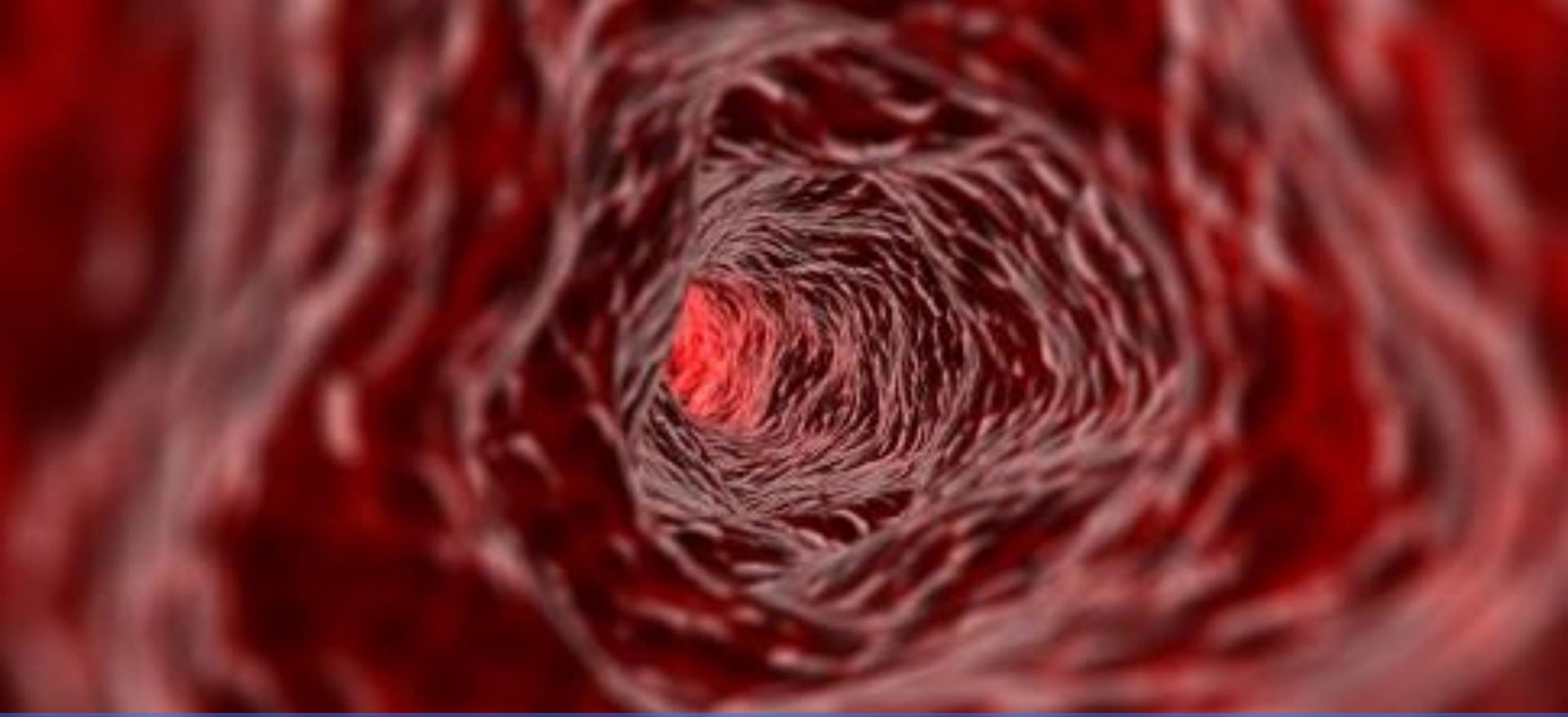

Alfredo Pinto

Predittività e Diagnosi Precoce di Preeclampsia e FGR

XIX CONGRESSO NAZIONALE A.G.E.O.

PREDITTIVITA' E DIAGNOSI PRECOCE IN OSTETRICIA E GINECOLOGIA"

Napoli 6 – 7 Giugno 2019

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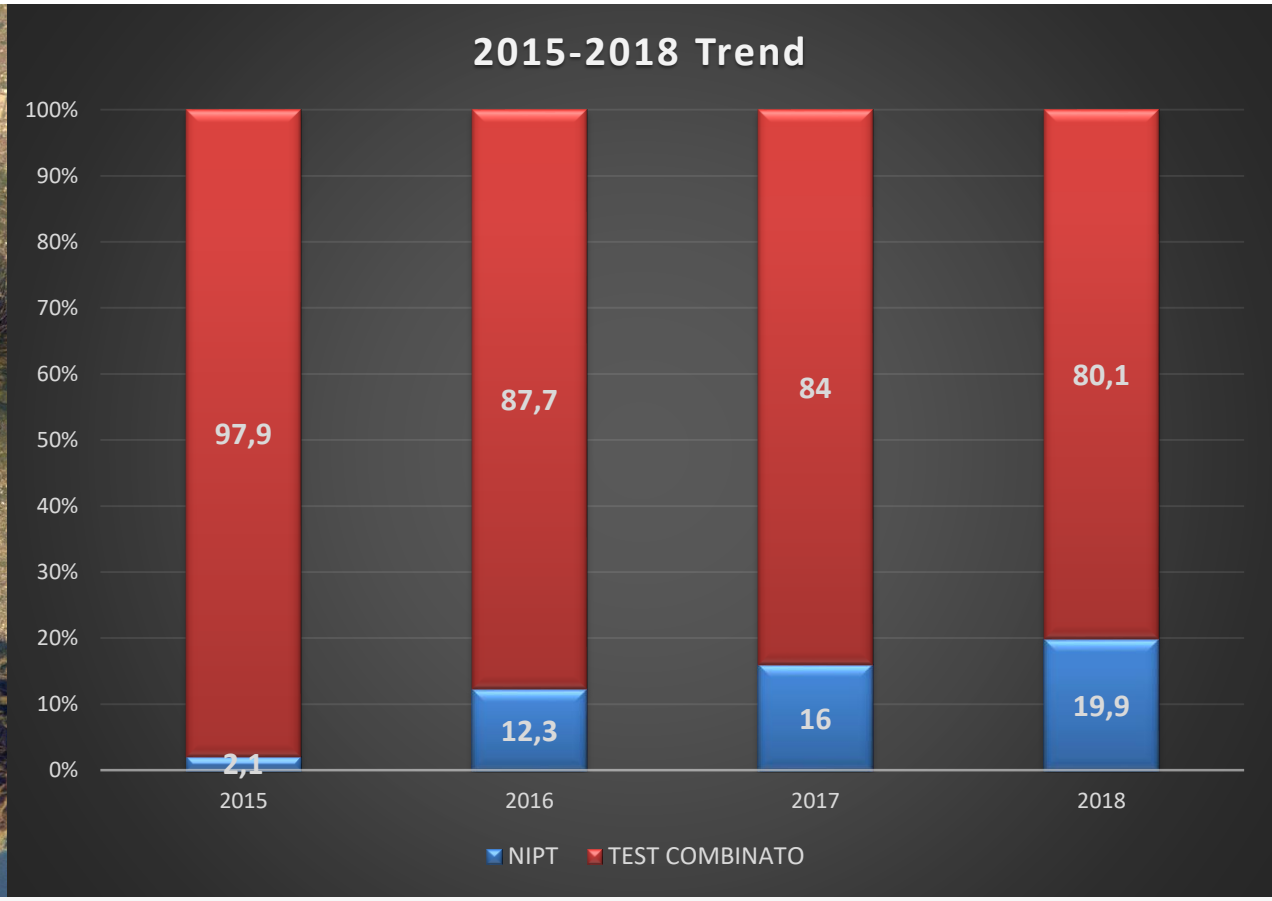
woman and fetal care

Non Invasive Prenatal Screening

NIPT vs Combined Test: Trend in Local Low Risk Population



ISTITUTO DIAGNOSTICO VARELLI

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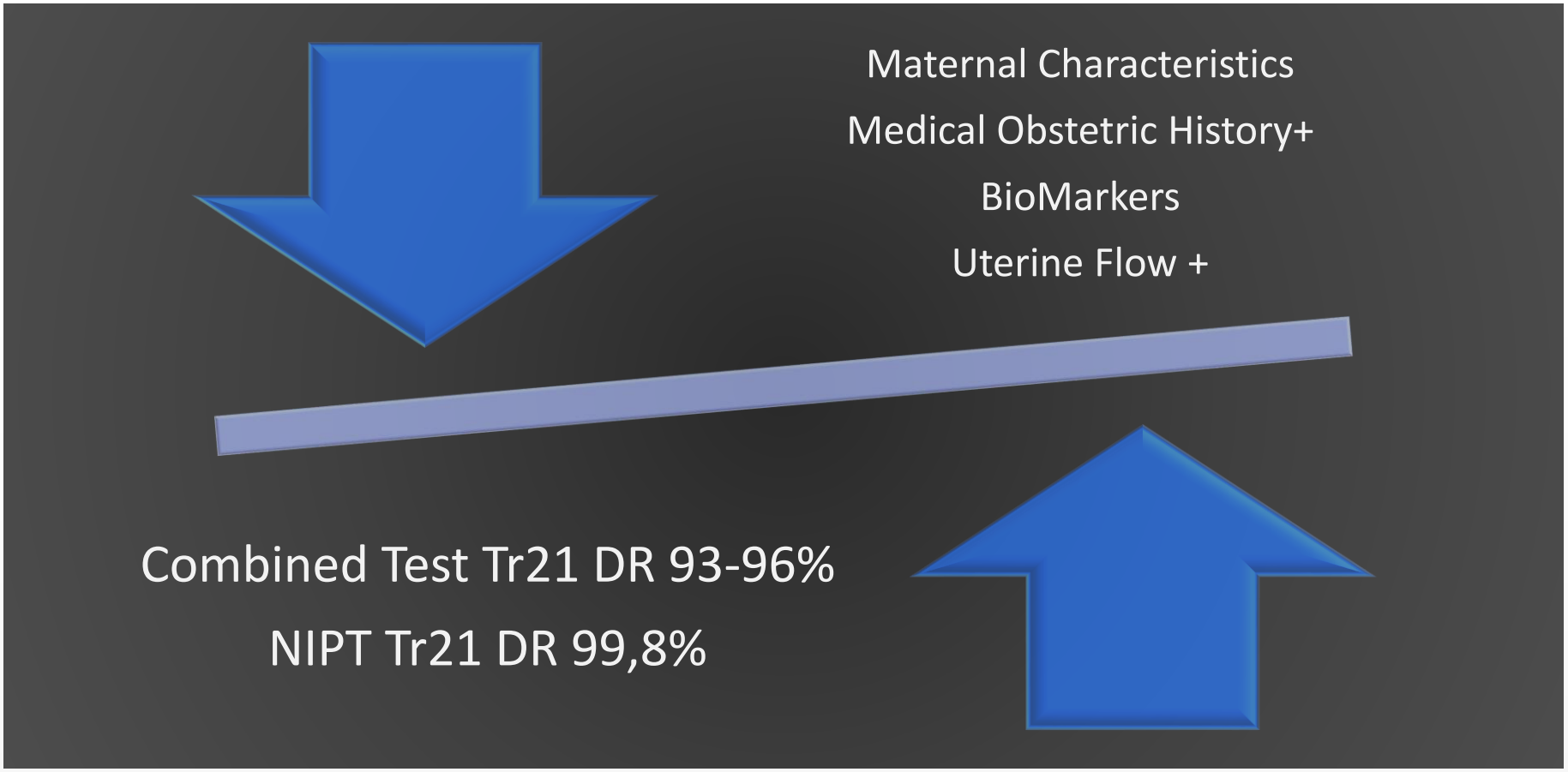
Non Invasive Prenatal Screening

