

# **Pre-eclampsia workup:**

## **More perspectives from Biomarkers?**

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# Hypertension



# The triumph of Love



# Being pregnant



# Being pregnant



# Maternal Mortality

	Developed countries	Africa	Asia	Latin America and the Caribbean
Number of datasets	5	8	11	10
Number of maternal deaths	2823	4508	16 089	11 777
Haemorrhage	13.4% (4.7–34.6)	33.9% (13.3–43.6)	30.8% (5.9–48.5)	20.8% (1.1–46.9)
Hypertensive disorders	16.1% (6.7–24.3)	9.1% (3.9–21.9)	9.1% (2.0–34.3)	25.7% (7.9–52.4)
Sepsis/infections	2.1% (0.0–5.9)	9.7% (6.3–12.6)	11.6% (0.0–13.0)	7.7% (0.0–15.1)
Abortion	8.2% (0.0–48.6)	3.9% (0.0–23.8)	5.7% (0.0–13.0)	12.0% (0.0–32.9)
Obstructed labour	0.0%* (0.0–0.0)	4.1% (0.0–10.3)	9.4% (0.0–12.0)	13.4% (0.0–38.9)
Anaemia	0.0%* (0.0–0.0)	3.7% (0.0–13.2)	12.8% (0.0–17.3)	0.1% (0.0–3.9)
HIV/AIDS	0.0%* (0.0–0.0)	6.2% (0.0–13.3)	0.0%* (0.0–0.0)	0.0%* (0.0–0.0)
Ectopic pregnancy	4.9% (0.4–7.4)	0.5% (0.0–3.3)	0.1% (0.0–3.9)	0.5% (0.0–4.5)
Embolism	14.9% (0.0–21.2)	2.0% (0.0–5.6)	0.4% (0.0–51.0)	0.6% (0.0–8.4)
Other direct causes	21.3% (0.0–33.9)	4.9% (0.0–10.3)	1.6% (0.0–25.9)	3.8% (0.0–27.9)
Other indirect causes	14.4% (0.0–51.2)	16.7% (9.1–29.3)	12.5% (0.0–29.2)	3.9% (0.0–25.3)
Unclassified deaths	4.8% (0.0–22.9)	5.4% (0.0–21.8)	6.1% (0.0–16.2)	11.7% (0.0–20.4)

Data are pooled percentages (range), unless stated otherwise. \*Zero indicates that the condition is not reported as a cause of death. Deaths from that cause could have occurred but listed under other or unclassified deaths.

Table 1: Joint distribution of causes of maternal deaths

Khan et al,  
Lancet 2006

**600.000 maternal deaths annually due to pregnancy complications**

**99% in developing countries**

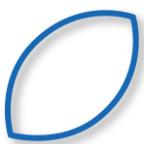
**50.000 caused by PE**

**Hypertensive pregnancy disorders cause 16% of all maternal deaths in developed countries**





## The definition of pre-eclampsia



Blood pressure	<ul style="list-style-type: none"><li>• Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure</li><li>• Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy</li></ul>
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and

Proteinuria	<ul style="list-style-type: none"><li>• Greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection)</li><li>or</li><li>• Protein/creatinine ratio greater than or equal to 0.3*</li><li>• Dipstick reading of 1+ (used only if other quantitative methods not available)</li></ul>
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Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:

Thrombocytopenia	<ul style="list-style-type: none"><li>• Platelet count less than 100,000/microliter</li></ul>
Renal insufficiency	<ul style="list-style-type: none"><li>• Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease</li></ul>
Impaired liver function	<ul style="list-style-type: none"><li>• Elevated blood concentrations of liver transaminases to twice normal concentration</li></ul>
Pulmonary edema	
Cerebral or visual symptoms	

\* Each measured as mg/dL.



## Prevalence of Pre-eclampsia

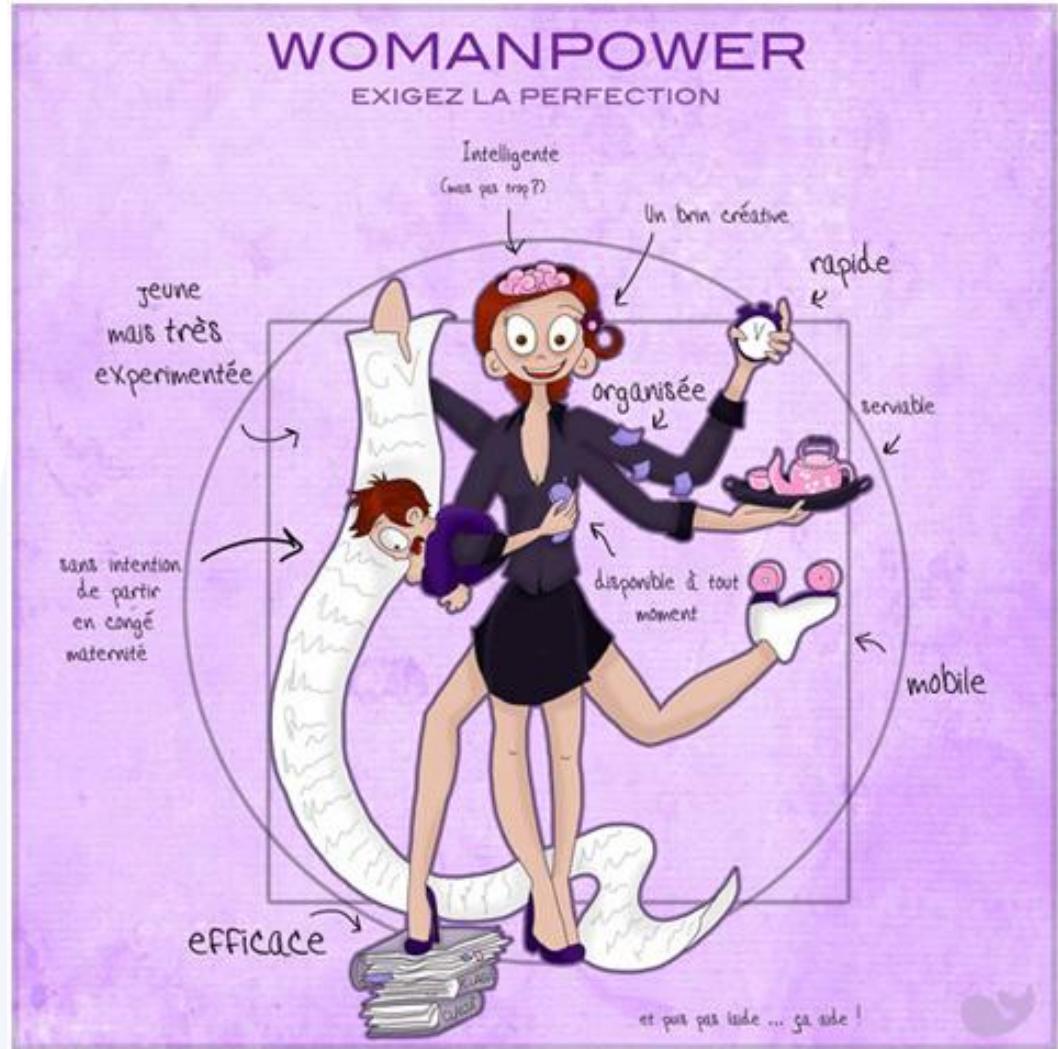
2-8%

**Incidence of 23.6 cases per 1,000 deliveries in the United States.**

Region	Number of data sets	Number of maternal deaths (denominator)	Proportion of maternal deaths caused by hypertensive disorders (%)
Developed countries	5	2,823	16.1
Africa	8	4,508	9.1
Asia	11	16,089	9.1
Latin America and Caribbean	10	11,777	25.7



# Prevalence of Pre-eclampsia



## **Impact of pre-eclampsia on mother and child**



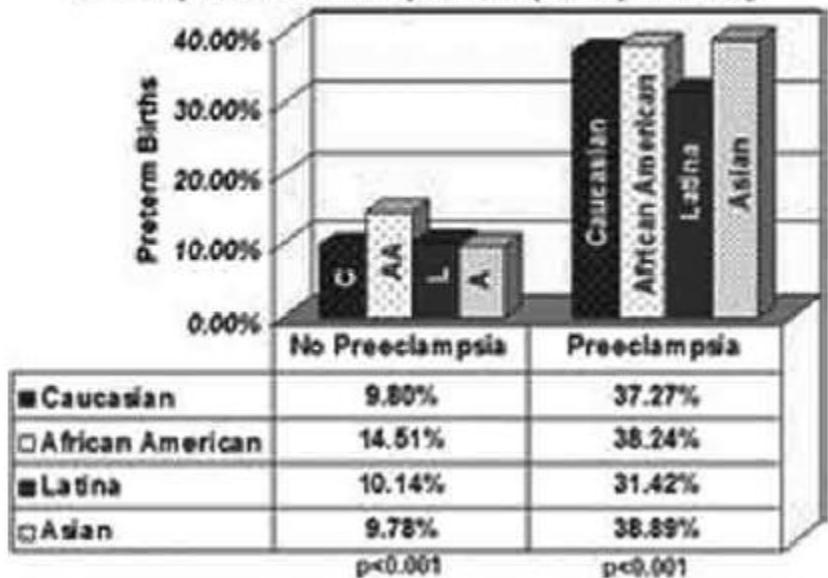
# Fetal Morbidity and Mortality – preterm birth



Hypertensive pregnancy disorders cause 15% of all preterm deliveries



Risk of preterm birth in preeclampsia by ethnicity



Vogel et al, BMJ 2010



# Fetal Morbidity and Mortality

## Long term effects

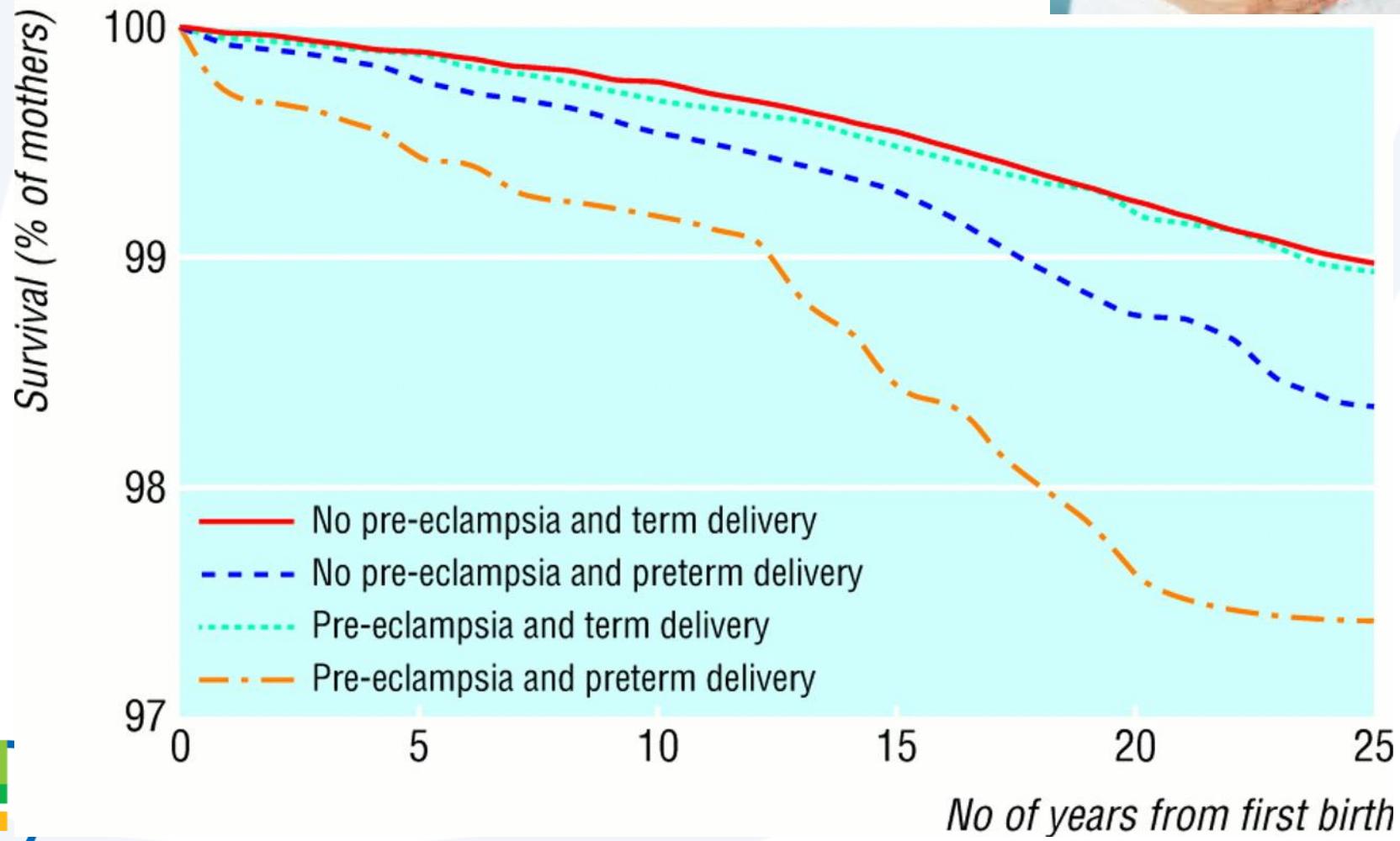


### « Fetal programming »

- ❖ Increased risk for hypertension and cardiovascular diseases in later life
- ❖ Increased prevalence of T2DM in later life



# Longterm hazard for children of pre-eclamptic mothers



# The mother – at risk for cardiovascular disease



Parameter	Term Control (n=50)	GH (n=20)	PE (n=50)	GH Versus Control (P Values)	PE Versus Control (P Values)	PE Versus GH (P Values)
MAP, mm Hg	83 (74–92)	109 (107–118)	113 (106–120)	0.0001	0.0001	0.4
CI, L/min/m <sup>2</sup>	3.2 (2.2–3.9)	2.8 (2.4–3.2)	2.9 (2.1–3.8)	0.6	0.6	0.5
TVRI, (dynes×s <sup>-1</sup> ×cm <sup>-5</sup> )/m <sup>2</sup>	645 (570–840)	951 (756–1086)	716 (574–1036)	0.003	0.012	0.7
Global diastolic dysfunction	7 (14)	2 (15)	20 (40)	0.9	0.007	0.031
Regional diastolic dysfunction†	3 (7)	0	9 (30)	0.6	0.022	0.028
Total LV geometric abnormality	12 (24)	15 (75)	34 (68)	0.0001	0.0001	0.7
Septal bulge	0	0	7 (14)	...	0.019	0.2
LV basal postsystolic shortening Index >25%	1 (2)	1 (5)	9 (18)	0.9	0.011	0.2

\*Values are given as median (interquartile) or no. of patients (percentage).

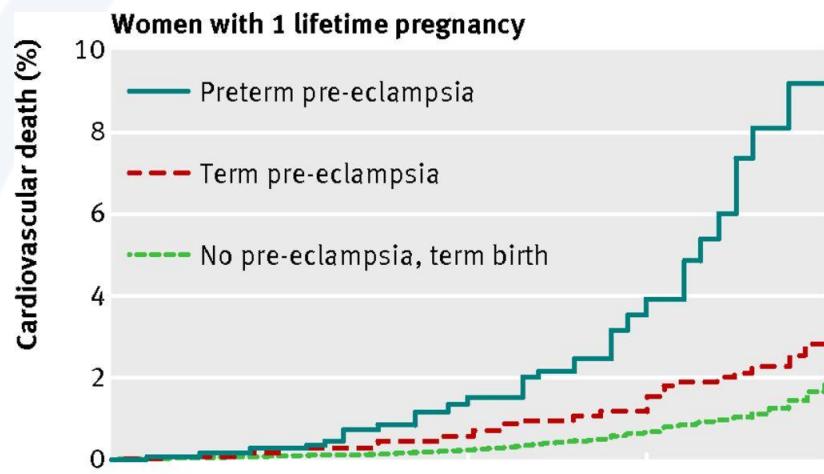
†Regional diastolic dysfunction is computed among patients with normal global diastolic function.

MAP indicates mean arterial pressure; CI, cardiac index; TVRI, total vascular resistance index.



Melchiorre et al., Hypertension 2011

# The mother – at risk for cardiovascular disease



- Women with preterm PE have persistent myocardial and ventricular dysfunction
- The majority of preterm PE women exhibits signs of (asymptomatic) cardiac impairment postpartum
- Preterm PE and cardiac impairment predispose to the development of essential hypertension
- OPPORTUNITY OF INTERVENTIONS





# Pathogenesis of pre-eclampsia

# **Maternal Preeclampsia**

**More an abnormal maternal response than an abnormal pregnancy**

**Arterial disease, hypertension, obesity, or diabetes**

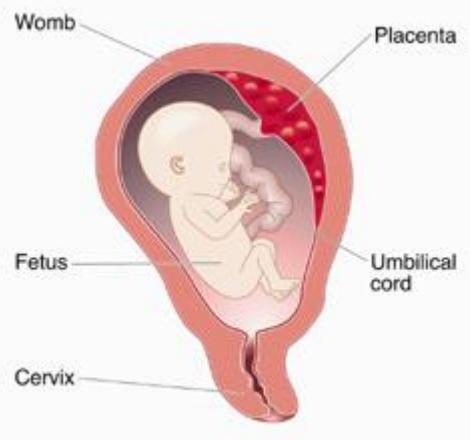
**Metabolic and vascular stress test**

**Low-grade systemic inflammatory response**

**Consistent with the higher incidence of ischemic heart disease, stroke, and hypertension that becomes evident many years after an episode of preeclampsia**



