

CLINICAL PREDICTORS AND BIOMARKERS IN PREECLAMPSIA: WHAT SHOULD WE TELL OUR PATIENTS?

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Montreal, QC

Canadian Society of Internal Medicine

Annual Meeting 2016

Montreal, QC

No Conflict Disclosures

Some of the drugs, devices, or treatment modalities mentioned
in this presentation are: aspirin

Canadian Society of Internal Medicine

Annual Meeting 2016

Montreal, QC

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E. Rey. CLINICAL PREDICTORS AND BIOMARKERS IN PREECLAMPSIA. 2016-10-29

OBJECTIVES

- **Identify** specific elements from past medical history, physical examination and obstetric history that can help **predict preeclampsia**
- **Select** patients that can benefit from imaging techniques to help **predict preeclampsia**
- **Recognize** the clinical utility of existing or promising biomarkers for **prediction of preeclampsia (PE)**

PLAN

- Physiology
- Predictors
 - Clinical risk factors
 - Biomarkers
 - Doppler
 - Cell-free fetal DNA
 - Podocyturia, Microalbuminuria
- Cases

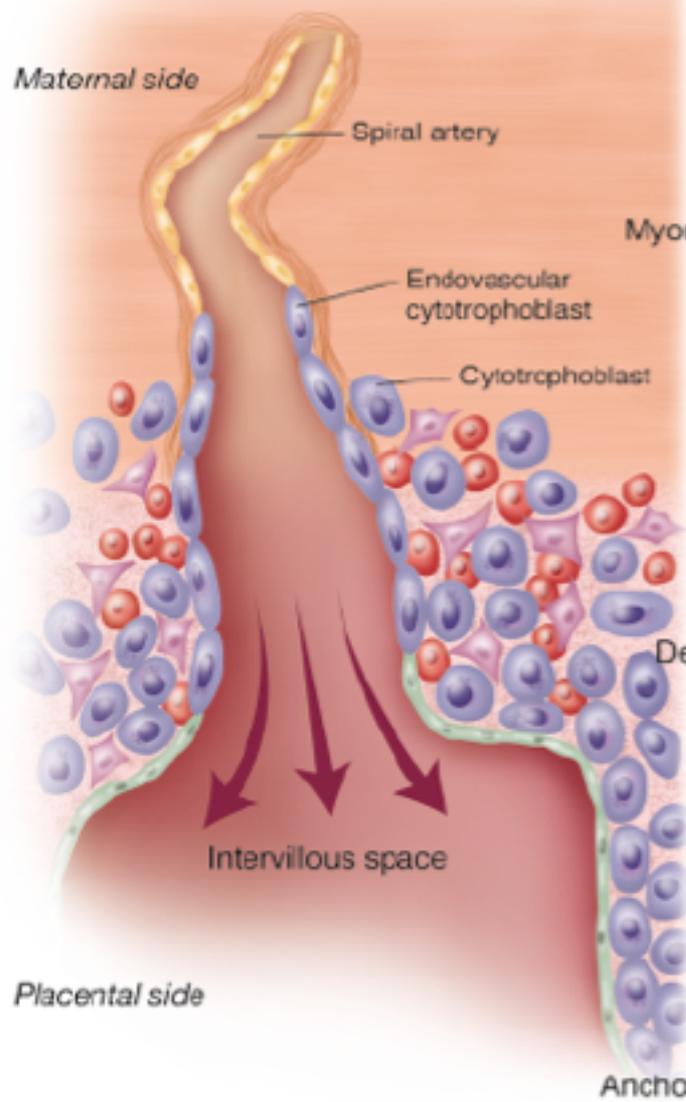
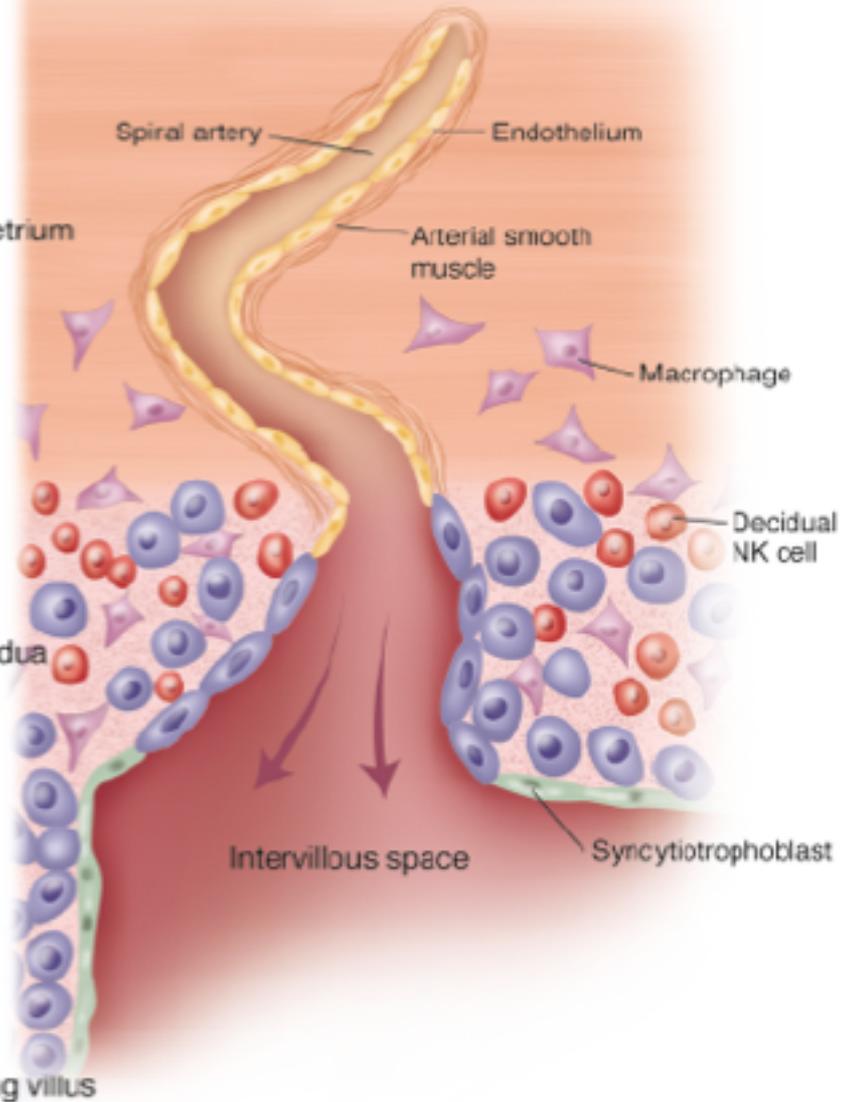
Stage 1

Partial maternal tolerance of
allogenic trophoblast

Stage 2

Poor placentation

Modified from Redman CW 2005

A**Normal placentation****B****Abnormal placentation**

Stage 1

Partial maternal tolerance of
allogenic trophoblast

Stage 2

Poor placentation

Oxidatively stressed
placenta

sFlt-1

Dysfunctional maternal
endothelium

Syncytiotrophoblast
debris/other factors

Maternal systemic
inflammatory response

Stage 3

Clinical signs of pre-eclampsia

Sub-clinical inflammation, genetics,
behavioral factors

Modified from Redman CW 2005

Stage 1

Partial maternal tolerance of
allogenic trophoblast

Stage 2

Poor placentation

Oxidatively stressed
placenta

Placental
markers

- ↓ PP13
- ↓ PAPP-A
- ↓ ADAM12
- ↓ Metastin
- ↓ β -hCG
- ↑ Activin-A
- ↑ Inhibin-A

Stage 3

sFlt-1
Dysfunctional maternal
endothelium

Syncytiotrophoblast
debris/other factors

Maternal systemic
inflammatory response

Clinical signs of pre-eclampsia

Sub-clinical inflammation, genetics,
Behavioral factors

Modified from Redman CW 2005

Stage 1

Partial maternal tolerance of
allogenic trophoblast

Stage 2

Poor placentation

Angiogenic F.

