Early screening for pre-eclampsia and growth-restriction

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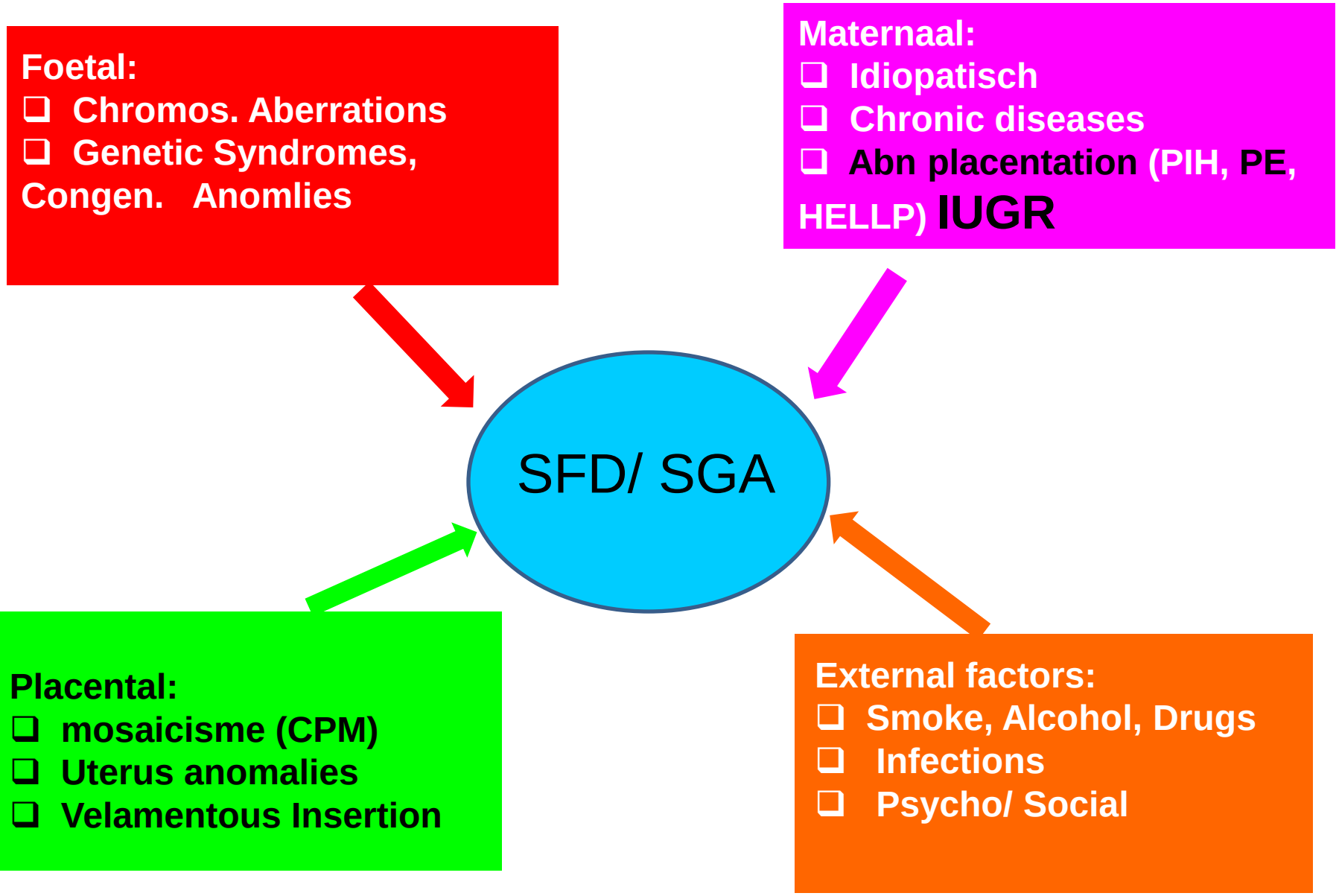
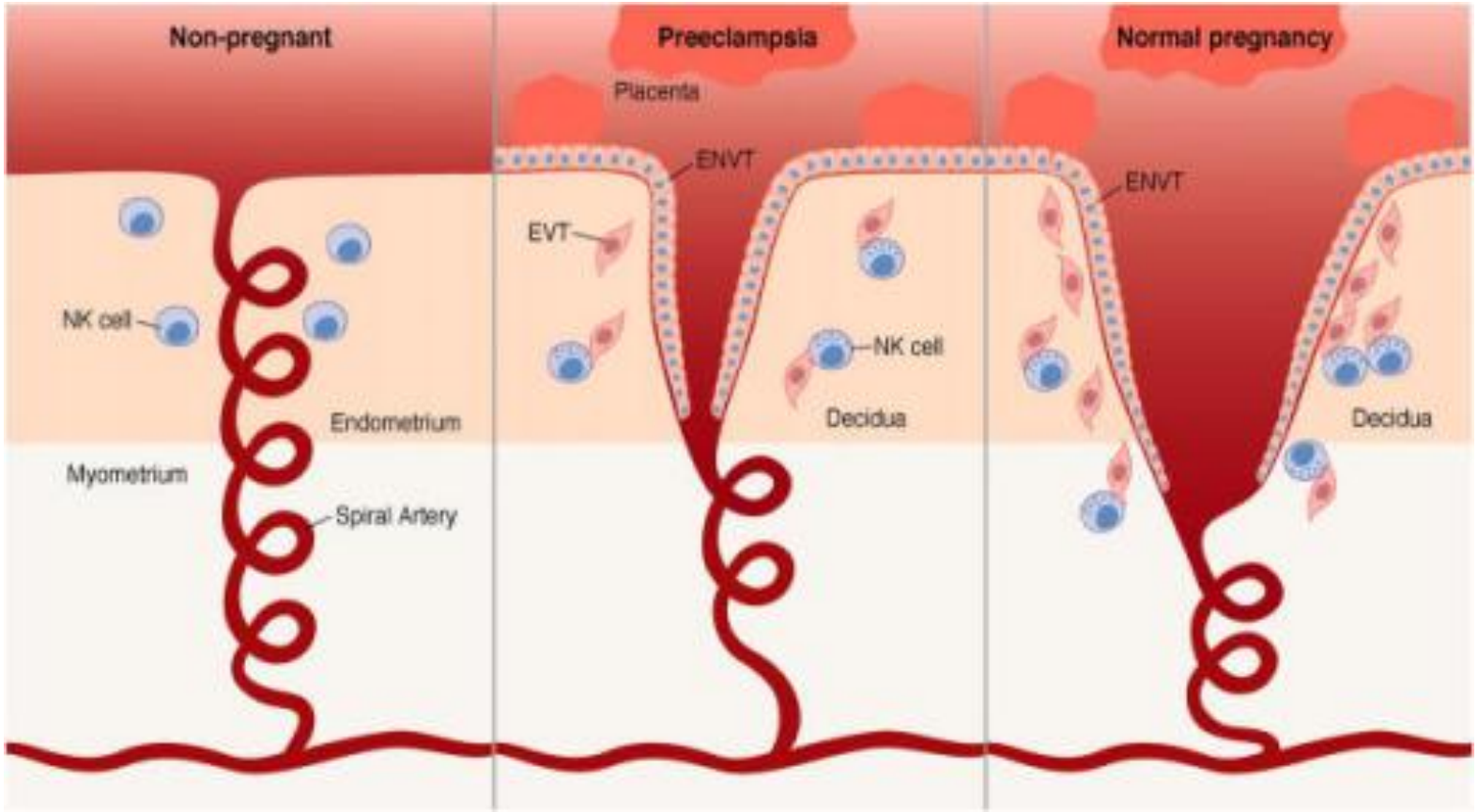
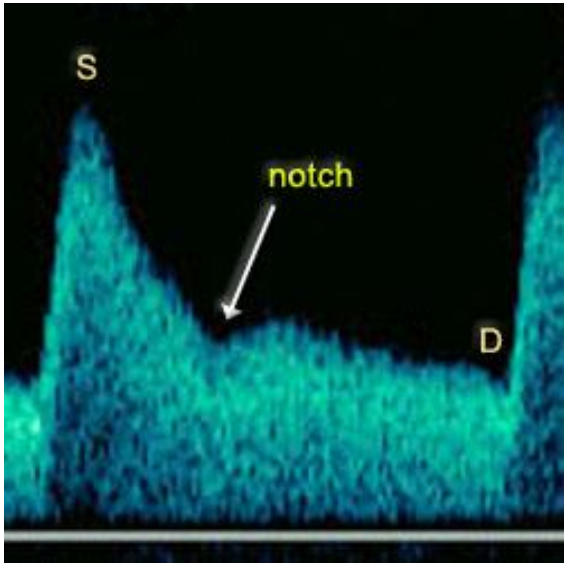
Causes of GR


