pacific region

Preeclampsia Awareness

2014 Survey Results Show:

PREECLAMPSIA foundation

High overall awareness of preeclampsia among expectant and new mothers*

83% had heard of preeclampsia

Yet despite high overall awareness, there is less knowledge of the symptoms

More than half
of respondents did not associate many known symptoms with preeclampsia

Most are also aware that this serious condition related to high blood pressure requires immediate medical evaluation

99% knew
preeclampsia is serious, even life-threatening, for mother and baby

88% knew
high blood pressure is a sign of preeclampsia

96% would call
their doctor or midwife if they experienced symptoms

Other important aspects of preeclampsia are also less known

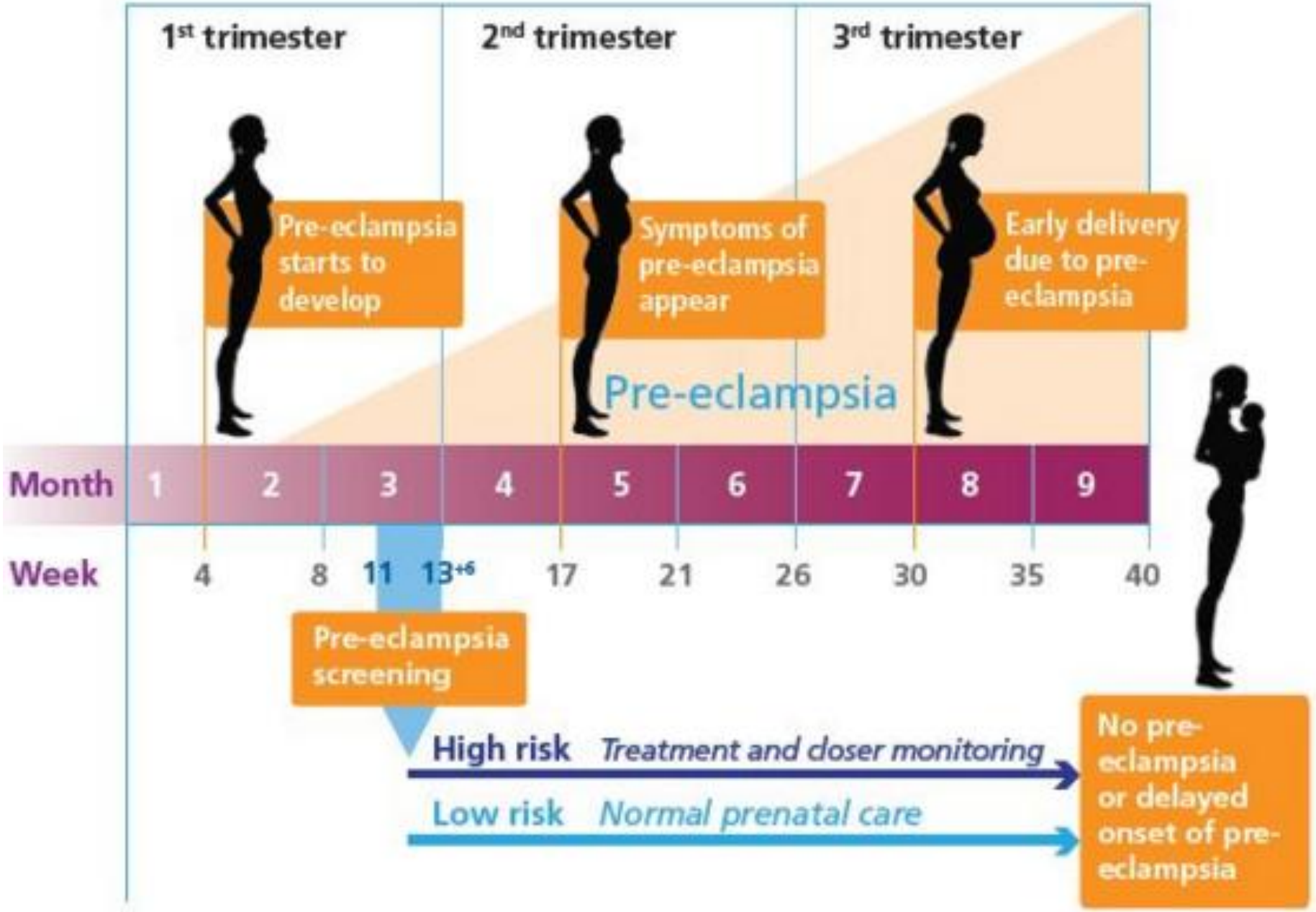
44% didn't know
that preeclampsia can occur up to six weeks after delivery

46% didn't know
that women with preeclampsia are at greater risk for future health problems

