

# Screening for Preeclampsia (PE) in 2<sup>nd</sup> & 3<sup>rd</sup> Trimester



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## Competing Risk Model at 19-24 Weeks

Original Research

ajog.org

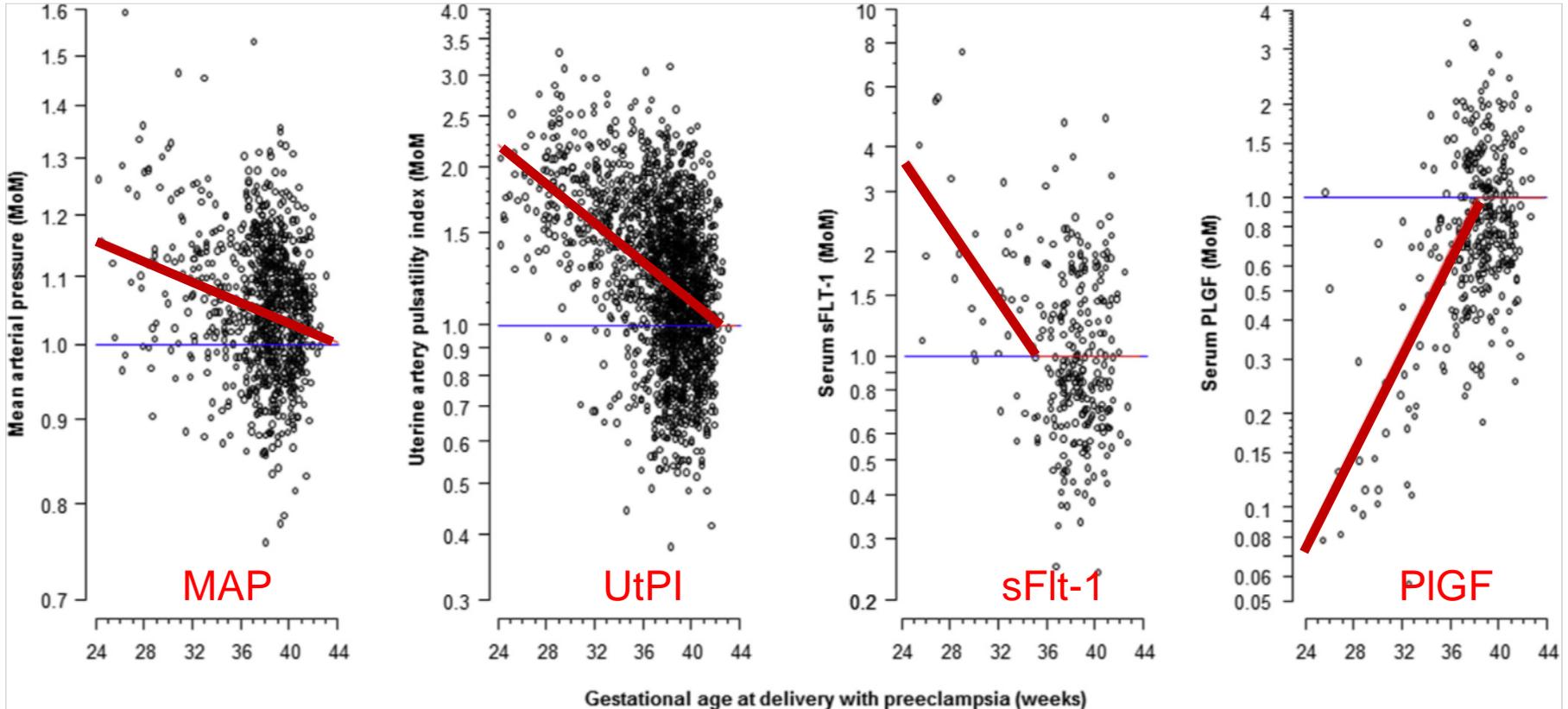
OBSTETRICS

### Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 19–24 weeks' gestation

Dahiana M. Gallo, MD; David Wright, PhD; Cristina Casanova, MD; Mercedes Campanero, MD; Kypros H. Nicolaides, MD

- ✓ Prospective Screening at 19-24 weeks
- ✓ 123,406 pregnancies
- ✓ Performance of screening based on PE requiring delivery <32, <37 & >37 weeks
- ✓ Combined screening with maternal history, MAP, UTPI, PIGF & sFlt-1

## Competing Risk Model at 19-24 Weeks



sFlt-1 higher, PIGF lower, UtPI higher, MAP higher



## Competing Risk Model at 19-24 Weeks

**TABLE 2**

**Empirical detection rate, at false-positive rate of 5% and 10%, in screening for preeclampsia with delivery at <37 and ≥37 weeks' gestation by maternal factors and combinations of biomarkers in the subgroup of 7748 pregnancies with complete data on all biomarkers**

Method of screening	Preeclampsia at <37 weeks				Preeclampsia at ≥37 weeks			
	FPR 5%		FPR 10%		FPR 5%		FPR 10%	
	n/N	% (95% CI) <sup>a</sup>	n/N	% (95% CI) <sup>a</sup>	n/N	% (95% CI) <sup>a</sup>	n/N	% (95% CI) <sup>a</sup>
History	21/62	34 (22, 47); 34	29/62	47 (34, 60); 47	55/206	27 (21, 33); 26	75/206	36 (30, 43); 37
MAP, UTPI, PLGF	45/62	73 (60, 83); 77	52/62	84 (72, 92); 85	58/206	28 (22, 35); 33	90/206	44 (37, 51); 46
MAP, UTPI, SFLT	46/62	74 (62, 84); 69	50/62	81 (69, 90); 79	57/206	28 (22, 35); 33	92/206	45 (38, 52); 46
MAP, PLGF, SFLT	37/62	60 (46, 72); 69	45/62	73 (60, 83); 79	56/206	27 (21, 34); 33	89/206	43 (36, 50); 46
UTPI, PLGF, SFLT	41/62	66 (53, 78); 74	50/62	81 (69, 90); 82	54/206	26 (20, 33); 28	74/206	36 (29, 43); 40
MAP, UTPI, PLGF, SFLT	46/62	74 (62, 84); 78	53/62	85 (74, 93); 86	56/206	27 (21, 34); 33	91/206	44 (37, 51); 46

- History has a bad performance
- Addition of sFlt-1 did not improve the detection
- Weak performance for late-onset