NIPT vs Combined Test: Trend in Local Low Risk Population



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Preeclampsia

Major cause of maternal and perinatal mortality and morbidity

Maternal death

- More than 70 000 women die every year throughout the world as a result of pre-eclampsia
  - WHO 2003 - 2009
    - Hemorrhagic causes, 19%
    - Hypertensive causes 14%

Mother Long Term Consequences:

- Doubling In Her Risk Of Major **Cardiovascular Disease**
  - 20% of women will develop hypertension (vs 2% without PE)

Neonate, short and long term conseguences:

- High risk of **perinatal death** and **cerebral palsy**
  - Associated **Fetal Growth Restriction**
  - **Premature Birth (**RDS, IVH, sepsis, neuropsychomotor deficit)
  - Adulthood Increased Risk Of **Cardiovascular Disease**

Preeclampsia Definition

International Society for Studies in Gestational Hypertension, 2018

Hypertension > 20w + ONE of the following conditions :

Proteinuria

Proteinuria/creatininuria above 0.3 mg/mg, or by 24-hour proteinuria above 300mg / 24h

Dysfunctions of maternal organs

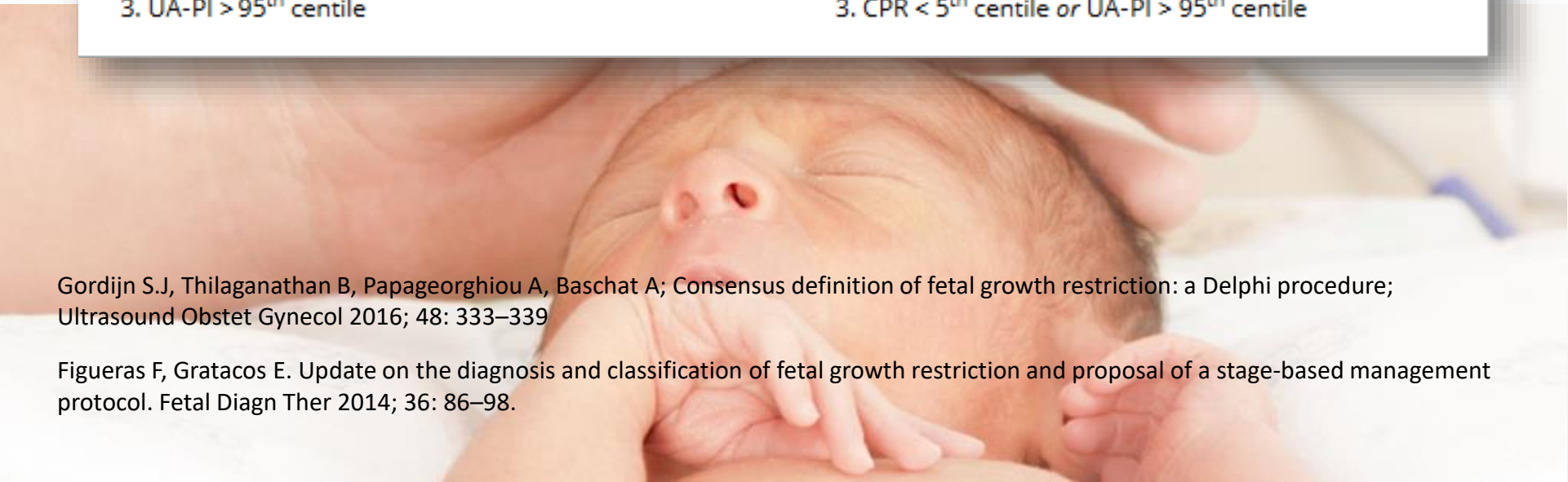
- Renal insufficiency (creatinine above 1.02 mg/dL)
- Hepatic impairment (elevation of transaminases > x2 normal levels), or pain in the right hypochondrium, or epigastralgia
- Neurological complications (scotomas or persistent cephalgia accompanied by hyperreflexia or confusional states or eclampsia or cerebrovascular accident or amaurosis
- Haematological complications (thrombocytopenia or hemolysis)

Uteroplacental dysfunctions

- Fetal growth restriction
- Changes in the Doppler velocimetry studies of the umbilical artery, especially if combined with alterations in uterine arteries

FGR Definition

Early FGR: GA < 32 weeks, in absence of congenital anomalies	Late FGR:GA ≥ 32 weeks, in absence of congenital anomalies
AC/EFW < 3rd centile *or* UA-AEDF	AC/EFW < 3rd centile
Or	*Or at least two out of three of the following*
1. AC/EFW < 10th centile *combined with*	1. AC/EFW < 10th centile
2. UtA-PI > 95th centile *and/or*	2. AC/EFW crossing centiles >2 quartiles on growth centiles*
3. UA-PI > 95th centile	3. CPR < 5th centile *or* UA-PI > 95th centile



Gordijn S.J, Thilaganathan B, Papageorghiou A, Baschat A; Consensus definition of fetal growth restriction: a Delphi procedure; Ultrasound Obstet Gynecol 2016; 48: 333–339

Figueras F, Gratacos E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. Fetal Diagn Ther 2014; 36: 86–98.

Screening of Preeclampsia

Reasons

There are no validated methods for prediction of PE

- Medical history
- Biomarkers
- Clinical diagnostic tests

Prediction

Maternal and perinatal morbidity and mortality: common

The only effective treatment: Early delivery: preterm birth in many cases

Prevention of PE: significant impact on maternal and infant health

Prevention

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Established method of screening for preeclampsia

Maternal History: ENG versus USA screening

NICE guidelines 2010

WHO recommendations 2011

NICE Performance

Prospective study
Heterogeneous population,
Nulli/multiparous
Early and late preeclampsia,
Detection rate of 37% and 28.9%
5% of false-positive
Poon L. C. Y., Journal of Human Hypertension. 2010;24