Foetal:
❑ Chromos. Aberrations
❑ Genetic Syndromes, Congen. Anomlies
Maternaal:
❑ Idiopatisch
❑ Chronic diseases
❑ Abn placentation (PIH, PE, HELLP) IUGR
SFD/ SGA
Placental:
❑ mosaicisme (CPM)
❑ Uterus anomalies
❑ Velamentous Insertion
External factors:
❑ Smoke, Alcohol, Drugs
❑ Infections
❑ Psycho/ Social

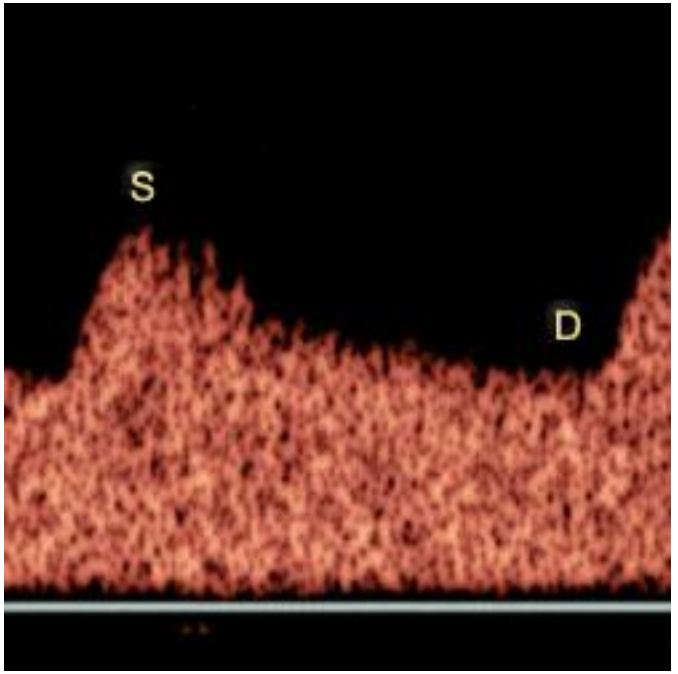
Defective Placentation



Screening uterine artety at 22-24 wks



High risk PE/ GR



Low-risk PE and IUGR

Early IUGR

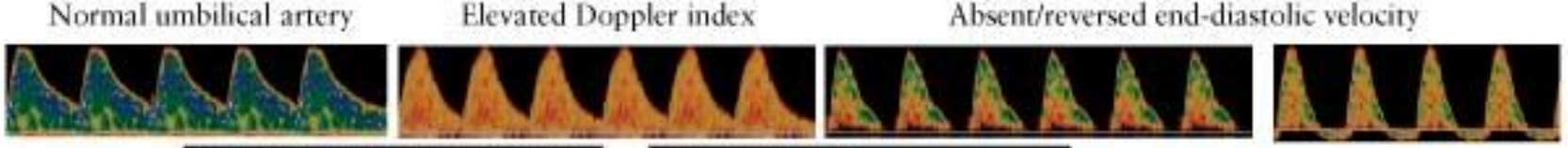
Late IUGR

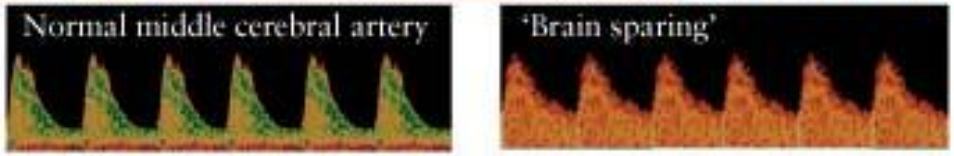
Failure of a fetus to reach its optimal growth potential

Soothill 1987, Economides 1989, Nicolaides 1989

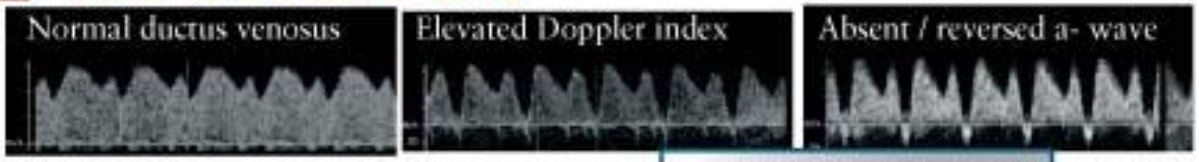
Blood Gases and Metabolites in the IUGR fetus :

↓PO2
↑PC02
↓Glucose
↑Triglycerids
↓ Essential Aminoacids





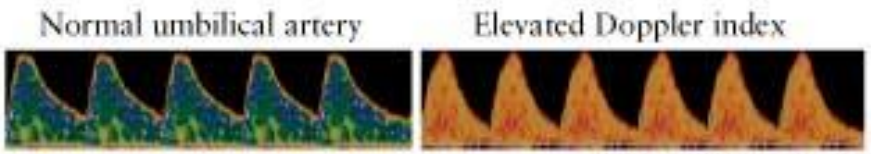
Early-onset FGR
Evolution over 4–6 weeks

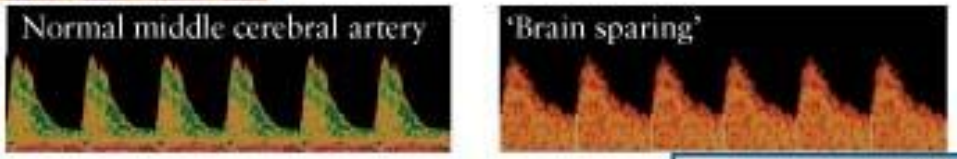


Early IUGR

Easy to identify, difficult to treat

- FHR variation loss
- Late decelerations
- Declining amniotic fluid volume
- Loss of breathing
- Loss of movement
- Loss of tone