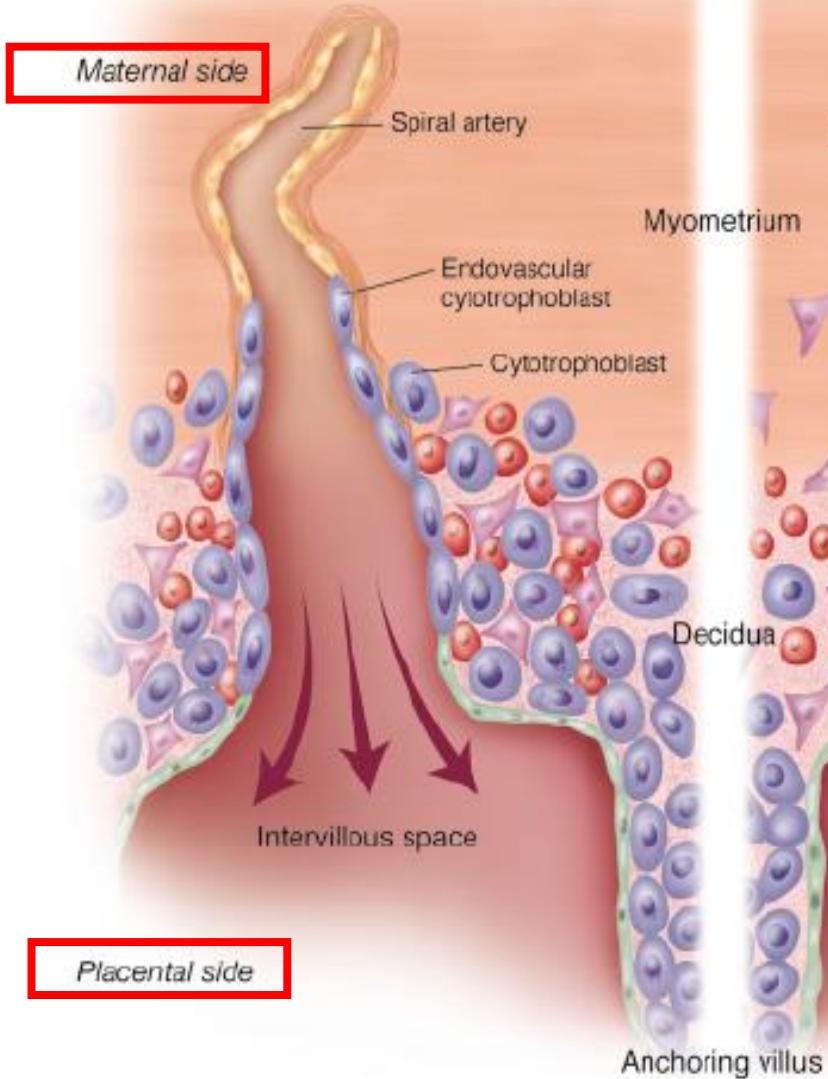
# Placental Preeclampsia



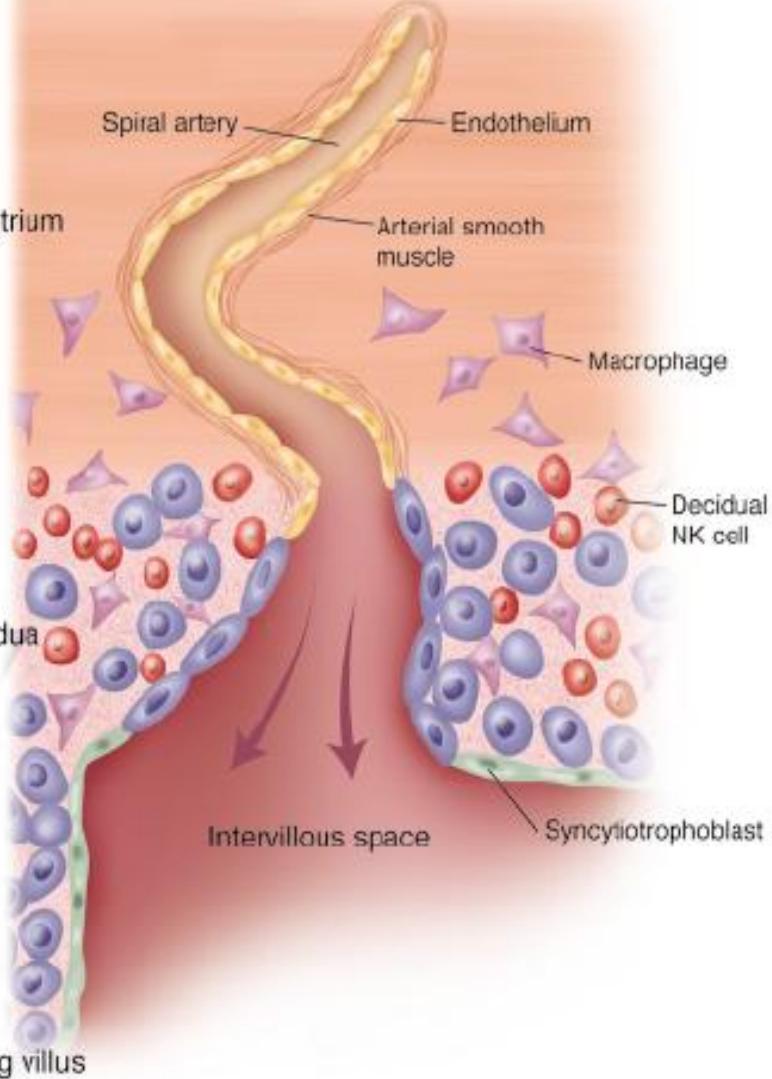
**<> Poor Placentation >>**



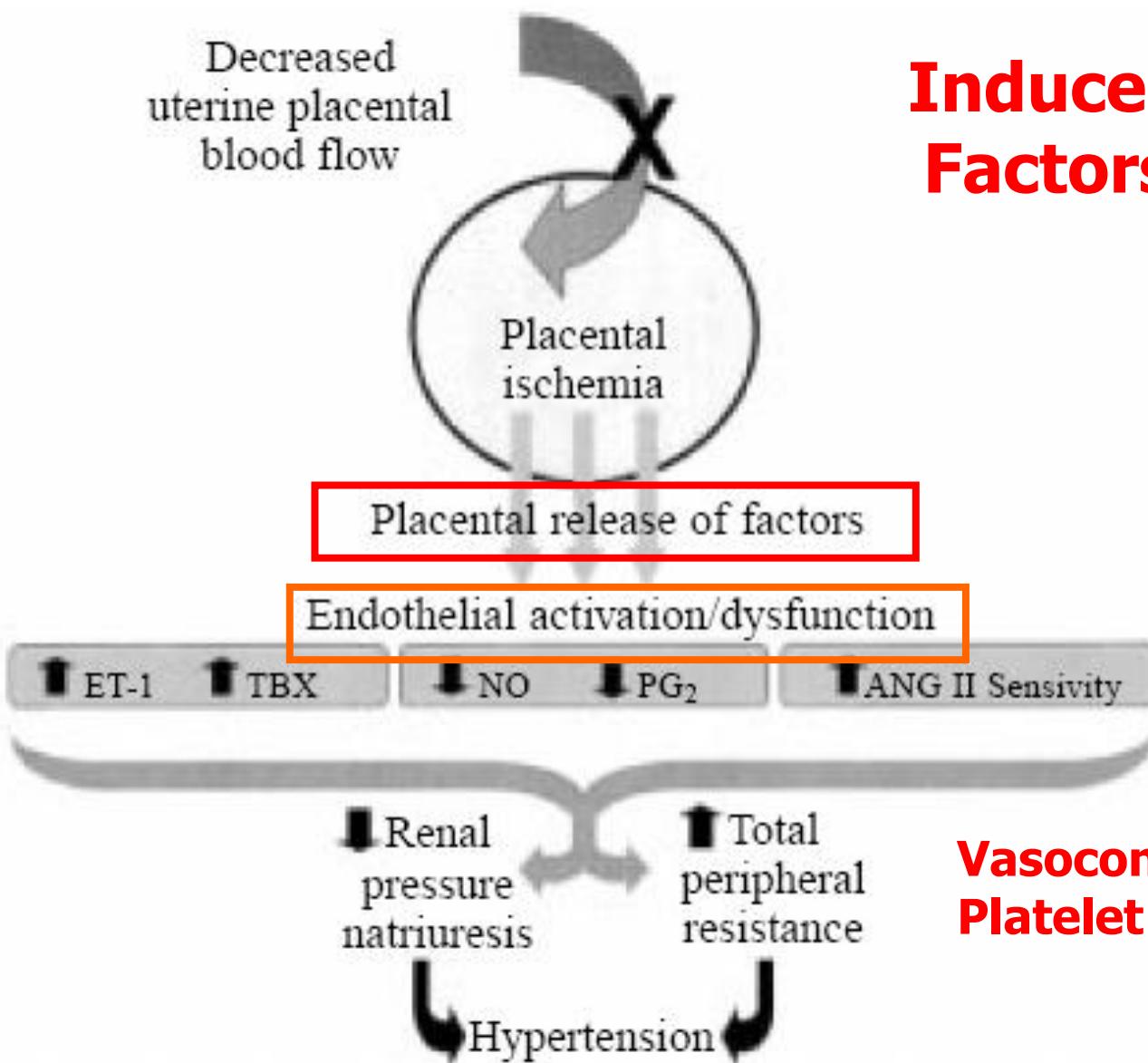
## Normal placentation



## Abnormal placentation



# Induced Factors



**Vasoconstriction  
Platelet activation**

## AIMS

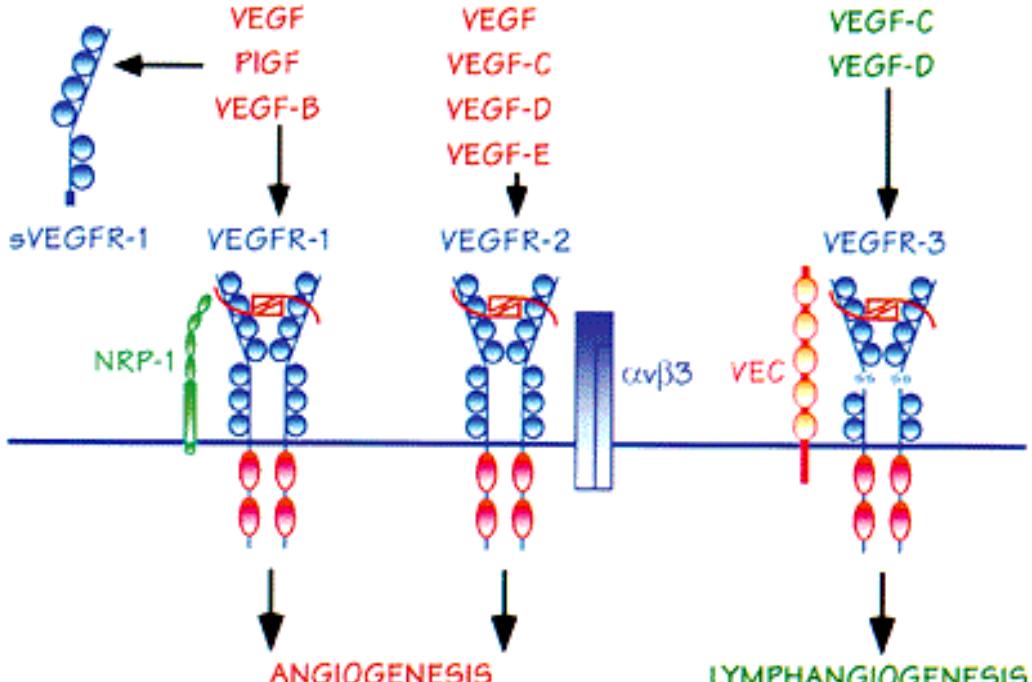
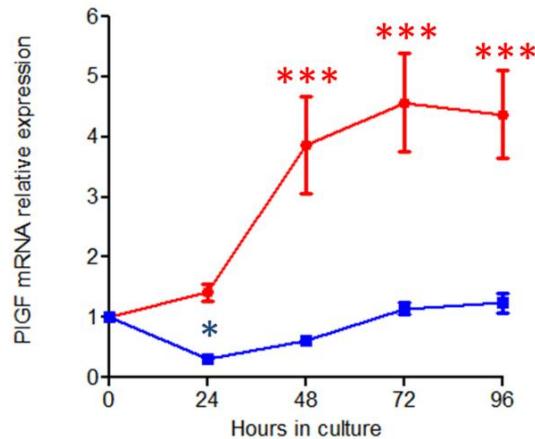
- (i)determine the effect of oxygen partial pressure on cytotrophoblast differentiation
- (i)measure mRNA expression and protein secretion from genes associated with placental angiogenesis; and
- (i)determine the reversibility of these effects at different oxygen partial pressures.

Term cytotrophoblasts were incubated at 21% and 2.5% O<sub>2</sub> for 96 hr, or were switched between the two oxygen concentrations after 48 hr.

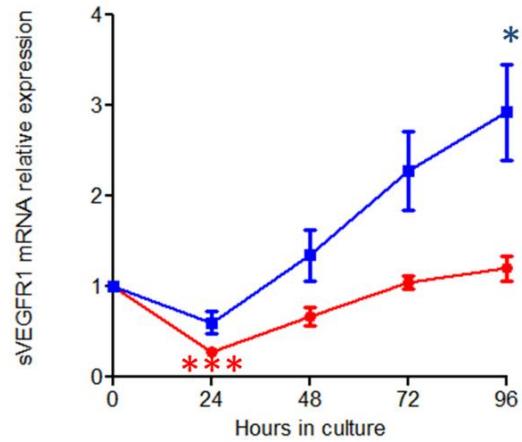


*Debiève F, Depoix C, Gruson D, Hubinont C. Mol Reprod Dev. 2013*

B



D



*Effect of normoxia and hypoxia on angiogenic factors mRNA expression. Freshly isolated cytotrophoblasts from at least 4 different placentae were cultured for 24h, 48h, 72h and 96h at 21% O<sub>2</sub> (red line) or 2.5% O<sub>2</sub> (blue line). VEGF (A), PIGF (B), VEGFR1 (C) and sVEGFR1 (D) mRNA expression were determined by RT-qPCR and normalized to RPLI mRNA. Experiments were done in duplicate and values are means  $\pm$  SEM and relative to plating day (0h) set to 1.0 ( $n \geq 4$ ). \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  compared to plating day (0h).*



**Excess placental soluble fms-like  
tyrosine kinase 1 (sFlt1) may contribute  
to endothelial dysfunction, hypertension,  
and proteinuria in preeclampsia**

See the related Commentary beginning on page 600.

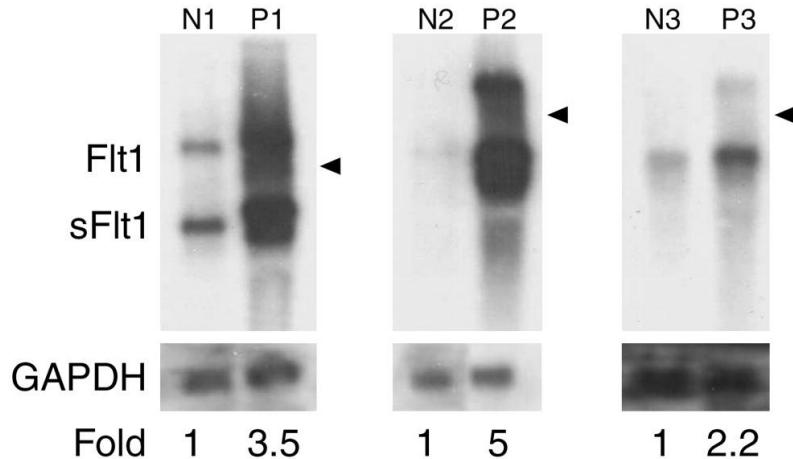
Preeclampsia: Overexpression of soluble form of  
VEGF receptor (sFLT-1)

Maynard S, J Clin Invest 2003



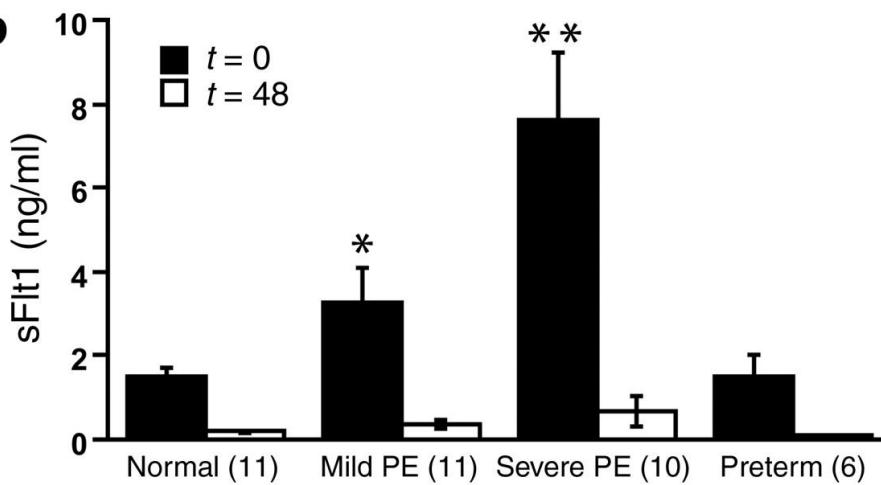
# Elevated placental sFlt1 production in PE

a



mRNA expression of placental sFlt1 from three patients with preeclampsia (P1, P2, and P3) and three normotensive term pregnancies (N1, N2, and N3).

b

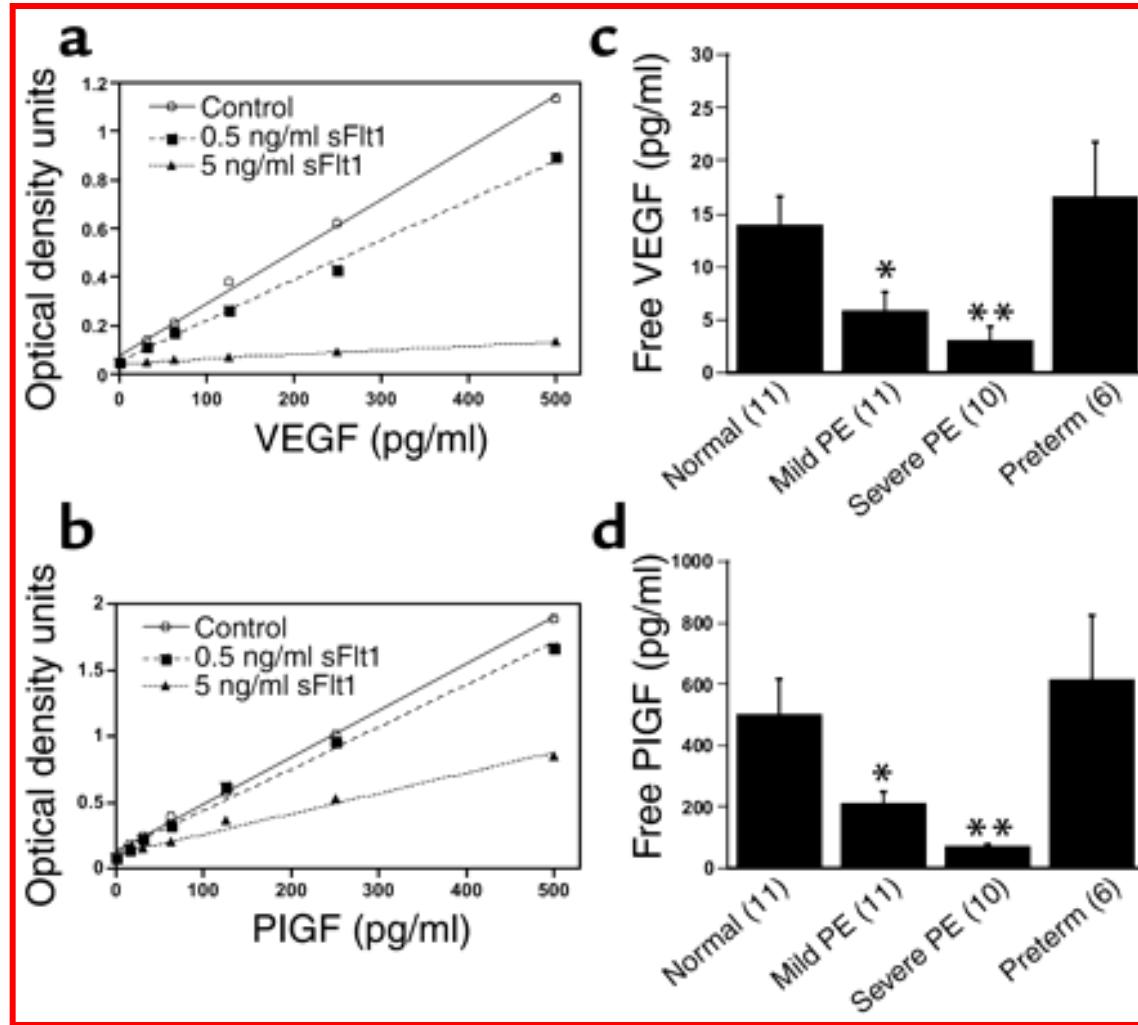


ELISA for sFlt1 on serum from patients with mild preeclampsia (PE), severe preeclampsia and from normotensive pregnant women at term (normal)