SCREEN POSITIVE

- *Any ONE High risk factors*
- *Any TWO OF FIVE moderate* risk factors

National Institute of Health and Care Excellence

ACOG 2013

Task Force on Hypertension in Pregnancy

ACOG Performance

DR of early PE was 46%
DR of preterm PE was 42%
SPR was 12%

SCREEN POSITIVE

- *ONE High risk factor*
- *Aspirin recommended*

American College Obstetrics and Gynecology

PreEclampsia Pathogenesis

Impaired remodeling of uterine spiral arteries

– Placental perfusion

– Trophoblast differentiation& invasion

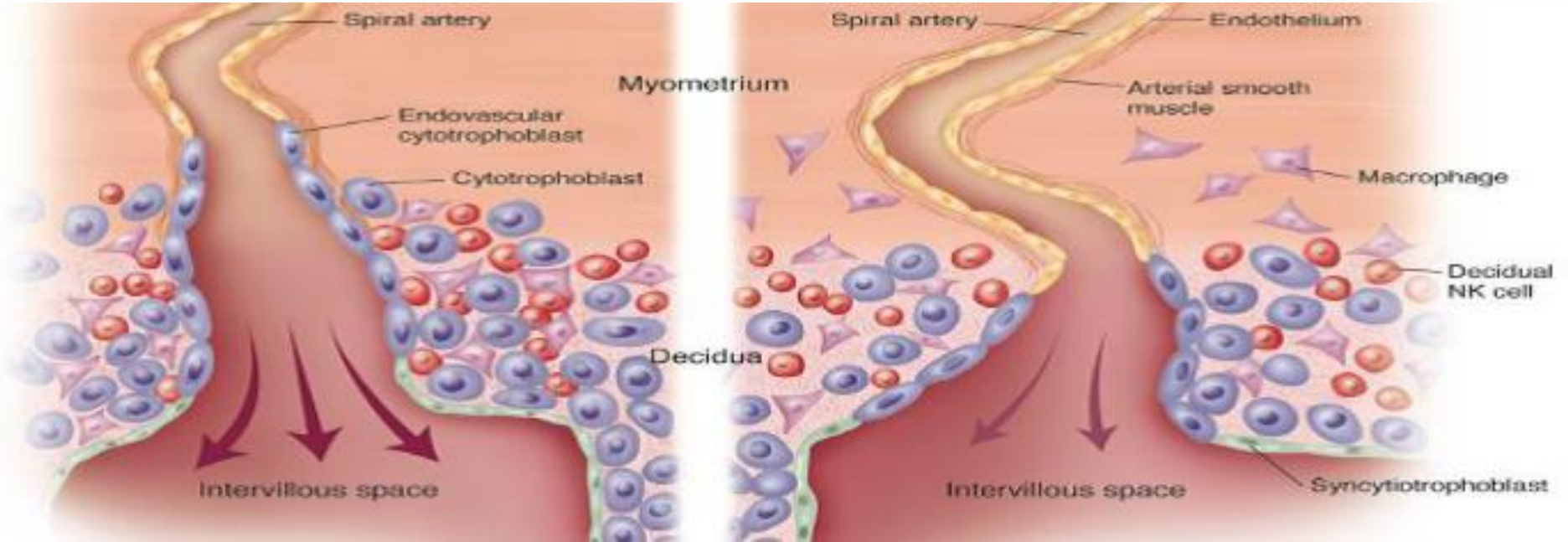
Placental & endothelial dysfunction

Immune maladaptation to paternal Antigens

Exaggerated systemic inflamatory response

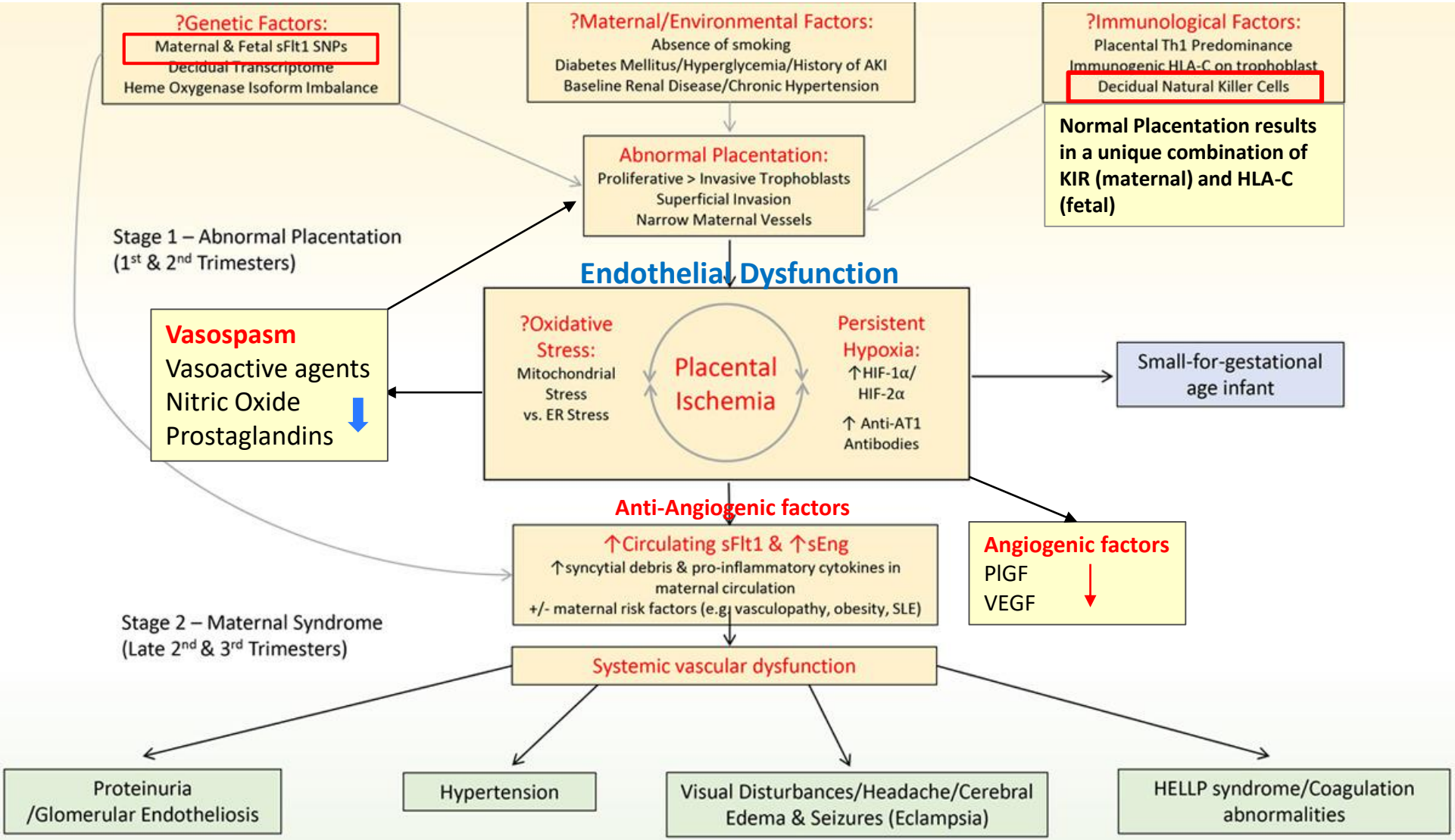
– Production of antiangiogenic factors

- *uncertainty whether pathogenesis of **PE with predominantly maternal component** is the same or differs from **PE with predominantly fetal component**.*



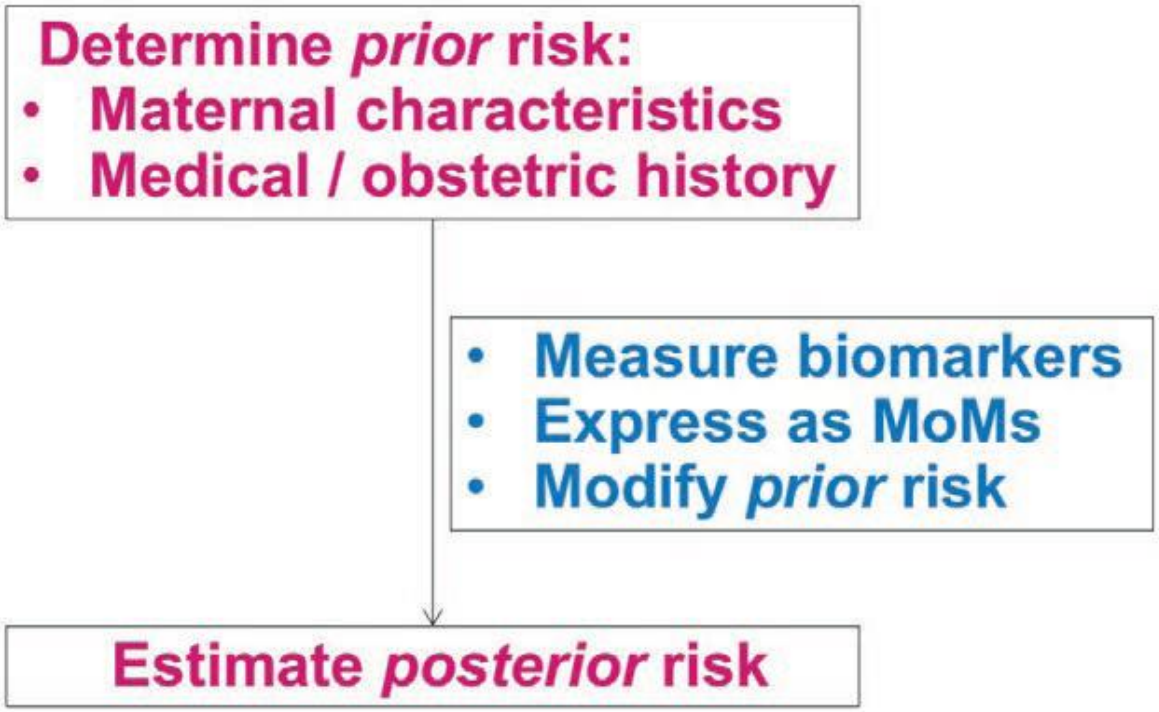
PreEclampsia & FGR Pathogenesis

Angiogenic Factors



Prediction of Preeclampsia

Fetal Medicine Foundation



Bayes Theorem to estimate the prior risk

- Derived from a multiple regression model of the various maternal risk factors
  - Each one of the factors is given its own separate importance
  - Takes into consideration the interrelationship between the different factors

Screening of Preeclampsia

Biochemical Predictors

HCG, AFP, Estriol

PAPP A, Inhibin A, Activin A

Placental protein 13 (PP13)

Corticotropin releasing hormone (CRH)

C reactive protein (CRP)

Anti phospholipid antibodies (APA)

Plasminogen activator inhibitor (PAI)

Anti thrombin 3 (ATIII)

Endothelins, homocysteine

Prostaglandins, thromboxanes

Angiogenic factors

- **placental growth factor (PlGF)**
- vascular endothelial growth factor (VEGF)
- **fms like tyrosine kinase receptor 1(FLT 1)**

Endoglin sEng

Atrial natriuretic peptide

Leptin

Beta 2 microglobulin

Free fetal DNA

Serum proteomic markers

Prediction of Preeclampsia

Biochemical Markers

Complexity of preeclampsia etiology

Isolated Maternal Factor Poor predictor

Major accuracy in **algorithms,** combining multiple factors

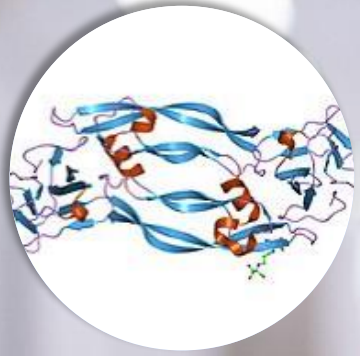
In **late PE**, which is the vast majority of cases, the screening biomarkers **results are modest.**

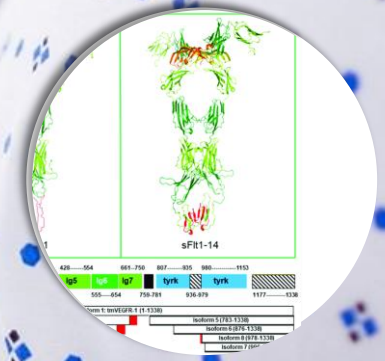
Biomarker	AUC (95%CI)	Reference
Maternal characteristics ∗	0.78 (0.71-085)	Goetzinger et al. [12]
PAPP-A	0.64 (0.57-0.72)	Goetzinger et al.
PAPP-A	0.54 (0.49-0.59)	Myatt et al.
ADAM-12	0,58 (0.50-0.67)	Goetzinger et al.
ADAM-12	0.58 (0.53-0.63)	Myatt et al.
PlGF	0.61 (0.56-0.66)	Myatt et al. [13, 14]
sFlt-1	0.54 (0.48-0.59)	Myatt et al.
PP13	0.51 (0.46-0.56)	Myatt et al
Maternal characteristics +PAPP-A+ADAM-12	0.79 (0.71-0.86)	Goetzinger et al.
Maternal characteristics∗∗+PlGF+PAPP-A+ADAM-12	0.73 (0.69-0.77)	Myatt et al.