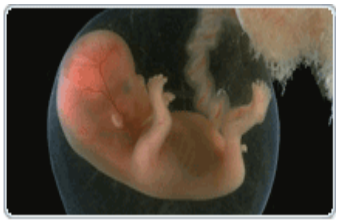


Late-onset FGR
Evolution over 6–9 weeks

Late IUGR

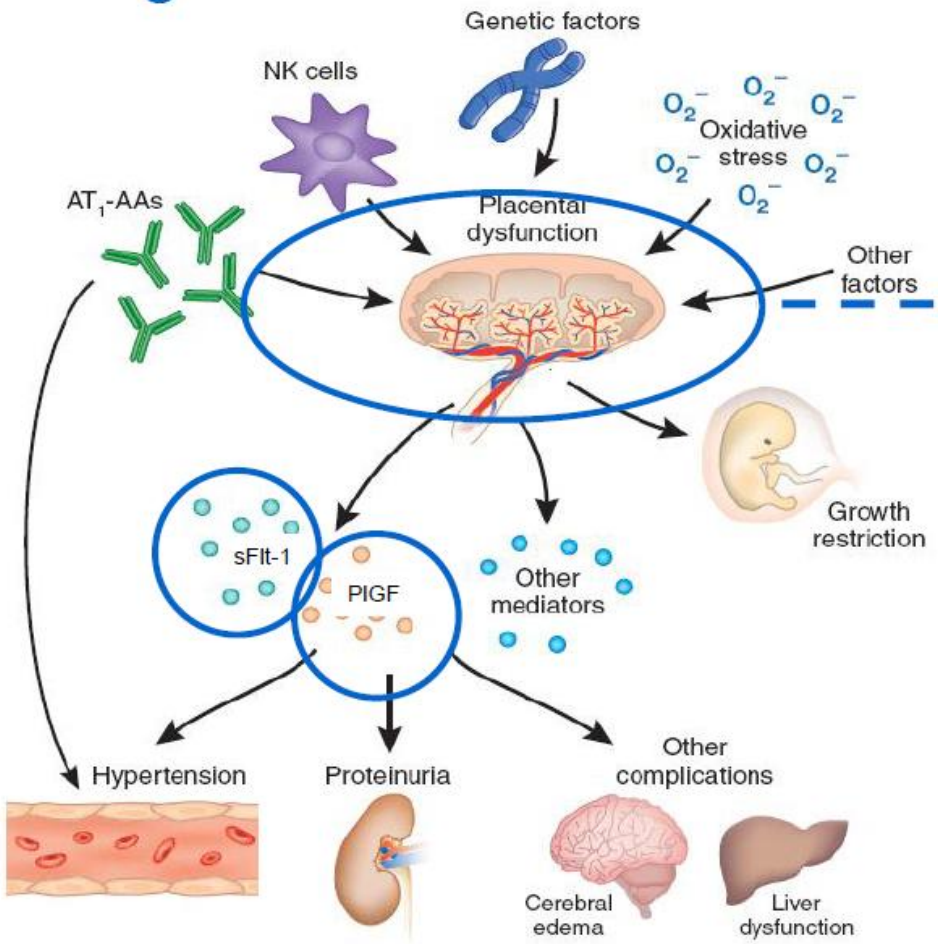
Difficult to identify, easy to treat

- Non-reactive FHR
- Declining AFI
- Loss of breathing



Central rol placenta

Pathogenesis of PE



Initial lesion, localized in the placenta

1st and early 2nd trimester

Preeclamptic syndrome, generalized defects

late 2nd and 3rd trimester

- **PE**
- **IUGR**
- **Preterm delivery**
- **Placental abruption**
- **IUFD**

Predictive value of angiogenic factors and uterine artery Doppler for early- versus late-onset pre-eclampsia and intrauterine growth restriction F. CRISPI et al. *Ultrasound Obstet Gynecol 2008*

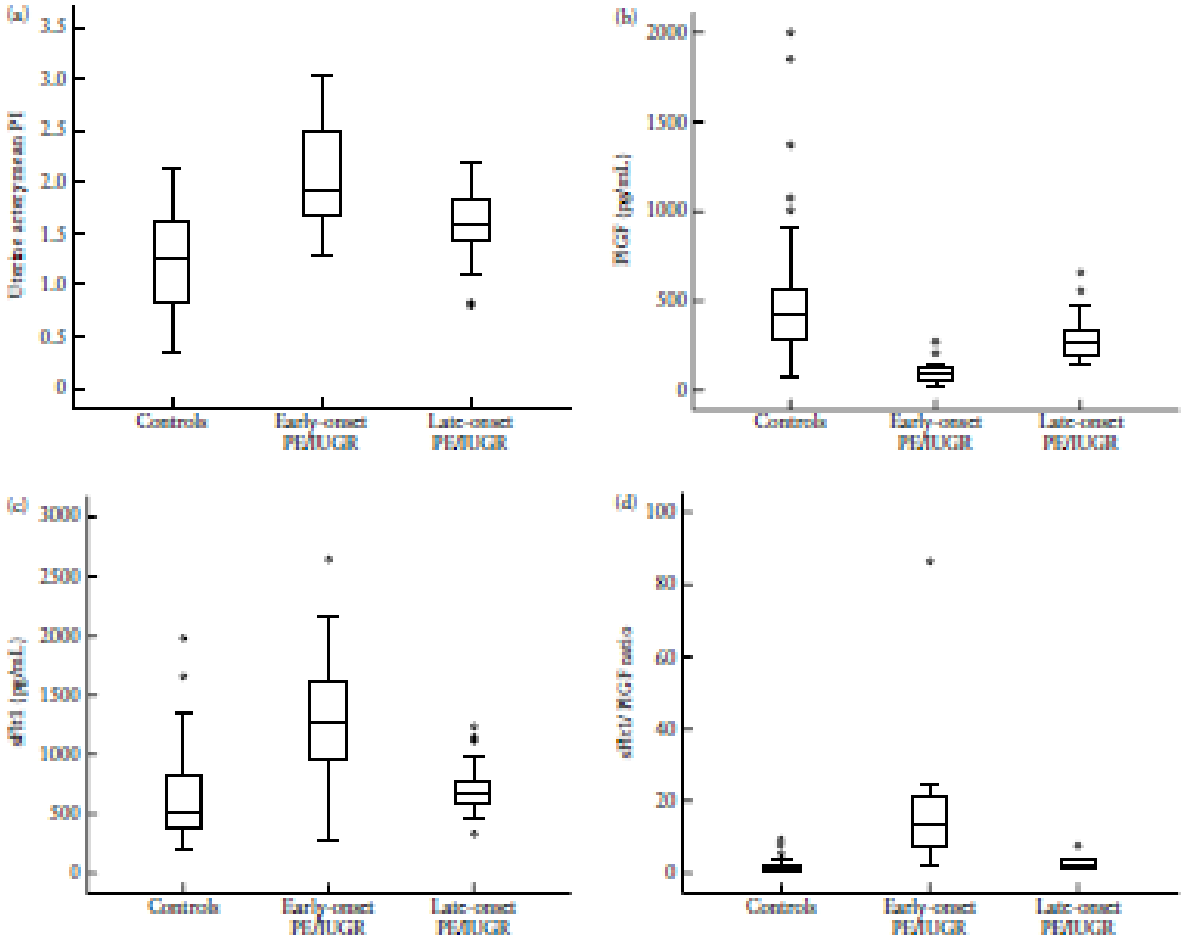


Figure 1 Uterine artery mean pulsatility index (PI) (a), maternal serum placental growth factor (PlGF) levels (b), soluble fms-like tyrosine kinase 1 (sFlt1) levels (c) and sFlt1/PlGF ratio (d) in healthy pregnant women (controls), those with early-onset (< 32 weeks) pre-eclampsia (PE) and/or intrauterine growth restriction (IUGR) and those with late-onset (≥ 32 weeks) PE/IUGR. Boxes show median and interquartile range (IQR). Whiskers represent either 1.5 × IQR or the extremes of the distribution, and circles represent values higher or lower than