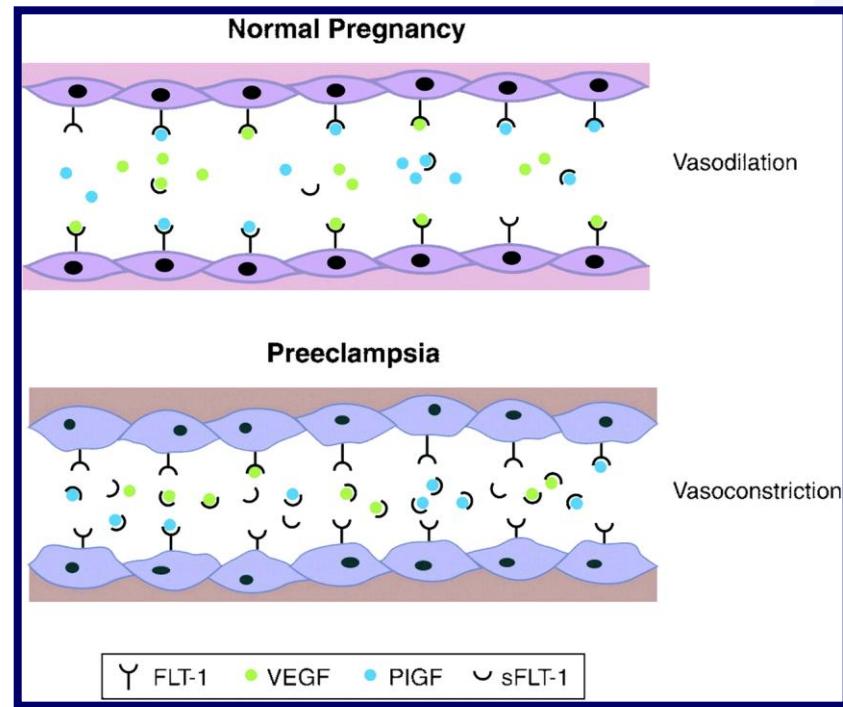
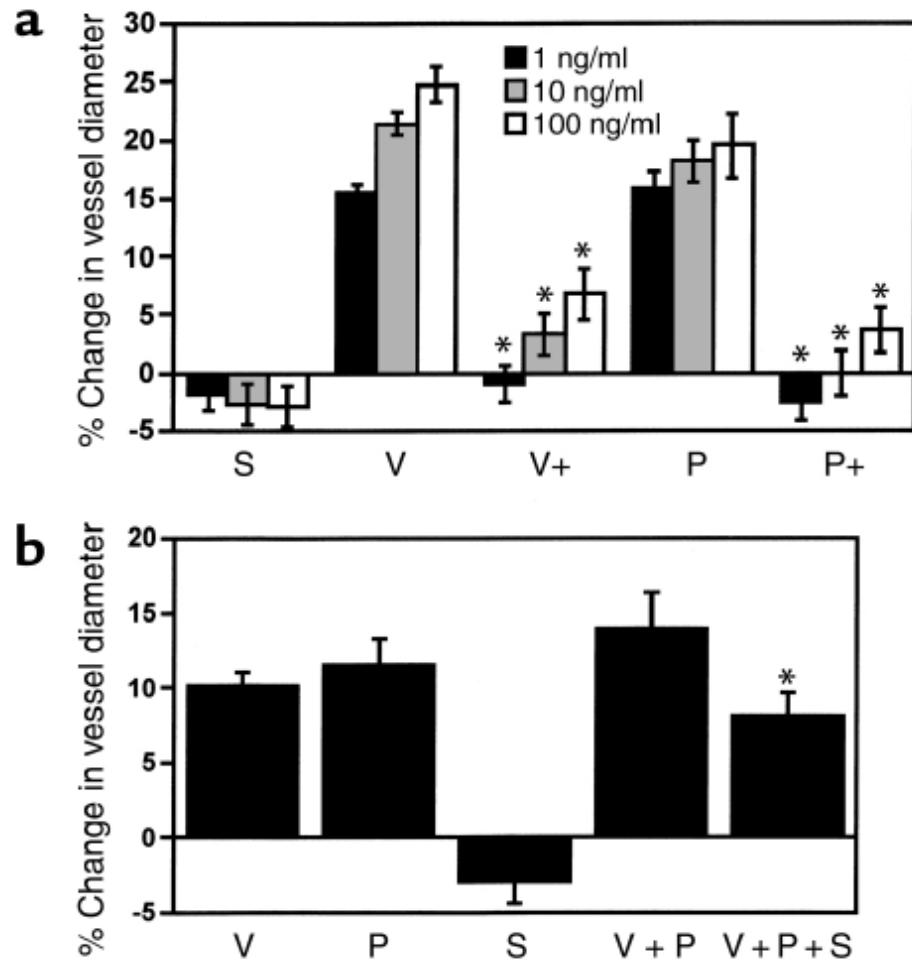
Maynard S, J Clin Invest 2003

# Decreased free VEGF and PIGF in patients with PE



Maynard S, J Clin Invest 2003

# Inhibition of VEGF and PIGF induced vasodilatation by sFlt1



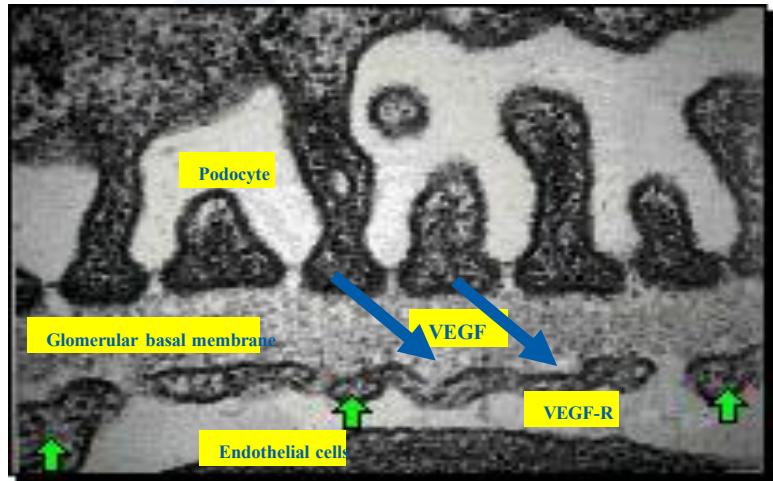
Maynard S, J Clin Invest 2003

## IN VIVO EFFECTS:

Recombinant adenovirus coding for sFlt1 induce a preeclampsia-like syndrome - hypertension, proteinuria and endotheliosis - in pregnant rats.

	n	PAM (mmHg)	Albumine/Créat
<i>Enceinte</i>			
contrôle	5	75 ± 11	62 ± 21
sFlt1	4	109 ± 19	6923 ± 658
<i>Non enceinte</i>			
contrôle	5	89 ± 6	138 ± 78
sFlt1	6	118 ± 13	12947 ± 2776

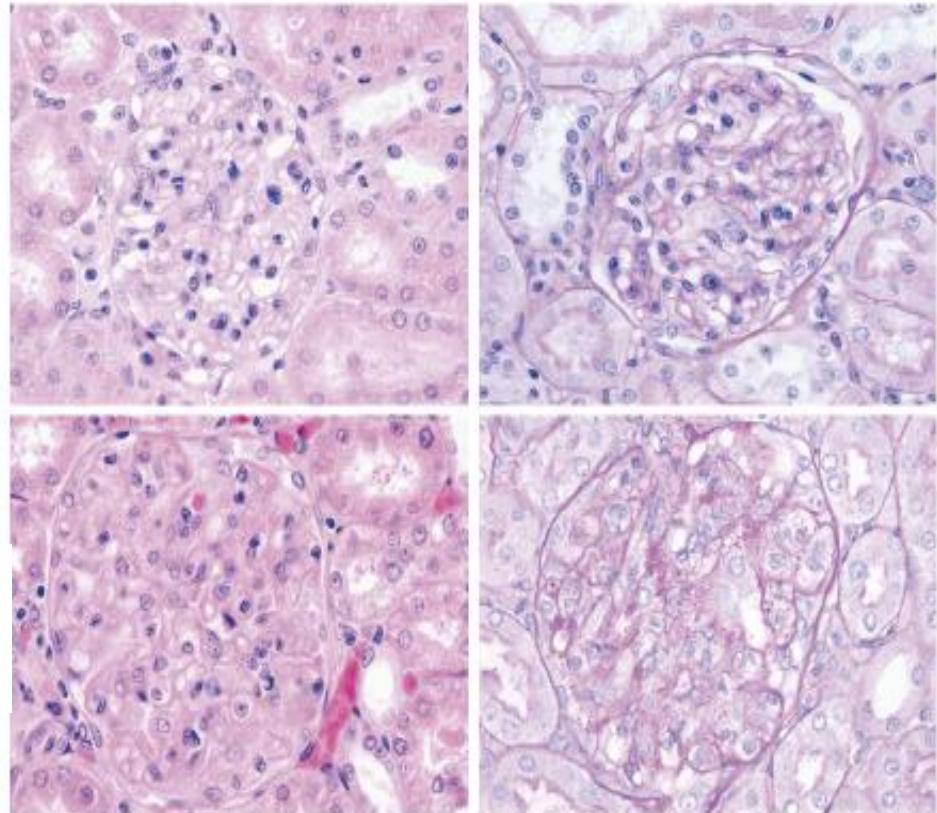
# Renal pathological changes due to sFlt1



**sFlt1 contributes to renal syndrome in PE (Increased endothelium permeability)**

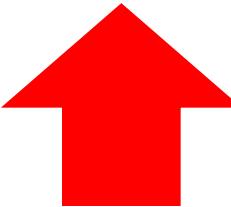
Controls

sFlt1



Maynard S, J Clin Invest 2003

# ENDOGLIN



Coreceptor for TGF-B1 and TGF-B3

Highly expressed on cell membranes  
of vascular endothelium and  
syncytiotrophoblast



## Preeclampsia

# sENDOGLIN

## Antiangiogenic

Venkatesha et al., 2006



Overexpression of sEndoglin in rodents  
through adenoviral vectors led to increased  
vascular permeability and hypertension

sEng may act in concert with sFlt1 to induce severe preeclampsia



# Risk stratification Of pre-eclampsia



# Maternal history: a priori risk

1. *First pregnancy*
2. *Multiple pregnancy*
3. *Pregnancy interval of more than 10 years*
4. *Age 40 or over*
5. *BMI > 35*
6. *Family history of preeclampsia*
7. *Diastolic blood pressure 80mmHg at first visit*
8. *Proteinuria at first visit*
9. *Previous preeclampsia*
10. *Long term medical condition*
  - *Hypertension*
  - *Renal disease*
  - *Diabetes*
  - *Antiphospholipid antibodies*



*Action on Pre-eclampsia. Pre-eclampsia Community Guideline (Precog); 2004.*



# An ideal biomarker for PE

- **Be easily measured and easily integrated with routine testing already performed as part of prenatal testing**
- **Delineate the risk of developing PE in the 1st trimester, thus creating a wide window of opportunity to implement treatment strategies which may facilitate normal placental development. This need to occur at an early stage when the placenta is capable of responding to corrective or moderating medications**
- **Ideally the biomarker might also serve as a plausible mediator of the underlying pathogenesis**



ORIGINAL ARTICLE

## Circulating Angiogenic Factors and the Risk of Preeclampsia

case-control study within the Calcium for Preeclampsia Prevention Trial

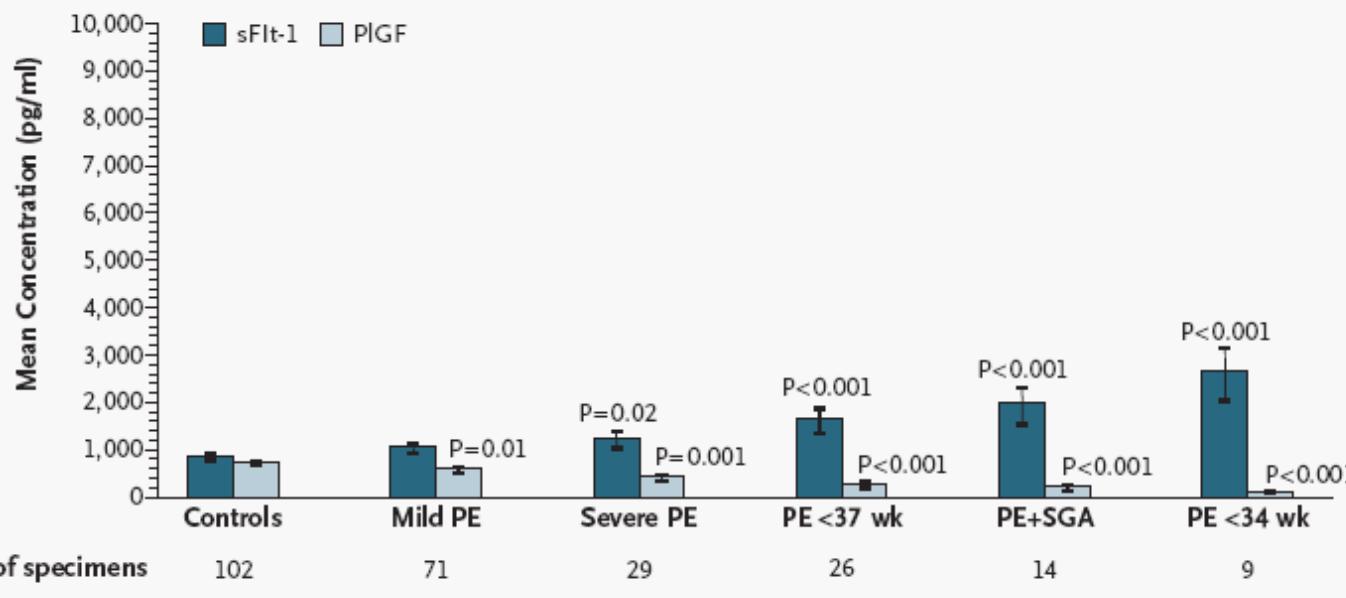
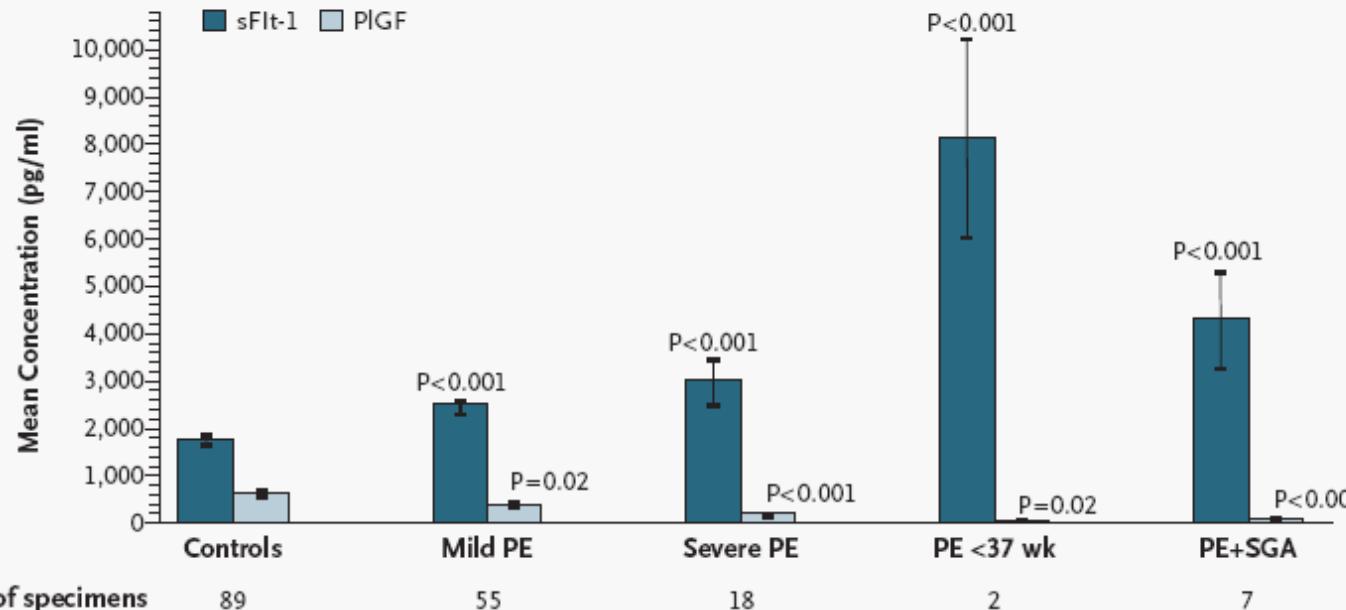
Each woman with preeclampsia was matched to one normotensive control

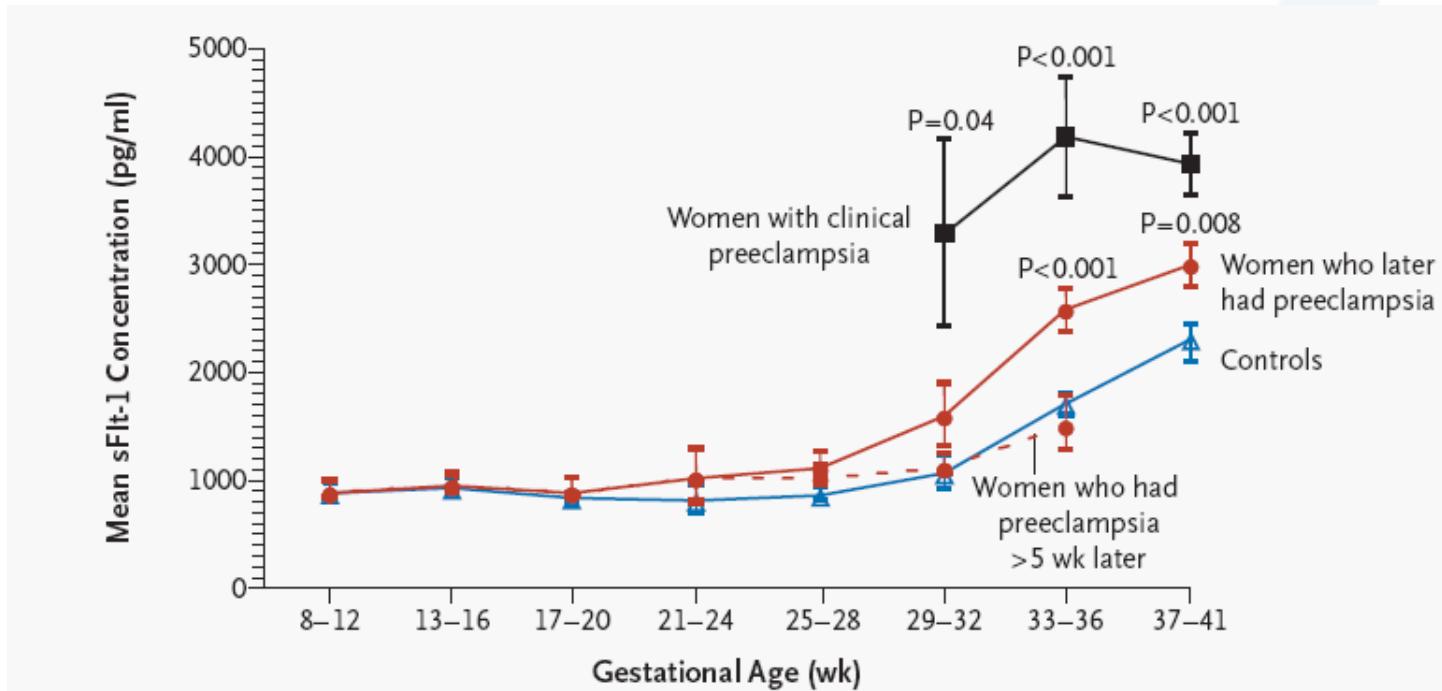
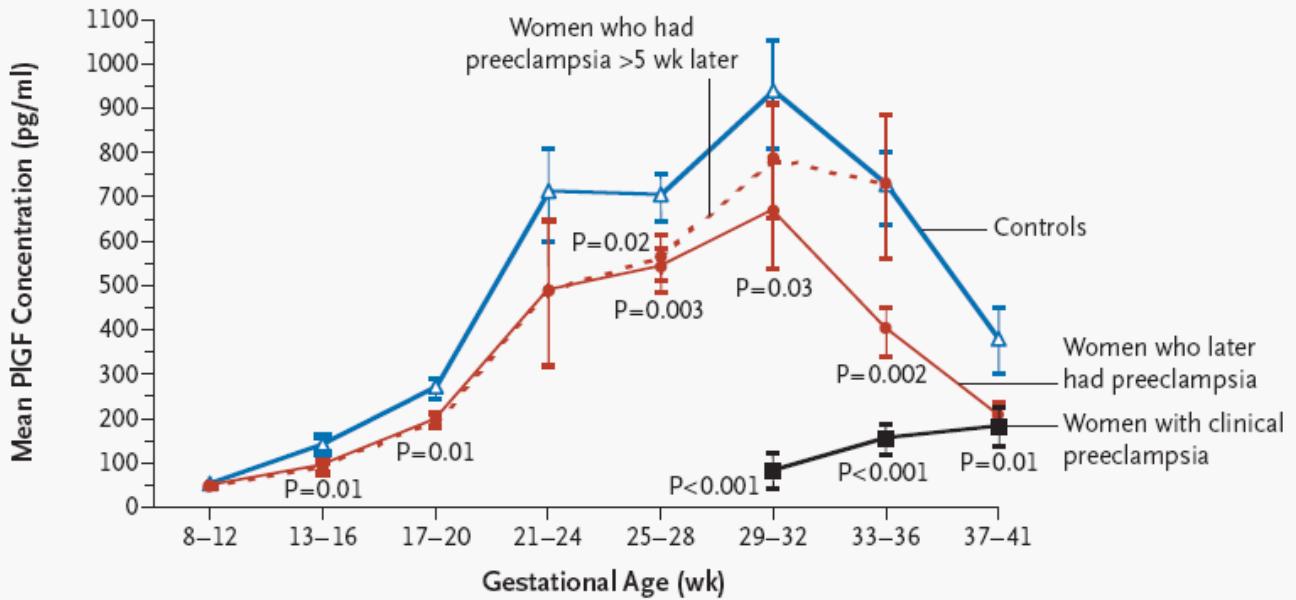
A total of 120 pairs of women were randomly chosen