## Competing Risk Model at 30-34 Weeks

### Original Research

ajog.org

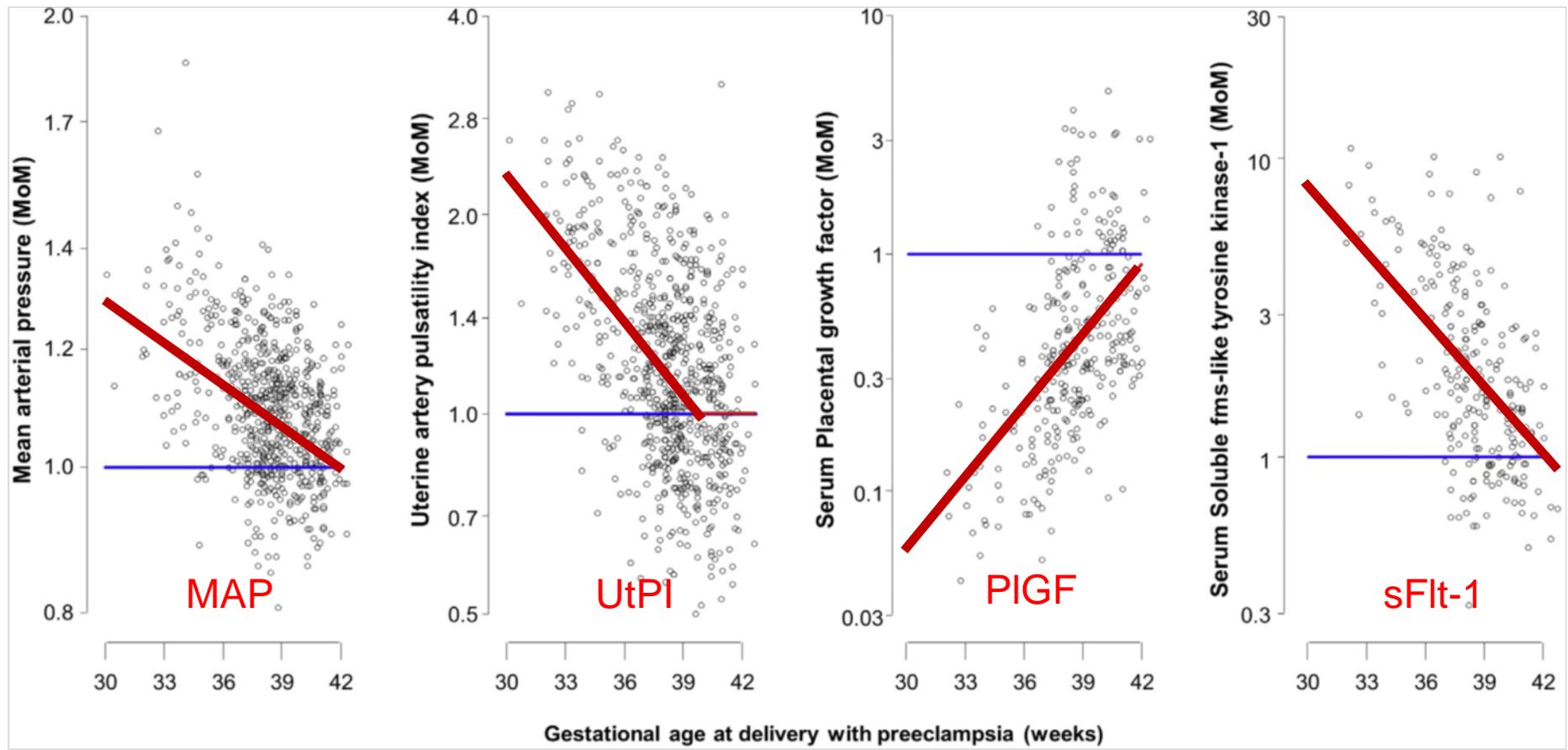
#### OBSTETRICS

## Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 30–34 weeks' gestation

Andreas Tsiakkas, MD; Youssef Saiid, MD; Alan Wright, PhD; David Wright, PhD; Kypros H. Nicolaides, MD

- ✓ Prospective Screening at 30-34 weeks
- ✓ 30,936 pregnancies
- ✓ Performance of screening based on PE requiring delivery <37 & >37 weeks
- ✓ Combined screening with maternal history, MAP, UTPI, PIGF & sFlt-1

## Competing Risk Model at 30-34 Weeks



sFlt-1 higher, PIGF lower, UTPI higher, MAP higher



## Competing Risk Model at 30-34 Weeks

TABLE 1

Empirical performance of screening for preeclampsia with delivery at < 37 and ≥ 37 weeks' gestation from all available data

Method of screening	Preeclampsia at < 37 wks				Preeclampsia at ≥ 37 wks			
	History		Combined		History		Combined	
	n/N	DR, % (95% CI)	n/N	DR, % (95% CI)	n/N	DR, % (95% CI)	n/N	DR %, (95% CI)
False-positive rate, 5%								
Maternal factors	61/179	34 (27, 42)	61/179	34 (27, 42); <b>34</b>	169/555	30 (27, 34)	169/555	30 (27, 34); <b>27</b>
MAP, UTPI, PLGF	15/52	29 (17, 43)	49/52	94 (84, 99); <b>95</b>	60/234	26 (20, 32)	110/234	47 (40, 54); <b>47</b>
MAP, UTPI, SFLT	13/44	30 (17, 45)	40/44	91 (78, 97); <b>97</b>	54/190	28 (22, 35)	86/190	45 (38, 53); <b>48</b>
MAP, PLGF, SFLT	13/45	29 (16, 44)	42/45	93 (82, 99); <b>97</b>	56/194	29 (23, 36)	104/194	54 (46, 61); <b>48</b>
UTPI, PLGF, SFLT	13/44	30 (17, 45)	40/44	91 (78, 97); <b>97</b>	55/192	29 (22, 36)	95/192	49 (42, 57); <b>50</b>
MAP, UTPI, PLGF, SFLT	13/44	30 (17, 45)	43/44	98 (88, 99); <b>98</b>	54/190	28 (22, 35)	104/190	55 (47, 62); <b>54</b>

- History has a bad performance
- Screening is superior to FTS
- Weak performance for late-onset



## Adverse Outcomes

*Ultrasound Obstet Gynecol* 2016; 47: 203–209

Published online 28 December 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.15663

### Biophysical and biochemical markers at 35–37 weeks' gestation in the prediction of adverse perinatal outcome

N. VALIÑO\*, G. GIUNTA\*, D. M. GALLO\*, R. AKOLEKAR\*† and K. H. NICOLAIDES\*

\*Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK; †Department of Fetal Medicine, Medway Maritime Hospital, Gillingham, Kent, UK

- ✓ Common findings are approved: for PE and SGA: increased UtPI, MAP, sFlt-1, reduced PIGF
- ✓ Screening with these markers can predict majority of cases with PE and SGA
- ✓ NOT useful in predicting fetal distress, CS, low cord blood pH, low Apgar, NNU admission
- ✓ Same results for 30. weeks



## Pitfalls and Advantages of These Models

- ✓ Large population
- ✓ Accurate measurements in short time
- ✓ Expression of values in MoMs after adjustment
- ✓ Bayes theorem to calculate patient specific risk
- ✓ Model which introduces optimistic bias
- ✓ Management options missing
- ✓ Could implementation improve perinatal outcome?
- ✓ Detection for how long?

## ACOG Recommendations



The American College of  
Obstetricians and Gynecologists  
WOMEN'S HEALTH CARE PHYSICIANS

### Hypertension in Pregnancy

*Report of the American College of Obstetricians and Gynecologists'  
Task Force on Hypertension in Pregnancy*

### Prediction of Preeclampsia

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#### TASK FORCE RECOMMENDATION

- Screening to predict preeclampsia beyond obtaining an appropriate medical history to evaluate for risk factors is not recommended.