Table 3 Area under the receiver–operating characteristics curve (AUC) and sensitivity of screening for early-onset pre-eclampsia and/or intrauterine growth restriction (< 32 weeks of gestational age) by uterine artery Doppler evaluation and maternal serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase (sFlt1)

Screening method	*AUC (95% CI)*	*Sensitivity (%) for a specificity of:*		
		95%	*90%*	*80%*
Uterine artery mean PI	0.851 (0.761–0.942)	47.4	52.6	73.3
PlGF	0.963 (0.911–0.989)	84.4	84.2	94.7
sFlt1	0.847 (0.735–0.958)	36.8	52.6	78.9
sFlt1/PlGF ratio	0.963 (0.926–1)	78.9	84.2	94.7
Uterine artery mean PI and PlGF	0.974 (0.944–1)	89.5	89.5	94.7
Uterine artery mean PI and sFlt1	0.940 (0.897–0.984)	63.2	73.7	100
PlGF and sFlt1	0.972 (0.941–1)	84.2	94.7	94.7
Uterine artery mean PI and sFlt1/PlGF ratio	0.979 (0.952–1)	84.2	89.5	100
Uterine artery mean PI, PlGF and sFlt1	0.981 (0.957–1)	89.5	89.5	100

PI, pulsatility index.

Conclusions Angiogenic factors and uterine artery *Doppler evaluation may be useful second-trimester screening tests for early-onset, but not late-onset, PE/IUGR*

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PE: Prediction at 11-13 wks

Maternal history: *a priori risk*

+

Biophysical markers

+

Biochemical markers

Adjusted risk

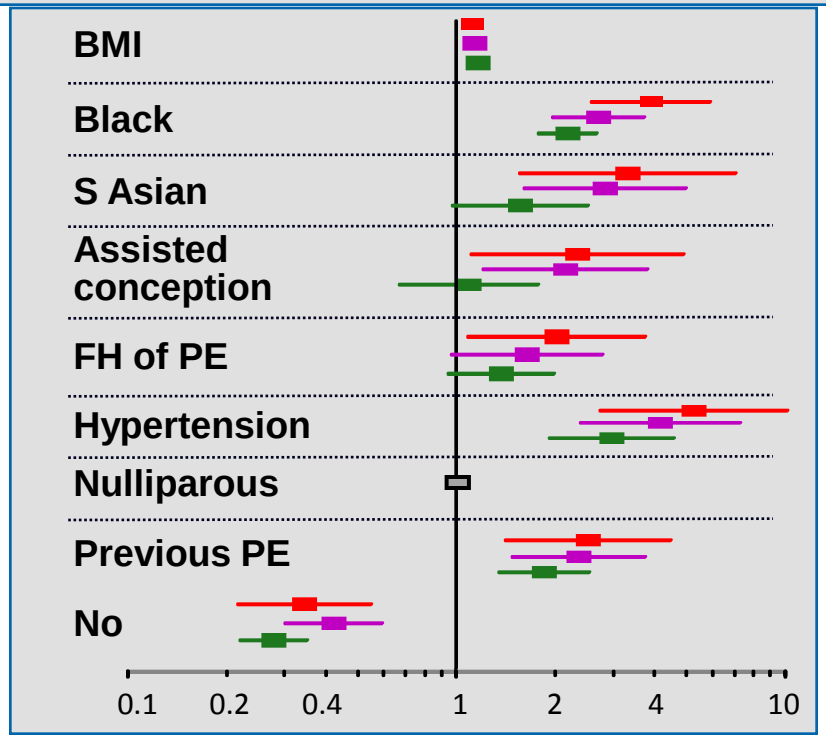
The Fetal Medicine Foundation

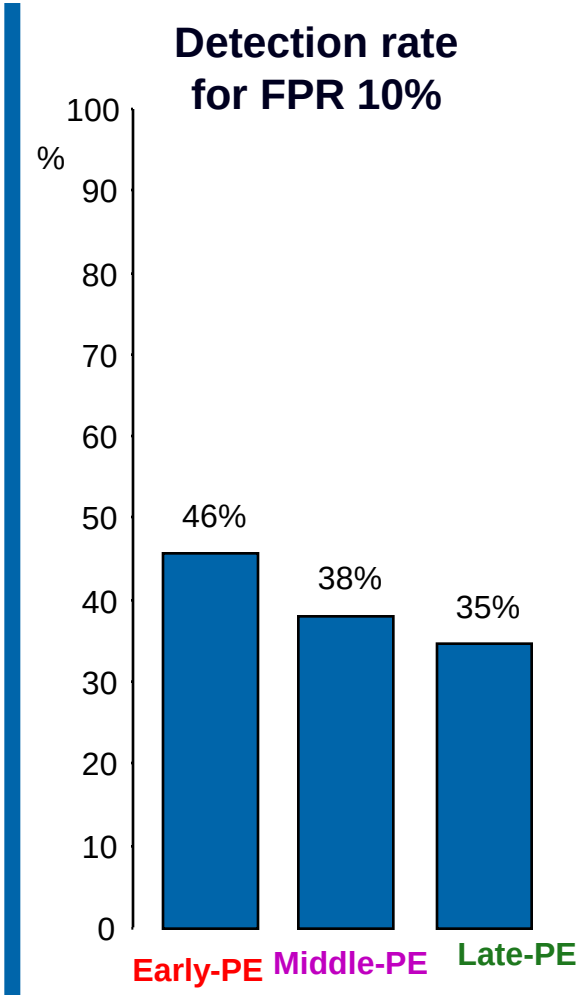
PE: Prediction at 11-13 wks

Maternal history: *a priori risk*

Prospective screening study at 11-13 wks: 35,486 singletons

- **Exclude miscarriage, termination, major defect, no FU n= 2,876**
- **Included n=32,610; No-PE n=31,884 (97.8%)**
- **Early-PE n=107 (0.3%), Middle-PE n=185 (0.6%), Late-PE n=434 (1.3%)**