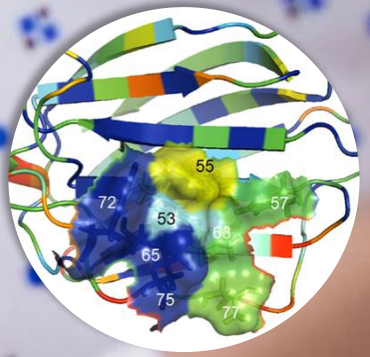
Tan M. Y., Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound in Obstetrics & Gynecology*. 2018;52(2):186–195

Prediction of Preeclampsia

Biochemical Markers



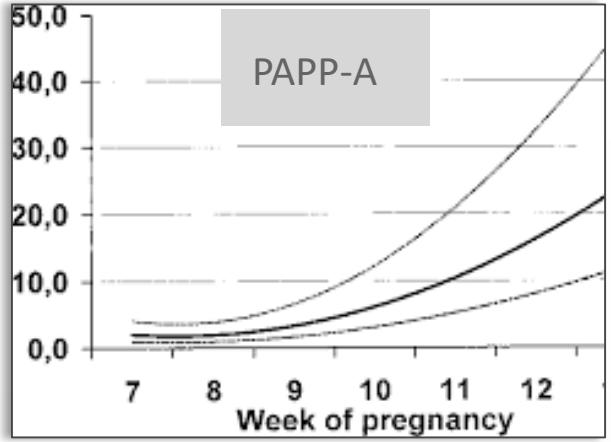




PAPP-A	PlGF	sFlt-1	PP-13

Screening of Preeclampsia

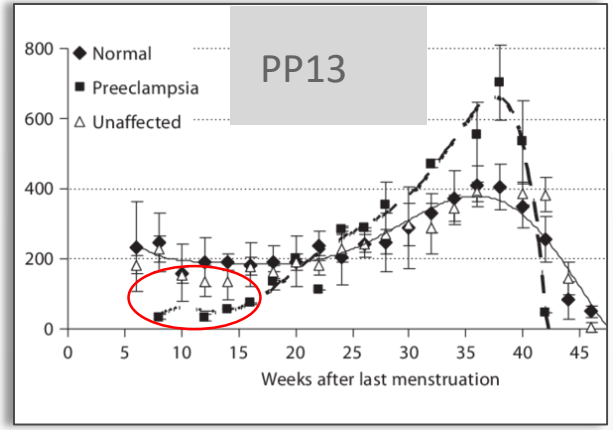
Biochemical Predictors



1628 aminoacid protease, produced by placental trophoblasts

Decreased levels of PAPP A in 1 Trim associated with increased levels of early onset PE, IUGR, SGA and PTD

Combined with UtPI, PE prediction of 70% at FP rates of 5%.



32 kDa dimeric protein produced by placental tissue

PP13 levels gradually increase in normal pregnancy

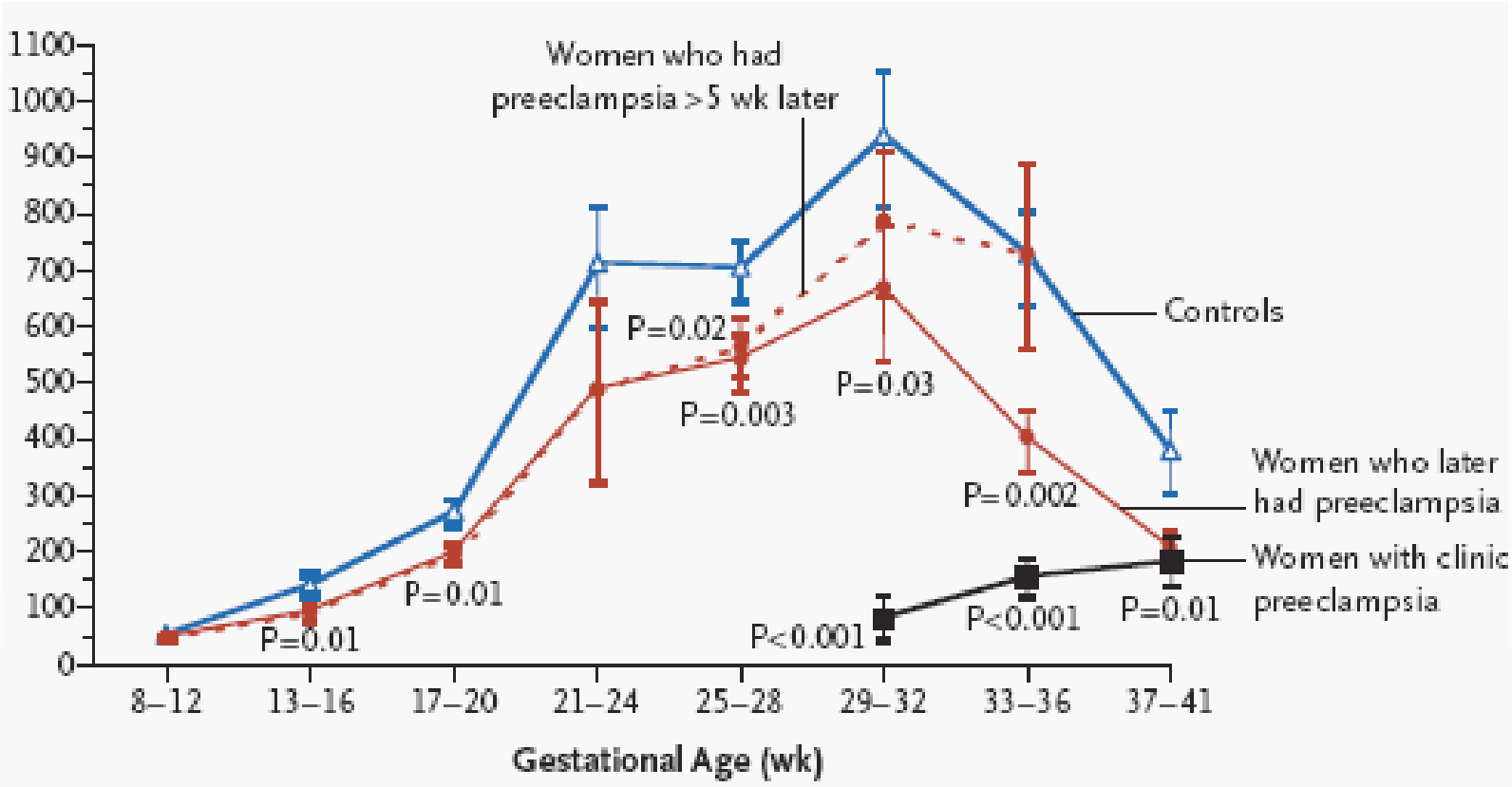
Abnormally low levels of PP13 in 1° trim. women who developed PE, IUGR and PTD in 2° & 3rd trimesters

Combined with UtPI, PE prediction of 71% at FP rate of 10%

D'Anna R, et al. First trimester serum PAPP-A and NGAL in the prediction of late-onset pre-eclampsia. Prenat Diagn 2009; 29 : 1066-8.

Angiogenic Markers

Mean **PlGF** concentration and gestational age



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sFlt-1

New Biochemical Predictors

s**Flt-1: soluble fms-like tyrosine kinase 1**

- anti-angiogenic soluble form of type -1 VEGF receptor

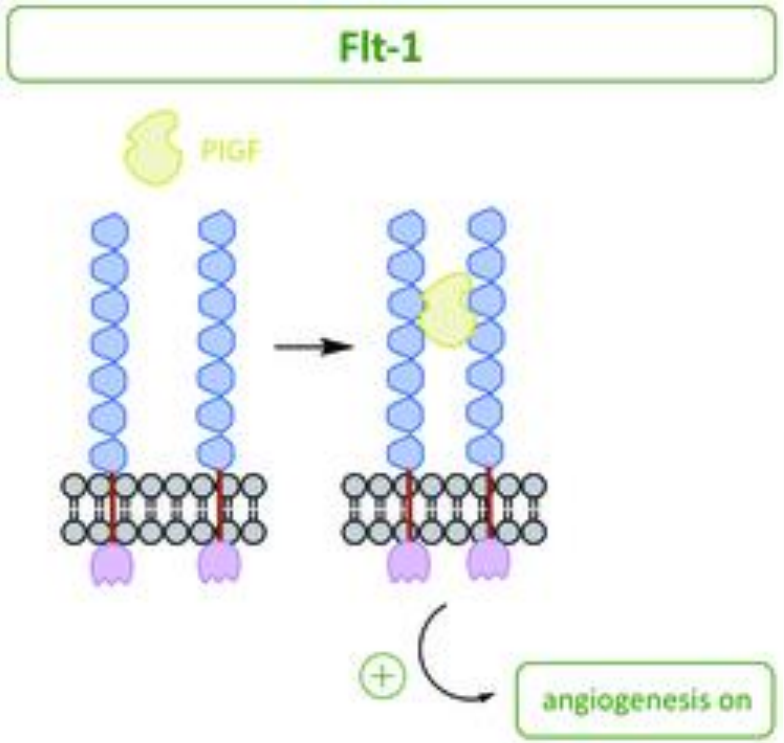
Serum sFlt1 binds with both VEGF and PlGF