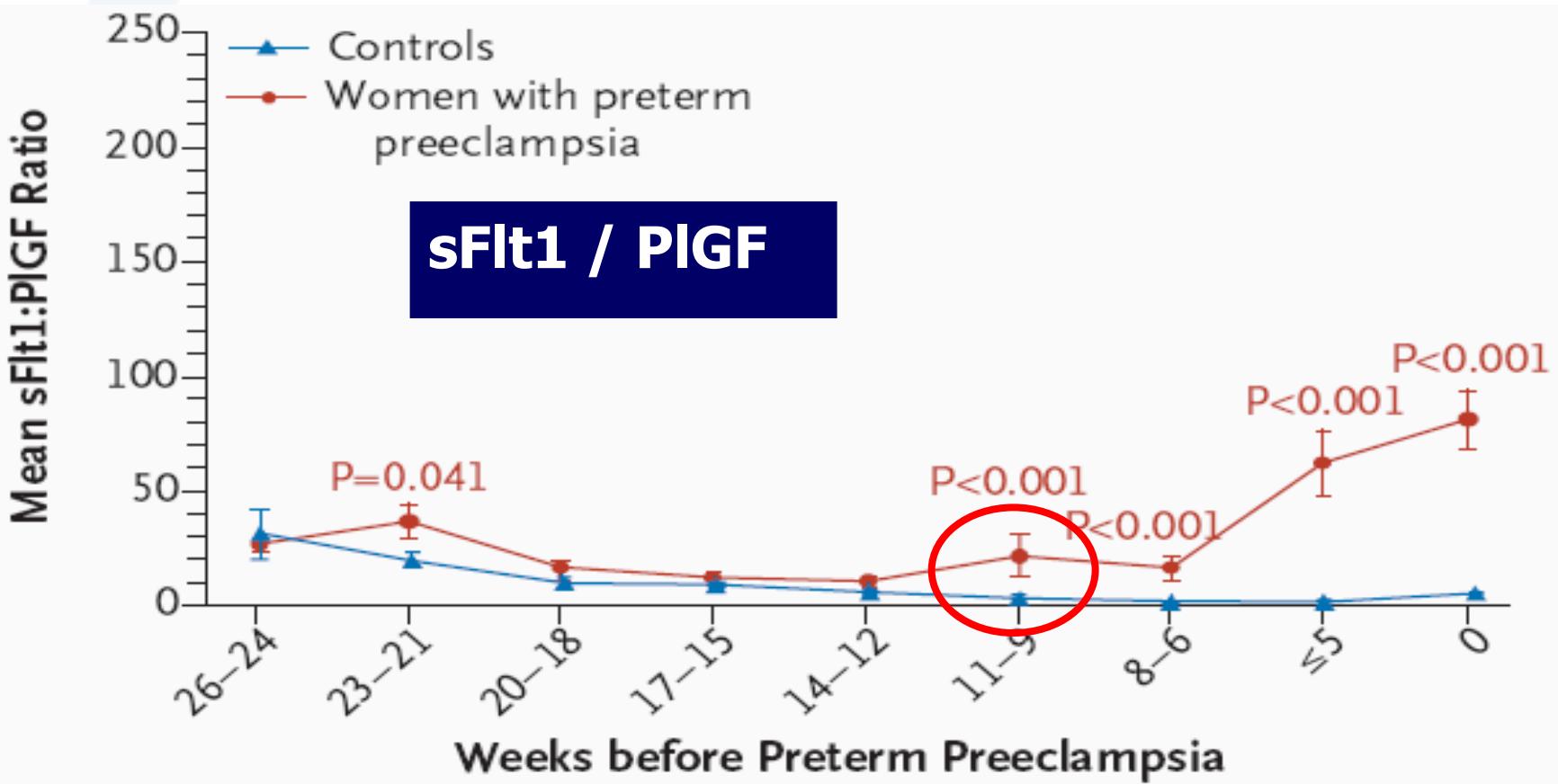
Serum concentrations of angiogenic factors (total sFlt-1, free PIGF, and free VEGF) were measured throughout pregnancy



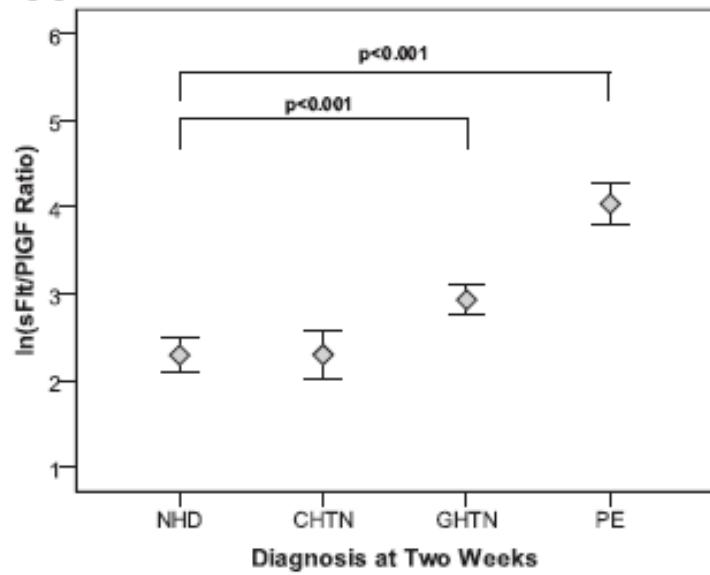
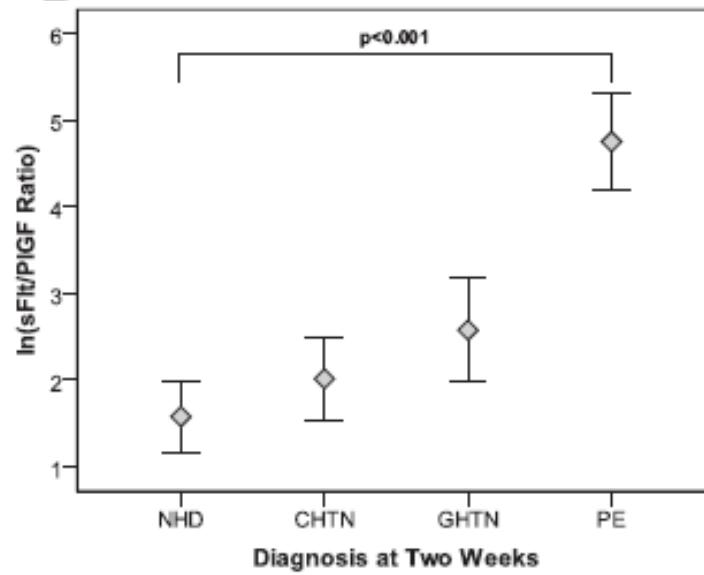
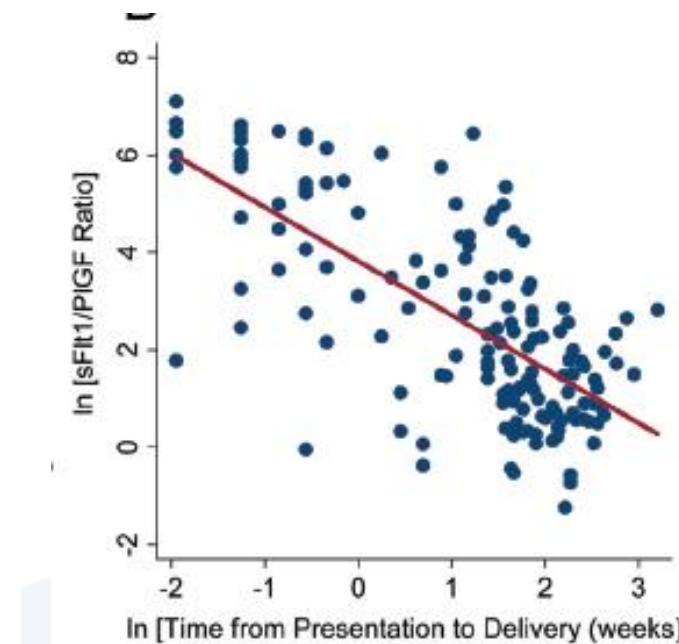
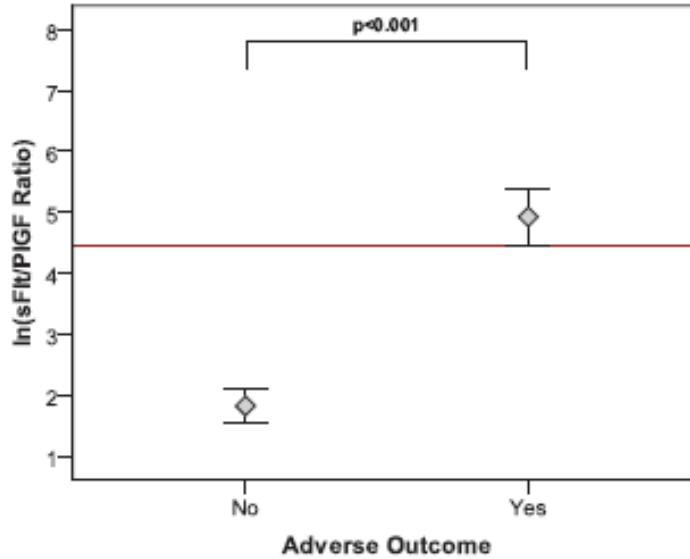
*Levine, nejm 2004*

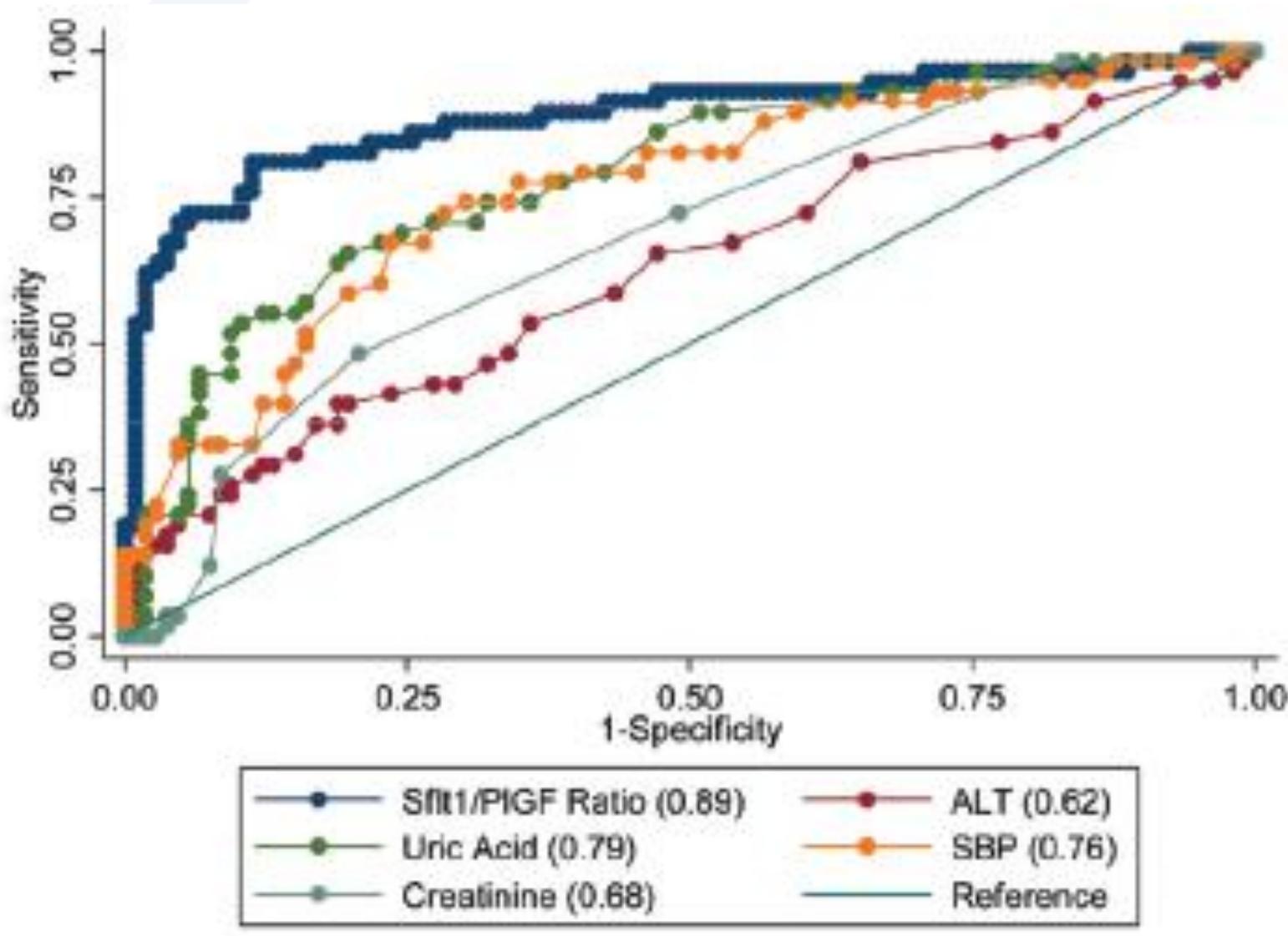
**A 21 to 32 Weeks****B 33 to 41 Weeks**