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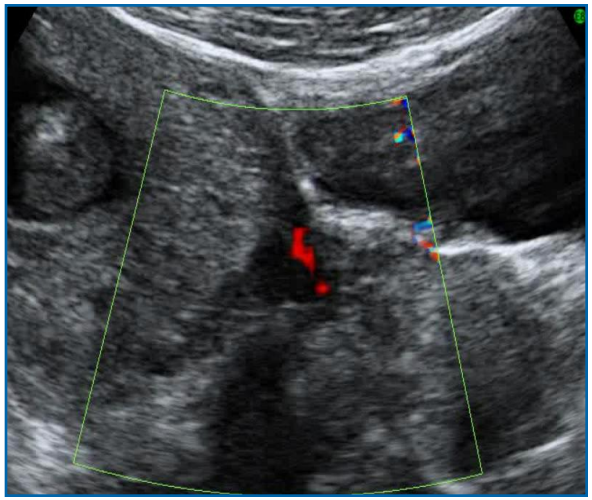
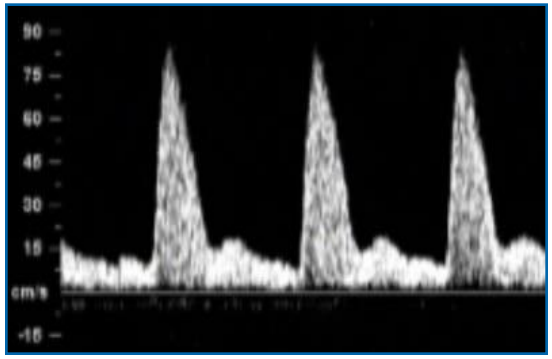
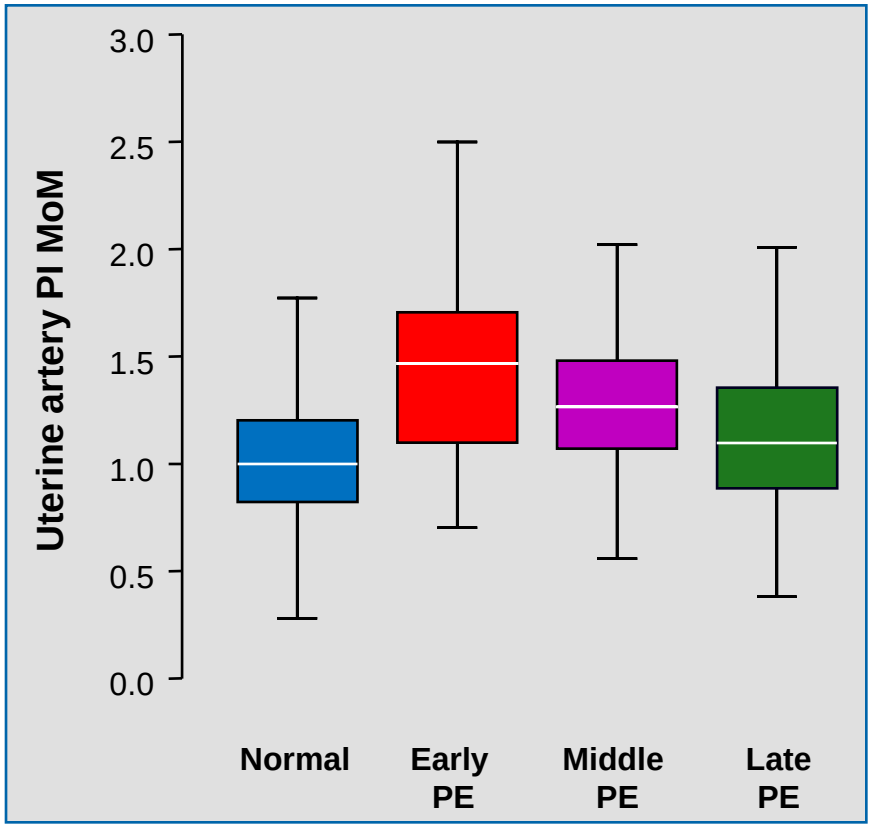
PE: Prediction at 11-13 wks

Uterine artery Doppler at 11-13 wks







- 20,798 pregnancies; Early-PE n= 84 (0.4%), Middle-PE 144 (0.7%), Late-PE 342 (1.6%)
- Mean uterine PI, adjusted for CRL, BMI, age, race

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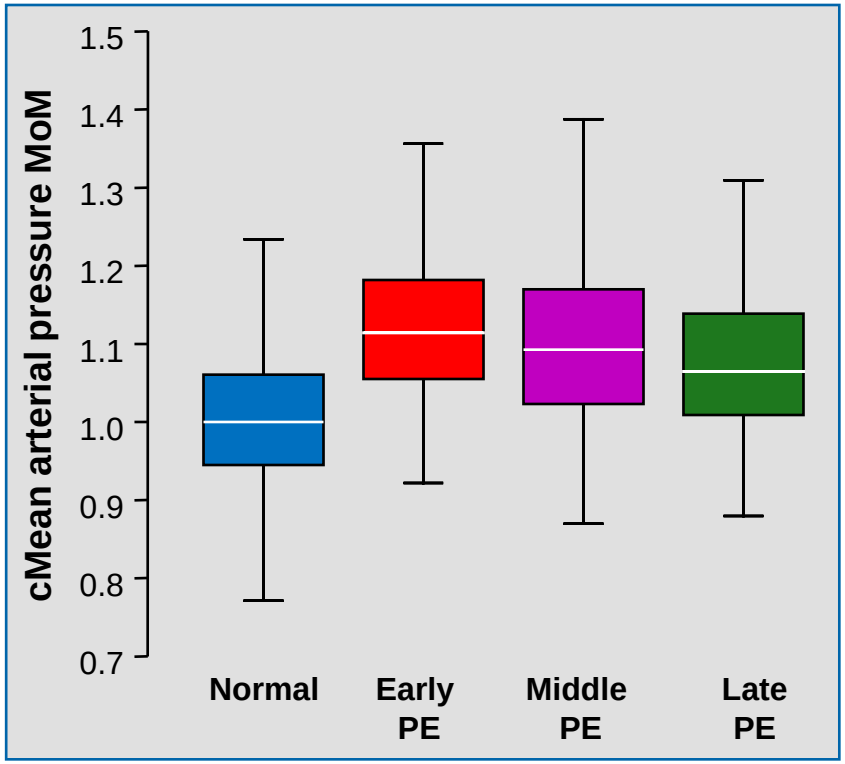
PE: Prediction at 11-13 wks

Blood pressure at 11-13 wks

MAP = Diastolic BP + (Systolic BP – Diastolic BP) / 3



- 13,712 pregnancies; Early-PE n=69 (0.5%), Middle-PE n=112 (0.8%), Late-PE n=246 (1.8%)
- MAP, adjusted for CRL, BMI, age, race and smoking

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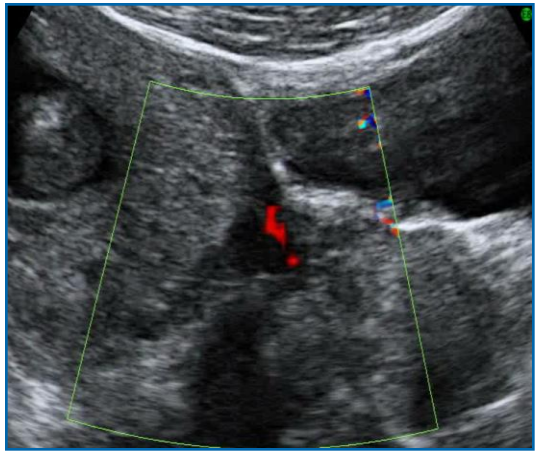
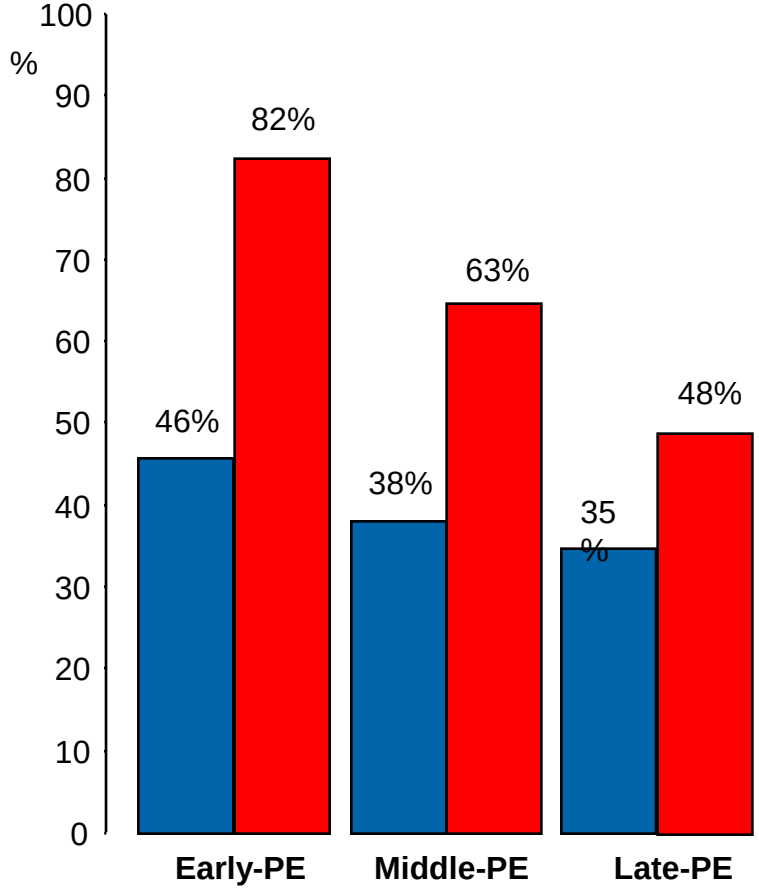
PE: Prediction at 11-13 wks