*Quality of evidence: Moderate*

*Strength of recommendation: Strong*

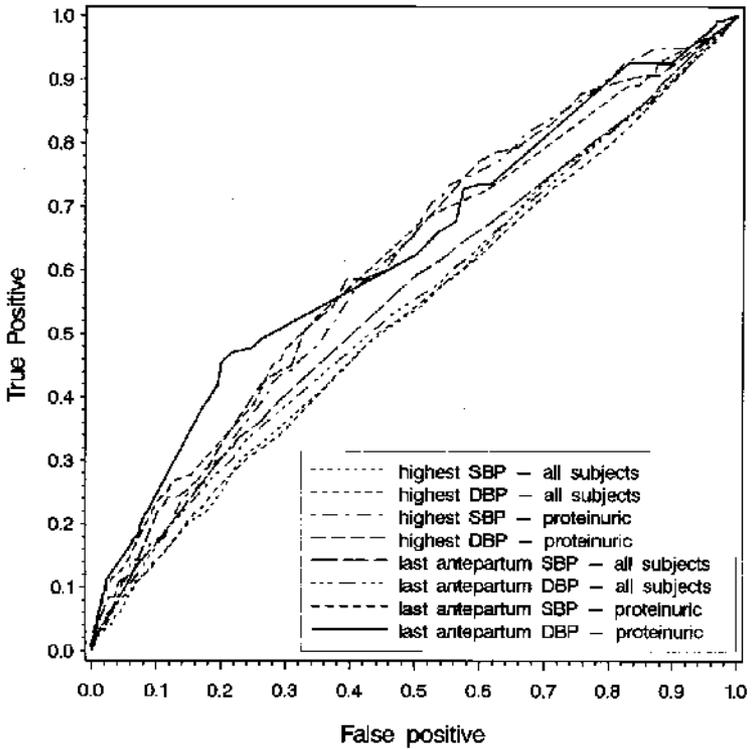
ACOG, Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy.

Obstet Gynecol 2013;122: 1122-31. 2013

## Diagnosis based on international guidelines

### Prediction of Adverse Outcomes by Common Definitions of Hypertension in Pregnancy

JUN ZHANG, PhD, MD, MARK A. KLEBANOFF, MD, MPH, AND JAMES M. ROBERTS, MD



Only ca. 30% PPV for adverse outcomes



## Pelican Study

### **636** Plasma placental growth factor (PIGF) in the diagnosis of women with pre-eclampsia requiring delivery within 14 days: the PELICAN study

Lucy Chappell<sup>1</sup>, Suzy Duckworth<sup>1</sup>, Melanie Griffin<sup>1</sup>, Paul Seed<sup>1</sup>, Christopher Redman<sup>2</sup>, Andrew Shennan<sup>1</sup>

<sup>1</sup>King's College London, Women's Health Academic Centre, London, United Kingdom, <sup>2</sup>University of Oxford, Nuffield Department of Obstetrics and Gynaecology, Oxford, United Kingdom

- ✓ Multicenter Study
- ✓ 607 pregnant women presenting between 20+0 – 40+6 weeks
- ✓ Suspected PE
- ✓ Diagnostic accuracy of PIGF was tested
- ✓ Delivery within 14 days
- ✓ Under 35 weeks: low PIGF rules in preterm delivery; high PIGF rules out preterm delivery within 14 days
- ✓ Under 35 weeks: Sensitivity 0.95; specificity 0.57; PPV 0.42



## Repetitive Measurements

### Journal of Perinatal Medicine

Official Journal of the World Association of Perinatal  
Medicine

### The importance of repeated measurements of the sFlt-1/PIGF ratio for the prediction of preeclampsia and intrauterine growth restriction

Katharina Schoofs<sup>1</sup> / Ulrike Grittner<sup>2</sup> / Theresa Engels<sup>1</sup> / Juliane Pape<sup>3</sup> / Barbara Denk<sup>4</sup> / Wolfgang Henrich<sup>1</sup> / Stefan Verlohren<sup>1</sup>

- ✓ Prospective Screening of 150 high-risk patients
- ✓ sFlt-1/PIGF—Ratio was higher in PE and IUGR
- ✓ An increase by repetitive measurements was observed in IUGR and PE which correlates with adverse outcomes
- ✓ Optimal time interval is yet unknown



## Consensus Statement

*Ultrasound Obstet Gynecol* 2015; 45: 241–246

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### Opinion

Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice

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- ✓ Large population needed
- ✓ Prospective studies needed
- ✓ Only one single platform tested
- ✓ It should be combined with other well-established methods
- ✓ It's screening performance is not yet tested
- ✓ Only high-risk populations tested



## Consensus Statement

### Statement 1: sFlt-1/PlGF < 38

sFlt-1/PlGF ratio < 38 rules out PE, irrespective of gestational age, for at least 1 week. Further management is according to the clinician's discretion.

### Statement 2: sFlt-1/PlGF ratio > 85 (early-onset PE) or > 110 (late-onset PE)

Diagnosis of PE or placenta-related disorder is highly likely. Management according to local guidelines. Severely elevated sFlt-1/PlGF ratios (> 655 at <34 + 0 weeks; > 201 at  $\geq 34 + 0$  weeks) are associated closely with the need to deliver within 48 h. Close surveillance and (if < 34 weeks) prompt initiation of antenatal corticoids to accelerate fetal lung maturation are mandatory.

### Statement 3: sFlt-1/PlGF ratio > 85 (early-onset PE) or > 110 (late-onset PE), repeat measurement

Re-measure after 2–4 days to determine trend and follow up according to clinician's discretion depending on severity.

The test frequency can be adapted to the clinical situation and trend in sFlt-1/PlGF ratio dynamics.

### Statement 4: sFlt-1/PlGF ratio 38–85 (early-onset PE) or 38–110 (late-onset PE)

The sFlt-1/PlGF ratio provides information about the patient before the onset of overt signs and symptoms. An sFlt-1/PlGF ratio of 38–85 or 38–110 provides extra information as to which women are at moderate risk or at high risk of developing PE within 4 weeks. Current PE or a placenta-related disorder can be ruled out, but women are at (high) risk (especially in the early-onset group).

**Early onset:** Consider a follow-up sFlt-1/PlGF test in 1–2 weeks, according to the individual clinical situation. Results are to be treated accordingly.

**Late onset:** An intermediate result of the sFlt-1/PlGF ratio is suggestive of impending placental dysfunction. Consider lowering the threshold for induction of delivery.

### Statement 5:

The sFlt-1/PlGF ratio has been proven as an aid in diagnosis for PE.

In a woman with PE already confirmed (high blood pressure and proteinuria) the sFlt-1/PlGF ratio may be useful to determine the severity of the disorder.