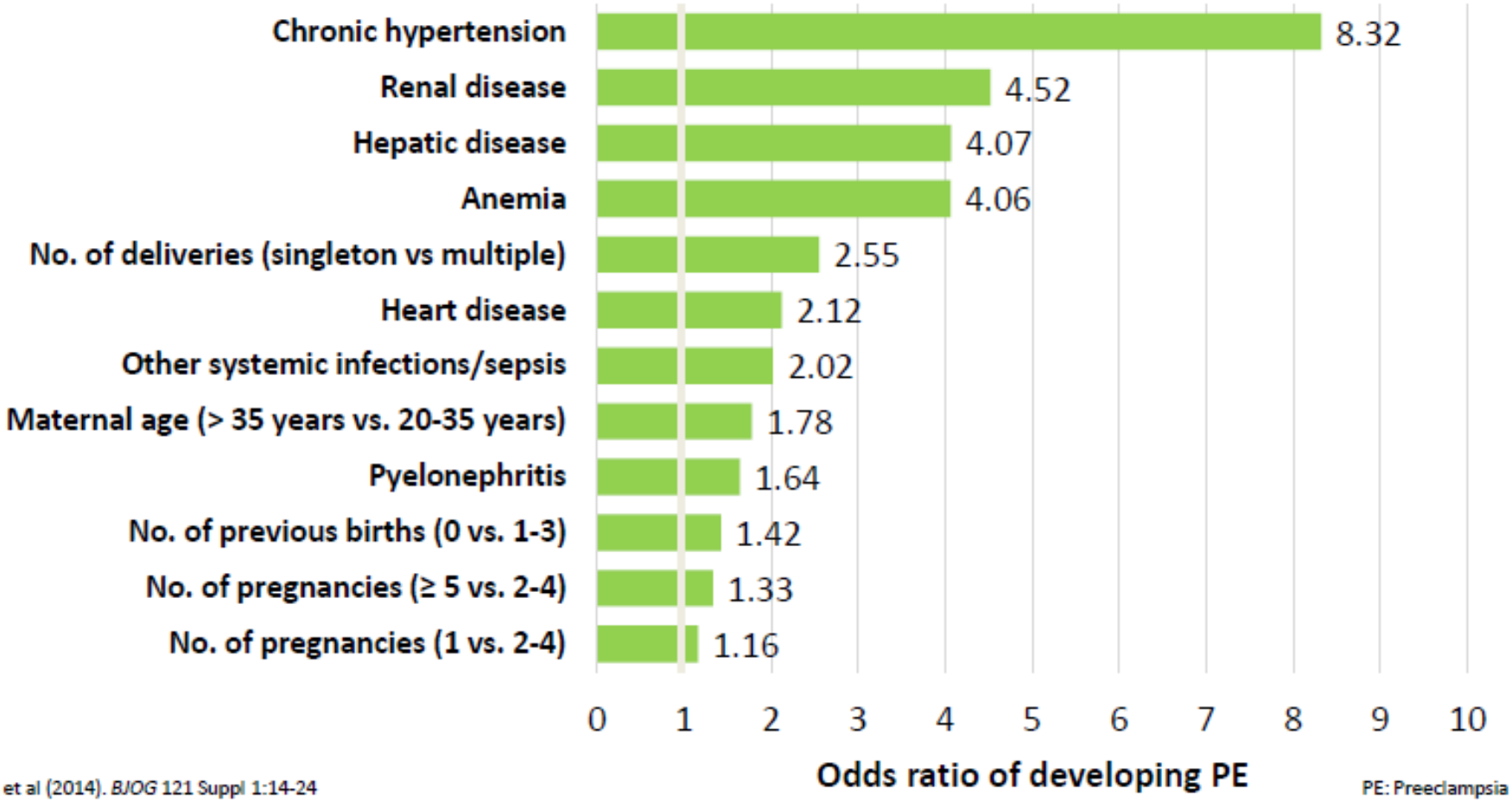
*Survey conducted among visitors to the BabyCenter website from January 17 to January 20, 2014. Total of 1,591 respondents completed the survey; qualified respondents defined as female U.S. residents, 18 years or older, who are pregnant or have at least one child three years of age or younger.

Survey by BabyCenter®

Design by rEVO Biologics Inc.


1st trimester
2nd trimester
3rd trimester
Pre-eclampsia starts to develop
Symptoms of pre-eclampsia appear
Early delivery due to pre-eclampsia
Pre-eclampsia
Month
1
2
3
4
5
6
7
8
9
Week
4
8
11
13+6
17
21
26
30
35
40
Pre-eclampsia screening
High risk
Treatment and doser monitoring
Low risk
Normal prenatal care
No pre-eclampsia or delayed onset of pre-eclampsia

Risk factors



Abalos et al (2014). *BJOG* 121 Suppl 1:14-24

PE: Preeclampsia

Before pregnancy

Primiparity

Previous preeclamptic pregnancy

Chronic hypertension, chronic renal disease, or both

History of thrombophilia

Multifetal pregnancy

In vitro fertilization

Family history of preeclampsia

Type I diabetes mellitus or type II diabetes mellitus

Obesity

Systemic lupus erythematosus

Advanced maternal age (older than 40 years)

Reprinted from American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Washington, DC: American College of Obstetricians and Gynecologists; 2013.

Risk factors and effective management of preeclampsia

Fred A English,[1] Louise C Kenny,[1] Fergus P McCarthy[1,2]

[1]Irish Centre for Fetal and Neonatal Translational Research (INFANT), Department of Obstetrics and Gynaecology, University College Cork, Cork, Ireland; [2]Women's Health Academic Centre, King's Health Partners, St Thomas' Hospital, London, UK

Risk factor	Mean RR (95% CI)
Antiphospholipid syndrome	9.72 (4.34–21.75)
Relative risk of preeclampsia	7.19 (5.85–8.83)
Previous preeclampsia	7.19 (5.85–8.83)
Insulin-dependent diabetes	3.56 (2.54–4.99)
Multiple pregnancy	2.93 (2.04–4.21)
Nulliparity	2.91 (1.28–6.61)
Family history of preeclampsia	2.90 (1.70–4.93)
Obesity	2.47 (1.66–3.67)
Age >40 years	1.96 (1.34–2.87)
Preexisting hypertension	1.38 (1.01–1.87)