Maternal history and biophysical testing

History

- BMI (Kg/m^2)
- Racial origin
  - White
  - Black
  - S Asian
- Parous
  - No previous PE
  - Previous PE
- Maternal history of PE
- History of hypertension
- Ovulation drugs





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PE: Prediction at 11-13 wks

Maternal history and Papp-A, PlGF

Impaired trophoblastic invasion of the maternal spiral arteries

↓

Placental hypoxia

↓

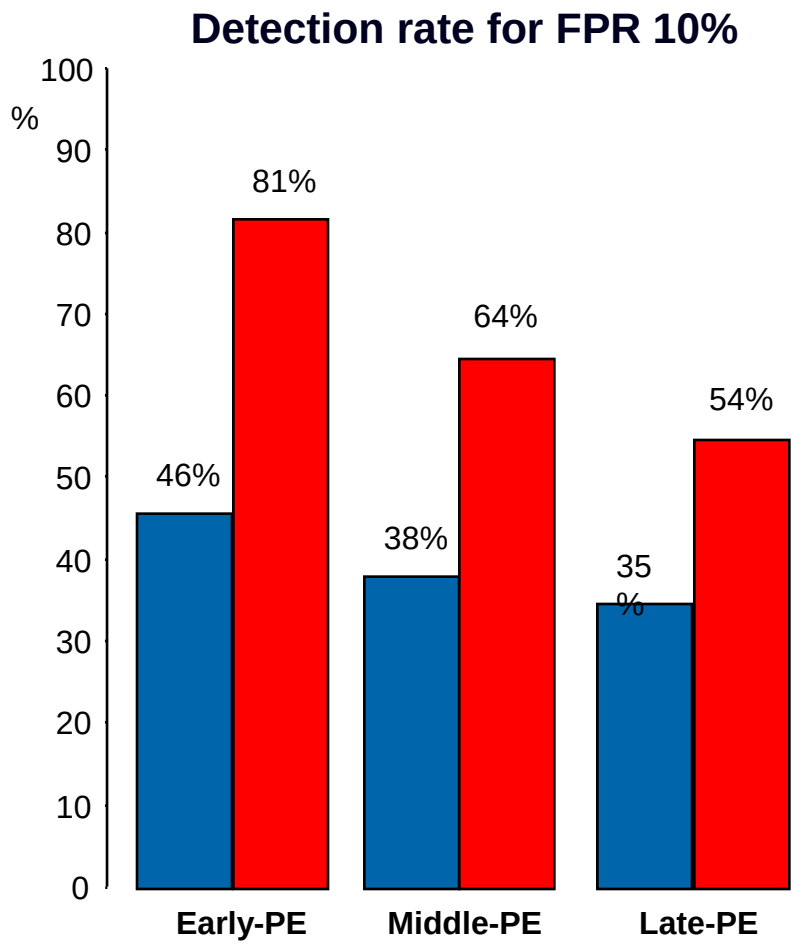
Release of inflammatory cytokines

↓

Platelet and endothelial cell activation and damage

↓

Clinical symptoms of preeclampsia



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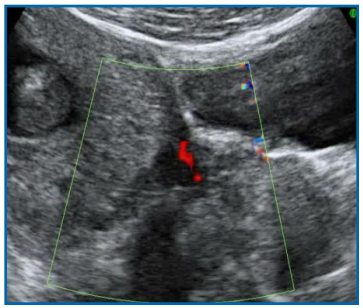
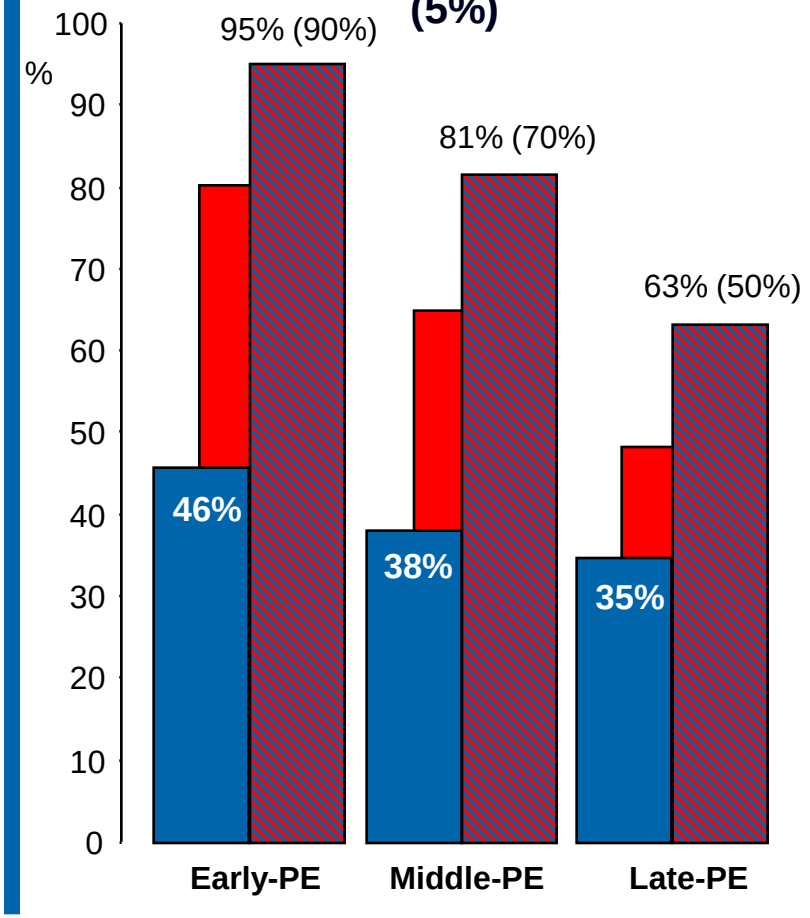
PE: Prediction at 11-13 wks

Combined testing

History

- BMI (Kg/m^2)
- Racial origin
  - White
  - Black
  - S Asian
- Parous
  - No previous PE
  - Previous PE
- Maternal history of PE
- History of hypertension
- Ovulation drugs





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First Trimester Screening

Hypertensive disorders in pregnancy: screening by biophysical and biochemical markers at 11–13 weeks

L. C. Y. POON, R. AKOLEKAR, R. LACHMANN, J. BETA and K. H. NICOLAIDES

UOG 2010

Results:

Multivariate logistic regression analysis demonstrated that significant prediction for **early PE** was provided by **maternal factors, MAP, uterine artery L-PI and serum PlGF**. Significant prediction of **late PE** was provided by **maternal factors, MAP, uterine artery L-PI, PlGF, activin-A and P-selectin**. The estimated detection rates, at a 5% false-positive rate, were **88.5%** (95% CI, 69.8–97.4%) **for early PE and 46.7%** (95% CI, 36.1–57.5%) **for late PE**.