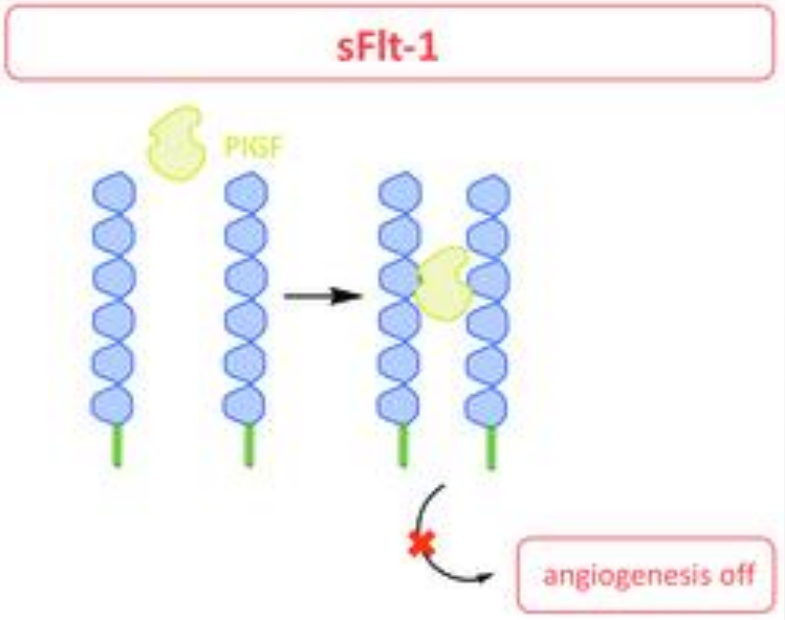
- **neutralize VEGF and PlGF**

Elevated level is associated **with onset of PE** and severity of illness

sFlt-1 increase is **observed approximately 5 weeks before onset of PE.**

Smokers have low sFlt-1levels & less Incidence of PE.





Angiogenic Markers

PlGF and sFlT-1 Levels in all trimesters

s**Flt-1** levels are stable during early & mid gestation then increase significantly during late stages

During 2° trimester low or **no increase in serum concentration of free PlGF** , VEGF & **higher concentration of sFlt-1** a strong predictor of **early PE**.

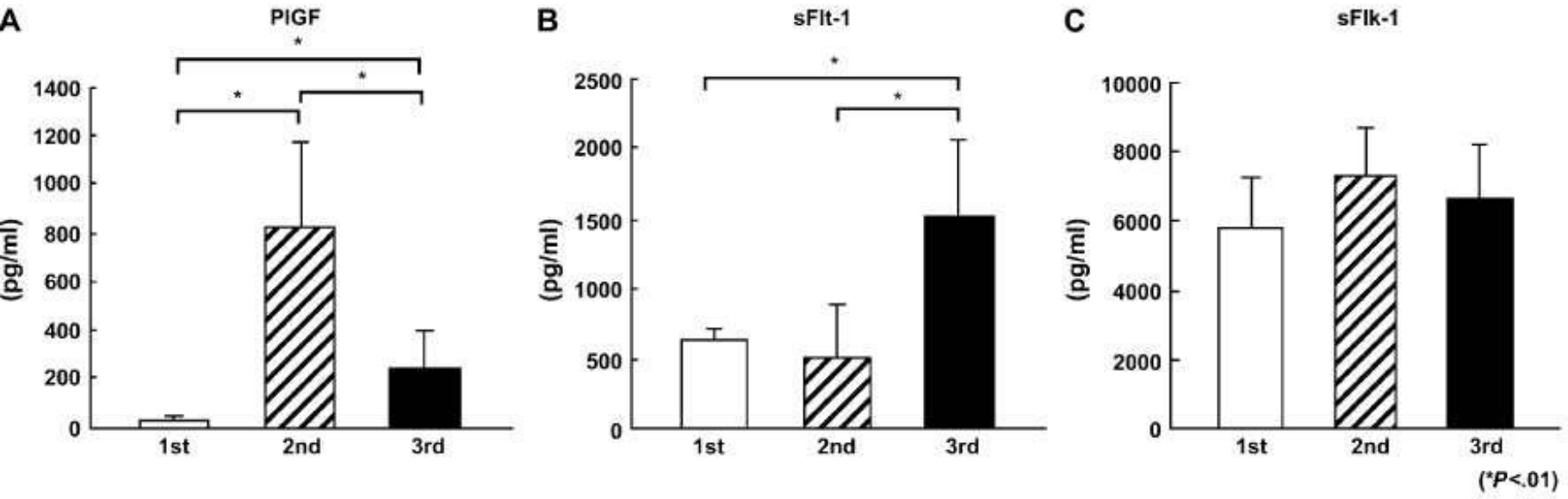
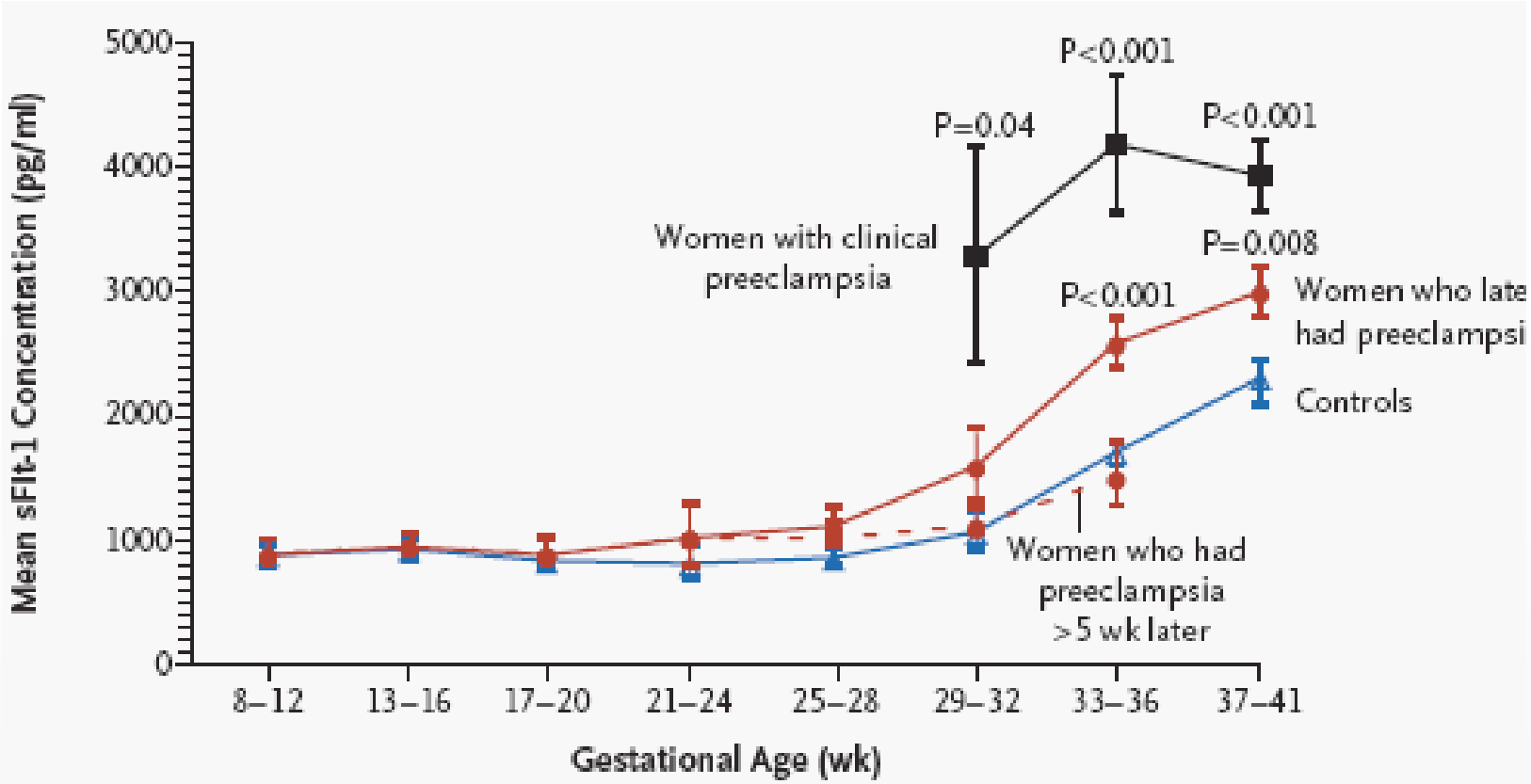


Figure 1 Serum levels of angiogenic factors **(A)** PlGF, **(B)** sFlt-1, and **(C)** sFlk-1 during normal pregnancy. Values are shown as mean ± SEM and the asterisks indicate $P < .01$.