## Study in Essen

- ✓ Prospective Screening population
- ✓ 28-40 weeks of pregnancy
- ✓ 2 years
- ✓ Over 900 pregnancies
- ✓ sFlt-1/PIGF – Ratio?
- ✓ Cut-offs?
- ✓ MoM-Values?
- ✓ Outcome measures: PE, IUGR
- ✓ BRAHMS GmbH
- ✓ Results: early 2017

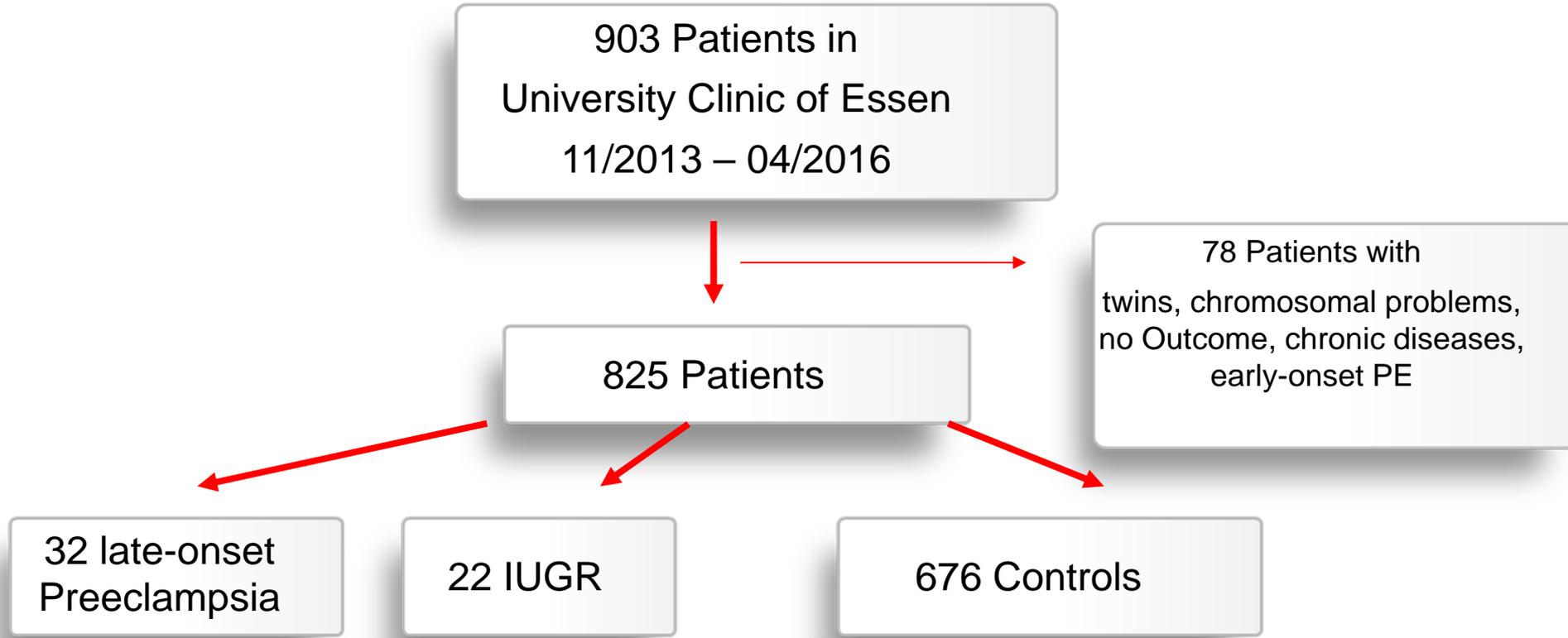


## Methods

- Prospective Analysis of the markers at 3. Trimester during the first visit between 28+1 – 40+0. weeks
- No signs of preeclampsia or IUGR at the time of visit
- 11/2013 – 04/2016
- Measurements with ELISA (B.R.A.H.M.S **KRYPTOR**® Compact)



## Methods



## Results – Patient Characteristics

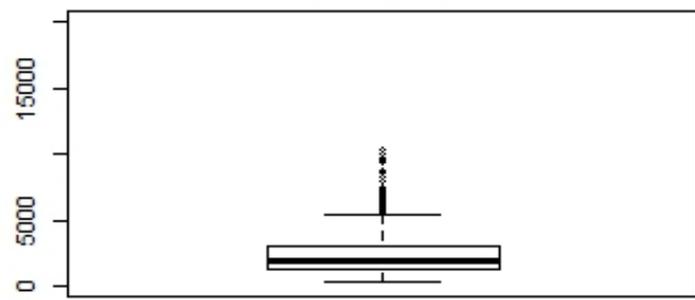
	Controls	IUGR*	PE
Number of Patients(%)	<b>676 (83.8%)</b>	<b>22 (2.7%)</b>	<b>32 (3.9%)</b>
Age <sup>1</sup>	<b>32.2 ± 5.5</b>	<b>32.5 ± 5.2</b>	<b>31.5 ± 5.2</b>
BMI <sup>1</sup>	<b>30.4 ± 8.8</b>	<b>27.9 ± 4.8</b>	<b>34.4 ± 7.3</b>
Birthweight <sup>1</sup>	<b>3340.0 ± 444.4</b>	<b>1897 ± 454</b>	<b>2527.0 ± 620.0</b>
Gestational week at analysis <sup>1</sup>	<b>34.6 ± 2.3</b>	<b>35.6 ± 2.5</b>	<b>34.4 ± 2.2</b>
Gestational week at birth <sup>1</sup>	<b>38.8 ± 1.7</b>	<b>33.4 ± 2.4</b>	<b>36.2 ± 2.4</b>
Smoking(%)	<b>64 (9.5%)</b>	<b>5 (22.7%)</b>	<b>2 (6.3%)</b>
sFlt-1 <sup>2</sup>	<b>1903.0 (1313.0-3021.0)</b>	<b>3688.0 (1501.0-6881.0)</b>	<b>6990.0 (4838.0-9964.0)</b>
PlGF <sup>2</sup>	<b>265.2 (144.4-486.3)</b>	<b>93.1 (39.2- 270.0)</b>	<b>38.7 (24.7-71.8)</b>
sFlt-1/PlGF-Ratio <sup>2</sup>	<b>7.0 (2.9-17.9)</b>	<b>50.4 (7.9- 179.5)</b>	<b>185.7 (77.9-427.8)</b>
PAPP-A <sup>2</sup>	<b>74280.0 (46130.0-119000.0)</b>	<b>71120 (47760-109800)</b>	<b>121900.0 (64950.0-313600.0)</b>
MR-proANP <sup>2</sup>	<b>38.7 (29.7-49.2)</b>	<b>59.7 (39.7- 163.0)</b>	<b>64.9 (36.3-105.2)</b>

<sup>1</sup> Mean ± Standard Deviation

<sup>2</sup> Median (Interquartilerange)