↓ VEGF

↓ PlGF

Oxidatively stressed
placenta

Vascular markers

sFlt-1

Syncytiotrophoblast
debris/other factors

Dysfunctional maternal
endothelium

Maternal systemic
inflammatory response

AntiAngiogenic F.

↑ sFlt-1

↑ sEndoglin

↑ sFlt-1/PlGF

Stage 3

Clinical signs of pre-eclampsia

Modified from Redman CW 2005

Stage 1

Partial maternal tolerance of
allogenic trophoblast

Stage 2

Poor placentation

Oxidatively stressed
placenta

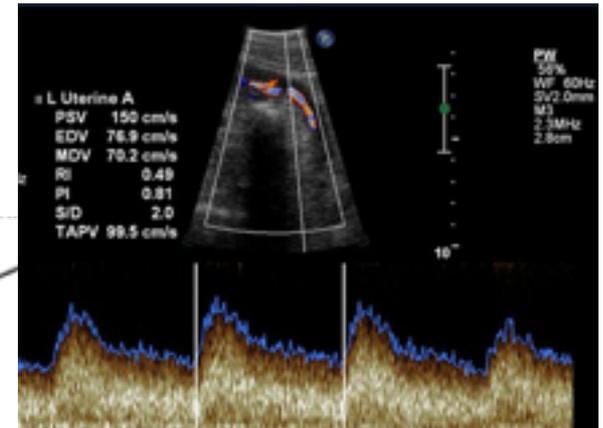
Imaging

sFlit-1

Dysfunctional maternal
endothelium

Clinical signs of pre-eclampsia

Stage 3



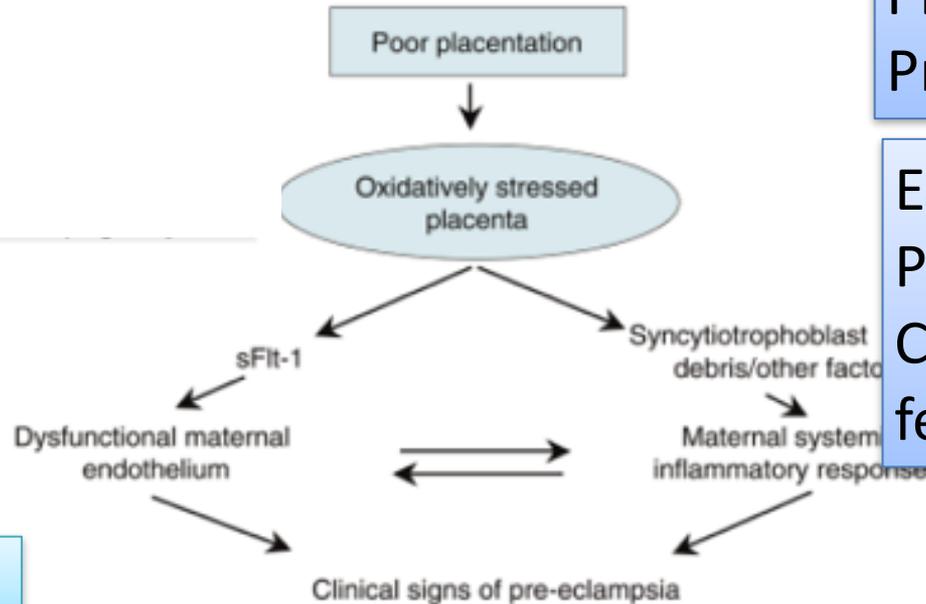
Modified from Redman CW 2005

Stage 1

Partial maternal tolerance of allogenic trophoblast

Prediction
Prophylaxis
Prevent occurrence
Prevent severity

Stage 2



Early diagnosis
Prognosis
Close maternal and fetal follow-up

Stage 3

Severity prediction,
Transfer, Delivery

Modified from Redman CW 2005

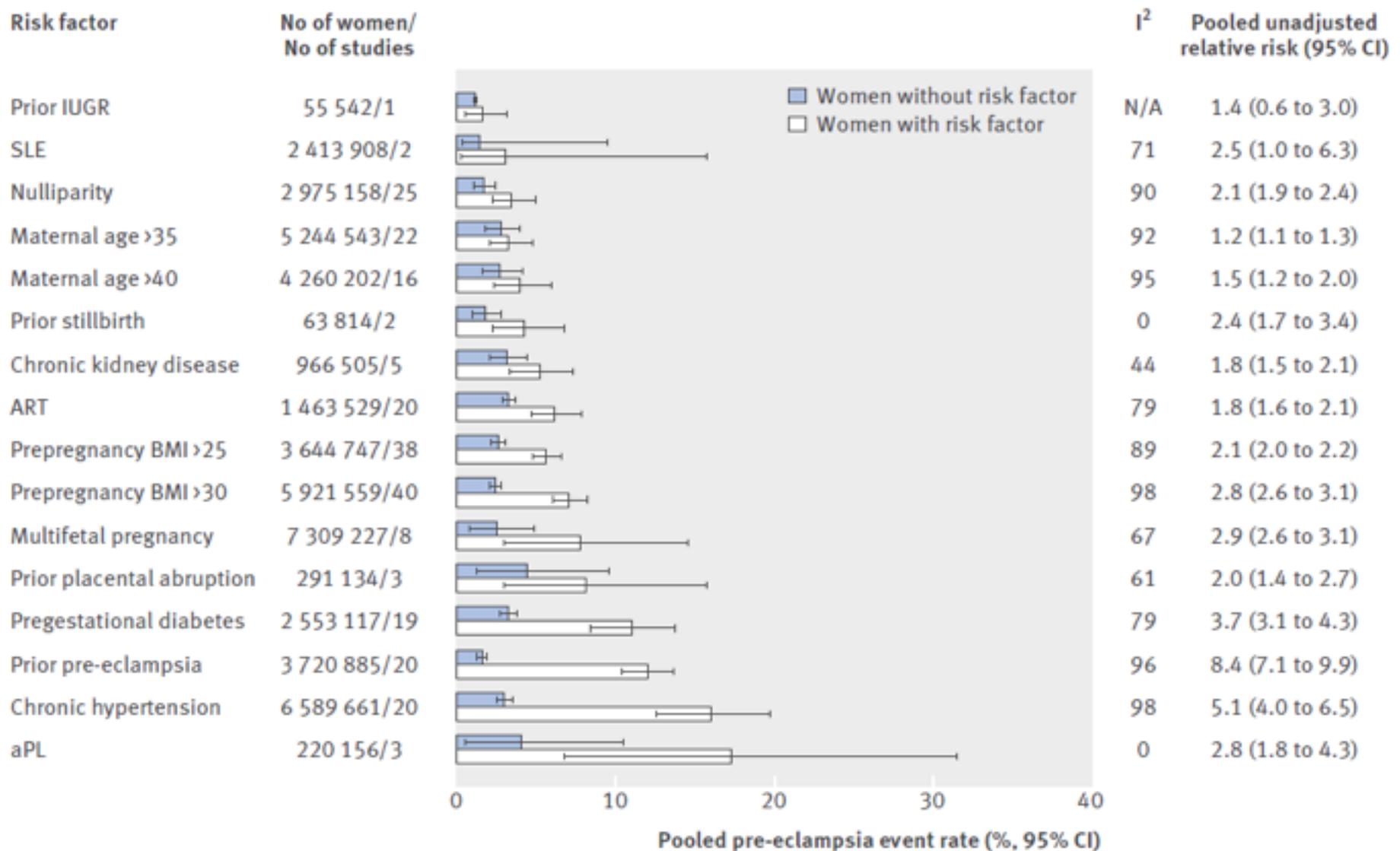
CLINICAL RISK FACTORS

- Family history
- Personal medical history
- Demographic characteristics
- Pregnancy-related factors