THE FIRST TRIMESTER

Early screening for preeclampsia

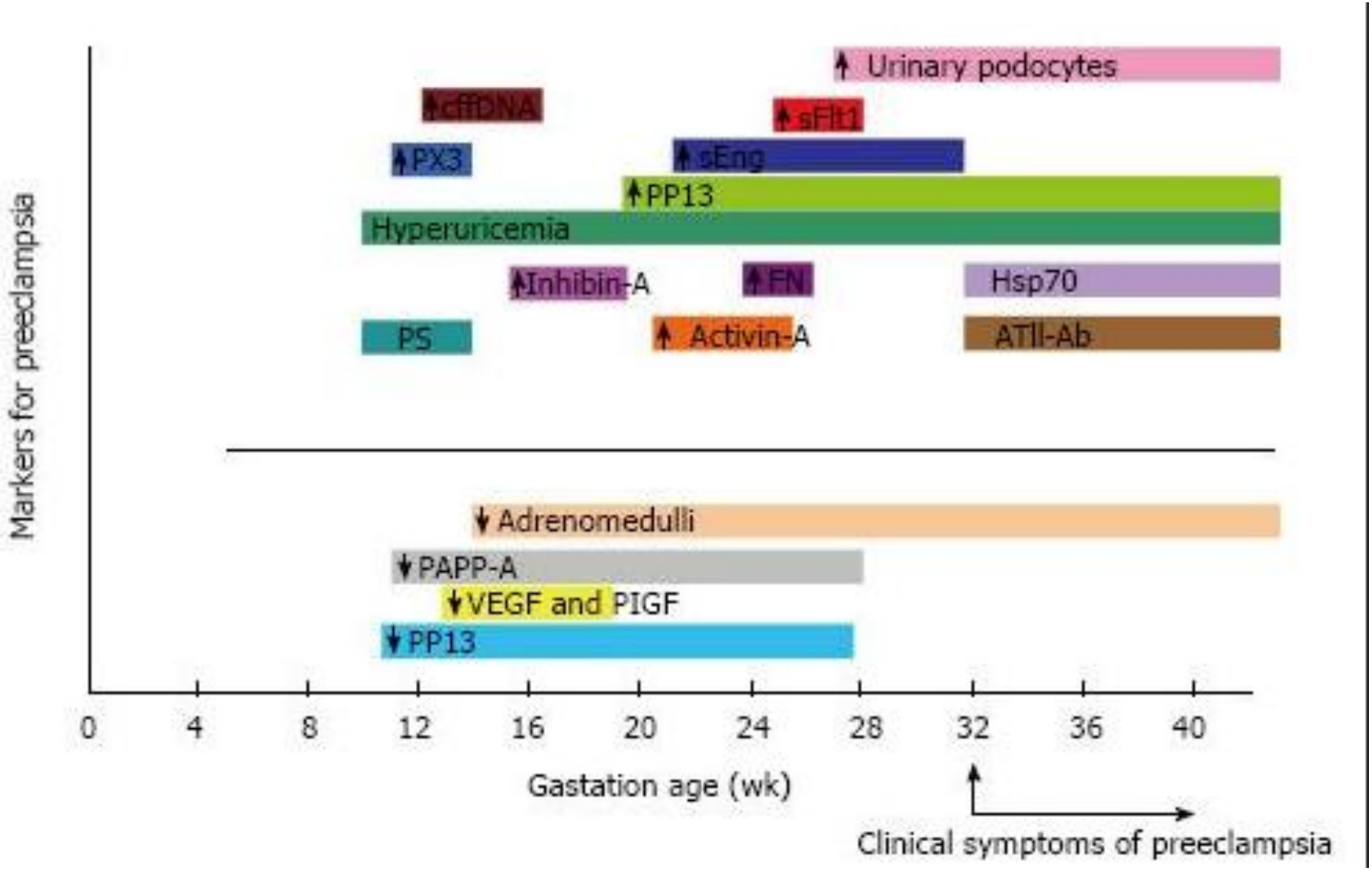
First trimester multiparametric model detection rates for early-onset PE

DR at 5% FPR	History	MAP	uA-PI	PAPP-A	PlGF	Reference
33	X					Yu et al.[66] Akolekar et al.[67]
38			X			Poon et al.[36]
47	X			X		Akolekar et al.[67]
54	X				X	Akolekar et al.[67]
60	X		X	X		Foidart et al.[68]
78	X		X		X	Foidart et al.[68]
78	X	X	X	X	X	Akolekar et al.[67]
84	X	X	X	X		Poon et al.[69]
89	X	X	X		X	Poon et al.[25]
93	X	X	X	X	X	Poon et al.[70]

History: body mass index, family history of PE, previous PE, ethnicity, smoking; MAP: mean arterial blood pressure; uA-PI: uterine artery pulsatility index.

Rev. Bras. Ginecol. Obstet. vol.33 no.11 Rio de Janeiro Nov. 2011

http://dx.doi.org/10.1590/S0100-72032011001100008


Markers for preeclampsia
Urinary podocytes
cffDNA
sFlt1
PX3
sEng
PP13
Hyperuricemia
Inhibin-A
FN
Hsp70
PS
Activin-A
ATII-Ab
Adrenomeduli
PAPP-A
VEGF and PIGF
PP13
0
4
8
12
16
20
24
28
32
36
40
Gastation age (wk)
Clinical symptoms of preeclampsia

AFTER THE 1ST TRIMESTER

Preeclampsia

Definition

Pregnancy disorder associated with

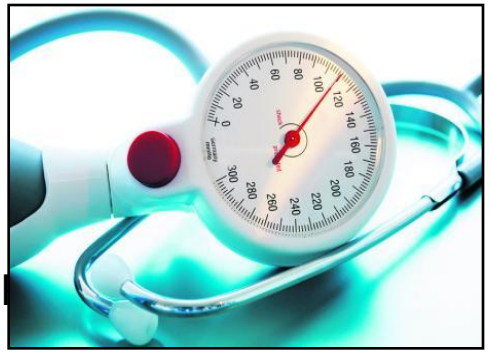
New onset of

→ **Hypertension** (>140 / 90 mmHg)

(Systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP
occasions ≥6 hour apart, but within 1 week) and

→ **Proteinuria** (≥ 0.3 g / 24 h)

after 20 weeks' gestation



Brown MA et al.: The Classification and Diagnosis of the Hypertensive Disorders of Pregnancy: Statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001; 20: ix–xiv

Diagnostic tools for PE

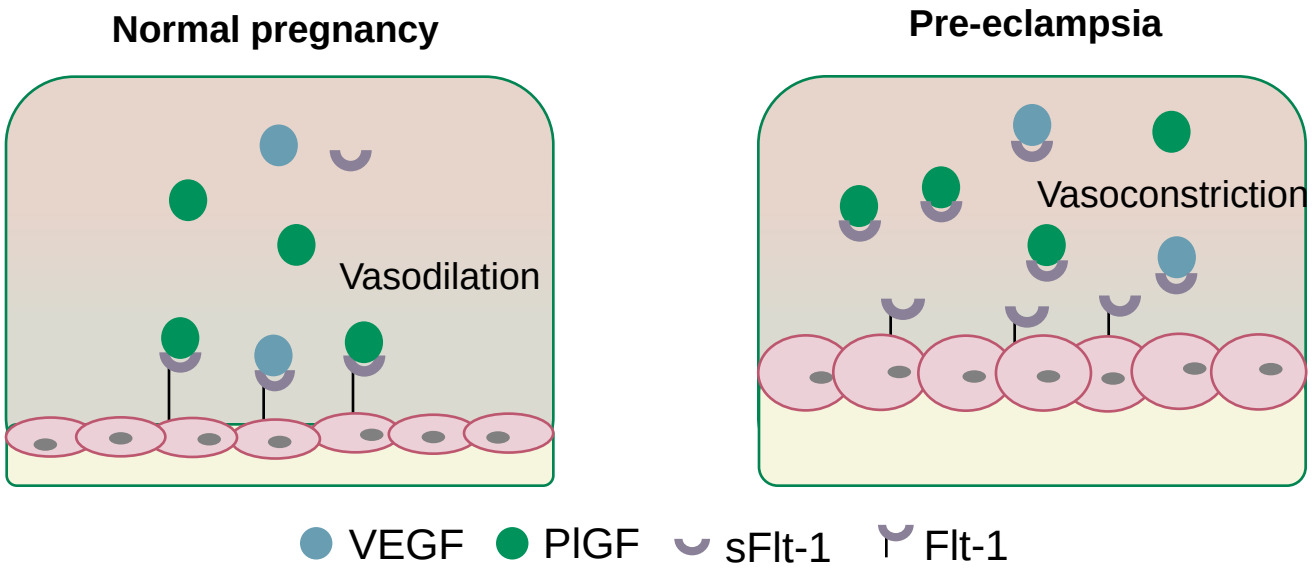
"Gold standard" tests have a low sensitivity and specificity for disease progression and severity

- Current clinical diagnosis is based on hypertension and proteinuria[1–3]
- Improved diagnostic tests are required for this complex syndrome
  - Measurement of proteinuria is prone to inaccuracies
  - PE complications often occur before proteinuria becomes significant
  - Diagnostic standards are poor in predicting PE-related adverse outcomes[4]

[1]NCCWCH. (2010). *NICE Clinical Guidelines* No. 107;
[2]WHO: Geneva. (2011). *WHO guidelines approved by the Guidelines Review Committee*;
[3]ACOG (2013). *Obstet Gynecol* 122, 1122–1131;
[4]Zhang, J., et al. (2001). *Obstet Gynecol* 97, 261–267.

Angiogenic markers play a role in pathogenesis of PE

- Disturbances in angiogenesis contribute to PE pathogenesis[1]
- ↑ anti-angiogenic sFlt-1and ↓ pro-angiogenic PlGF = ↑ **sFlt-1/PlGF ratio**



[1]Maynard, S.E., et al. (2003). *J Clin Invest* 111, 649–658.

PROGNOSIS

Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study

Zeisler et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. New Engl J Med 2016;374:13–22

PROGNOSIS:

Prediction of Short-Term Outcome in Pregnant Women with Suspected

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.

PROGNOSIS:

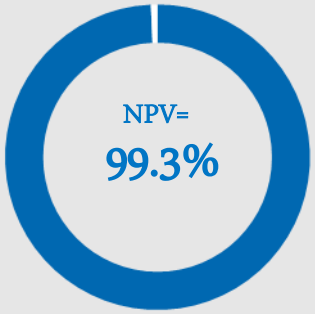
investigating the sFlt-1/PlGF ratio as a predictive tool for preeclampsia

New Engl J Med 2016; 374: 13–22

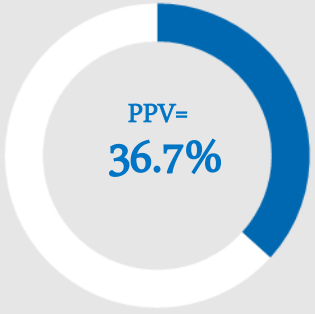
PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase 1

Executive summary

PROGNOSIS is the first study to demonstrate that the Roche ELECSYS® immunoassay sFlt-1/PlGF ratio ≤38 is useful for predicting the short-term absence of preeclampsia in women with clinical suspicion of the syndrome



for *ruling out*
preeclampsia within 1 week



for *ruling in*
preeclampsia within 4 weeks

An sFlt-1/PlGF ratio >38 may help predict whether pregnant women with suspicion of preeclampsia will develop preeclampsia within 4 weeks

Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

New Gestational Phase–Specific Cutoff Values for the Use of the Soluble fms-Like Tyrosine Kinase-1/Placental Growth Factor Ratio as a Diagnostic Test for Preeclampsia

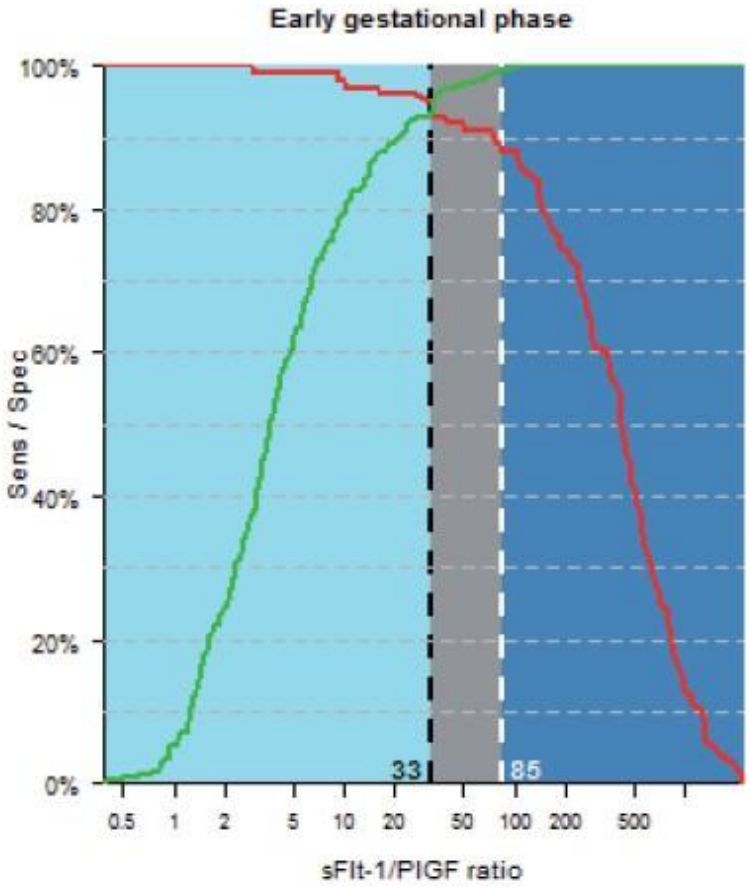
Stefan Verlohren, Ignacio Herraiz, Olav Lapaire, Dietmar Schlembach, Harald Zeisler, Pavel Calda, Joan Sabria, Filiz Markfeld-Erol, Alberto Galindo, Katharina Schoofs, Barbara Denk and Holger Stepan

sFlt-1/PlGF ratio: *data published*

Early gestational phase

(20+0 – 33+6 wks)

sFlt-1/PlGF ratio	sensitivity	specificity
Rule out cut-off 33	**95.00%**	94.00%
Rule in cut-off 85	88.00%	**99.50%**