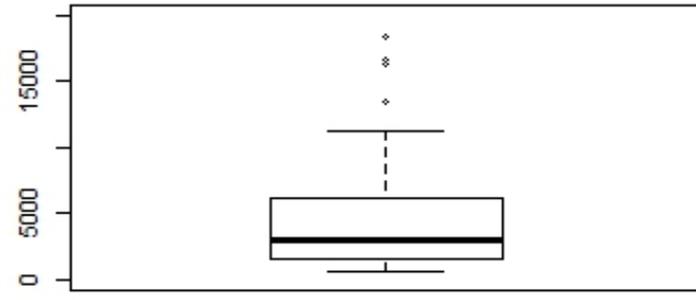
## Results – sFlt-1 - Boxplots

### Controls



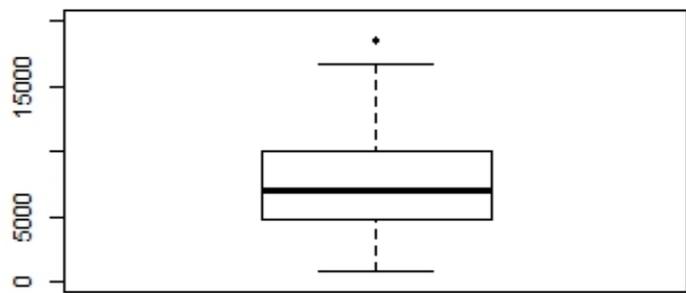
sFlt.1

### IUGR



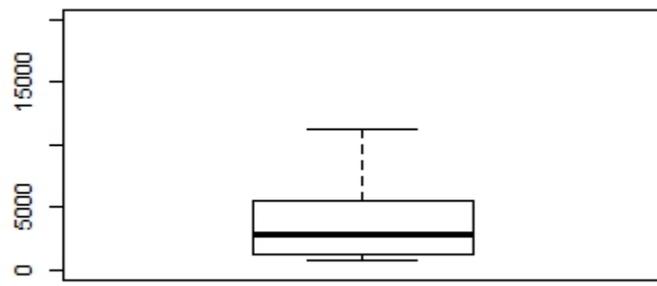
sFlt.1

### Pre-eclampsia



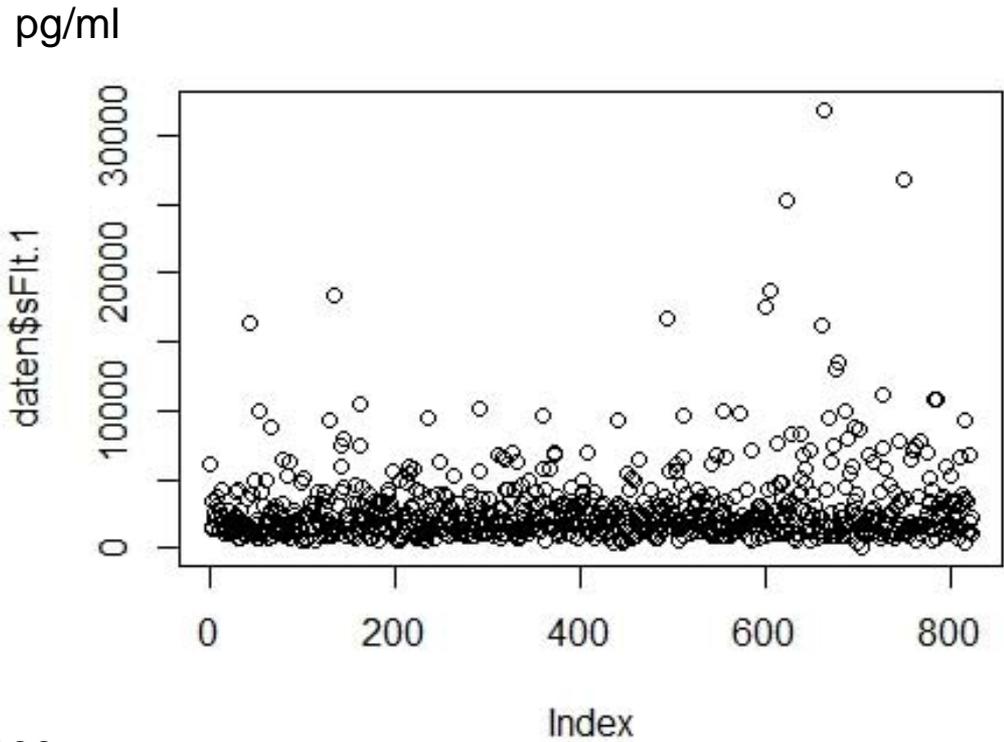
sFlt.1

### SIH



sFlt.1

## sFlt-1



Cut-off 20,000

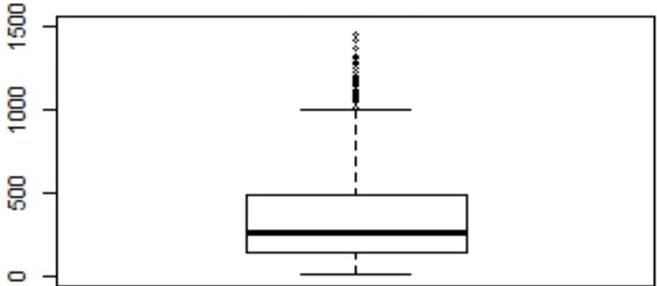


## sFlt-1 - Linear Regression Analysis\*

	<b>exp(<math>\beta</math>)</b>	<b>Lower 95%-CI</b>	<b>Upper 95%-CI</b>	<b>p value</b>
<b>PE</b>	3.29	2.69	4.04	<0.00001
<b>IUGR</b>	1.75	1.36	2.26	<0.0001