Table 5
Risk markers for preeclampsia.*

Demographics and family history	Past medical or obstetric history	Current pregnancy	
		First trimester	Second or third trimester
	Previous preeclampsia Anti-phospholipid antibody syndrome Pre-existing medical condition(s) <ul style="list-style-type: none"> • Pre-existing hypertension or booking diastolic BP \geq 90 mmHg • Pre-existing renal disease or booking proteinuria • Pre-existing diabetes mellitus 	Multiple pregnancy	
Maternal age ^f \geq 40 years	Lower maternal birthweight and/or preterm delivery	Overweight/obesity	Elevated BP (gestational hypertension) [†]
Family history of preeclampsia (mother or sister)	Heritable thrombophilias [‡]	First ongoing pregnancy	Abnormal AFP, hCG, inhA or E ₃ ^{***}
Family history of early-onset cardiovascular disease	Increased pre-pregnancy triglycerides	New partner	Excessive weight gain in pregnancy
	Non-smoking	Short duration of sexual relationship with current partner	Infection during pregnancy (e.g., UTI, periodontal disease)
	Cocaine and metamphetamine use	Reproductive technologies ^{**}	Abnormal uterine artery Doppler IUGR
	Previous miscarriage at \leq 10 weeks with same partner	Inter-pregnancy interval \geq 10 years	Investigational laboratory markers [§]
		Booking sBP \geq 130 mmHg, or booking dBP \geq 80 mmHg	
		Vaginal bleeding in early pregnancy	
		Gestational trophoblastic disease	
		Abnormal PAPP-A or free β hCG	
		Investigational laboratory markers	

Magee LA SOGC 2008



Bartsch E. BMJ 2016

CLINICAL RISK FACTORS

Predictor Models

Metaanalysis AL-Rubaie ZTA et al BJOG 2016

Parity

Previous PE

Ethnicity

cHT

Conception method

Mean BP

EPE

Sensitivity 70%

Specificity 70%

BLOOD PRESSURE

Table 3: Comparison of the performance of screening for preeclampsia and gestational hypertension by systolic blood pressure, diastolic blood pressure, and mean arterial pressure and their combination with the disease-specific maternal factor-derived *a priori* risk.

Screening test	Early preeclampsia	Late preeclampsia	Gestational hypertension
Detection rate with (95% CI) for a fixed false-positive rate of 10%			
Maternal risk factor	47.0 (22.5–65.0)	41.4 (32.8–50.4)	30.7 (23.2–39.1)
Systolic blood pressure	56.8 (39.5–72.9)	31.2 (23.4–40.0)	30.7 (23.2–39.1)
Diastolic blood pressure	51.4 (34.4–68.1)	33.6 (25.5–42.5)	33.6 (25.8–42.0)
Mean arterial pressure	59.5 (42.1–75.2)	36.7 (28.4–45.7)	35.7 (27.8–44.2)
Maternal risk factor plus			
Systolic blood pressure	70.3 (53.0–84.1)	52.3 (43.3–61.2)	44.3 (35.9–52.9)
Diastolic blood pressure	67.6 (50.2–82.0)	48.4 (39.5–57.4)	47.9 (39.4–56.5)
Mean arterial pressure	75.7 (58.8–88.2)	52.3 (43.3–61.2)	47.9 (39.4–56.5)

Poon et al *Hypertension in Pregnancy*, 30:93–107, 2011

UA DOPPLER VELOCIMETRY

1stT

- Sensitivity 48%, specificity 92%
- Not alone
- Not done routinely in Canada

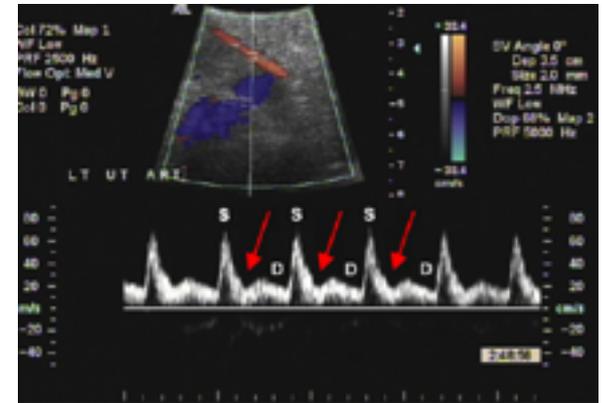
When?

Lausman A. JOGC 2013

Any time if IUGR

19-20 w

- If abnormal biomarkers: usefulness?
- If risk of IUGR



BIOMARKERS

- Availability
- Aneuploidy screening
 - 1T PAPP-A
 - 2T -hCG
 - alphaFP
 - Estriol
 - Inhibin-A