Conclusion

Combined biophysical and biochemical testing at 11–13 weeks could effectively identify women at high risk for subsequent development of hypertensive *disorders in pregnancy.*

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Competing Risks Model in Early Screening for Preeclampsia by Biophysical and Biochemical Markers

Akolekar et al.2012

Table 3. Estimated detection rates of PE requiring delivery before 34, 37 and 42 weeks' gestation, at false-positive rates (FPR) of 5 and 10%

Screening test	FPR %	PE <34 weeks (n = 214)		PE <37 weeks (n = 568)		PE <42 weeks (n = 1,426)	
		risk cutoff	detection n (%)	risk cutoff	detection n (%)	risk cutoff	detection n (%)
Maternal characteristics	5.0	1:93	78 (35.5)	1:35	186 (32.7)	1:9	419 (29.4)
	10.0	1:143	108 (50.5)	1:51	246 (43.3)	1:12	574 (40.3)
Uterine artery PI	5.0	1:88	127 (59.3)	1:31	227 (40.0)	1:9	445 (31.2)
	10.0	1:164	161 (75.2)	1:52	313 (55.1)	1:12	602 (42.2)
MAP	5.0	1:88	125 (58.4)	1:31	250 (44.0)	1:8	532 (37.3)
	10.0	1:159	156 (72.9)	1:52	337 (59.3)	1:12	763 (53.5)
PAPP-A	5.0	1:88	93 (43.6)	1:33	212 (37.3)	1:9	449 (31.5)
	10.0	1:151	117 (54.7)	1:52	274 (48.2)	1:12	601 (42.1)
PLGF	5.0	1:95	127 (59.3)	1:33	232 (40.8)	1:9	415 (29.1)
	10.0	1:170	155 (72.4)	1:55	309 (54.4)	1:12	572 (40.1)
Uterine artery PI and MAP	5.0	1:96	171 (79.9)	1:31	310 (54.6)	1:7	498 (34.9)
	10.0	1:197	192 (89.7)	1:57	406 (71.5)	1:12	807 (56.6)
PAPP-A and PLGF	5.0	1:101	129 (60.3)	1:34	243 (42.8)	1:9	433 (30.4)
	10.0	1:181	159 (74.3)	1:56	317 (55.8)	1:12	582 (40.8)
Uterine artery PI, MAP and PAPP-A	5.0	1:105	175 (81.8)	1:26	298 (52.5)	1:7	514 (36.0)
	10.0	1:216	198 (92.5)	1:65	424 (74.6)	1:12	811 (59.9)
Uterine artery PI, MAP and PLGF	5.0	1:126	187 (87.4)	1:36	344 (60.6)	1:8	536 (37.6)
	10.0	1:261	205 (95.8)	1:67	439 (77.3)	1:12	755 (52.9)
Uterine artery PI, MAP, PAPP-A and PLGF	5.0	1:128	200 (93.4)	1:36	347 (61.1)	1:8	539 (37.8)
	10.0	1:269	206 (96.3)	1:67	435 (76.6)	1:12	764 (53.6)

Competing risks

- Other cause birth (e.g. Normal birth no PE)
- PE event

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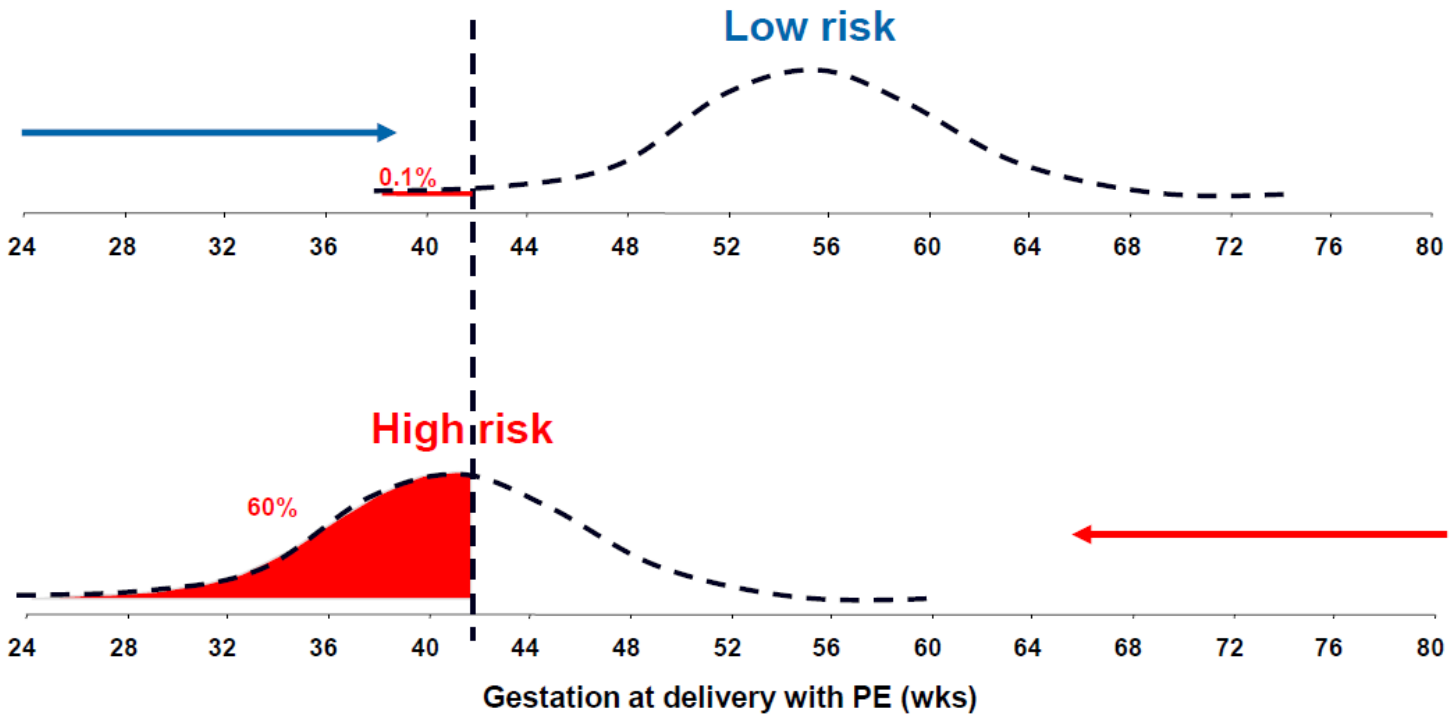
Competing risk model



Wright *et al.*, 2012: A competing risks model in early screening for preeclampsia. Fetal Diagn Ther