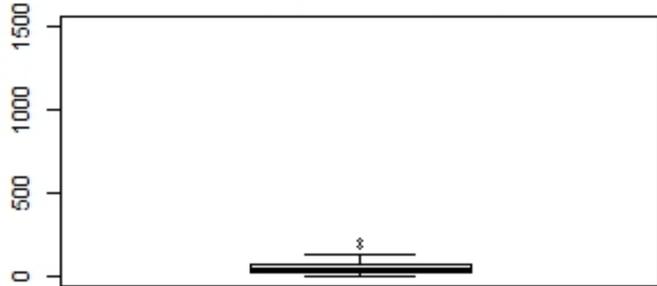
## PIGF - Boxplots

**Controls**



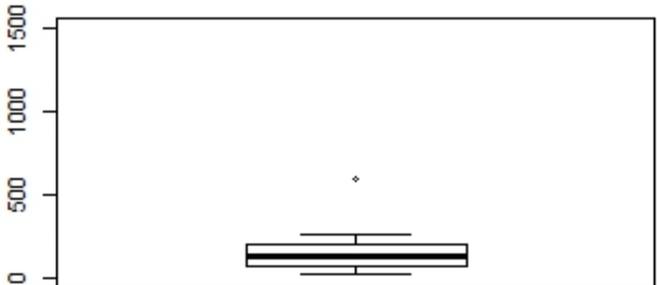
PIGF

**Pre-eclampsia**



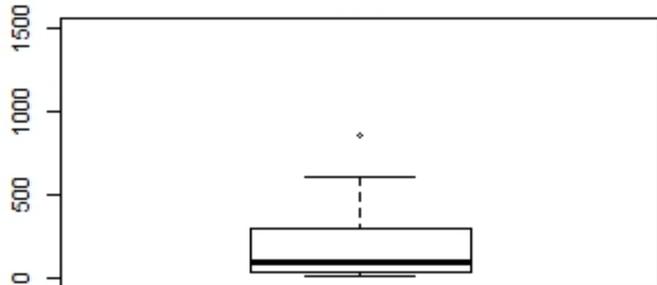
PIGF

**SIH**



PIGF

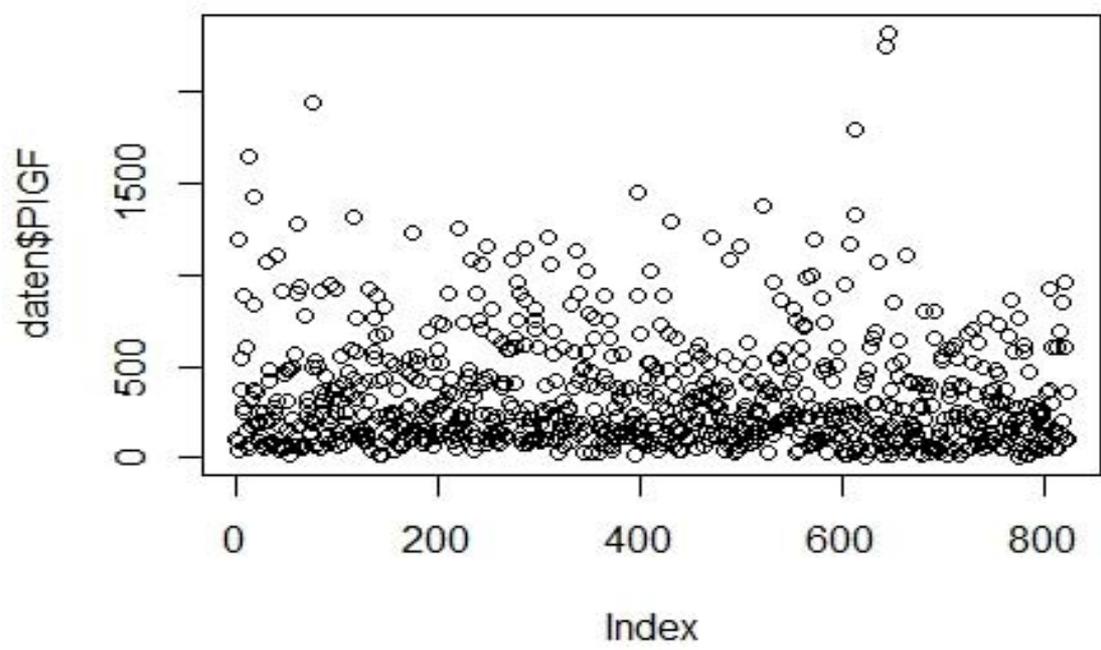
**IUGR**



PIGF

## PIGF

pg/ml



Cut-off 1,500

## PIGF - Linear Regression Analysis\*

	<b>exp(<math>\beta</math>)</b>	<b>Lower 95%-CI</b>	<b>Upper 95%-CI</b>	<b>p value</b>
<b>Preeclampsia</b>	0.18	0.13	0.24	<0.00001
<b>IUGR</b>	0.39	0.26	0.57	<0.00001



## sFlt-1/PIGF – Linear Regression Analysis\*

	exp( $\beta$ )	Lower 95%-CI	Upper 95%-CI	p value
<b>Preeclampsia</b>	15.59	10.64	22.84	<0.00001
<b>IUGR</b>	4.13	2.56	6.66	<0.00001

## PAPP-A & MR-proANP – Linear Regression Analysis\*

PAPP-A	exp( $\beta$ )	Lower 95%-CI	Upper 95%-CI	p value
Preeclampsia	1.48	1.15	1.89	0.002
IUGR	0.83	0.61	1.13	0.23

MR-proANP	exp( $\beta$ )	Lower 95%-CI	Upper 95%-CI	p value
Preeclampsia	1.56	1.34	1.81	<0.00001
IUGR	1.43	1.20	1.71	0.0001

## Logistic Regression Analysis\* for Preeclampsia

	OR per IQR*	95%-CI		p-value
		Lower	Upper	
sFlt-1	4,10	2,90	6,20	<0.0001
PIGF <sup>1</sup>	0,968	0,956	0,978	<0.0001
sFlt-1/PIGF Ratio	1,48	1,32	1,70	<0.0001
PAPP-A	1,83	1,26	2,60	0,001
MR-proANP	2,35	1,78	3,13	<0.0001

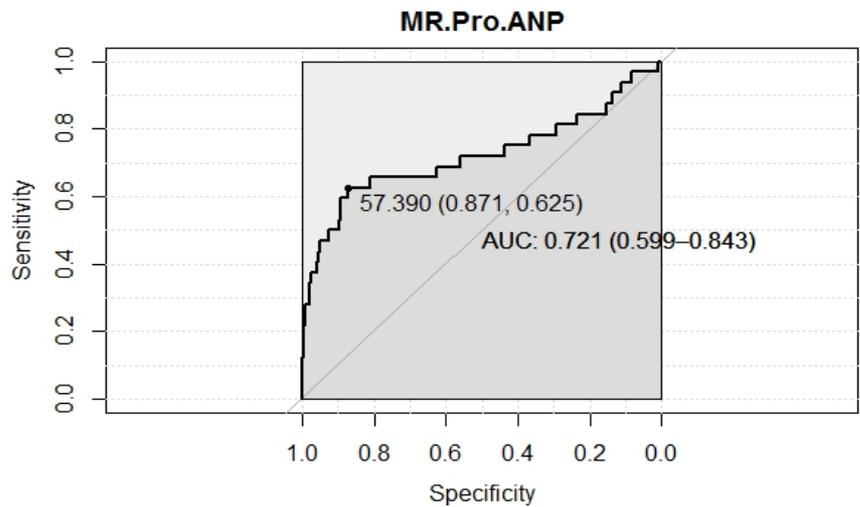
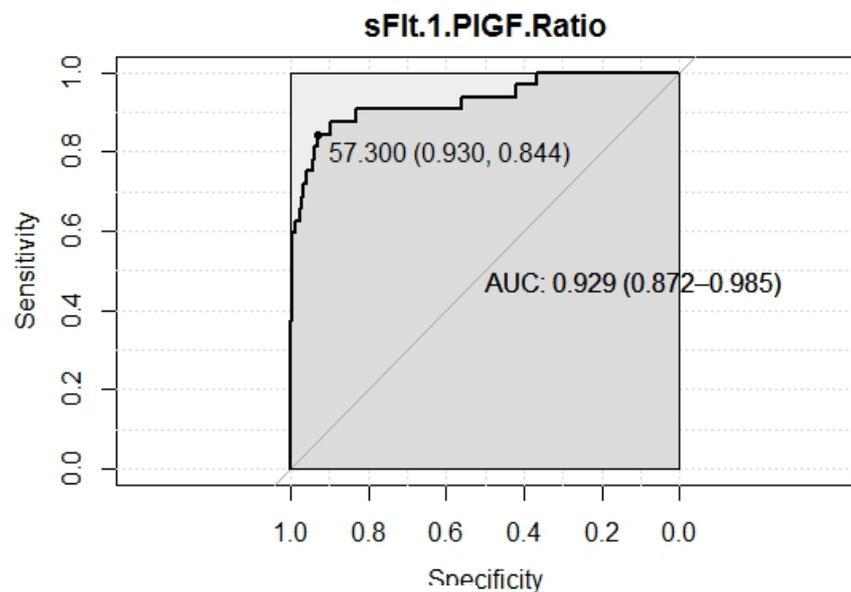
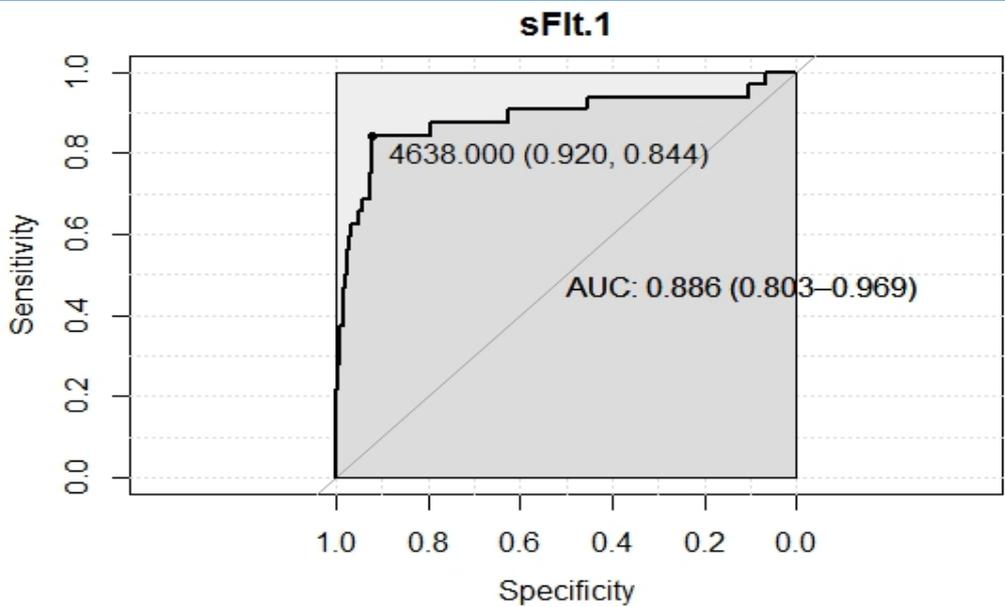
<sup>1</sup> OR und 95%-CI PIGF-Unit