Angiogenic Markers

Mean sFlt-1 concentration and gestational age



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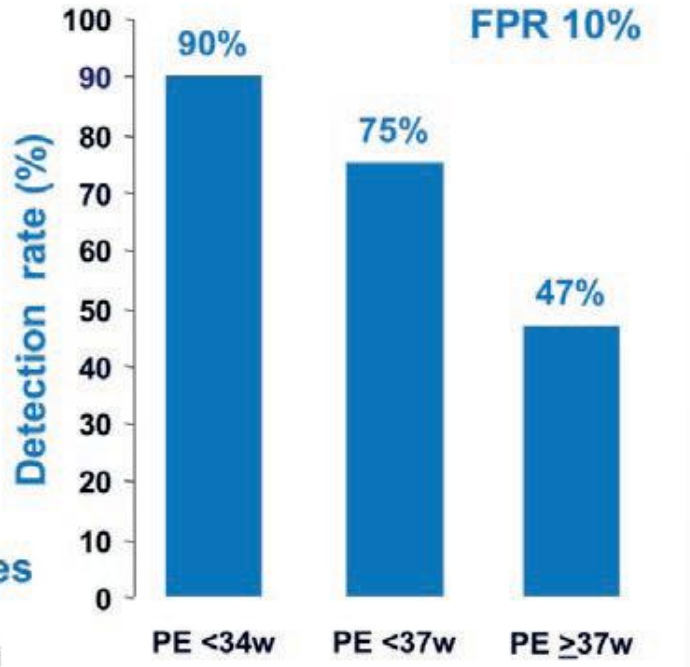
Prediction of Preeclampsia

Fetal Medicine Foundation

Maternal risk factors

- Age: every 10 years above 30 y
- Weight: every 10 kg above 70 kg
- Racial origin
  - Afro-Caribbean
  - South Asian
- Obstetric history
  - First pregnancy
  - Previous preeclampsia
- Family history of preeclampsia
- Conception by IVF
- Chronic hypertension
- Diabetes mellitus
- Autoimmune : SLE / APS

Screening in 35,948 pregnancies



AJOG American Journal of Obstetrics & Gynecology

O' Gorman et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks. Am J Obstet Gynecol 2016; 214: 103

- **History** + **MAP** (Mean Arterial Pressure) + **Uterine Artery PI**
- + Biochemical Markers
  - **PAPP-A (**Pregnancy Associated Plasma Protein A)
  - **PlGF** (Placental Growth Factor)

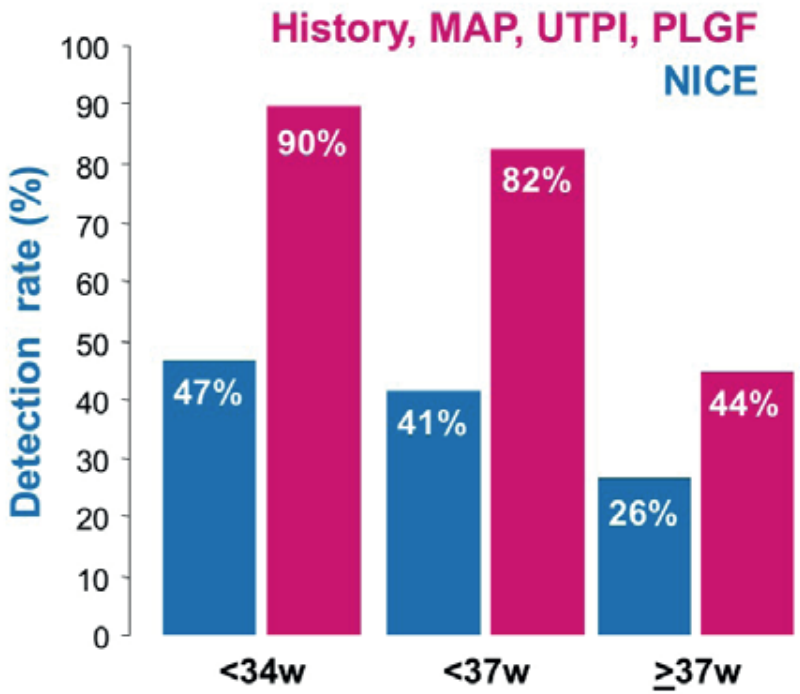
Prediction of Preeclampsia

Validation of FMF Algorithm: SPREE Study Versus NICE

Screening for Preeclampsia

- 7 NHS hospitals in England
- Routine screening at 11-13 w
- Non-intervention study
- 16,747 singleton pregnancies
- Comparison of NICE vs. FMF
- Coordinated by UCL CCTU

National Institute For Health Research
Efficacy and Mechanism Evaluation Programme



ULTRASOUND in Obstetrics & Gynecology

Tan *et al*. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. Ultrasound Obstet Gynecol2018, doi: 10.1002/uog.19039.

Multicenter study funded by British government; Non Intervention Study

Combined test performed, without giving results to the patients or managing clinicians

NICE guidelines: Screen positive rate of 10%, : overall detection rate of all pre-eclampsia was about 30%

Prediction of Preeclampsia

Measurement of Mean Arterial Pressure

Automated devices (3BTO-A2; Microlife)

Doctors with appropriate training

Seating position, with arms supported at the level of the heart

Appropriate Cuff: small (<22 cm), normal (22-32 cm) or large (33-42 cm)

Rest for 5 min

Two recordings of blood pressure were made in both arms simultaneously.

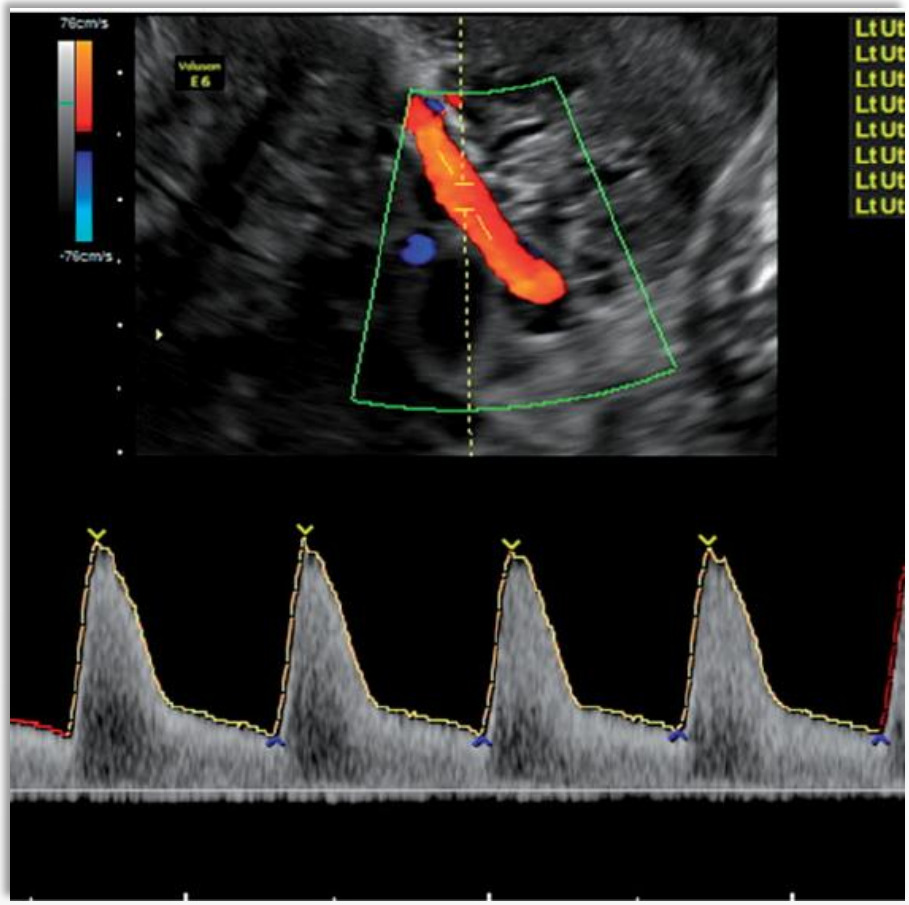
Final MAP calculated as the average of all four measurements

- Prediction Rate; heterogeneous population (nulli/multiparous); Early and late preeclampsia 58% and 44%, (5% FP)

Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH: Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. Fetal Diagn Ther 2012;31:42-48.

Prediction of Preeclampsia

Doppler of the Uterine Arteries; Unselected Population; Isolated Marker



Second Trimester (23w); Early PE Prediction

Increase UA resistance: sensitivity 42.8%

No clinical applicability for screening test

First trimester (11-14w) Early & Late PE Prediction;

Detection rate: 59% and 40% (5% FP)