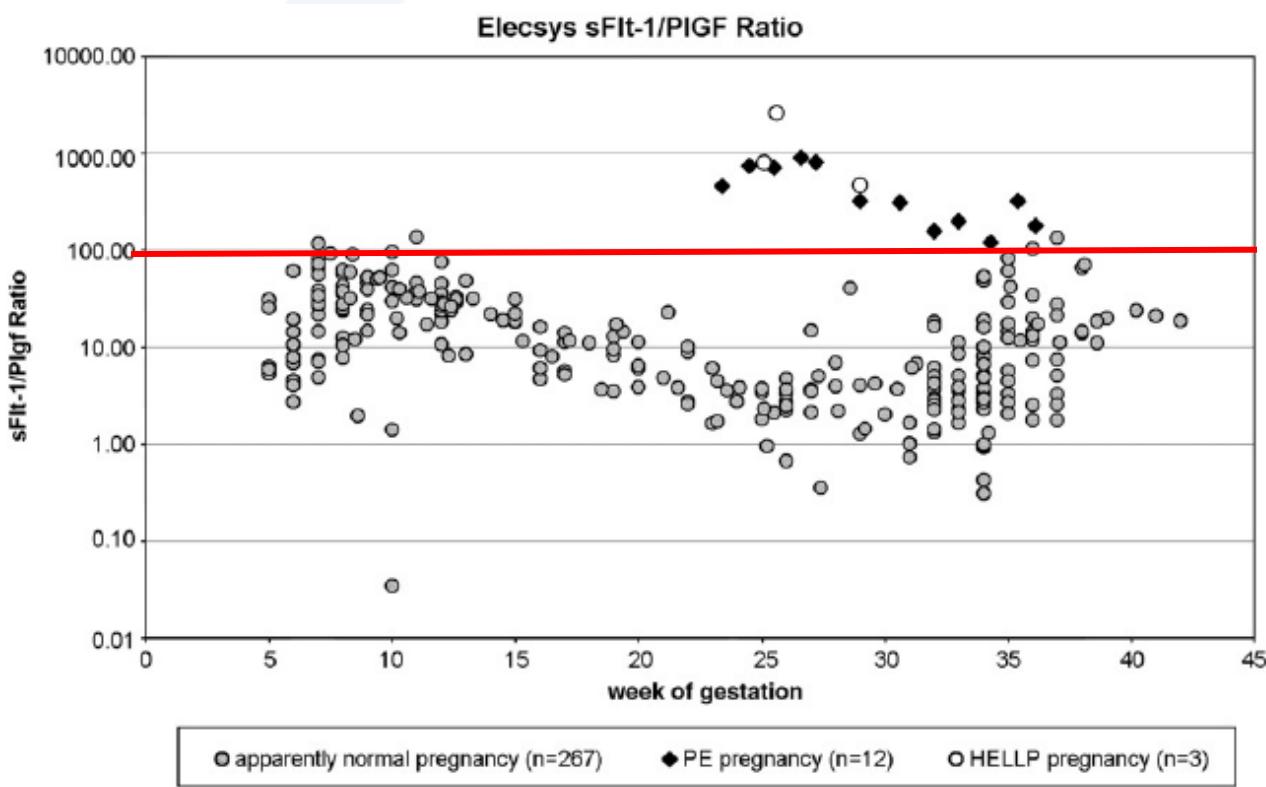


*Levine, nejm 2007*

**A****B****B**

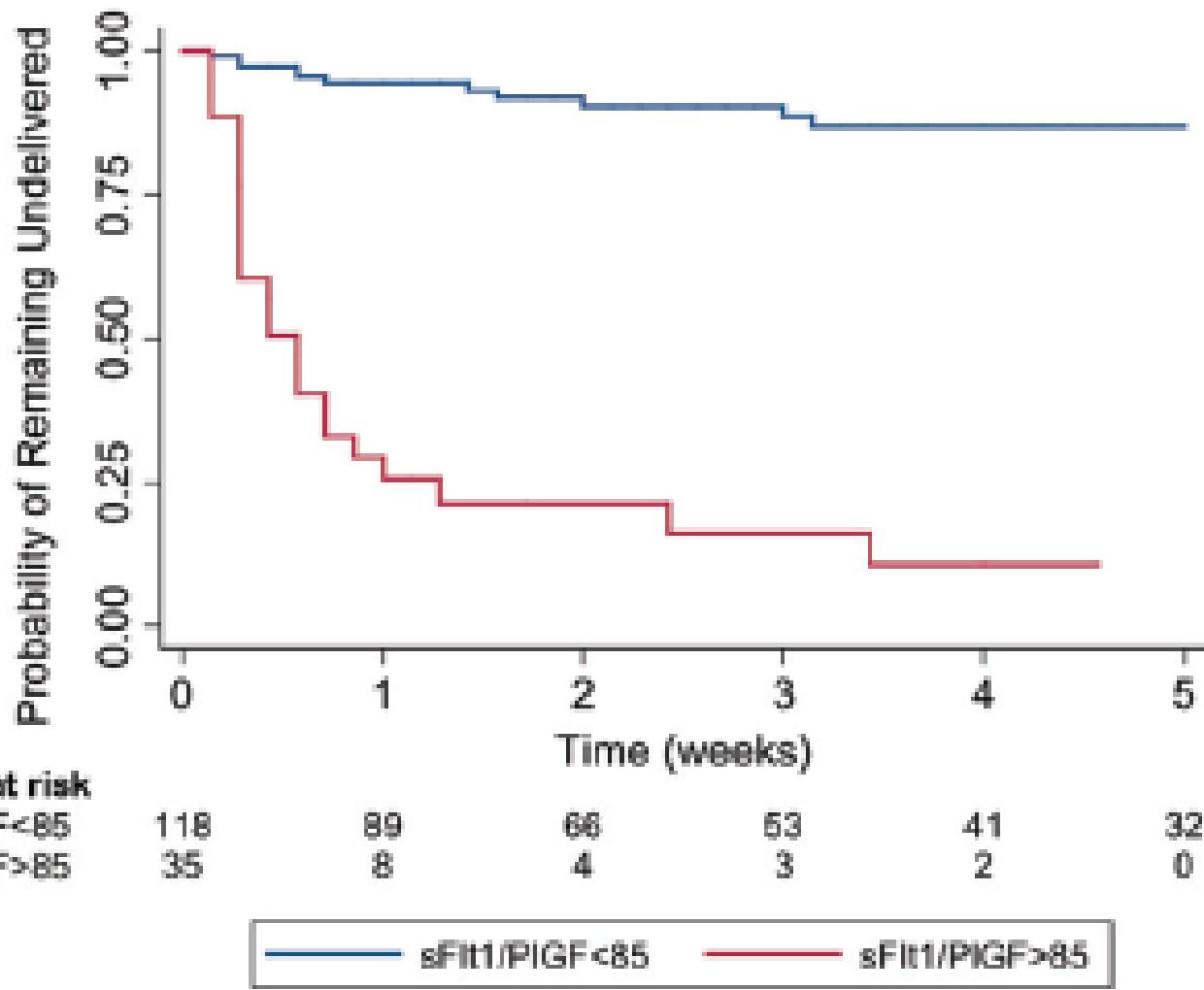


Rana et al., Circulation 2011

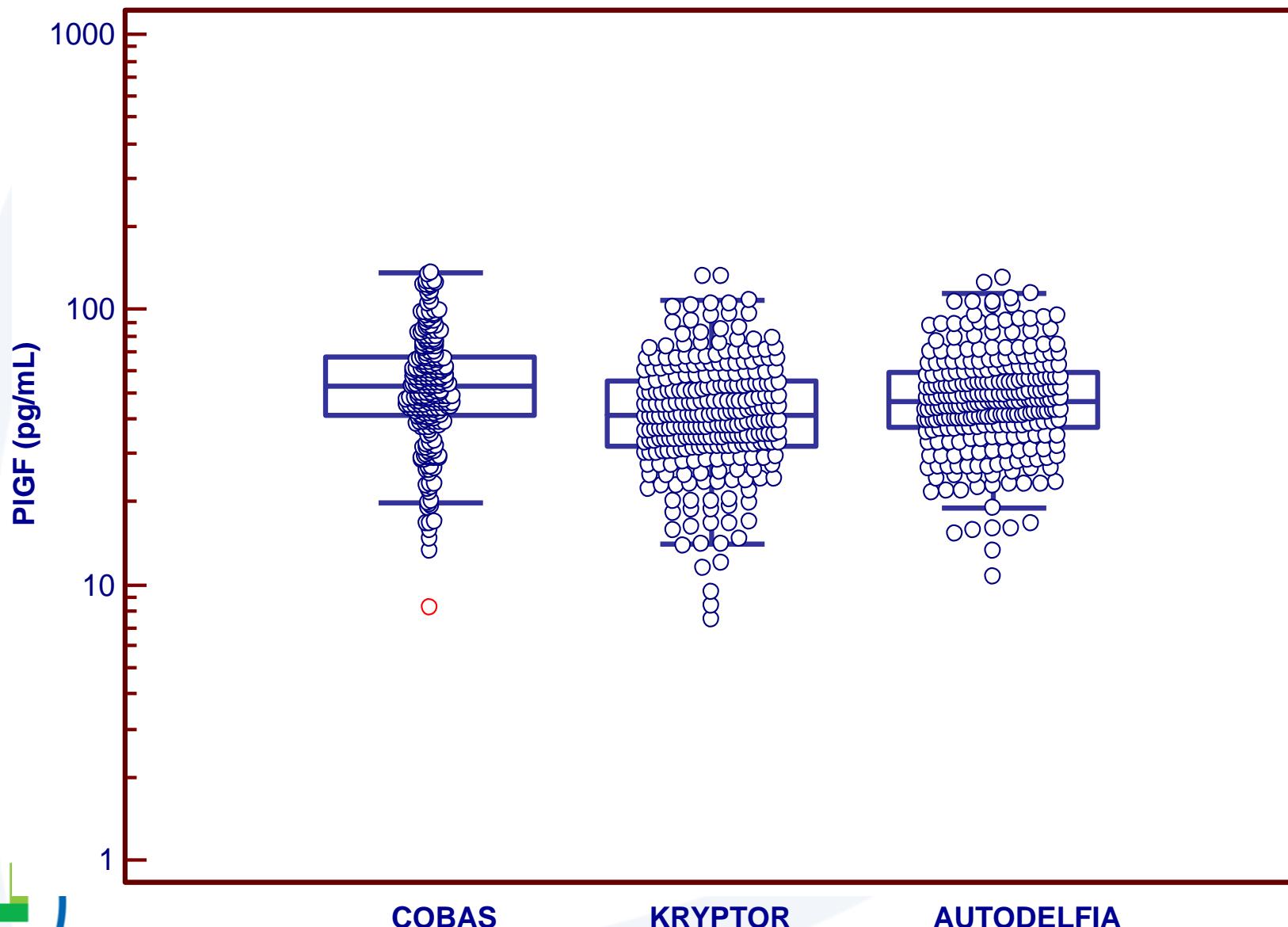


**Table 2**  
Utility of different sFlt-1/PIGF ratio cut-off values in preeclampsia.

Study	Number of patients with PE (control)	Patients	Cut-off used	Sensitivity (%)	Specificity (%)
De Vivo et al. [58]	52 (52)	All patients	38.46	88.5	88.5
Sunderji et al. [57]	39 (388)	All patients	137	96	97
Kim et al. [49] <sup>a</sup>	46 (100)	All patients	1.4	80.4	78
Verlohren et al. [15] <sup>b</sup>	37 (268)	Early-onset PE	85	89	97
	34 (268)	Late-onset PE	85	74	89
	71 (268)	All patients	85	82	95
Ohkuchi et al. [59] <sup>ab</sup>	15 (144)	Early-onset PE	45	100	95
	19 (144)	Late-onset PE	45	95	95
	34 (144)	All patients	45	97	95
Stepan et al. [60] <sup>b</sup>	12 (38)	All patients	3.15	62	51
	9 (38)	Early-onset PE	3.15	67	51

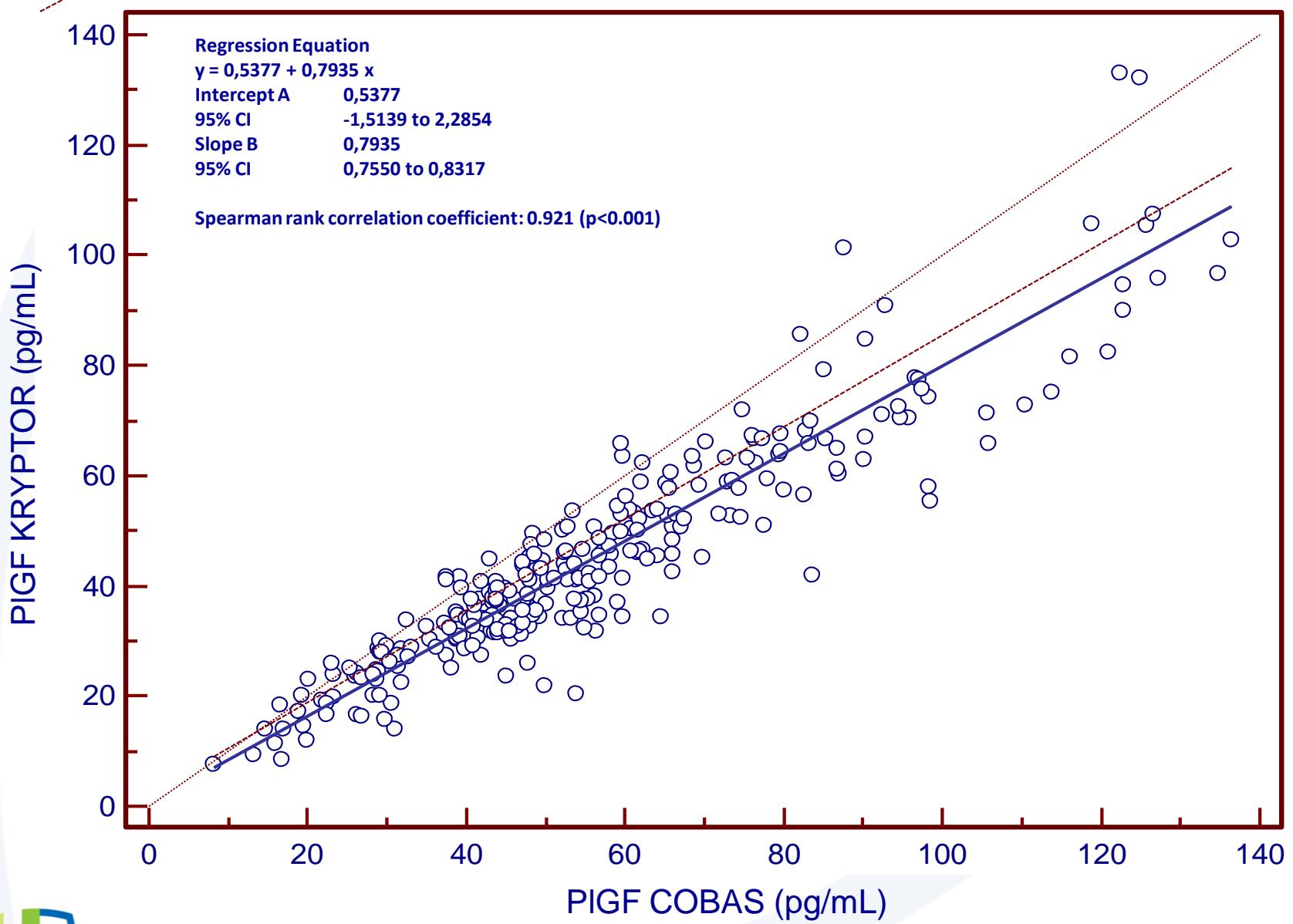


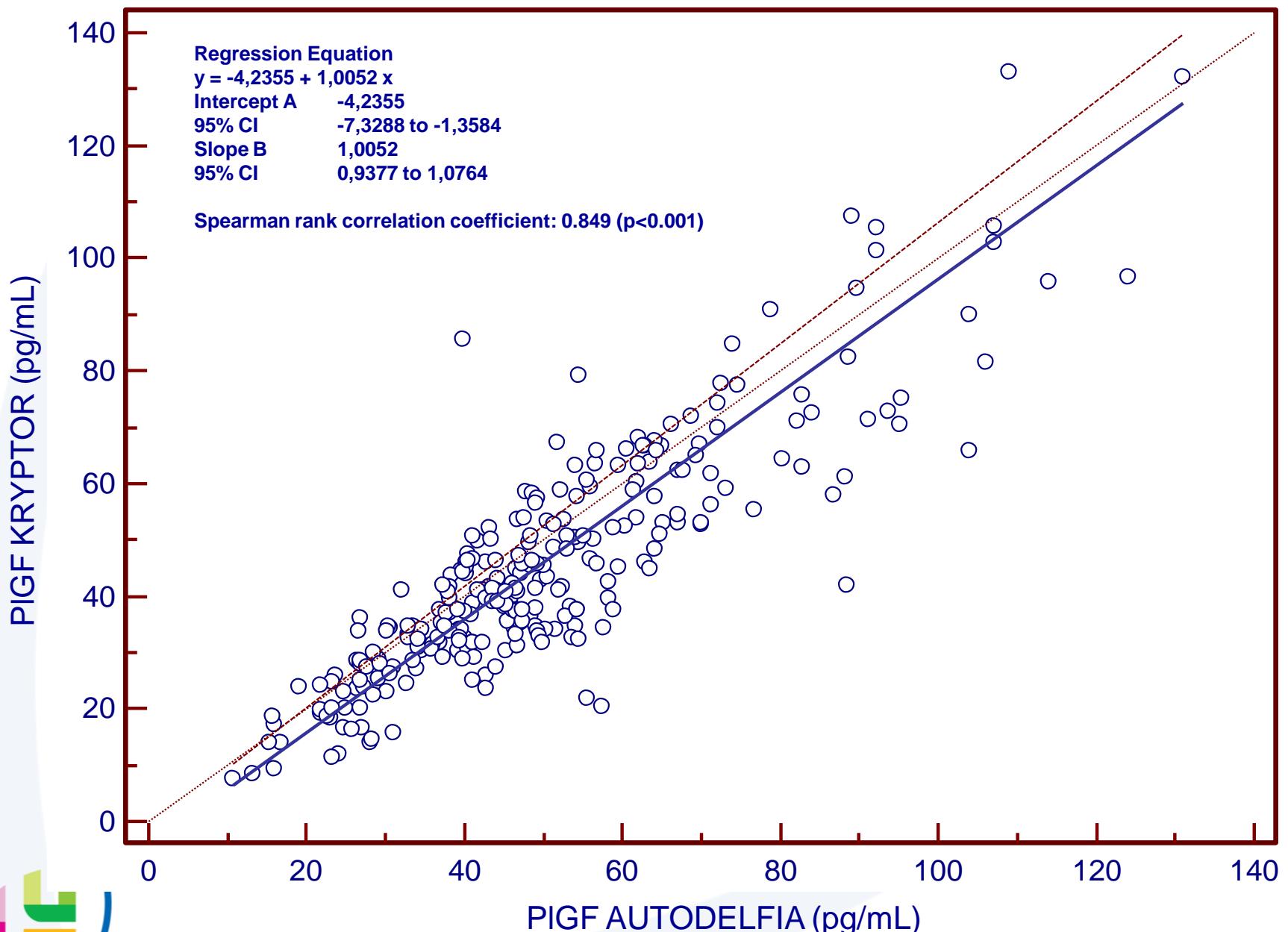
# Distribution of the PIGF circulating levels obtained with the three immunoassays

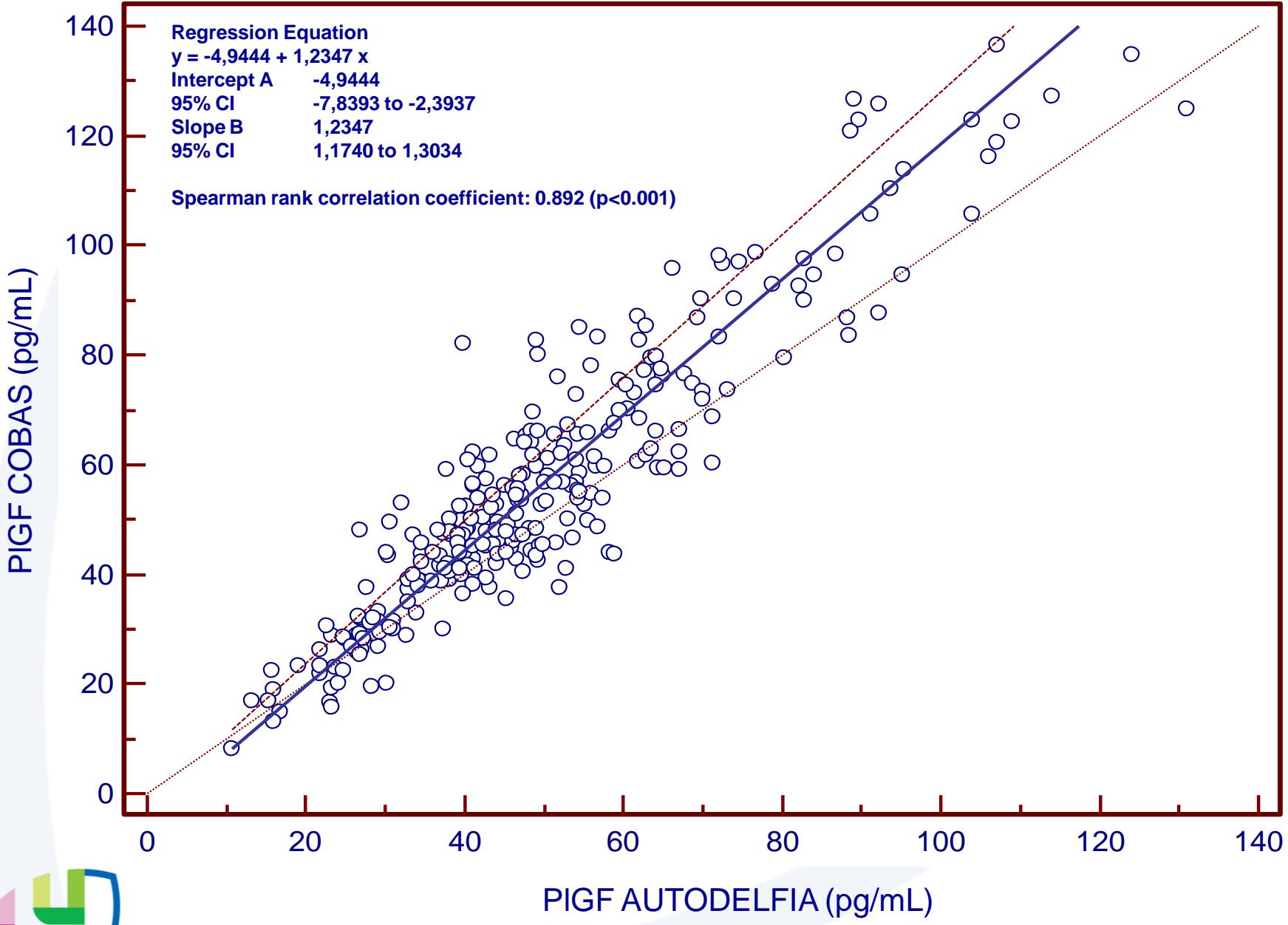


Gruson et al., FMF 2013

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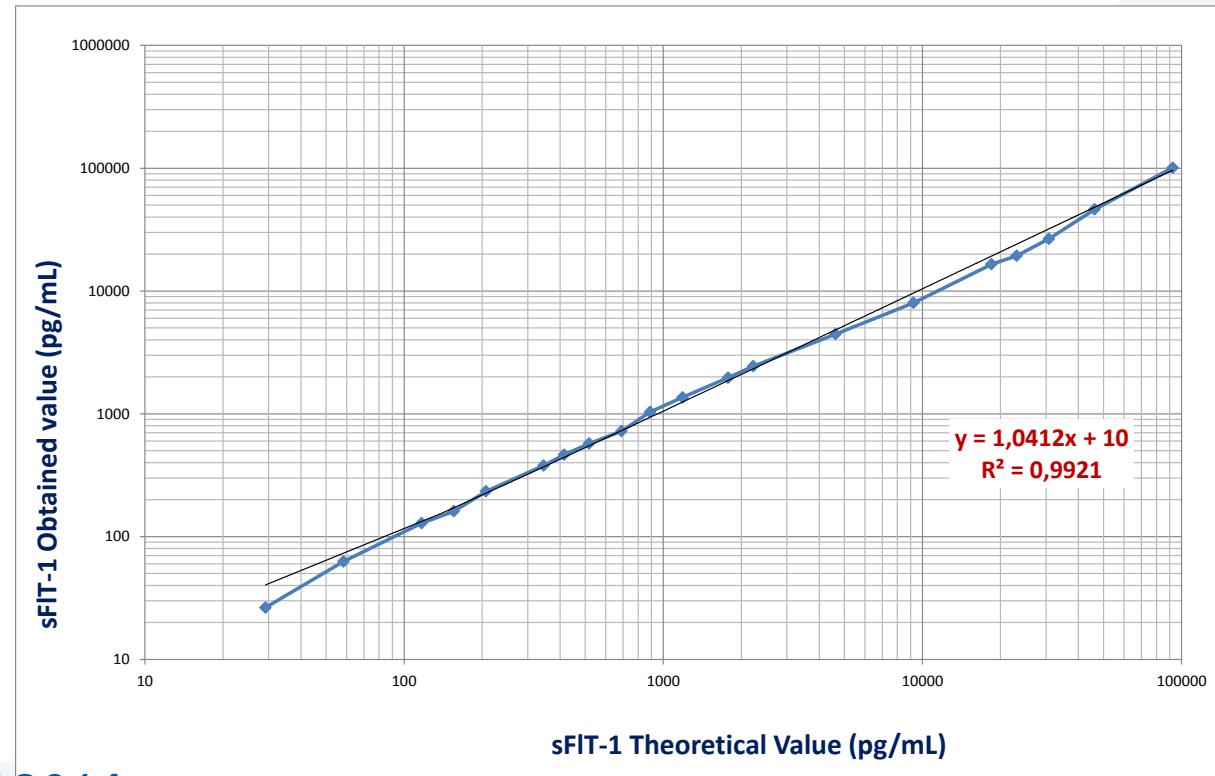