## ROC for Preeclampsia

	AUC (95%-CI)	Threshold	Sensitivity (%)	Specificity (%)
sFlt-1	0.89 (0.80-0.97)	4638,0	84,4	92,0
PIGF	0.94 (0.89-0.97)	80,7	84,4	90,4
sFlt-1/PIGF-Ratio	0.93 (0.87-0.99)	57,3	84,4	93,0
PAPP-A	0.63 (0.52-0.74)	139575,0	50,0	80,2
MR-proANP	0.72 (0.59-0.84)	57,4	62,5	87,1

## ROC for Preeclampsia



## Logistic Regression Analysis\* for IUGR

	OR per IQR*	95%-CI		p-value
		Lower	Upper	
sFlt-1	2,15	1,59	3,00	<0.0001
PIGF <sup>1</sup>	0,996	0,992	0,998	0,01
sFlt-1/PIGF-Ratio	1,23	1,13	1,39	<0.0001
PAPP-A	0,85	0,43	1,50	<b>0,61</b>
MR-proANP	1,97	1,41	2,76	<0.0001

<sup>1</sup> OR und 95%-CI PIGF-Unit

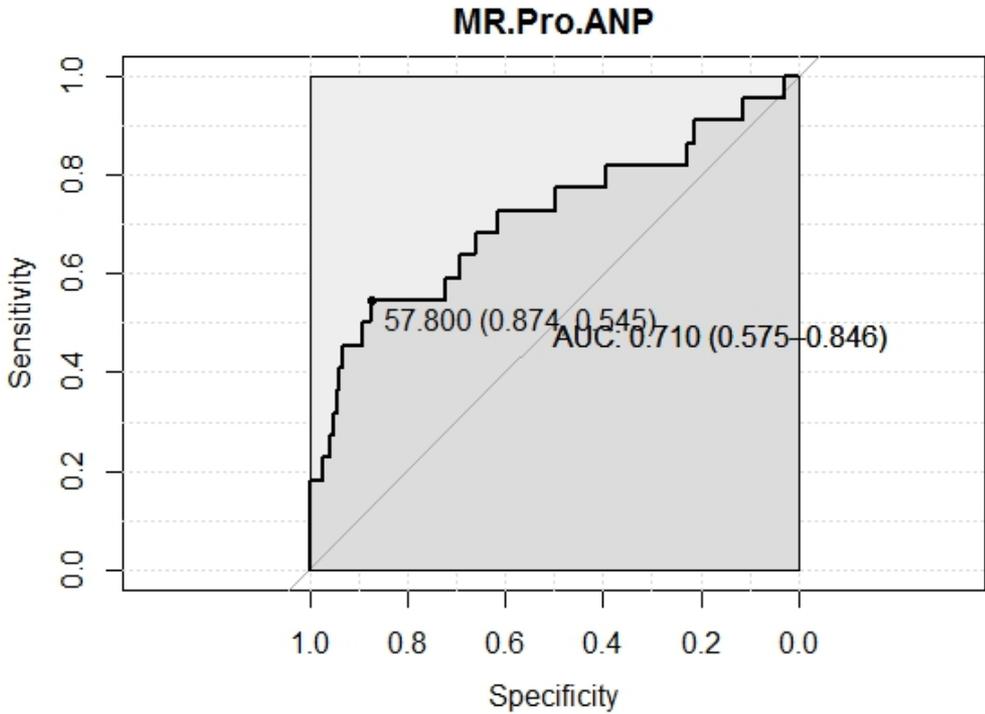
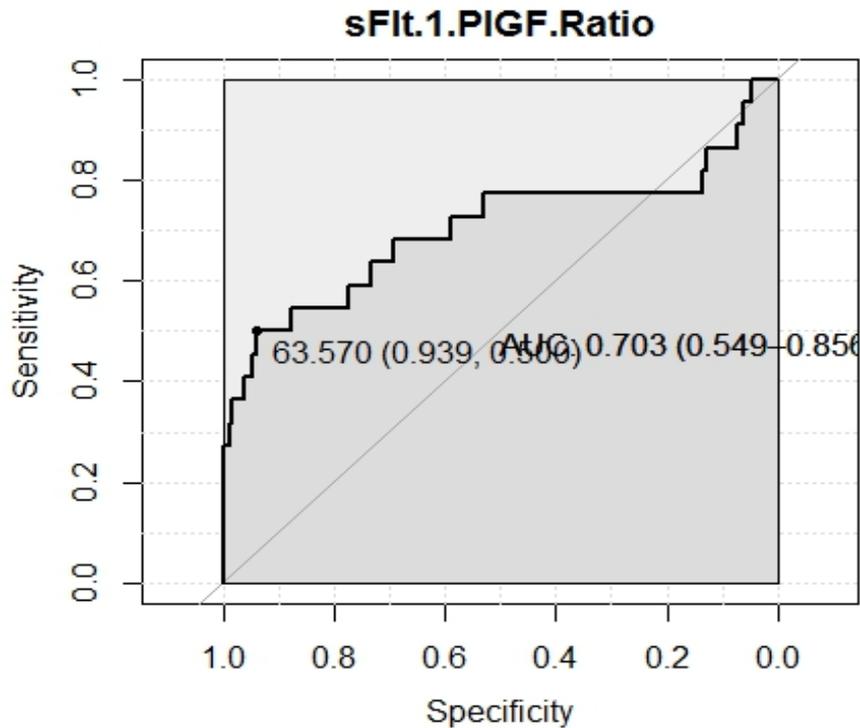