BIOMARKERS

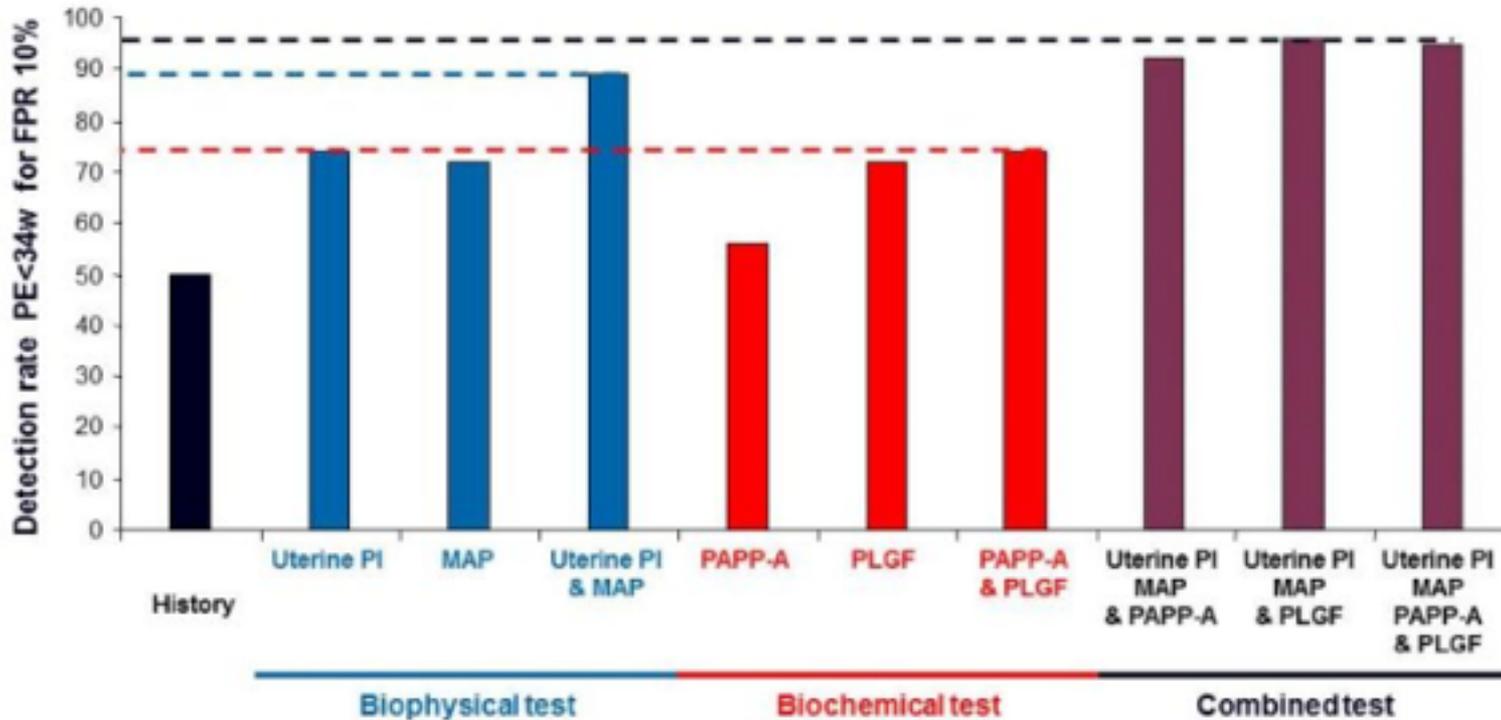
1st T/early second trimester

- PAPP-A
- Inhibin-A
- PIGF

New

Early prediction of preeclampsia <34w

Maternal history and biophysical & biochemical testing



Nicolaides 2008

Maternal factors

Maternal characteristics

Date of birth

Height cm ft in

Weight kg lbs

Racial origin

Conception method

Smoking during pregnancy Yes No

Mother of the patient had PE Yes No

Medical history

Chronic hypertension

Diabetes type I

Diabetes type II

Systemic lupus erythematosus

Anti-phospholipid syndrome

Obstetric history

Nulliparous (no previous pregnancies ≥ 24 weeks)

Parous (at least one pregnancy ≥ 24 weeks)

Pregnancy dating (select one of the methods below)

Fetal crown-rump length (45-84mm)

Fetal head circumference (158-226mm)

Manual (any gestation)

Gestational age weeks

Date of measurement

This application allows calculation of risks for PE based on maternal factors alone and in combination with any of the biomarkers. Biophysical and biochemical markers should be obtained within the same gestational age block (11⁺⁰ to 14⁺¹, 19⁺⁰ to 24⁺⁶, 30⁺⁰ to 34⁺⁶, 35⁺⁰ to 37⁺⁶ weeks).

Biophysical measurements

Useful markers for all three trimesters are MAP and mean UTPI

Date of measurement

Weight kg lbs

MAP (mmHg)

Mean UTPI

Biochemical measurements

Useful markers in the first trimester are PLGF and PAPP-A and in the second and third trimesters are PLGF and SFLT

Date of measurement

Weight kg lbs

PLGF (MoM)

PAPP-A (MoM)

SFLT (MoM)

Calculate risk

EPE

- Parity
- Previous PE
- Ethnicity
- cHT
- Conception
- Mean BP

LPE

- +
- Family H PE
- Age
- BMI

Table 3 Comparison of reported and observed performance of prediction models for early (< 34 weeks' gestation) and late (\geq 34 weeks' gestation) pre-eclampsia (PE)

<i>Reference</i>	<i>Reported PE rate*</i>	<i>Sensitivity (%) at fixed 10% FPR</i>		<i>Probability score</i>	
		<i>Reported</i>	<i>Observed</i>	<i>Cut-off</i>	<i>Optimal cut-off</i>
Early pre-eclampsia					
Parra-Cordero ⁷	2619/17	47	29	0.0319465	0.0119318
Scazzocchio ¹⁰	5170/26	81	43	0.0347586	0.0090969
Poon ⁸	8366/37	89	53	0.0045660	0.0020121
Poon ¹³	<u>8366/37</u>	<u>95</u>	<u>52</u>	0.0032741	0.0008496
Odibo ¹²	452/12	68	80	0.0172392	0.0948812
Caradeux ¹⁵	627/9	63	30	0.0882681	0.0539006
Late pre-eclampsia					
Parra-Cordero ⁷	2619/53	29	18	0.4106497	0.0982396
Scazzocchio ¹⁰	5170/100	40	31	0.1643843	0.0488402

Oliviera N et al. Ultrasound Obstet Gynecol 2014

TABLE 6

Sensitivity and positive likelihood ratio of different combinations of maternal characteristics, PIGF, PAPP-A, Inhibin-A, and uterine artery Doppler at 11-13 weeks' gestation, for a fixed 10% false-positive rate

Variable	Preeclampsia			Severe preeclampsia			Early-onset preeclampsia		
	Sensitivity	LR ⁺	LR ⁻	Sensitivity	LR ⁺	LR ⁻	Sensitivity	LR ⁺	LR ⁻
Maternal characteristics alone	30.0	3.0	0.78	45.5	4.5	0.60	55.6	5.6	0.49
Maternal characteristics plus:									
L-PI	35.1	3.5	0.72	42.1	4.2	0.64	50.0	5.0	0.55
PIGF	40.9	4.1	0.66	61.5	6.1	0.43	75.0	7.5	0.28
PAPP-A	32.5	3.2	0.75	54.5	5.4	0.50	55.6	5.6	0.49
Inhibin-A	35.0	3.5	0.72	50.0	5.0	0.55	55.6	5.6	0.49
PIGF, PAPP-A	40.9	4.1	0.66	53.8	5.4	0.51	75.0	7.5	0.28
PIGF, Inhibin-A	40.9	4.1	0.66	53.8	5.4	0.51	75.0	7.5	0.28
PAPP-A, Inhibin-A	32.5	3.2	0.75	54.5	5.5	0.50	55.6	5.6	0.49
PIGF, Inhibin-A, PAPP-A	31.8	3.2	0.76	53.8	5.4	0.51	75.0	7.5	0.28
Inhibin, PAPP-A, L-PI	32.4	3.2	0.75	52.6	5.3	0.53	37.5	3.7	0.69
PIGF, Inhibin-A, PAPP-A, L-PI	40.0	4.0	0.67	54.5	5.5	0.50	100.0	10.0	0.00

All models including PIGF are based on 531 women only, including 498 unaffected, 22 with preeclampsia (13 severe, 4 early-onset).

L-PI, lowest of uterine artery Doppler pulsatility indices; LR⁺, likelihood ratio for a positive test; PAPP-A, pregnancy-associated plasma protein-A; PIGF, placental growth factor.

Audibert. Screening for preeclampsia using first-trimester serum markers and uterine artery Doppler. *Am J Obstet Gynecol* 2010.

EFFICACY OF THE MODELS?