Gruson et al., FMF 2013

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**B·R·A·H·M·S sFlt-1 KRYPTOR (Thermo Scientific)**

	<b>sFlt-1 (pg/mL)</b>	<b>Between-run CV</b>
Sample 1	<b>33.6</b>	<b>12.4%</b>
Sample 2	<b>49.4</b>	<b>8.9%</b>
Sample 3	<b>474</b>	<b>1.6%</b>
Sample 4	<b>1471</b>	<b>1.4%</b>
Sample 5	<b>9471</b>	<b>1.9%</b>
Sample 6	<b>20619</b>	<b>1.9%</b>
Sample 7	<b>65187</b>	<b>2.6%</b>

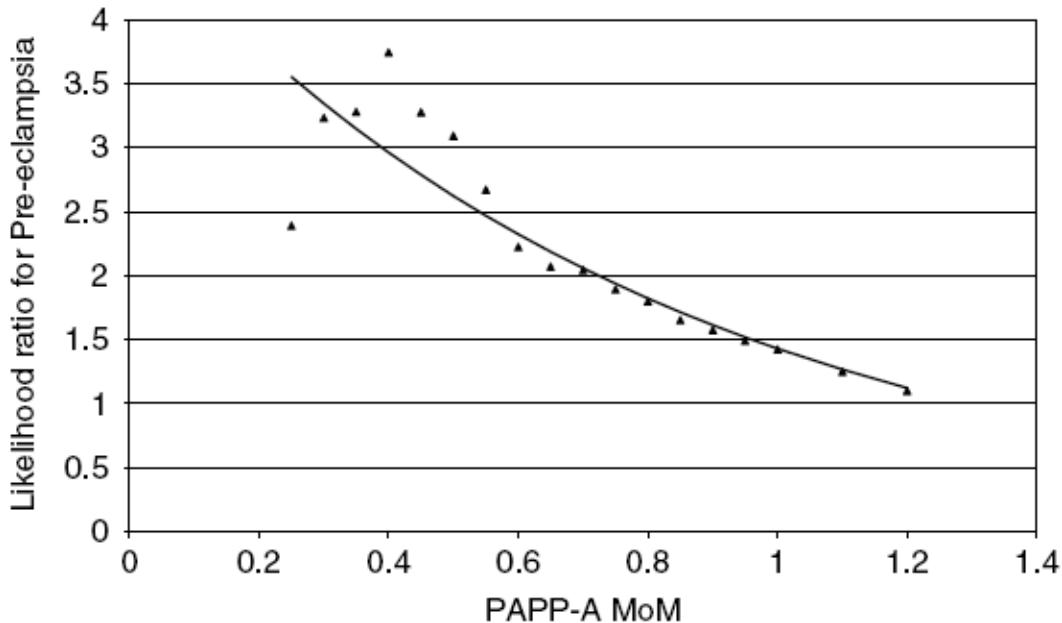


Gruson et al., FMF 2014

Study	Pre-eclampsia		PAPP-A				Free $\beta$ -hCG			
	<i>N</i>	MoM	5th centile		<0.5 MoM	MoM	5th centile		<0.2 MoM	
			OR or RR	DR			OR or RR	DR		
Ong <i>et al.</i> , 2000	80	0.903			11.1	0.879			7.4	
Smith <i>et al.</i> , 2002	331	0.963	2.1	7.6			1.1		4.1	
Yaron <i>et al.</i> , 2002	27				1.7					
Dugoff <i>et al.</i> , 2004	764		1.54	7.85						
Spencer <i>et al.</i> , 2005b	64	0.844				0.923			7.8	

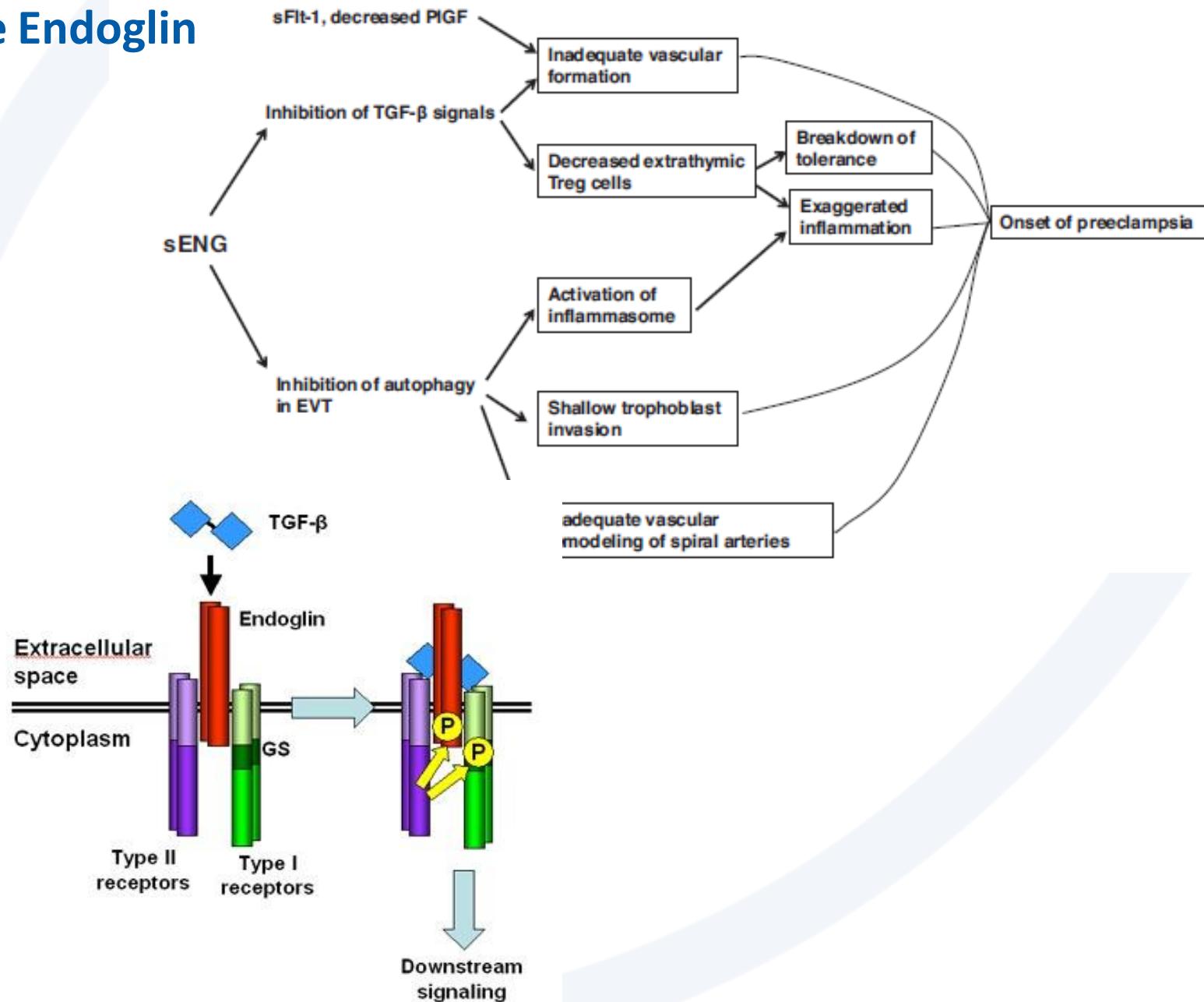
  

Variable	Normal outcome ( <i>n</i> = 47 770)	Pre-eclampsia ( <i>n</i> = 222)
Age, mean (SD) (years)	31.5 (5.5)	29.7 (5.6)
Nulliparity %	43.2%	65%
Ethnicity %		
Caucasian	86%	85%
Asian	6%	3%
African	5%	10%
Other	5%	2%
GA at enrolment, mean (SD) (days)	84 (4.2)	86 (4.4)
GA delivery (SD) (weeks)	39.6 (1.2)	36.9 (2.5)
Birth weight (SD) (g)	3510 (410)	2285 (590)



Spencer *et al.*, 2008

# Soluble Endoglin



ORIGINAL ARTICLE

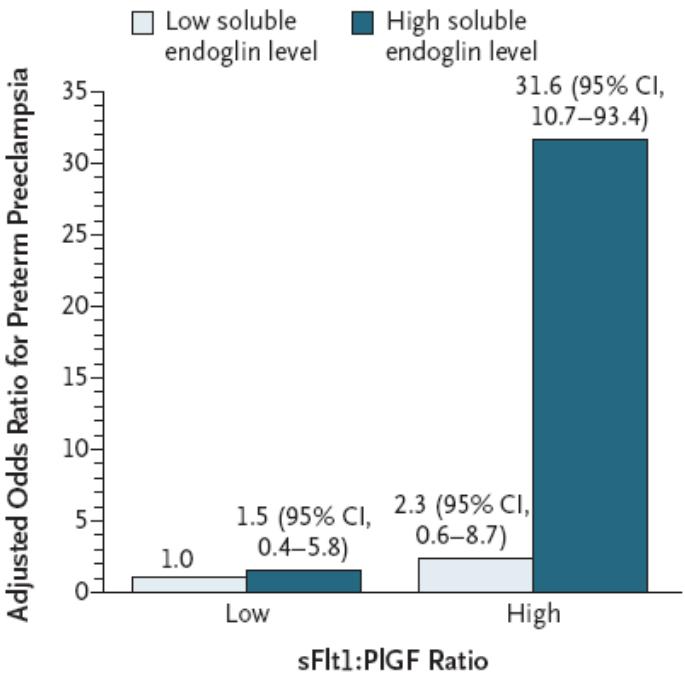
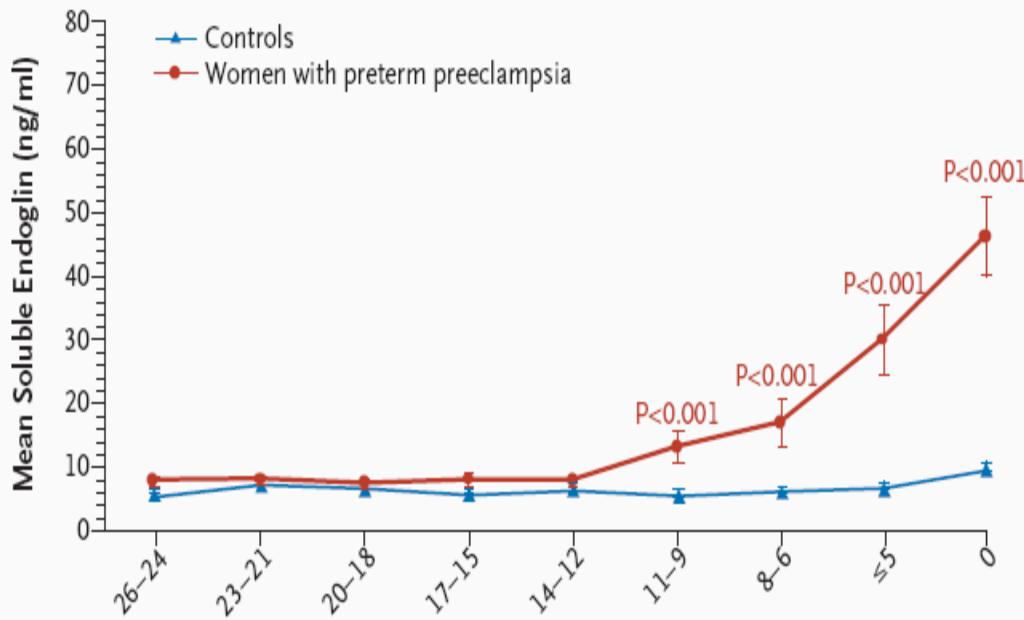
## Soluble Endoglin and Other Circulating Antiangiogenic Factors in Preeclampsia

Richard J. Levine, M.D., M.P.H., Chun Lam, M.D., Cong Qian, M.S.,  
Kai F. Yu, Ph.D., Sharon E. Maynard, M.D., Benjamin P. Sachs, M.B., B.S., D.P.H.,  
Baha M. Sibai, M.D., Franklin H. Epstein, M.D., Roberto Romero, M.D.,  
Ravi Thadhani, M.D., M.P.H., and S. Ananth Karumanchi, M.D.,  
for the CPEP Study Group\*

***Case-control study of healthy nulliparous women within the Calcium for Preeclampsia Prevention trial.***

***The study included all 72 women who had preterm preeclampsia (<37 weeks), as well as 480 randomly selected women — 120 women with preeclampsia at term (at ≥37 weeks), 120 women with gestational hypertension, 120 normotensive women who delivered infants who were small for gestational age, and 120 normotensive controls who delivered infants who were not small for gestational age.***

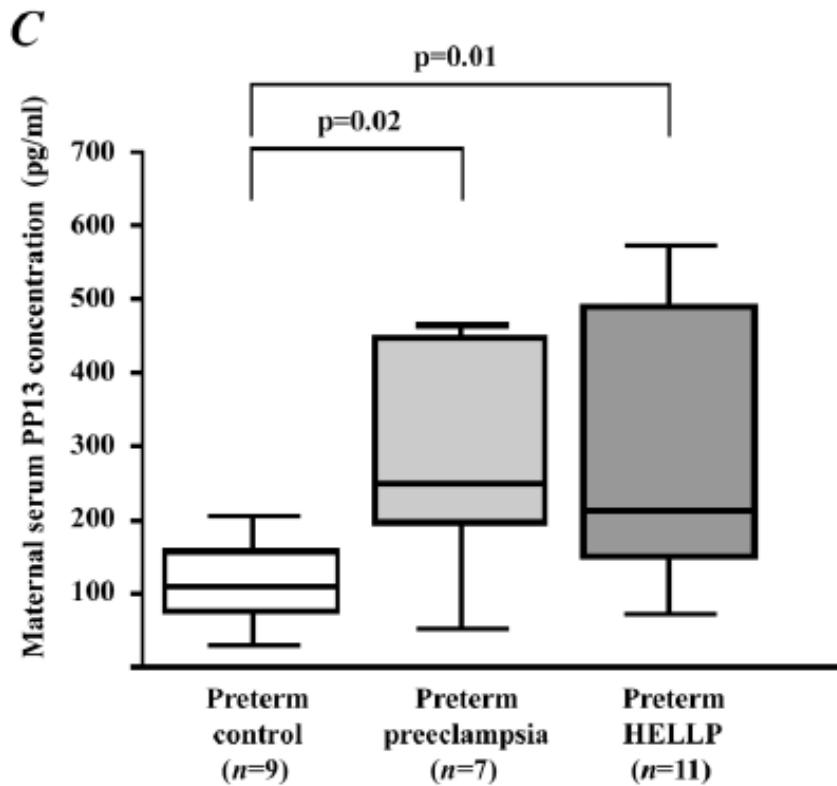
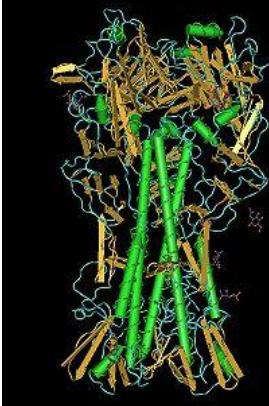




**Rising circulating levels of soluble endoglin and ratios of sFlt1:PIGF herald the onset of preeclampsia.**



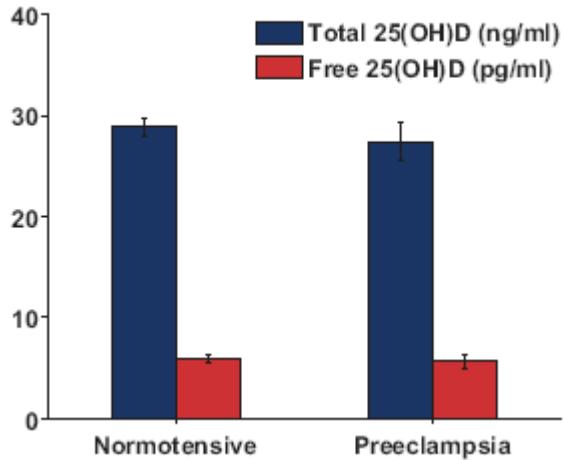
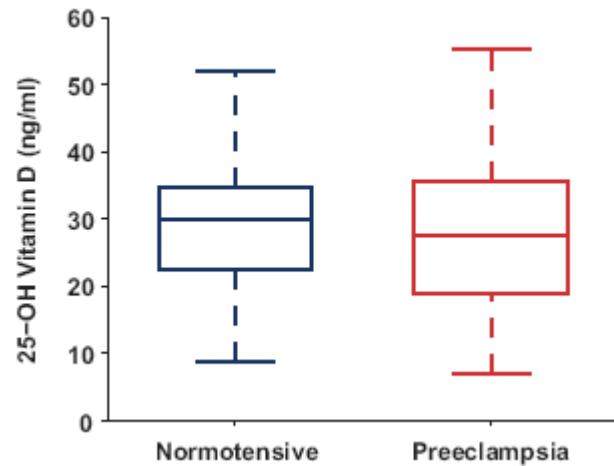
Placental Protein 13 (galectin-13) has decreased placental expression but increased shedding and maternal serum concentrations in patients presenting with preterm preeclampsia and HELLP syndrome



1) preeclampsia with ( $n=12$ ) or 2) without HELLP syndrome ( $n=20$ ), and 3) a second subset of controls ( $n=30$ ), which consisted of term ( $n=20$ ) and preterm controls ( $n=10$ ). Term controls had no medical or obstetrical complications and delivered at term ( $GW \geq 37$ ) a newborn with birth-weight appropriate for gestational age.