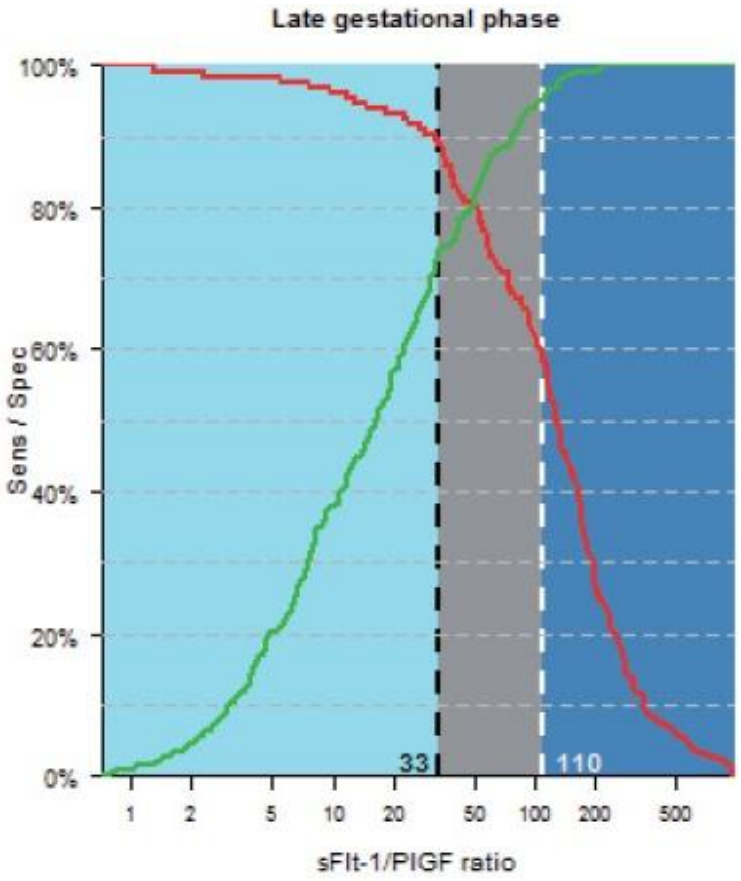


sFlt-1/PlGF ratio: *data published*

Late gestational phase

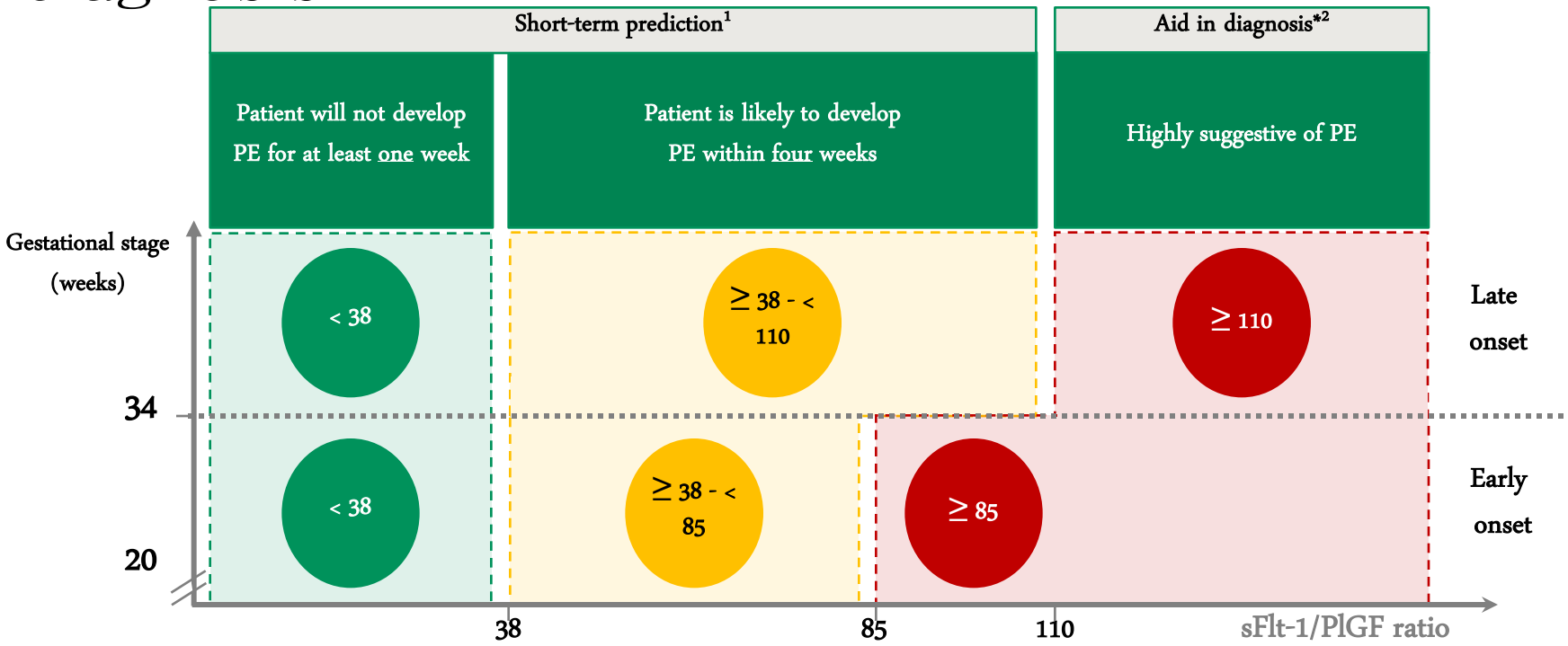
(34+0 wks – delivery)

sFlt-1/PlGF ratio	sensitivity	specificity
Rule out cut-off 33	**89.55%**	73.13%
Rule in cut-off 110	58.21%	**95.52%**



sFlt-1/PlGF ratio

Short-term prediction of PE and aid in diagnosis



Using gestational age-specific cut-offs, the sFlt-1/PlGF ratio can aid in the diagnosis and short-term prediction of PE

1. Zeisler et al (2014). 20th COGI World Congress 2014
2. Verlohren et al (2014). *Hypertension* 63:346-352

* Used in addition to other accepted diagnostic tools and clinical information

PE: Preeclampsia; PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1

The sFlt-1/PlGF ratio* helps guide clinical management

A low sFlt-1/PlGF ratio requires low intensity management

Routine visit

Low sFlt-1/PlGF ratio **(< 38)**

PE ruled out for one week

Low intensity management

Patient managed in midwife-led hospital outpatient setting with an average weekly appointment for routine tests including:

- Proteinuria
- Blood pressure

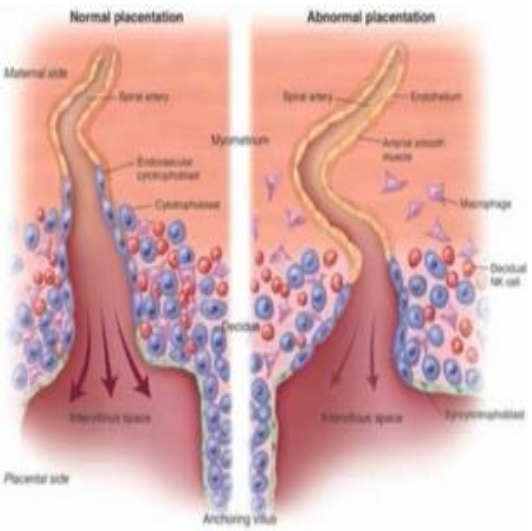
* Roche Elecsys® immunoassay sFlt-1/PlGF ratio

PE: Preeclampsia; PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1

1. NICE (2011). Hypertension in pregnancy: the management of hypertensive disorders during pregnancy
2. Stepan et al (2015). *Ultrasound Obstet Gynecol* 45:241-246

The sFlt-1/PlGF ratio* helps guide clinical management

A high sFlt-1/PlGF ratio requires high intensity management



Routine visit

Early onset PE: high sFlt-1/PlGF ratio **(> 85)**[1]

Late onset PE: high sFlt-1/PlGF ratio **(> 110)**[1]

sFlt-1 **PlGF**

Diagnosis of PE or placenta-related disorder is highly likely

High intensity management

Patient admitted to hospital for monitoring of:

- Proteinuria (daily)
- Blood pressure (at least four times per day)
- Following blood tests two to three times per week:
  - Kidney function
  - Electrolytes
  - Full blood count
  - Transaminases
  - Bilirubin
- Patient receives oral labetalol twice daily

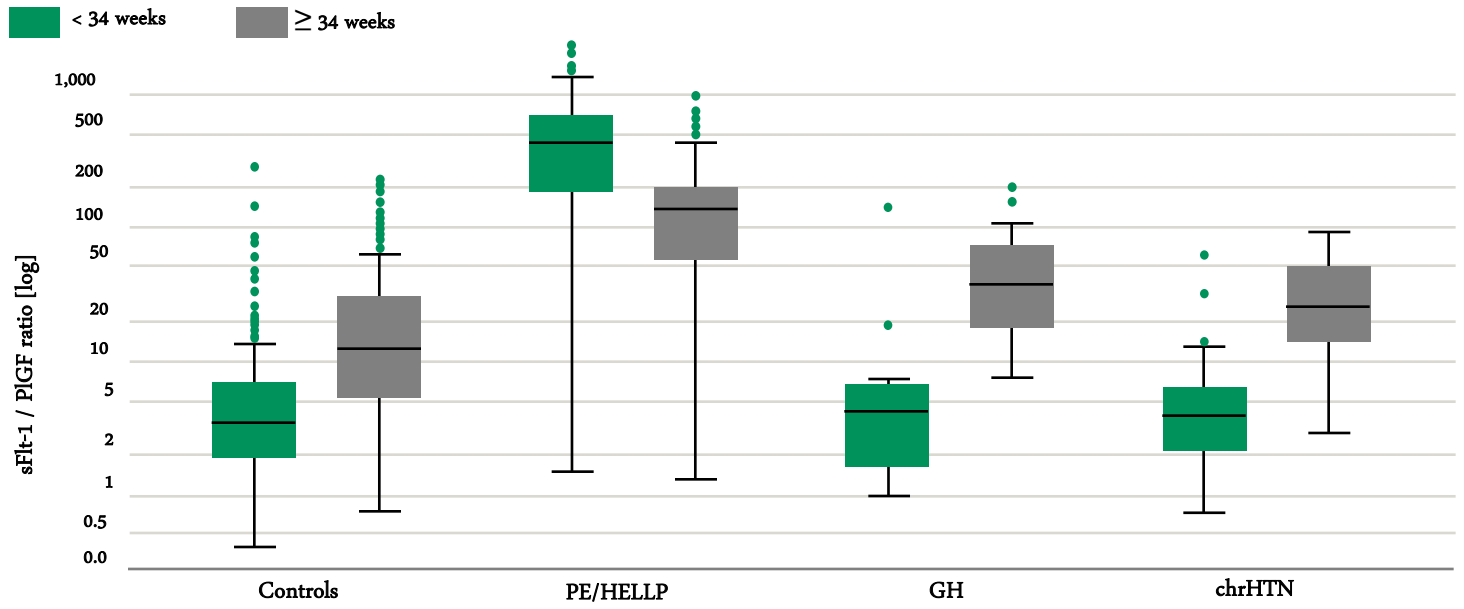
* Roche Elecsys® immunoassay sFlt-1/PlGF ratio

1. NICE (2011). Hypertension in pregnancy: the management of hypertensive disorders during pregnancy.
2. Stepan et al (2015). *Ultrasound Obstet Gynecol* 45:241-246

PE: Preeclampsia; PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1

sFlt-1/PlGF ratio can support differential diagnosis by distinguishing PE from other hypertensive disorders of pregnancy

sFlt-1/PlGF ratio in patients with PE/HELLP, GH, chrHTN, and healthy controls



The sFlt-1/PlGF ratio can reliably discriminate between different types of pregnancy-related hypertensive disorders

chrHTN: Chronic hypertension; GH: Gestational hypertension; HELLP: Hemolysis, elevated liver enzymes, low platelets; PE: Preeclampsia PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1

Verlohren et al (2012). *Am J Obstet Gynecol* 206:58.e1-8

sFlt-1/PlGF ratio can identify women with a higher risk of adverse pregnancy outcomes

Early onset PE: high sFlt-1/PlGF ratio **(> 85)**[1]

Late onset PE: high sFlt-1/PlGF ratio **(> 110)**[1]

Adverse outcomes[2]

- Placental abruption
- Elevated liver enzymes
- Low platelets
- Small for gestational age birth weight
- Abnormal uterine artery doppler

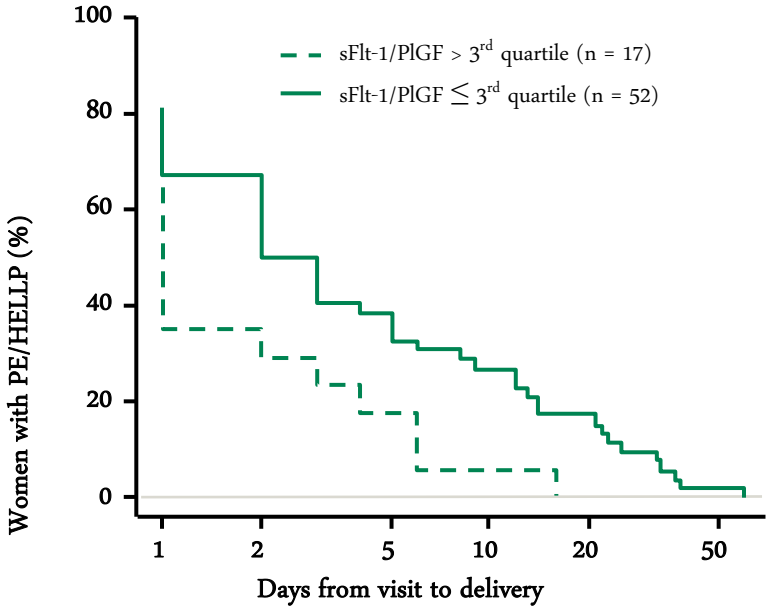
Women with a high sFlt-1 ratio at presentation have a higher risk of adverse pregnancy outcomes[2]