## ROC for IUGR

	AUC (95%-CI)	Threshold	Sensitivity (%)	Specificity (%)
sFlt-1	0.67 (0.52-0.83)	3369,0	59,1	81,7
PIGF	0.72 (0.59-0.86)	60,4	45,5	95,3
sFlt-1/PIGF-Ratio	0.70 (0.55-0.86)	63,6	50,0	93,9
PAPP-A	0.53 (0.41-0.65)	141150,0	90,9	19,8
MR-proANP	0.71 (0.58-0.85)	57,8	54,5	87,4



## ROC for IUGR



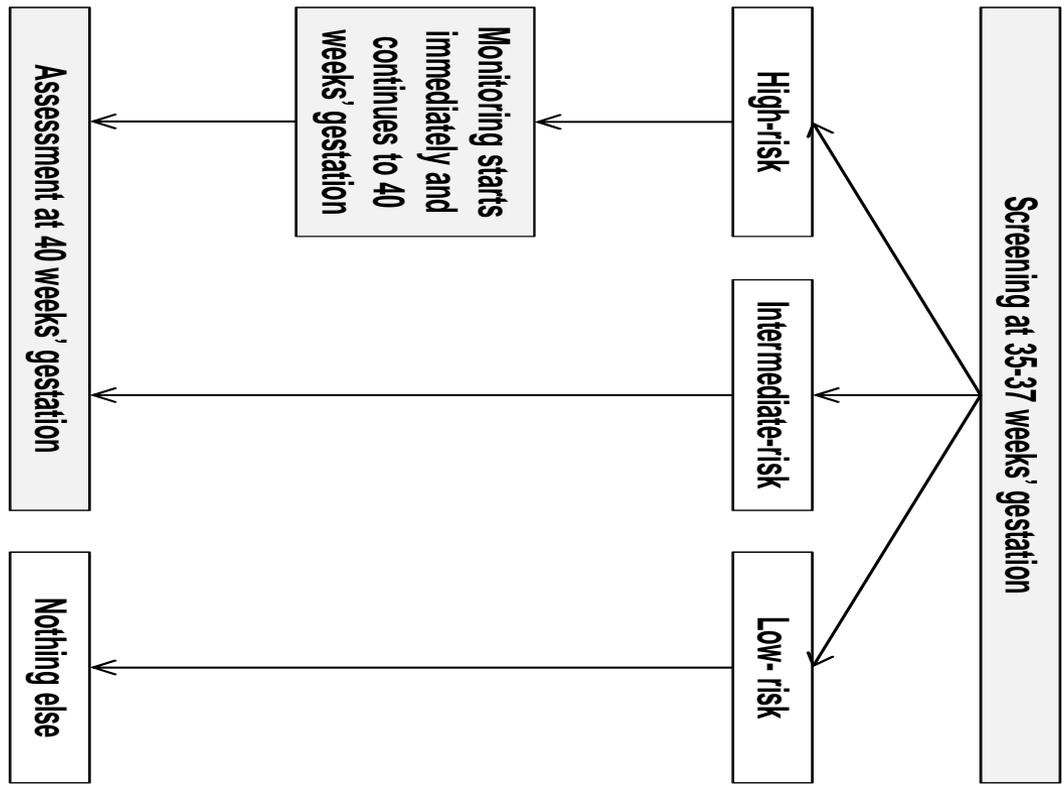


## sFlt-1/PIGF – Ratio of 38

	Threshold	Sensitivity (%)	Specificity (%)
sFlt-1/PIGF-Ratio	38	37,6	85,9

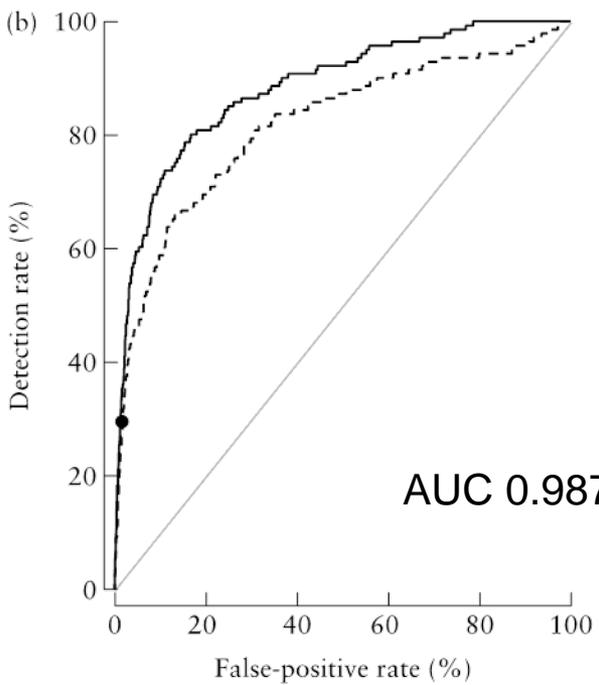
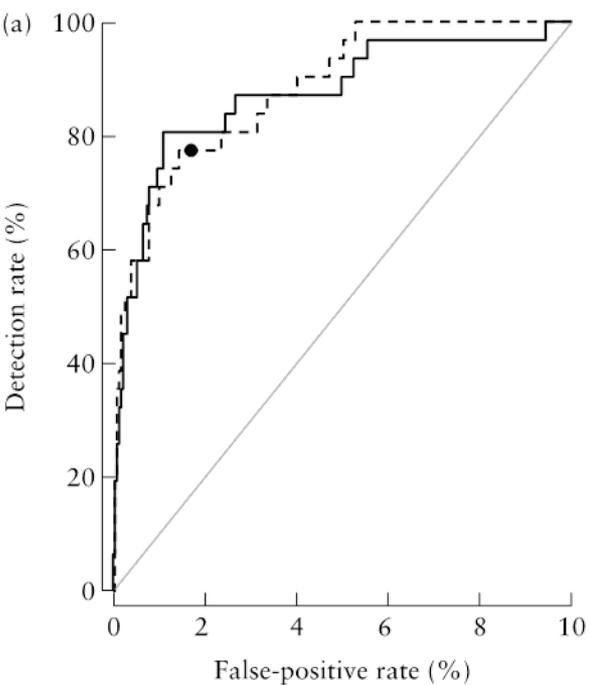
## Future Perspectives

Proposed clinical management of pregnancies after combined screening for preeclampsia at 35-37 weeks' gestation



## Comparison

Comparison of screening for pre-eclampsia at 31–34 weeks' gestation by sFlt-1/PlGF ratio and a method combining maternal factors with sFlt-1 and PlGF



AUC 0.987 (95%CI) vs. AUC 0.988 (95%CI)



Thank you