Than et al., 2008

# And what about Vitamin D?



Powe et al., Hypertension 2010

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# Pre-eclampsia: Risk Prediction

## IN THE SPOTLIGHT

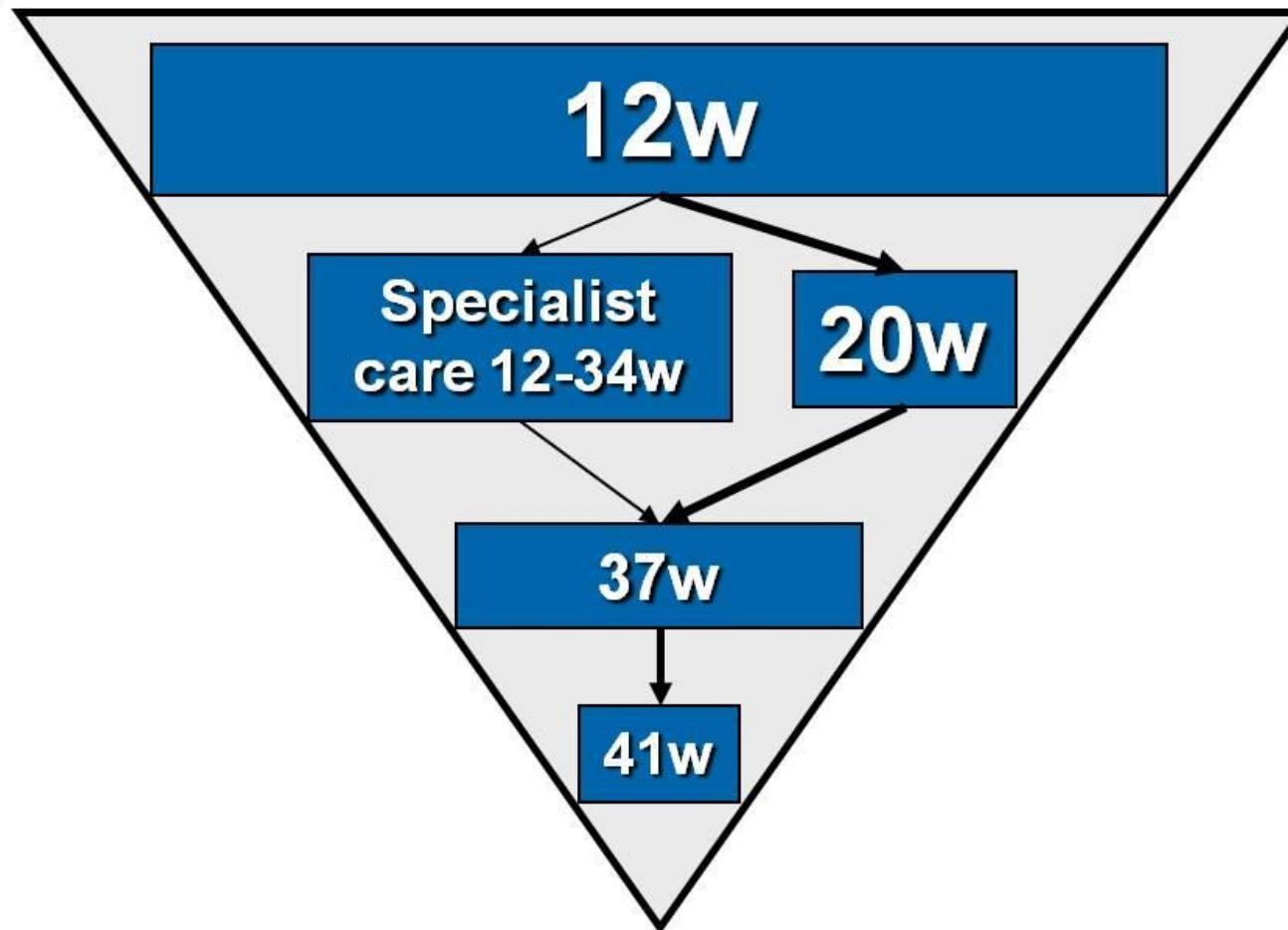
- Since actor Angelina Jolie, pictured, revealed her preventive double mastectomy in May there has been a **400 per cent** increase in Canberra women seeking genetic screening.



- Women have a **1 in 500** chance of carrying the faulty BRCA 1 or 2 gene linked to breast and ovarian cancer.
- Men can also carry the BRCA 1 and 2 gene which puts them at increased risk of breast, prostate and pancreatic cancer.
- **5 per cent** of all breast cancers are diagnosed in BRCA 1 or 2 carriers.
- **44** Canberra women have opted for preventative mastectomies over the past ten years – ten within the last three years.
- **153** Canberra women are currently undergoing annual MRI scans to manage their BRCA 1 or 2 condition. Eight have gone on to develop cancer in the past five years.

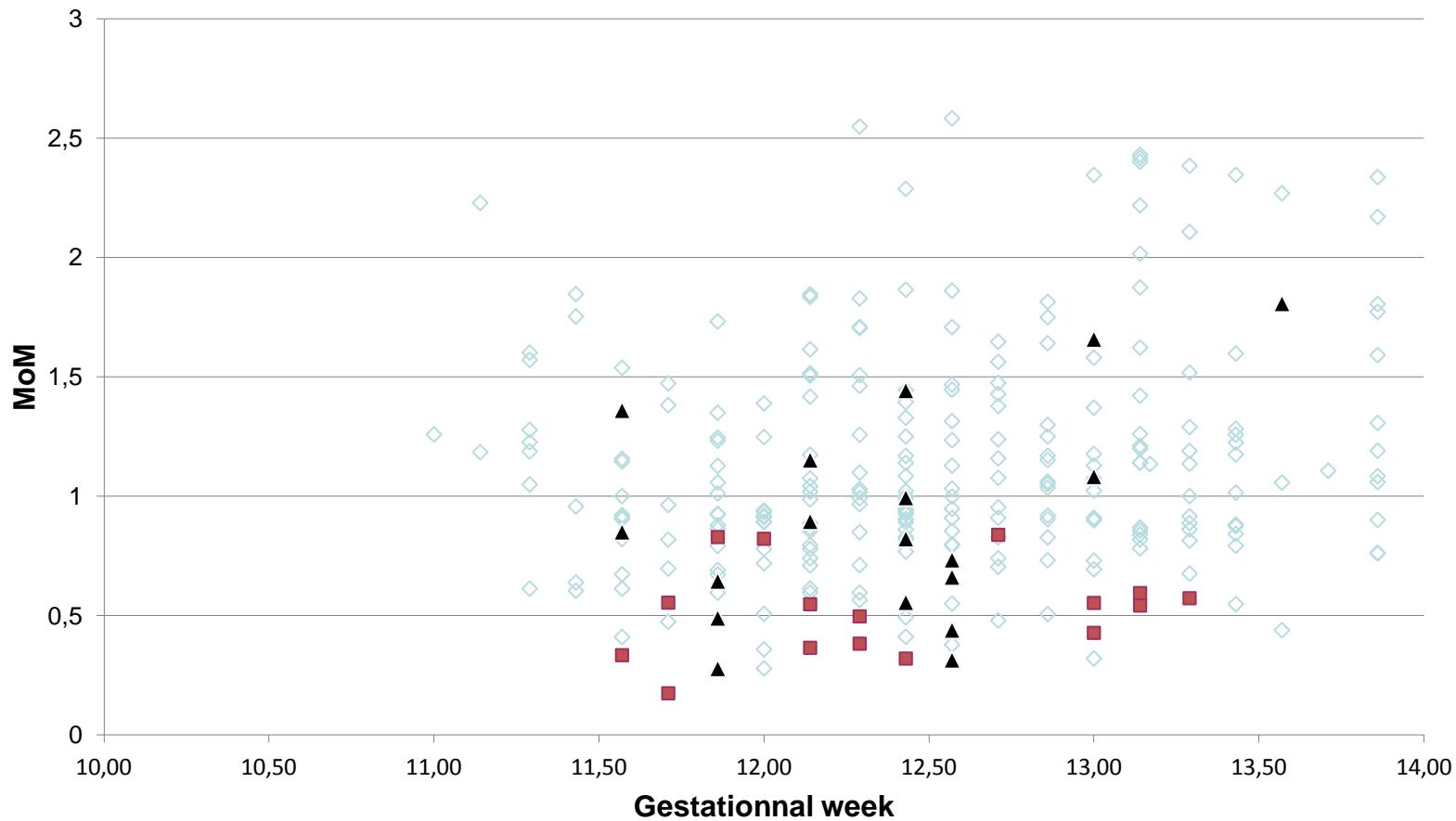


# Pre-eclampsia: Prediction at 11 – 13 weeks



# Pre-eclampsia: Prediction at 11 – 13 weeks

## MoM PIGF COBAS

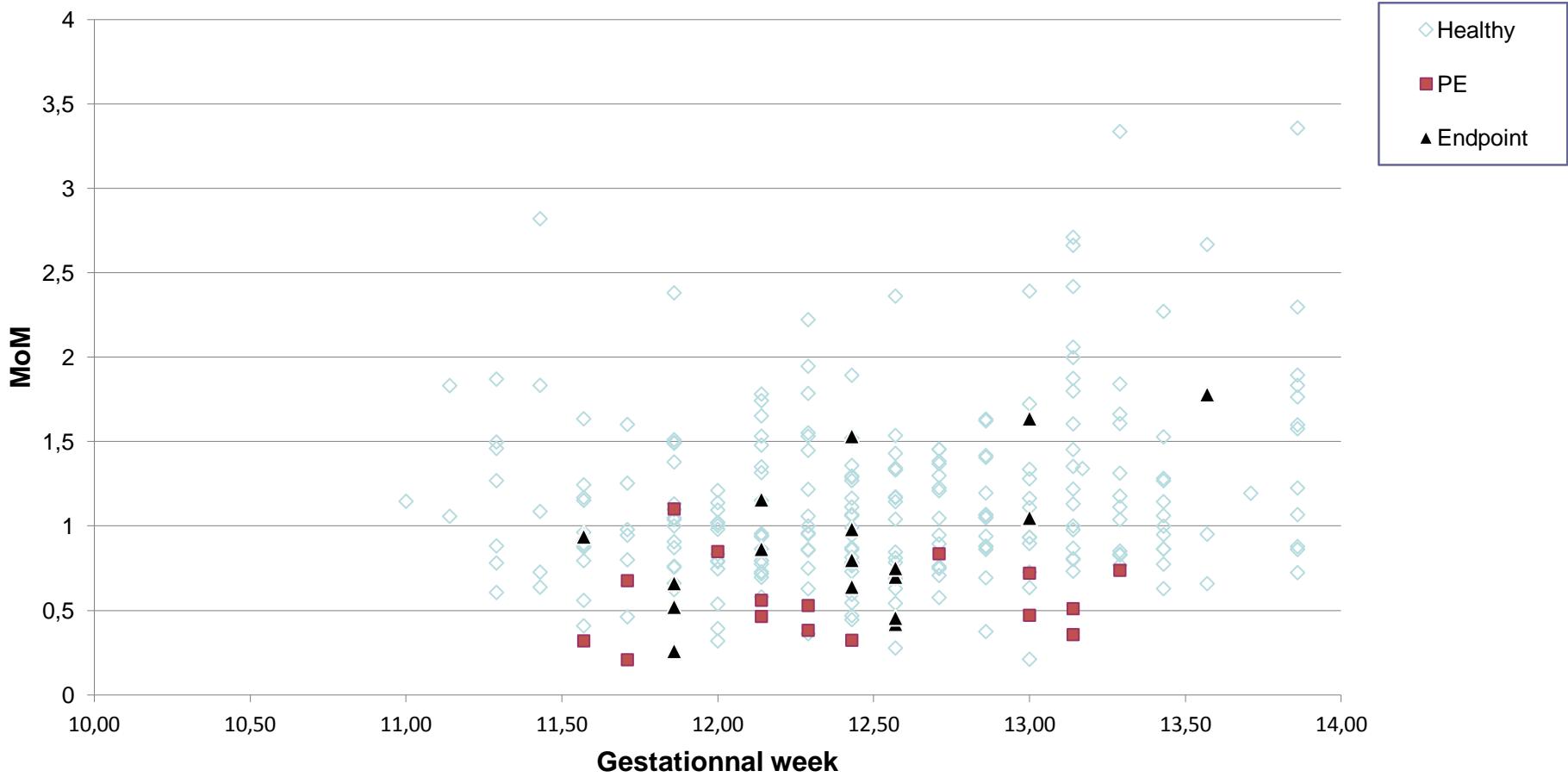


Gruson et al., FMF 2013

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# Pre-eclampsia: Prediction at 11 – 13 weeks

## MoM PIGF KRYPTOR

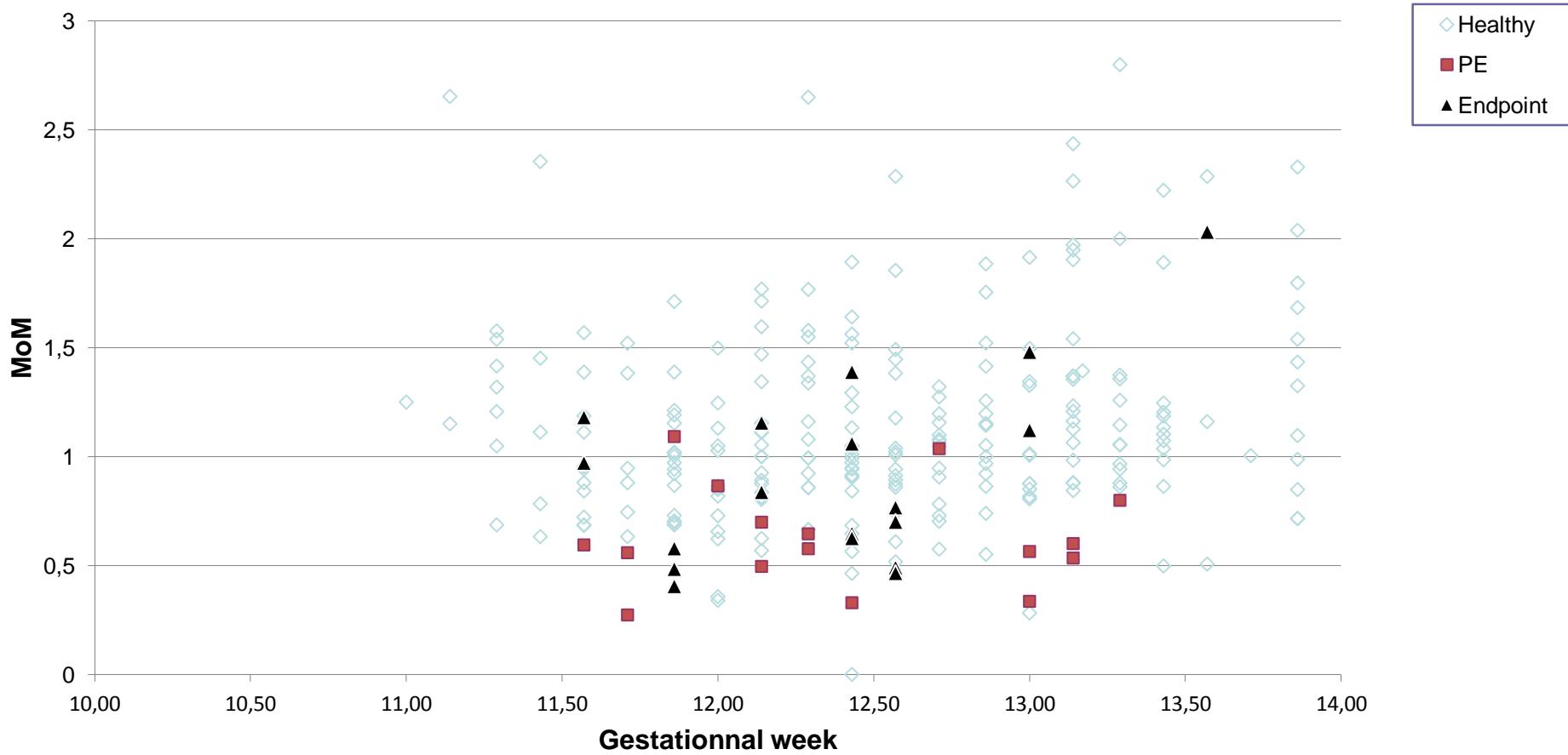


Gruson et al., FMF 2013

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# Pre-eclampsia: Prediction at 11 – 13 weeks

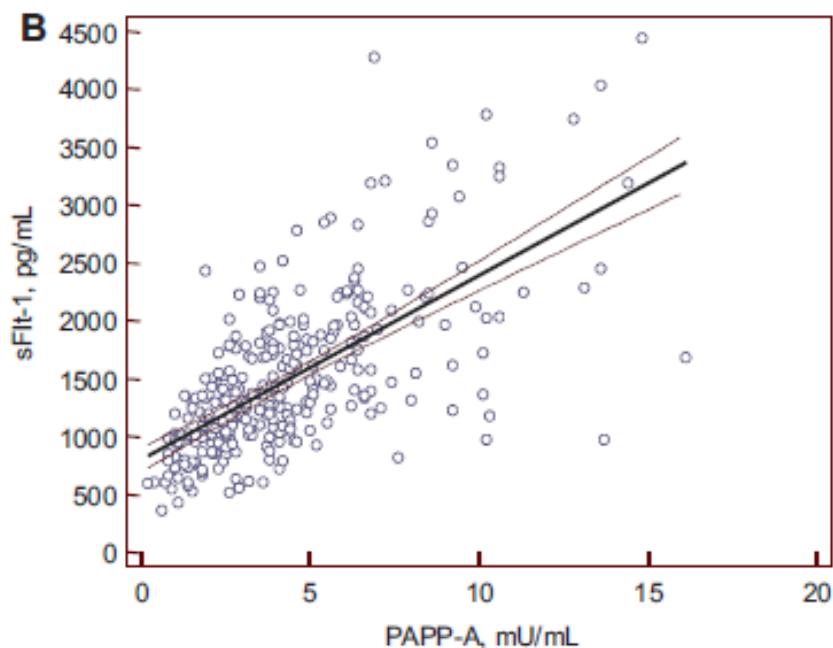
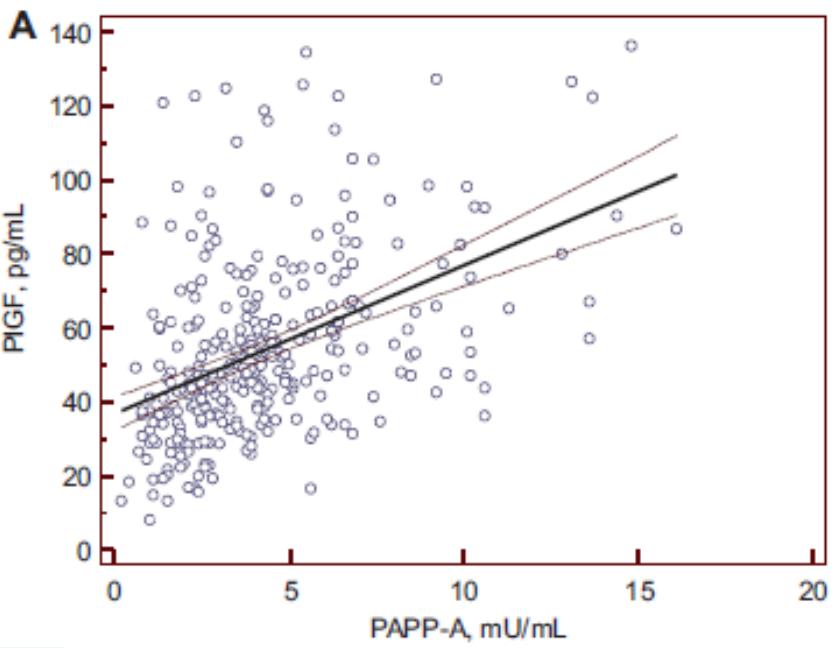
## MoM PIGF AUTODELFIA



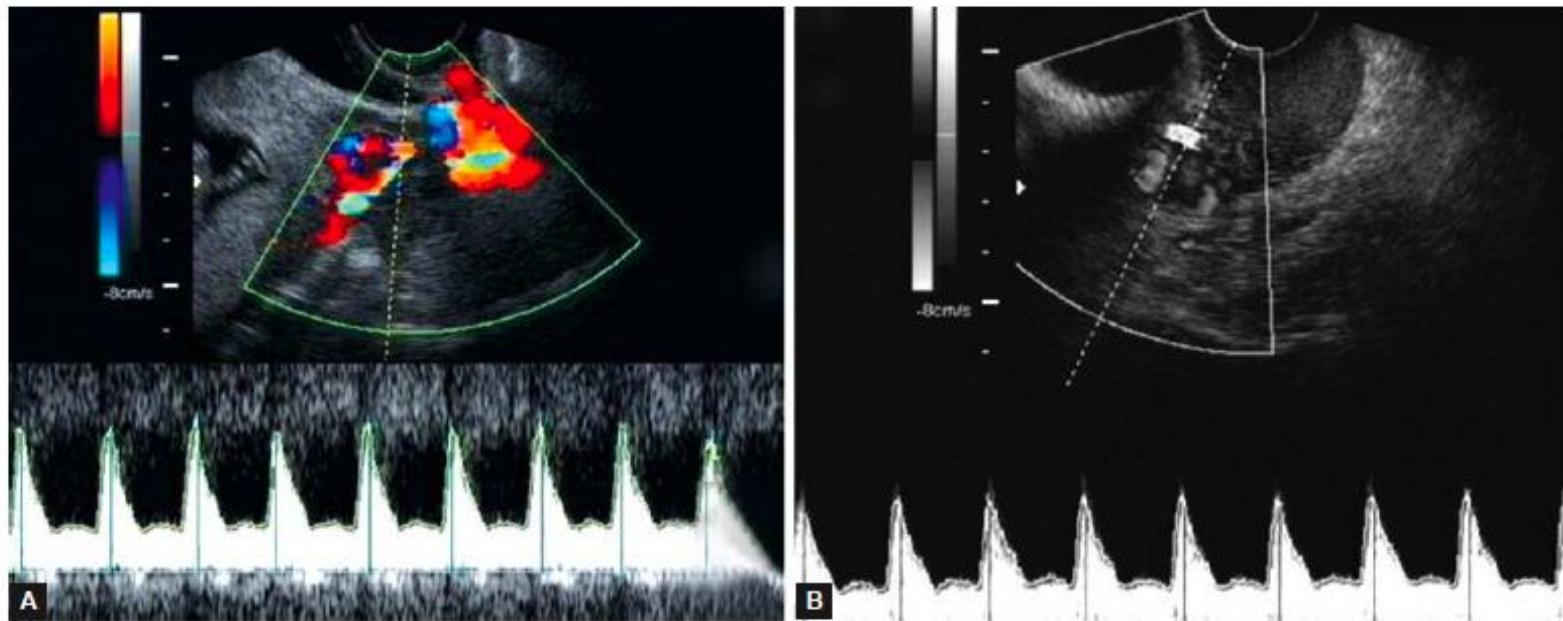
Gruson et al., FMF 2013

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# Integrated Risk Estimation