1. Verlohren et al (2014). *Hypertension* 63:346-352
2. Rana et al (2012). *Circulation* 125:911-919

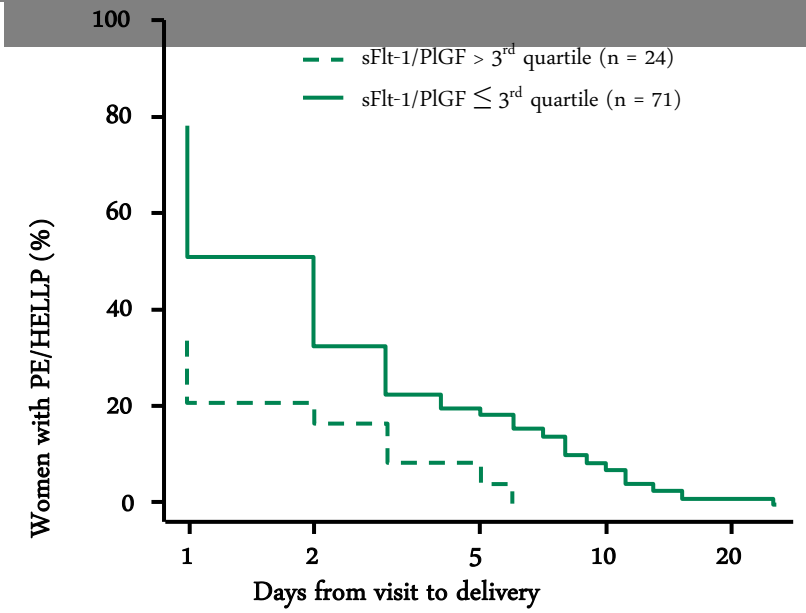
PE: Preeclampsia; PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1

sFlt-1/PlGF ratio can indicate an increased risk of imminent delivery

Time to delivery in women with PE/HELLP < 34 wks



Time to delivery in women with PE/HELLP ≥ 34 wks



A high sFlt-1/PlGF ratio is associated with a significantly increased risk for immediate delivery

HELLP: Hemolysis, elevated liver enzymes, low platelets;
PE: Preeclampsia; PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1

Verlohren et al (2012). *Am J Obstet Gynecol* 206,58:e1-8

Cost saving

sFlt-1/PlGF ratio

Aid in short-term prediction

sFlt-1/PlGF ratio enables clinicians to avoid unnecessary hospitalisations by reliably excluding PE for at least one week. Expecting mothers are therefore saved from the stress of intensive monitoring and the disruption to their home life caused by a hospital stay. Furthermore, the cost of unnecessary care is reduced, and clinicians can focus on those patients who need more attention and care.

Supporting statements

- Using the sFlt-1/PlGF ratio, an sFlt-1/PlGF ratio < 38 rules out PE for at least one week, irrespective of gestational age, providing reassurance to the physician and the patient. With more than 80% of patients belonging to this patient group, clinicians are able to exclude the majority of patients, keeping them in routine antenatal care, and focus on those who need more attention and care.[1,2]
- Use of the sFlt-1/PlGF test for screening and prediction of PE is recommended by the German clinical and diagnostic guidelines (DGGG)[3]
- Using sFlt-1/PlGF ratio, a saving in health-care costs of GBP 399 per patient can be made by reducing the number of women who are hospitalised[4]

1. Stepan et al (2015). *Ultrasound Obstet Gynecol* 45:241-24
2. Zeisler et al (2014). 20th COGI World Congress 2014
6. DGGG Clinical and Diagnostic Guidelines in Hypertension in Pregnancy (2013, diagnostic details updated 2014). Available at: http://www.awmf.org/leitlinien/detail/ll/015-018.html last accessed June 2015
4. Strunz-McKendry et al (2014). 20th COGI World Congress 2014

GBP: British pound; PE: Preeclampsia; PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1

sFlt-1/PlGF ratio may enable cost savings through a significant improvement in PE diagnostic accuracy

UK[1]	Germany[2]	USA[3,4]
With sFlt-1/PlGF ratio: False-negative reduction: **67%** False-positive reduction: **71%**	**With sFlt-1/PlGF ratio:** False-negative reduction: **67%** False-positive reduction: **71%**	**With sFlt-1/PlGF ratio:** False-positive reduction: **91%** True-negative increase: **63%**
Cost saving per patient: **GBP 945**	Cost saving per patient: **EUR 637**	Cost saving per patient: **USD 1,215**
Country saving per year: **GBP 730 million**	Country saving per year: **EUR 436 million**	Country saving per year: **USD 4.8 billion***

*Calculated from number of births in the USA in 2013 (3,932,181)

EUR: Euro; GBP: British pound; PE: Preeclampsia; PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1; USD: Unites States dollar

1. Hadker et al (2010). *J Med Econ* 13:728-737
2. Hadker et al (2013). *Hypertens Pregnancy* 32:105-119
3. Schnettler et al (2013). *BJOG* 120:1224-32
4. CDC (2013). Births and natality.
   Available at http://www.cdc.gov/nchs/fastats/births.htm Last accessed June 2015

Management

Severe preeclampsia-management algorithm