- No RCT
- **ASPRE**
- Cohorts comparison *Parks et al 2015*

Table 2 Pregnancy outcome in women screened for pre-eclampsia (PE) at 11 to 13 + 6 weeks' gestation according to those who received no treatment (observational group) and those who were administered low-dose aspirin if at high risk (interventional group)

<i>Outcome</i>	<i>Observational group (n = 3066)</i>	<i>Interventional group (n = 2717)</i>	<i>P</i>
PE (percent based on number of live births)	71 (2.36)	38 (1.42)	0.01
Delivered \geq 37 weeks	46 (1.53)	28 (1.05)	0.11
Delivered < 37 weeks	25 (0.83)	10 (0.37)	0.03
Delivered at 34 + 0 to 36 + 6 weeks	13 (0.43)	9 (0.34)	0.57
Delivered < 34 weeks	12 (0.40)	1 (0.04)	< 0.01

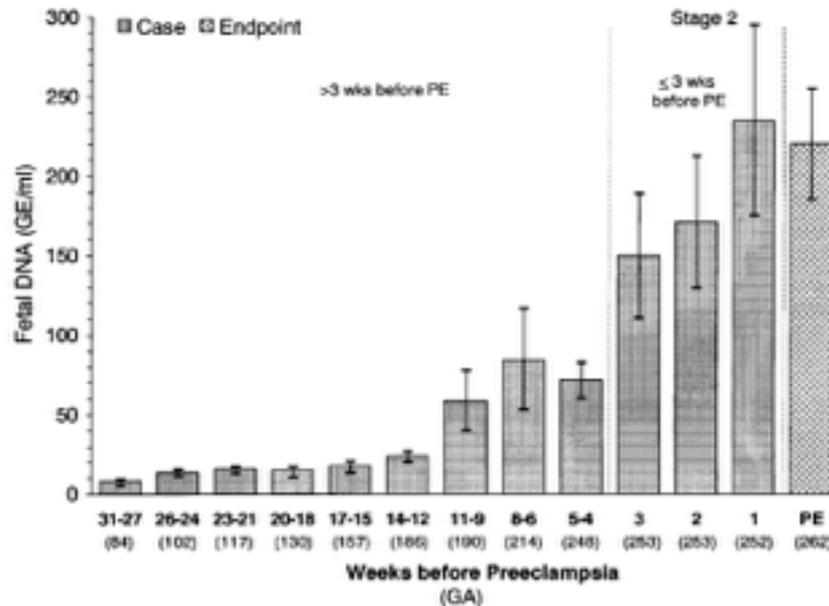
Table 3 Pregnancy outcome in women screened as being at high risk for pre-eclampsia (PE) at 11 to 13 + 6 weeks' gestation according to those who received no treatment (observational group) and those who were administered low-dose aspirin if at high risk (interventional group)

<i>Outcome</i>	<i>Observational group (n = 301)</i>	<i>Interventional group (n = 264)</i>	<i>P</i>
NND delivered > 34 weeks	1 (0.33)	1 (0.38)	0.93
No PE	270 (89.70)	247 (93.56)	0.08
PE	31 (10.30)	17 (6.44)	0.10
Delivered \geq 37 weeks	14 (4.65)	10 (3.79)	0.61
Delivered < 37 weeks	17 (5.65)	7 (2.65)	0.08
Delivered at 34 + 0 to 36 + 6 weeks	6 (1.99)	6 (2.27)	0.82
Delivered < 34 weeks	11 (3.65)	1 (0.38)	< 0.01

Park F et al. Ultrasund Obstet Gynecol 2015;46:419

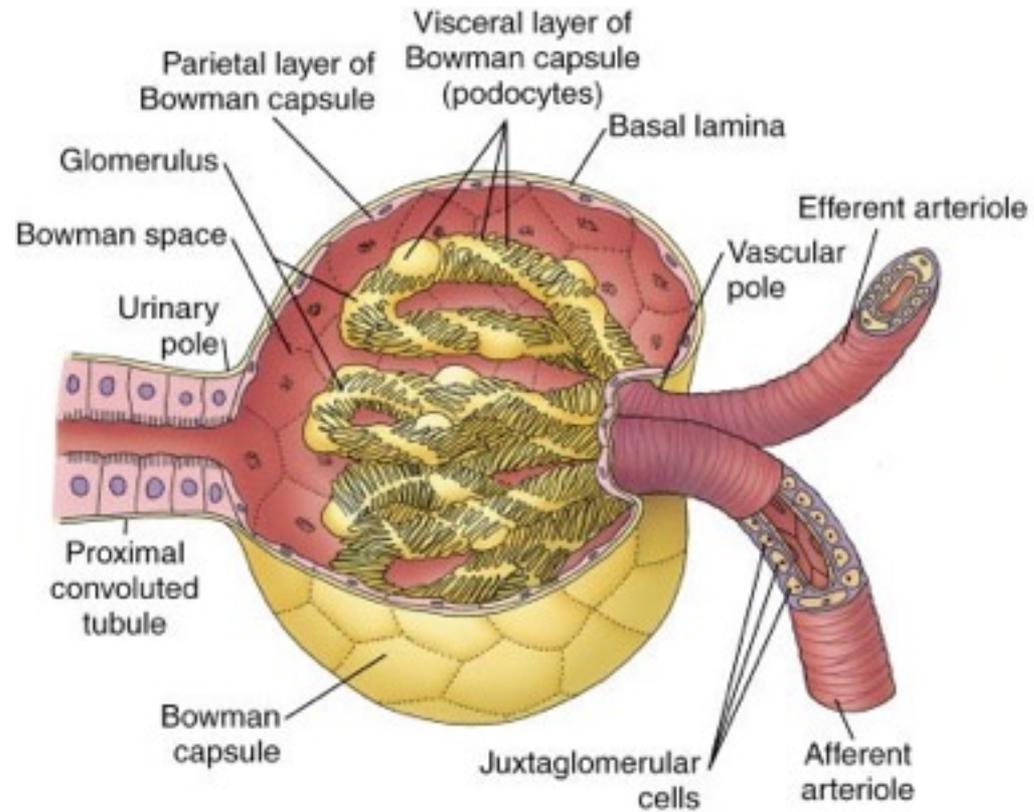
Cell-free FETAL DNA

- Increases with markers of placenta size
- Marker for trophoblastic cell death
- *Yu H 2013*: Increases at 11-14w in EPE: sensitivity 90% specificity 85%