UA Doppler Performance Limits

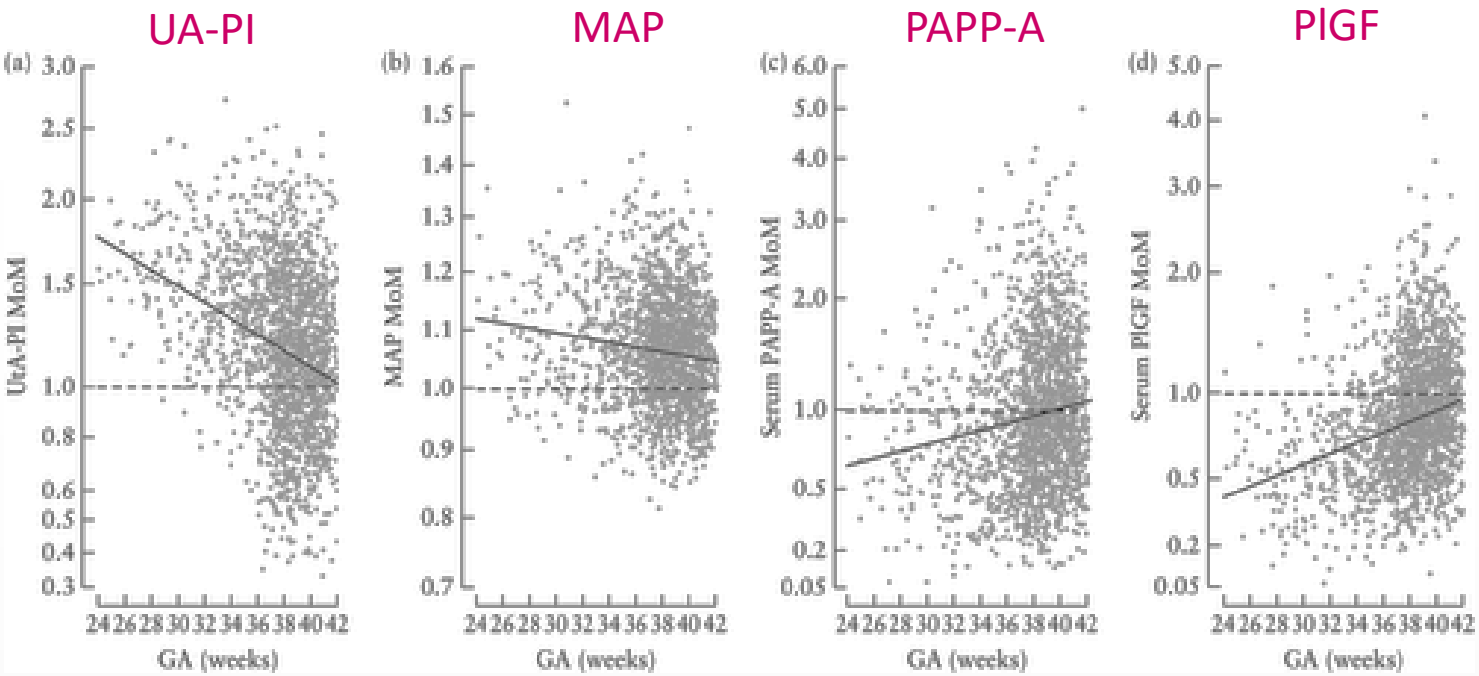
Availability of the ultrasound device, Examiner, Expertise and training

Restricts its use on a large scale

Yu C. K. H., An integrated model for the prediction of preeclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women. *American Journal of Obstetrics & Gynecology*. 2005;193(2):429–436.

Prediction of Preeclampsia

Risk factor Performance according to Gestational Age



All markers showed **more separation at earlier** than later gestations and this is reflected in **their superior performance at detection of early than late PE**

Regression lines for **UtA-PI** and **PAPP-A** intersect 1 MoM close to term and, therefore, these biomarkers **perform poorly in screening for late PE.**

Tan M.Y. et al; Ultrasound Obstet Gynecol 2018; 52 (2) 186-195

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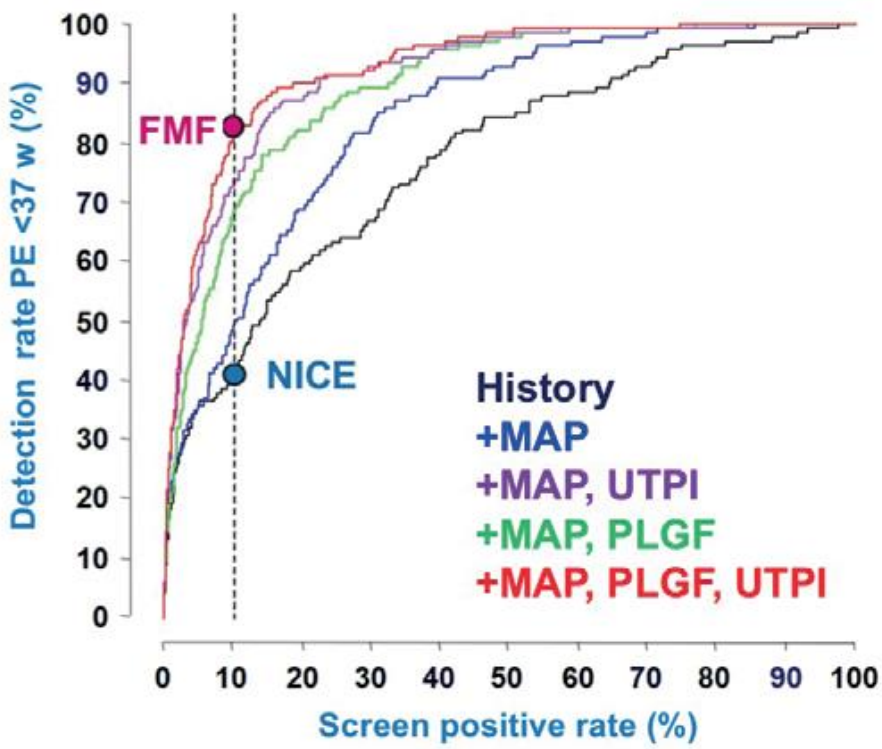
Prediction of Preeclampsia

Performance of each individual marker or combinations of different markers



Tan M.Y. et al; UOG 2018; 52 (2) 186-195

Method of screening	DR %
History	45
+ MAP	51
+ MAP, PAPP-A	56
+ MAP, UTPI	68
+ MAP, UTPI, PAPP-A	68
+ MAP, PLGF	66
+ MAP, UTPI, PLGF	**75**
+ MAP, UTPI, PLGF, PAPP-A	75

Detection of PE < 37 w

Summary of first trimester screening in singleton pregnancies at 11 - 13 weeks

Pregnancies: n = 61174 Preeclampsia: Total: n = 1770 (2,9%); <37w: n = 493 (0,8%)

Best combination: mean arterial pressure, uterine artery pulsatility index and PlGF

PAPP-A did not provide significant improvement to any combination which included PlGF

Software for estimation of patient-specific risk for PE by any combination of biomarkers is accessible freely (www.fetalmedicine.org).

Prediction of Preeclampsia

Cut Off for therapy

Risk assessment

Risk for preeclampsia

Report date	03-06-2019
Examination date	17-04-2019
Gestational age	12^{+2} weeks

40D07B559868BE

Maternal characteristics

Age in years	36.4
Height in cm	164
Weight in kg	71
Racial origin	White
Smoking during pregnancy	No
Family history of preeclampsia	No
Method of conception	Spontaneous
Singleton or twins	Singleton

Medical history

Chronic hypertension	No
Diabetes type I	No
Diabetes type II	No
Systemic lupus erythematosus	No
Anti-phospholipid syndrome	No

Obstetric history

Parity	Nulliparous

Biophysical measurements

Mean arterial pressure	89 mmHg (1.021 MoM)
Uterine artery PI	1.3 (0.768 MoM)
Measurement date	17-04-2019

Biochemical measurements

PLGF	1.07 MoM
Measurement date	18-04-2019

Preeclampsia risk from history only

< 37 weeks: 1 in 143

Preeclampsia risk from history plus MAP, UTPI, PLGF

< 37 weeks: 1 in 556

FMF Risk calculator

Race:

Caucasian

Cut-off:

1:150

HighRisk group:

Beneficial effect of aspirin

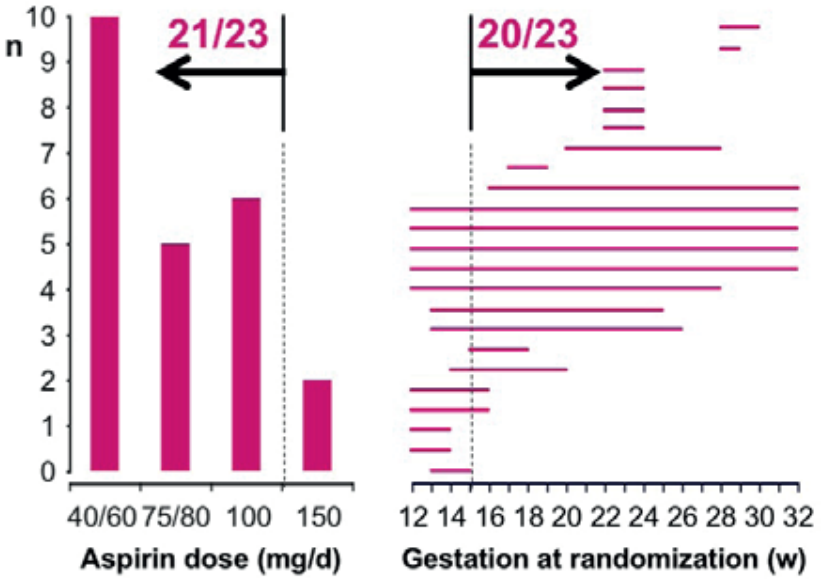
Prevention of Preeclampsia

Aspirin; Meta-Analysis Lancet 2007

Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data

Askie *et al.* Lancet 2007; 369: 1791

- Meta-analysis of individual patient data from **32,217 women in 31 RCTs (aspirin 23)**
- RR for PE: **0.90** (95% CI 0.84-0.97)
- RR for birth <34 w: **0.90** (95% CI 0.83-0.98)

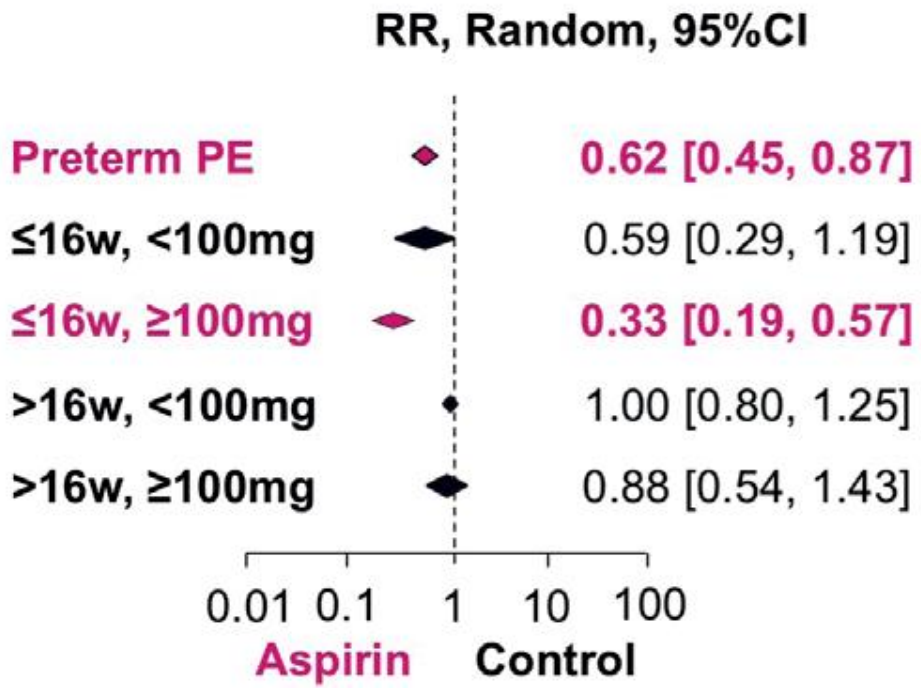


Use of aspirin in high risk women has only a mild or moderate effect in reducing the risk of pre-eclampsia by about 10%