# Uterine artery pulsatility index

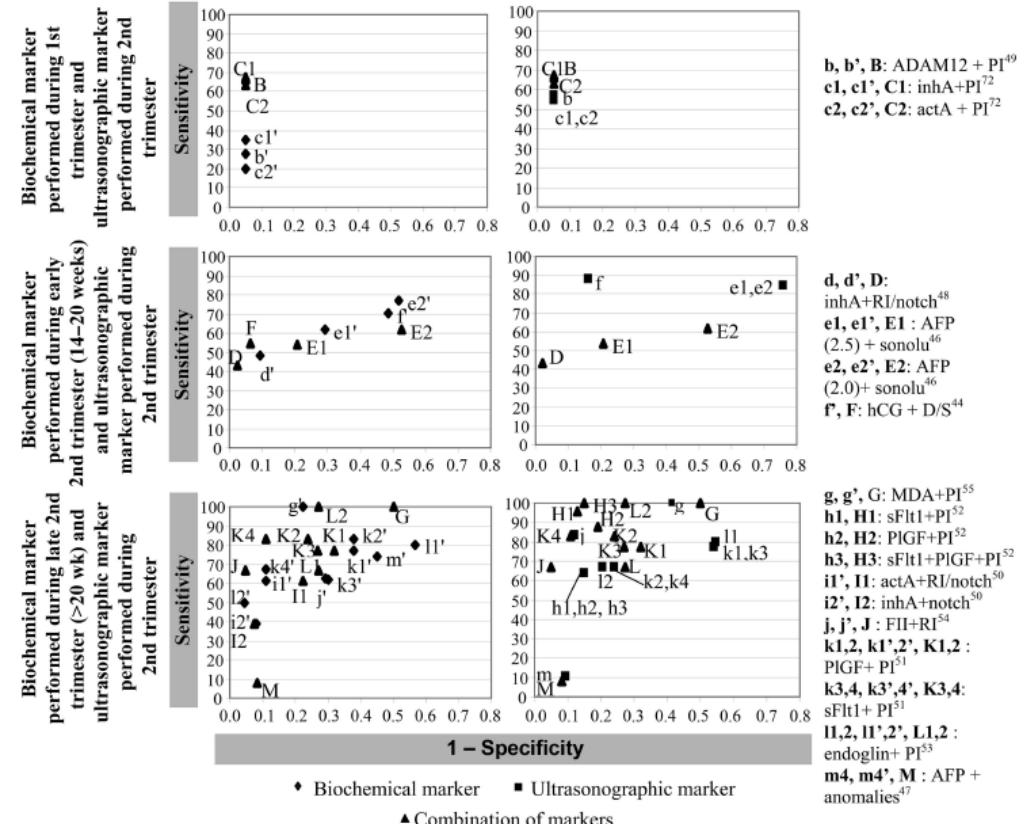


Figs 2A and B: Uterine artery flow measurement transvaginally lateral to the uterine cervix at the level of the internal cervical (first trimester)

*Uterine artery Doppler studies both in the second and the first trimester can predict pregnancies at increased risk of the complications of impaired placentation. The sensitivity for predicting severe preeclampsia ranges between 80 and 90% for a false positive rate of 5 to 7%.*



# Integrated Risk Estimation



*In low-risk populations, combinations including placental protein 13 (PP13), pregnancy-associated plasma protein A (PAPP-A), a disintegrin and metalloprotease-12 (ADAM12), activin A, or inhibin A measured in first or early second trimester and uterine artery Doppler in second trimester appear promising (sensitivity 60%–80%, specificity 80%).*

*In high-risk populations, the combination of PP13 and pulsatility index in first trimester showed 90% sensitivity and 90% specificity in a single study limited to severe preeclampsia.*



# Pre-eclampsia: Prediction at 11 – 13 weeks

**Table 1.** Fitted regression model for marker  $\log_{10}$  MoM values on gestation at time of delivery for pregnancies with PE

Marker	Intercept	SE	P	Slope	SE	P
Uterine artery PI	0.642102	0.038479	<0.0001	-0.015173	0.0010191	<0.0001
MAP	0.114859	0.014798	<0.0001	-0.002115	0.0003917	<0.0001
PAPP-A	-0.656448	0.078707	<0.0001	0.015555	0.0020837	<0.0001
PLGF	0.861296	0.089182	<0.0001	0.020221	0.0023705	<0.0001

Study population	False-positive rate	Detection rate
Total	5,572/57,458 (9.7)	432/568 (76.1)
Caucasian all	3,012/42,514 (7.1)	181/281 (64.4)
Caucasian nulliparous	2,077/21,785 (9.5)	130/187 (69.5)
Caucasian parous	935/20,729 (4.5)	51/94 (54.3)
Afro-Caribbean all	2,007/9,268 (21.7)	200/224 (89.3)
Afro-Caribbean nulliparous	1,061/3,638 (29.2)	93/96 (96.9)
Afro-Caribbean parous	946/5,630 (16.8)	107/128 (83.6)

*Akolekar et al., 2013*



Please record the following information and then press calculate.

Maternal age  years

Maternal weight  kg

Maternal height  cm

Racial origin

- Pre-existing diabetes mellitus type I
- Chronic hypertension
- Cigarette smoker in this pregnancy
- Systemic lupus erythematosus
- Family history of preeclampsia

Method of conception

Obstetric history

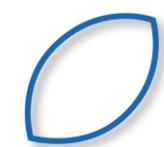
Fetal crown-rump length  mm

Uterine artery PI  MoM The uterine artery PI MoM is derived from your measurements by the [FMF calculator](#)

Mean arterial pressure  MoM The mean arterial pressure MoM is derived from your measurements by the [FMF calculator](#)

Maternal serum PAPP-A  MoM

Maternal serum PIGF  MoM PIGF MoM is derived from your measurements by the [FMF calculator](#)



# Pre-eclampsia: Prediction at 11 – 13 weeks

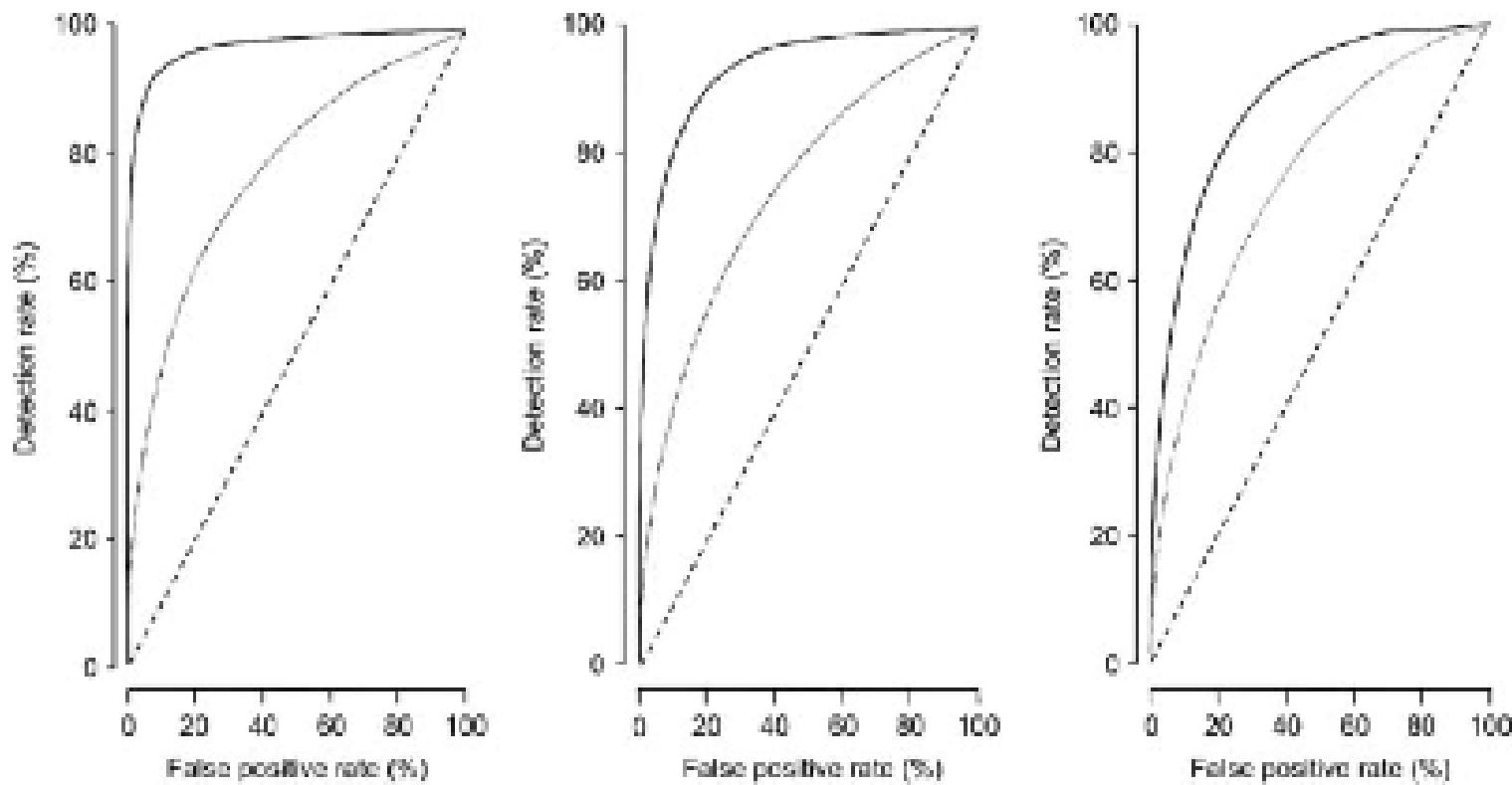


Figure 1—Receiver operating characteristic (ROC) curves in the prediction of early (left), intermediate (middle) and late pre-eclampsia (PE) by maternal factors only (-----) and by a combination of maternal factors, biochemical and biophysical markers (—)

In screening for PE by maternal factors only at a fixed false positive rate of 5%, the estimated detection rates were 33.0% for early PE, 27.8% for intermediate PE and 24.5% for late PE.

The respective detection rates in screening by a combination of maternal factors, biophysical and biochemical markers were 91.0, 79.4 and 60.9%.

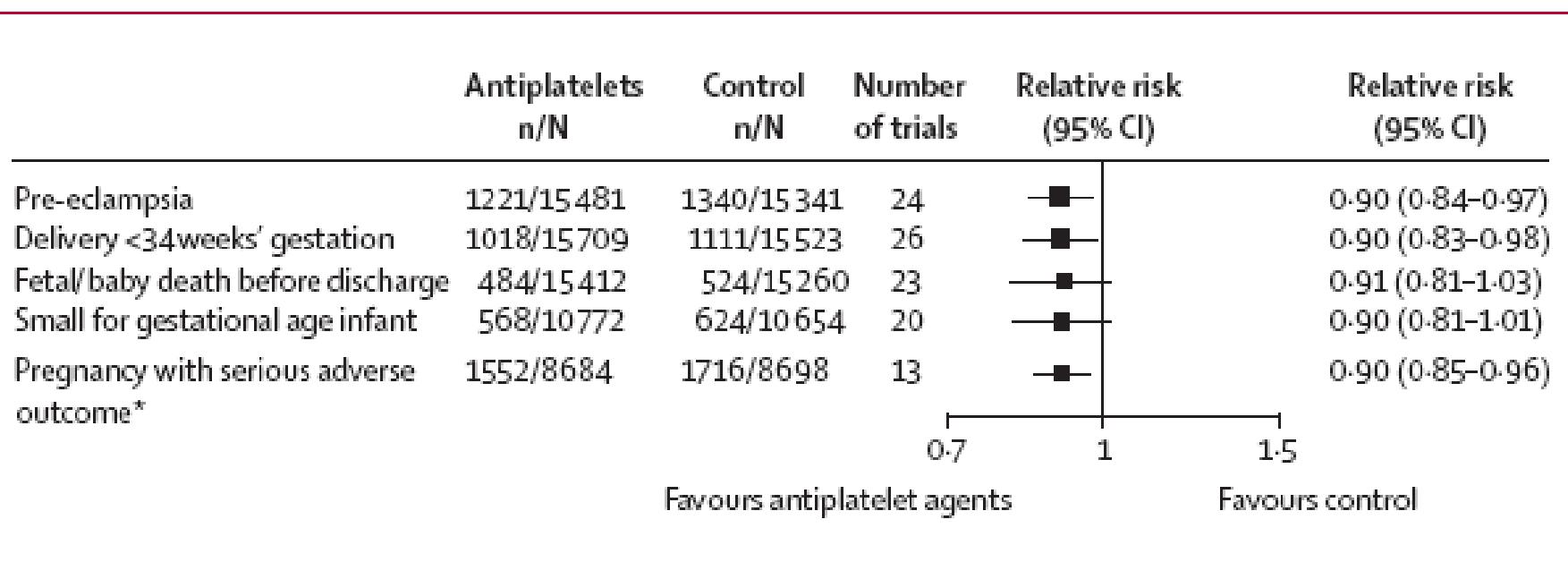


# Pre-eclampsia

## Treatment ?

*The only cure is delivery*



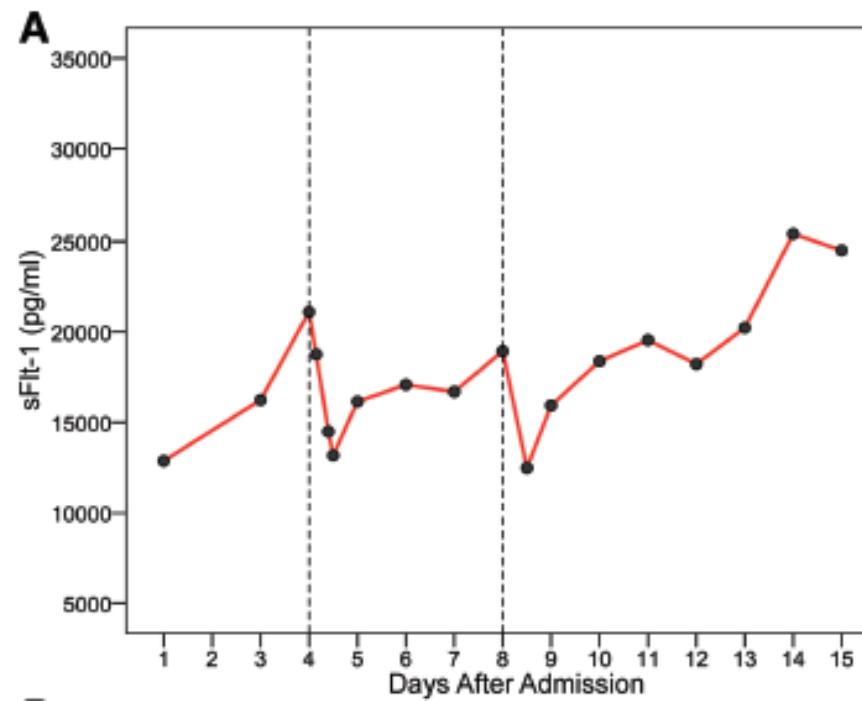


**Askie et al., Lancet 2007**

# sFlt-1 removal: a semi-causative therapy of PE

## RAAPID TRIAL

*Dextran Sulfate Apheresis fro Pre-Eclampsia*



*Thadanit et al., Circulation 2011.*

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# PRELIMINARY PROGRAMME

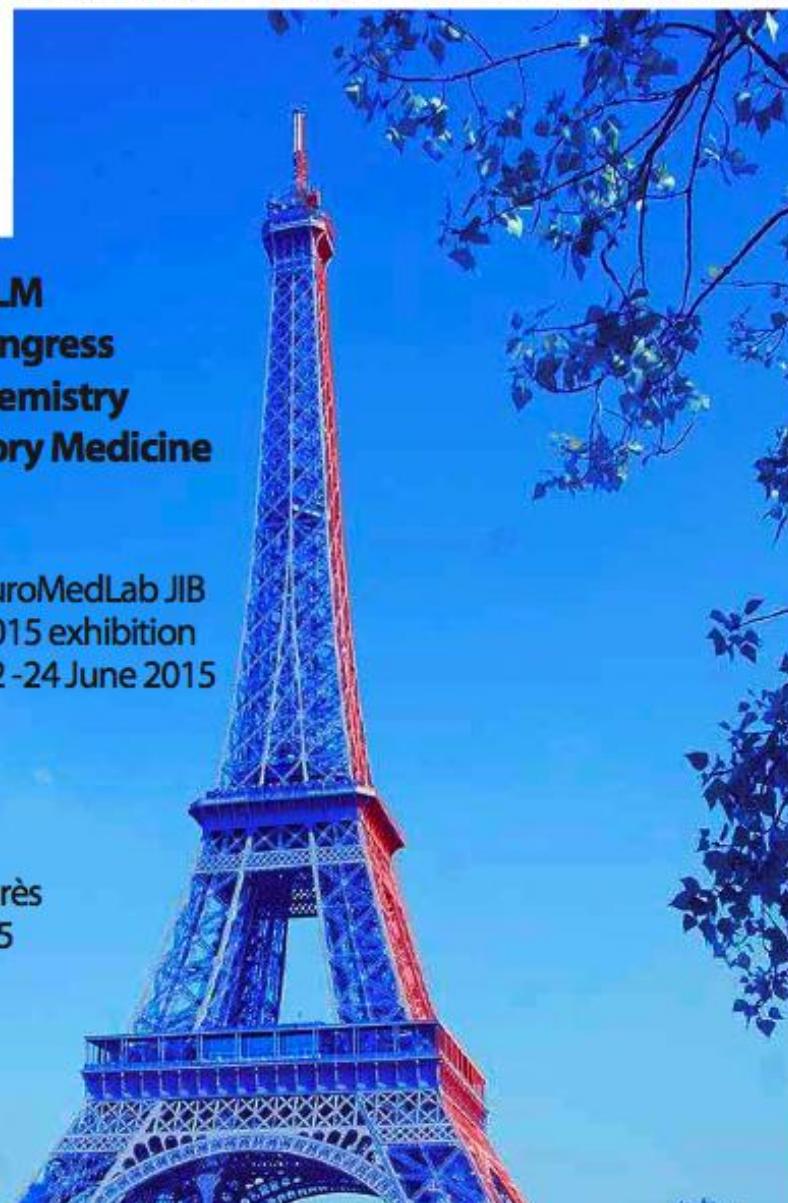


## 21<sup>st</sup> IFCC - EFLM European Congress of Clinical Chemistry and Laboratory Medicine



EuroMedLab JIB  
2015 exhibition  
22-24 June 2015

Paris, France  
Palais des Congrès  
21-25 June 2015



# **Thank you very much....**



**...for your attention !**

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