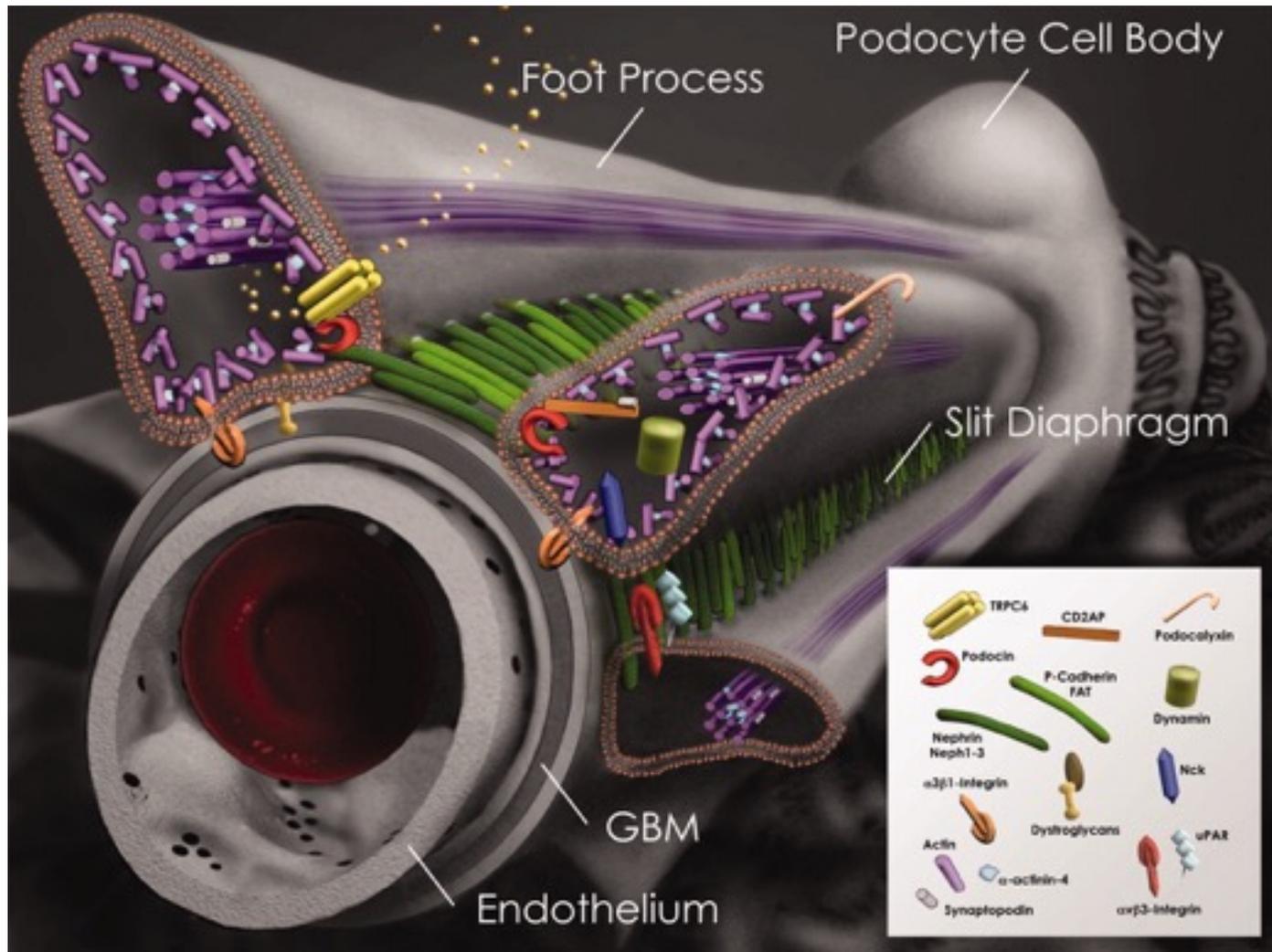


Levine RJ AJOG 2004

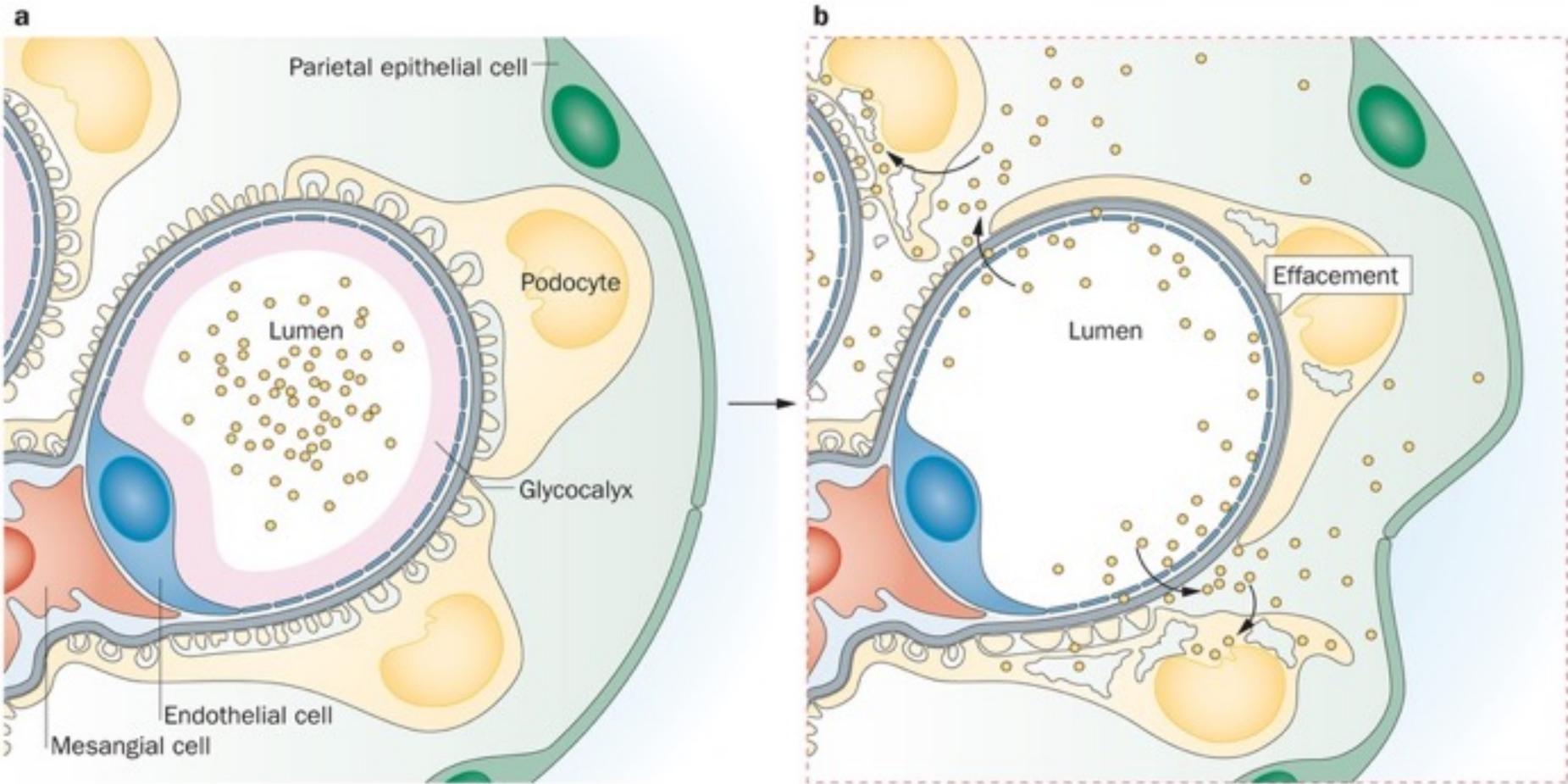
NEXT MARKER?



Medical dictionnary 2011



Moller CC et al. J Am Soc Nephrol 2009



PODOCYTURIA

Table 4. Test Characteristics for Angiogenic Markers and Podocyturia in the Second Trimester and at Delivery

Variable	PE, gHTN vs NTP			PE vs gHTN, NTP			PE vs gHTN			PE vs NTP		
	Cutoff	Sensitivity, %	Specificity, %	Cutoff	Sensitivity, %	Specificity, %	Cutoff	Sensitivity, %	Specificity, %	Cutoff	Sensitivity, %	Specificity, %
Prediction of preeclampsia at median 27 gestational weeks (IQR, 25–28)												
Podocyturia, no. of cells/mg creatinine	0.30	54	100	0.30	100	100	0.30	100	100	0.30	100	100
Diagnosis of preeclampsia at median 39-5 gestational weeks (IQR, 39–40)												
Podocyturia, number of cells/mg creatinine	4.00	83	100	8.00	100	93	8.00	100	63	8.00	100	100

Late entry in the study

Craici et al. Hypertension 2013:1289-96

MICROALBUMINURIA

< 20 wks

- Low risk: **no**
- cHt or previous Preeclampsia
 - higher level
 - Laura-Gonzalez 2003: **20mg/l**
 - Sensitivity 79% et specificity 63%
 - PPV 46% NPV 88%

Coté AM Current Hypertension reviews 2010

MICROALBUMINURIA IN DB

- Strong risk factor for PE
- Jensen DM Diab Care 2010: 846 women T1DB
 - No MicroA: **12% PE vs**
 - MicroA: **40% PE**
 - MicroA: ORa 4**, nulliparity ORa 3
- Castiglioni MT Pregnancy Hyper 2014
 - cHT OR 17 (3-91), **MicroA OR 3.8 (1.2-11.6)**, **1T GHc OR 2.8 (1.1-7)**