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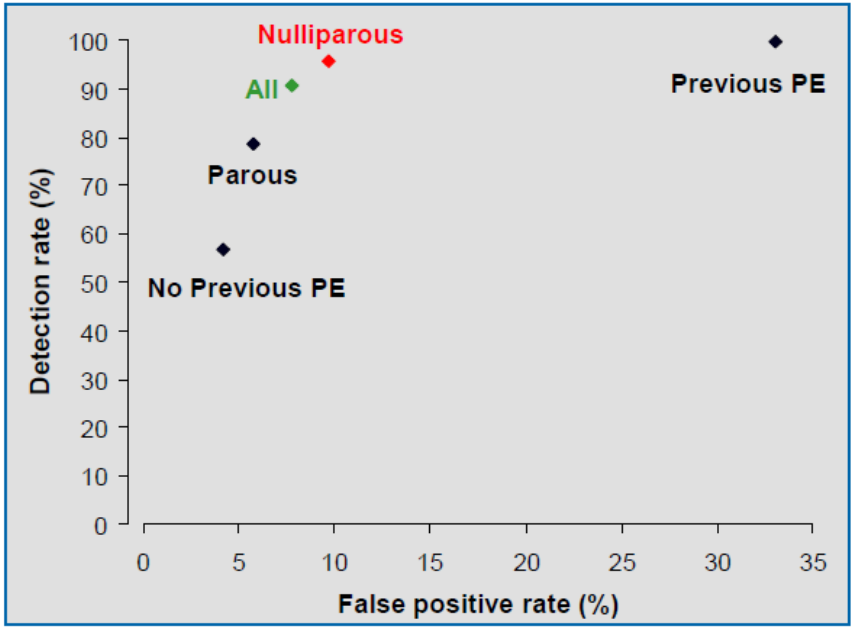
Algorithm for early-PE risk cut-off 1:200 and algorithm for preterm-FGR risk cut-off 1:150



	Caucasian		African	
	FPR	DR	FPR	DR
All	7.7	91	24.9	100
Nulliparous	9.6	96	30.8	100
Parous	5.7	79	21.1	100
Previous PE	33.0	100	64.1	100
No previous PE	4.1	57	18.3	100

Performance of screening depends on patient characteristics

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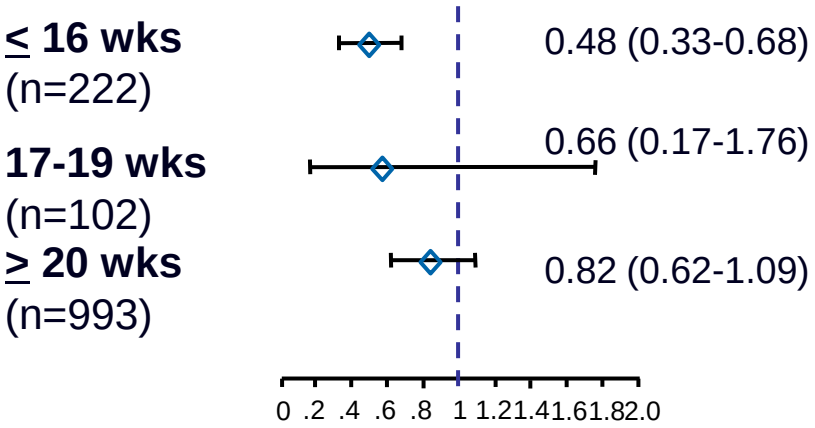
PE: Prediction at 11-13 wks

Meta analysis on prophylactic aspirin
31 randomized studies, 32217 patients

- Preeclampsia 0.90 (95% CI 0.84-0.97)

Askie et al, Lancet 2007



Bujold 2009

Aspirine started before 16 wks gives a 50% reduction in the risk of developing PE

Early Administration of Low-Dose Aspirin for the Prevention of Preterm and Term Preeclampsia: A Systematic Review and Meta-Analysis

Stéphanie Roberge[a] Pia Villa[d] Kypros Nicolaides[f] Yves Giguère[c]

Fetal Diagn Ther 2012

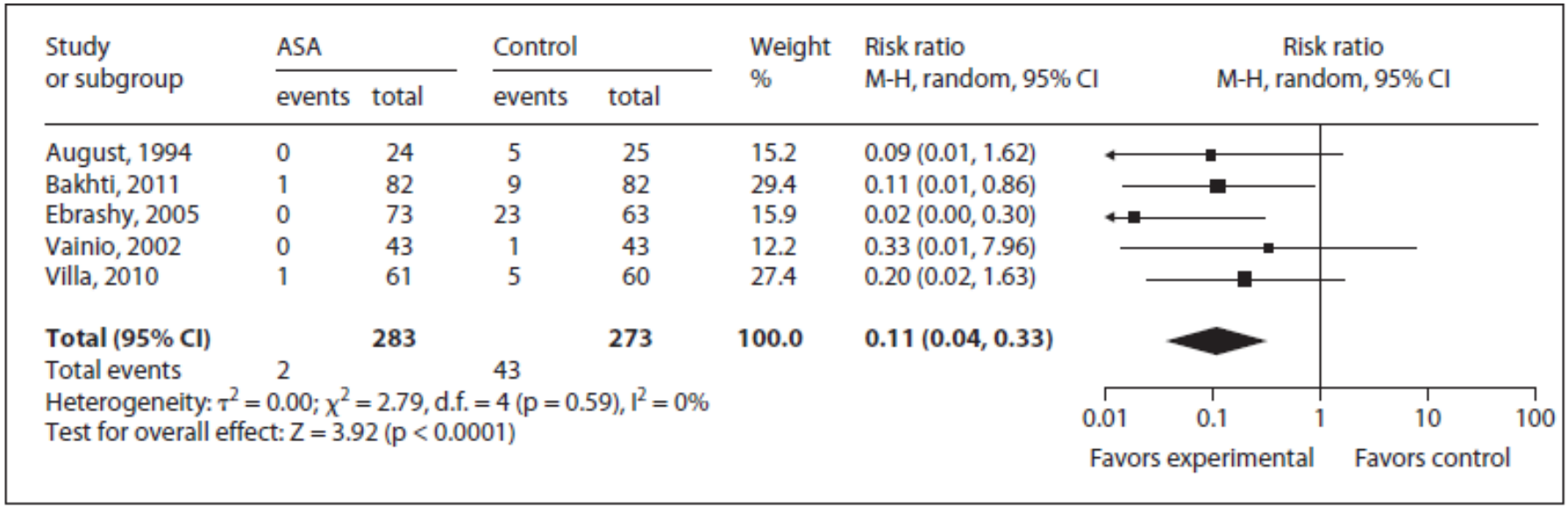


Fig. 2. Forest plot of the effect of low-dose aspirin initiated at or before 16 weeks' gestation on the risk of preterm preeclampsia.

RESULTS:

ONLY FIVE TRIALS ON A COMBINED TOTAL OF 556 WOMEN FULFILLED THE INCLUSION CRITERIA. ASPIRIN INITIATED AT OR BEFORE 16 WEEKS OF GESTATION WAS ASSOCIATED WITH A MAJOR REDUCTION OF THE RISK OF PRETERM PREECLAMPSIA (RR 0.11, 95% CI 0.04–0.33)

CONCLUSION:

LOW-DOSE ASPIRIN ADMINISTRATED AT OR BEFORE 16 WEEKS OF GESTATION REDUCES THE RISK OF PRETERM BUT NOT TERM PREECLAMPSIA.

What happens in the western world

- Screening for PE is not yet performed in a standardized way

- Many obstetricians already prescribe Aspirin to pregnant women, as if it was …..water

- Many pregnant women use Aspirin on their own initiative, without medical prescription or supervision

- No uniformity or information on use, dosage, compliance

- This has made difficult to perform a large randomized CT

The still unanswered questions

- **Is screening for PE equally effective in the "real world"?**
- **Which is the most cost-effective algorithm?**
- **Is Aspirin really effective ?**
- **Is it safe?**
- **Is it the best therapeutic strategy?**

More evidence is necessary, a RCT is necessary to assess the real therapeutic value of aspirin

funded by EU FP7
ASPRE
project

Trial Identifiers

- **FP7-HEALTH-2013-INNOVATION-2**
- **EudraCT Number:** 2010-023659-26
- **ISRCTN:** ISRCTN13633058
- **WHO UTN:** U1111-1140-4837

Thanks!