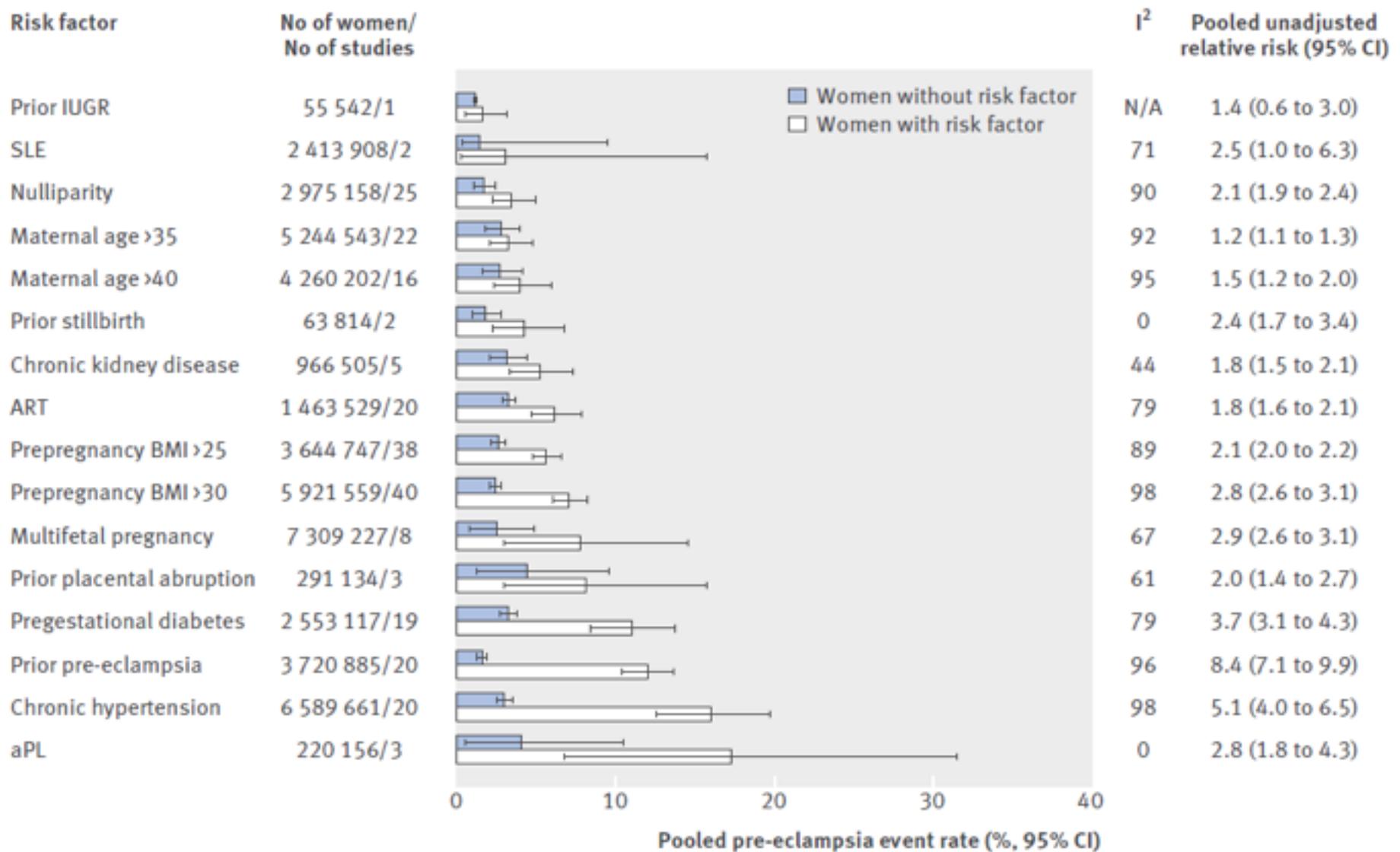


Case 1

- Kimberly, 29y, G1 P0,
- Essential chronic hypertension
- Black race
- BMI 36
- 154/104 at 12w

Risk of preeclampsia ?

.5-10%
.10-20%
.20-30%
. > 30%



Bartsch E. BMJ 2016

Table 6| Estimated incidence and prediction intervals of adverse pregnancy outcomes for women with chronic hypertension: studies conducted in United States compared with US general population data²¹

Outcome	No of studies	Estimated incidence (%) (95% CI)	Prediction interval (95%)	US general population incidence (%)	Risk ratio (95% CI)	Heterogeneity τ^2
Superimposed pre-eclampsia	38	29.2 (21.6 to 38.2)	6.6 to 70.3	3.8	7.7 (5.7 to 10.1)	0.623
Caesarean section	27	42.4 (35.0 to 50.1)	18.4 to 70.7	32.9	1.3 (1.1 to 1.5)	0.258
Pre-term delivery (<37 weeks)	30	33.0 (23.7 to 44.0)	7.8 to 74.1	12.2	2.7 (1.9 to 3.6)	0.526
Birth weight <2500 g	14	22.2 (15.4 to 30.9)	5.1 to 60.5	8.2	2.7 (1.9 to 3.8)	0.225
Neonatal intensive care	16	19.3 (13.4 to 27.0)	5.0 to 51.9	6.1	3.2 (2.2 to 4.4)	0.246
Perinatal death	27	4.6 (3.0 to 7.1)	1.0 to 18.9	1.1	4.2 (2.7 to 6.5)	0.429

95% prediction intervals show uncertainty of range of possible incidence percentages for new study population, whereas 95% confidence intervals show uncertainty about estimate of average percentage incidence across study populations.

Bramham K. BMJ 2014

Maternal factors

Maternal characteristics

Date of birth

Height cm ft in

Weight kg lbs

Racial origin

Conception method

Smoking during pregnancy Yes No

Mother of the patient had PE Yes No

Medical history

- Chronic hypertension
- Diabetes type I
- Diabetes type II
- Systemic lupus erythematosus
- Anti-phospholipid syndrome

Obstetric history

- Nulliparous (no previous pregnancies ≥ 24 weeks)
- Parous (at least one pregnancy ≥ 24 weeks)

Pregnancy dating (select one of the methods below)

Fetal crown-rump length (45-84mm)

Fetal head circumference (158-226mm)

Manual (any gestation)

Gestational age weeks

Date of measurement

This application allows calculation of risks for PE based on maternal factors alone and in combination with any of the biomarkers. Biophysical and biochemical markers should be obtained within the same gestational age block (11⁴⁰ to 14⁴¹, 19⁴⁰ to 24⁴⁶, 30⁴⁰ to 34⁴⁶, 35⁴⁰ to 37⁴⁶ weeks).

Biophysical measurements

Useful markers for all three trimesters are MAP and mean UTPI

Date of measurement	Weight ⁴	MAP (mmHg) ⁴	Mean UTPI ⁴
<input type="text" value="dd-mm-yyyy"/>	<input type="text"/> kg <input type="text"/> lbs	<input type="text"/>	<input type="text"/>

Biochemical measurements

Useful markers in the first trimester are PLGF and PAPP-A and in the second and third trimesters are PLGF and SFLT

Date of measurement	Weight ⁴	PLGF (MoM) ⁴	PAPP-A (MoM) ⁴	SFLT (MoM) ⁴
<input type="text" value="dd-mm-yyyy"/>	<input type="text"/> kg <input type="text"/> lbs	<input type="text"/>	<input type="text"/>	<input type="text"/>

Biochemical measurements

Date of measurement	Weight	PAPP-A
01-04-2016	93 kg	0.69 MoM

Abnormal if < 0.4 MoM

Preeclampsia risk from history only

- < 32 weeks: 4.1 %
- < 37 weeks: 16 %
- ≥ 37 weeks: 28 %

Preeclampsia risk from history plus PAPP-A

- < 32 weeks: 4.8 %
- < 37 weeks: 18 %
- ≥ 37 weeks: 30 %

Case 2

- Sandra, 37y, G1,
- Type 2 DB x 10y. Not smoking
- White race
- BMI 44
- BP 114/76 at 15w

Risk of preeclampsia ?

.5-10%

.10-20%

.20-30%

. > 30%

OTHER INFORMATION?

GH

Sandra =7.9%

Microalbuminuria

Sandra =none

MICROALBUMINURIA IN DB

- Strong risk factor for PE
- Jensen DM Diab Care 2010: 846 women T1DB
 - No MicroA: **12% PE vs**
 - MicroA: **40% PE**
 - MicroA: ORa 4**, nulliparity ORa 3
- Castiglioni MT Pregnancy Hyper 2014
 - cHT OR 17 (3-91), **MicroA OR 3.8** (1.2-11.6), **1T GHc OR 2.8 (1.1-7)**

Biochemical measurements

Date of measurement	Weight	PAPP-A
03-03-2016	121 kg	0.5 MoM

Abnormal if < 0.4 MoM

Preeclampsia risk from history only

- < 32 weeks: 1.4 %
- < 37 weeks: 7.2 %
- ≥ 37 weeks: 17 %

Preeclampsia risk from history plus PAPP-A

- < 32 weeks: 2.5 %
- < 37 weeks: 11 %
- ≥ 37 weeks: 20 %

Case 3

- Mandy, 35y, G2 P1
- Previous EPE 25w + IUGR. CS 27w.
- Black race, BMI 25
- BP 130/80

Risk of preeclampsia ?

.10-20%

.20-30%

.30-40%

. > 40%

OTHER INFORMATION?

- Placenta
- Recurrence
- Vascular malperfusion lesions associated with recurrence

Weiner E. Prenatal Diagnosis 2015

Date of measurement

14-02-2016

Weight

73 kg

PAPP-A

0.8 MoM

Abnormal if < 0.4 MoM**Preeclampsia risk from history only**

< 32 weeks: 20 %

< 37 weeks: 48 %

 \geq 37 weeks: 53 %**Preeclampsia risk from history plus PAPP-A**

< 32 weeks: 20 %

< 37 weeks: 48 %

 \geq 37 weeks: 54 %

Preeclampsia risk?

	Dany	Suzy	
Age	22	29	Hypothyroidism Non smoking G1 No FH of PrE
BMI	30.2	24.8	
Race	White	Black	
BP 12 sem	120/50	120/80	
PAPP-A	0.34	1.72	

Clinical F.	4.8%	6.9%
+ MAP AND PAPP-A	2.1%	7.3%

CONCLUSIONS

- **HIGH RISK** defined by **CLINICAL FACTORS:**
REMAIN MAJOR TOOL
- Impact of biomarkers on this group of women?
- Biomarkers in moderate risk women more useful?

HAVE A LOOK! GEMOQ.CA



JOIN US AT the NASOM/GEMOQ meeting

Without previous EPE

Date of measurement

14-02-2016

Weight

73 kg

PAPP-A

0.8 MoM

Preeclampsia risk from history only

< 32 weeks: 1 in 141

< 37 weeks: 4.3 %

≥ 37 weeks: 12 %

Preeclampsia risk from history plus PAPP-A

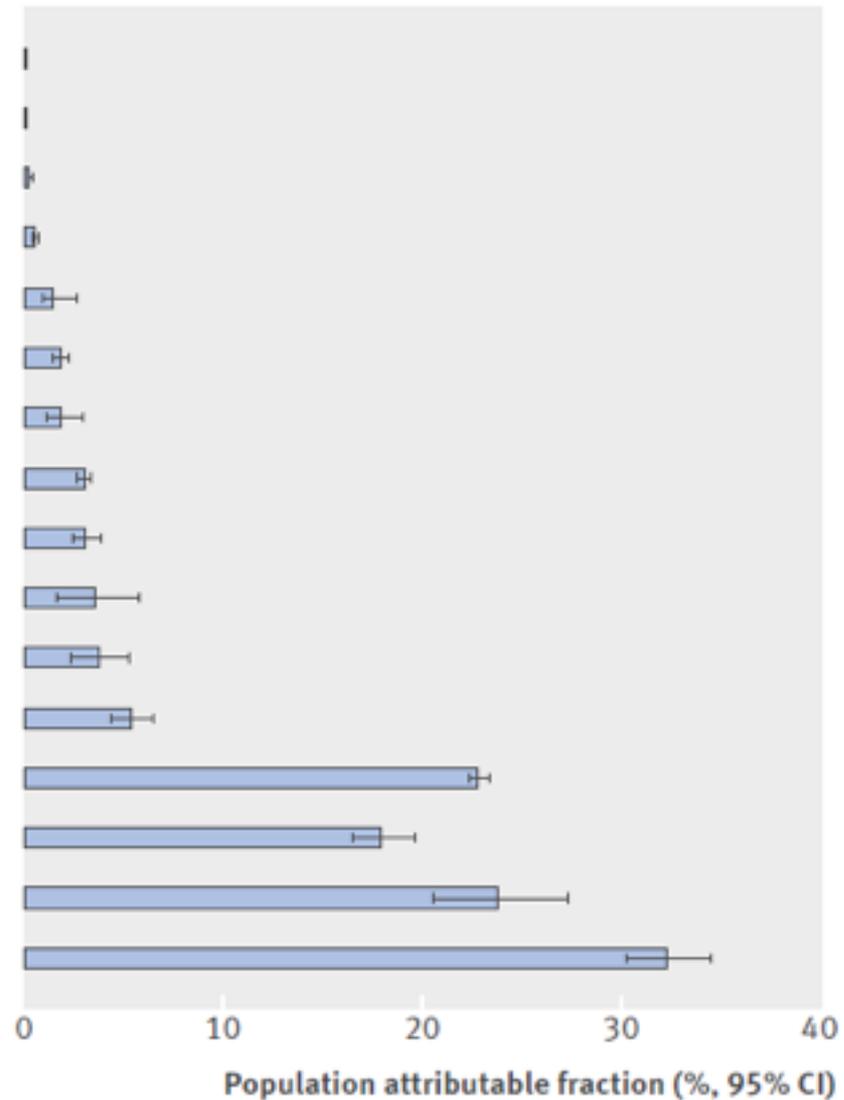
< 32 weeks: 1 in 139

< 37 weeks: 4.6 %

≥ 37 weeks: 13 %

Risk factor **No of women/
No of studies**

SLE	2 413 908/2
aPL	220 156/3
Prior IUGR	55 542/1
Prior placental abruption	291 134/3
Prior stillbirth	63 814/2
Pregestational diabetes	2 553 117/19
Chronic kidney disease	966 505/5
Maternal age >40	4 260 202/16
Maternal age >35	5 244 543/22
ART	1 463 529/20
Multifetal pregnancy	7 309 227/8
Chronic hypertension	6 589 661/20
Prior pre-eclampsia	3 720 885/20
Prepregnancy BMI >30	5 921 559/40
Prepregnancy BMI >25	3 644 747/38
Nulliparity	2 975 158/25



Bartsch E.
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