- **Limits**
- Many different selecting criteria of the high-risk group
- 14 different definitions of pre-eclampsia
- **Dose of aspirin varied from 40 to 160 milligrams**
- Starting point of therapy in the majority of the **studies beyond 16 weeks**

Prevention of Preeclampsia

Dose and Timing of Aspirin administration



AJOG American Journal of Obstetrics & Gynecology

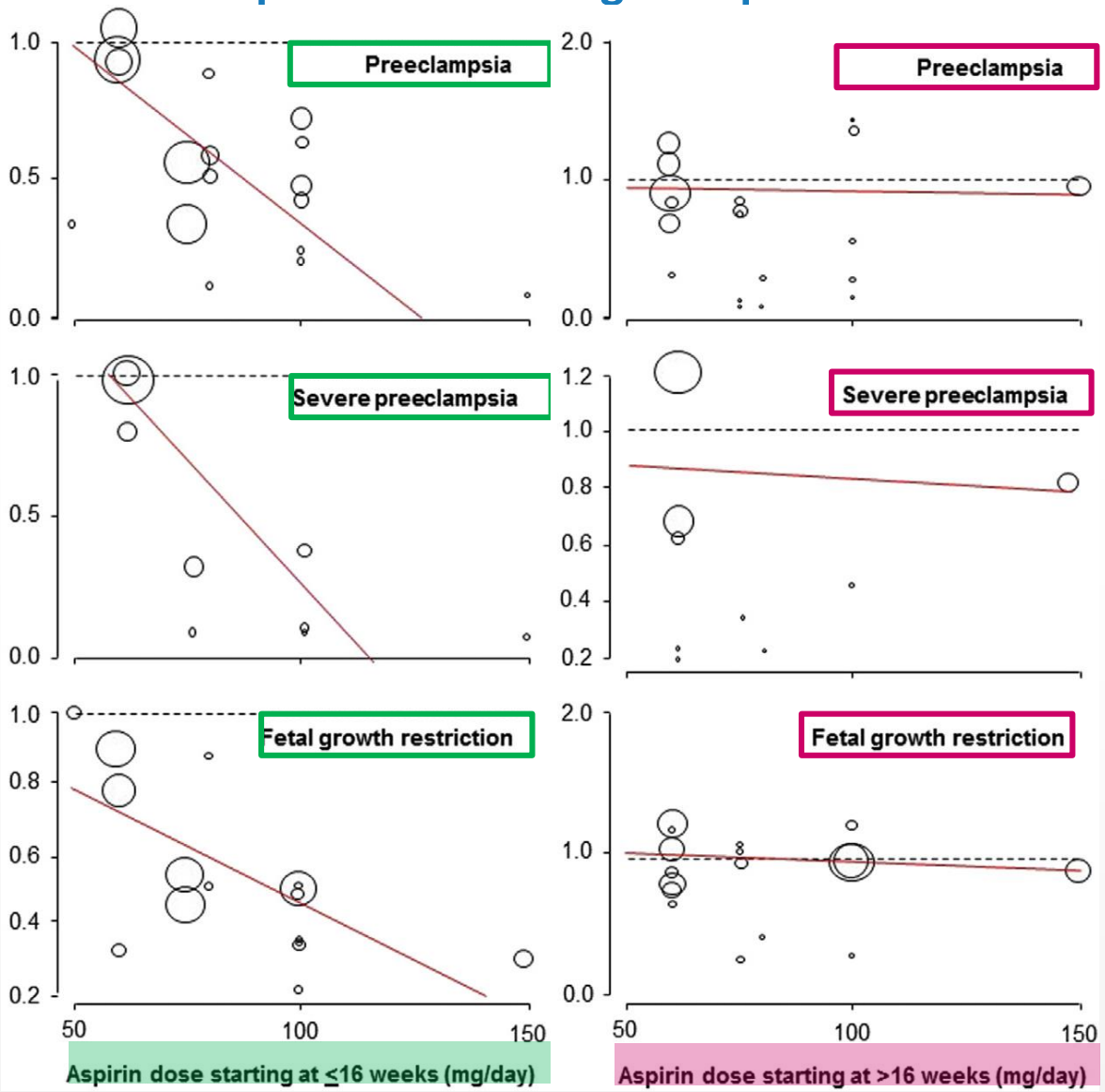
Roberge S, Bujold E, Nicolaides K. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol 2017;pii: S0002-9378(17)32326-8.

Meta-Analisys: 16 studies, 18907 participants

- Aspirin, at less than 100 milligrams, started after 16 weeks, does not reduce the rate of preterm PE
- **Aspirin at a minimum dose of 100 milligrams, and starting before 16 weeks, reduces the rate of preterm PE by 67%.**

Prevention of Preeclampsia

Dose- Response and Timing of Aspirin administration; Relative Risk



Aspirin < 16w:

Significant reduction in the prevalence:

- PE, severe PE, and FGR

Dose-response relationship

Aspirin >16w

No significant effect on the Prevalence:

- PE or FGR

No dose-response relationship

Rationale:

Normal pregnancies

physiological transformation of uterine spiral arteries is completed by 16-18

Term and mild PE

Consequences of other pathologic Maternal processes

Roberge. Aspirin's dose for prevention of PE. Am J Obstet Gynecol 2017.

Prevention of Preeclampsia

funded by EU FP7 ASPRE project

Aspirin; ASPRE Trial 2017

The NEW ENGLAND JOURNAL of MEDICINE

Rolnik DL, Wright D, Poon L, et al. Aspirin versus placebo in pregnancies at high risk of preterm preeclampsia. N Engl J Med 2017;377:613-22.

DOSE: 150 mg / day — **Aspirin resistance: 30% at 81mg and 5% at 160 mg**
Caron et al: J Obstet Gynaecol Can 2009;31:1022-7

START: 12 weeks

FINISH: 36 weeks — **Avoid potential hemorrhage for neonate**

TIME: Bed time — **RCT aspirin 100 mg vs placebo morning, afternoon, night**
Aspirin at night: lower PE, FGR, PTB or IUD
Ayala DE, Ucieda R, Hermida RC: Chronobiol Int 2013; 30:260-279

OUTCOME: — **Preterm PE**

STUDY POPULATION: — **High-risk group defined by FMF algorithm**

Multicenter European Union trial (UK, Spain, Belgium, Italy, Greece)

150 mg: lower doses of aspirin will find high proportions of non-responders

start treatment before

Start < 16w: placentation is completed by 16 weeks, and therapy could act only if it is still ongoing

Stop 36w: brain hemorrhage or other haemorrhagic events for fetus and neonate

Bedtime: greatest effectiveness in prevention of PE achieved if assumed in the evening

Prevention of Preeclampsia

funded by EU FP7 ASPRE project

Aspirin; ASPRE Trial 2017

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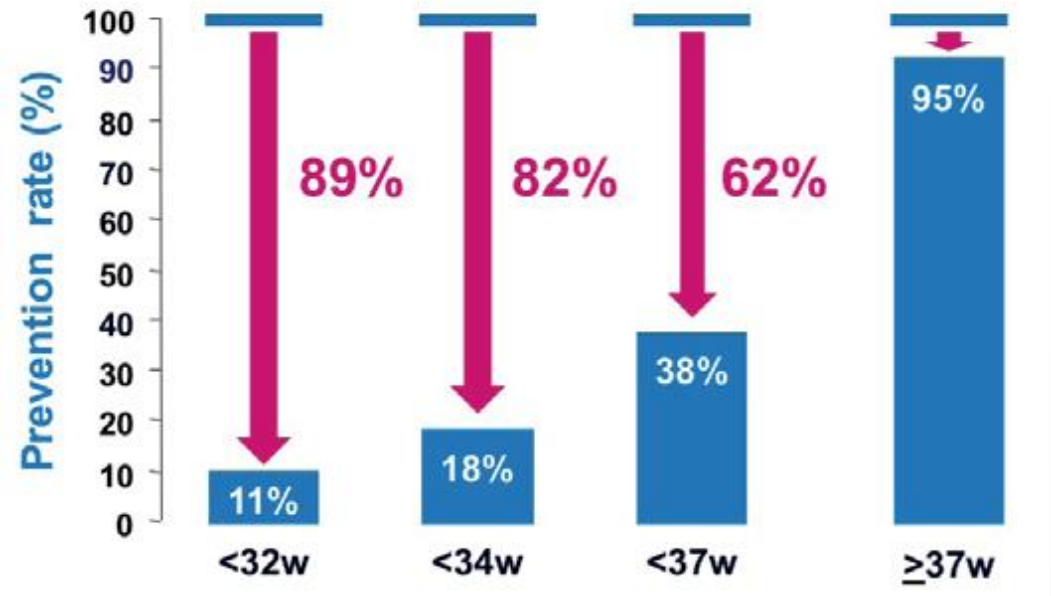


Overall reduction in rate of preterm pre-eclampsia of more than 60%

- **Reduction of early pre-eclampsia <32 weeks of nearly 90%**

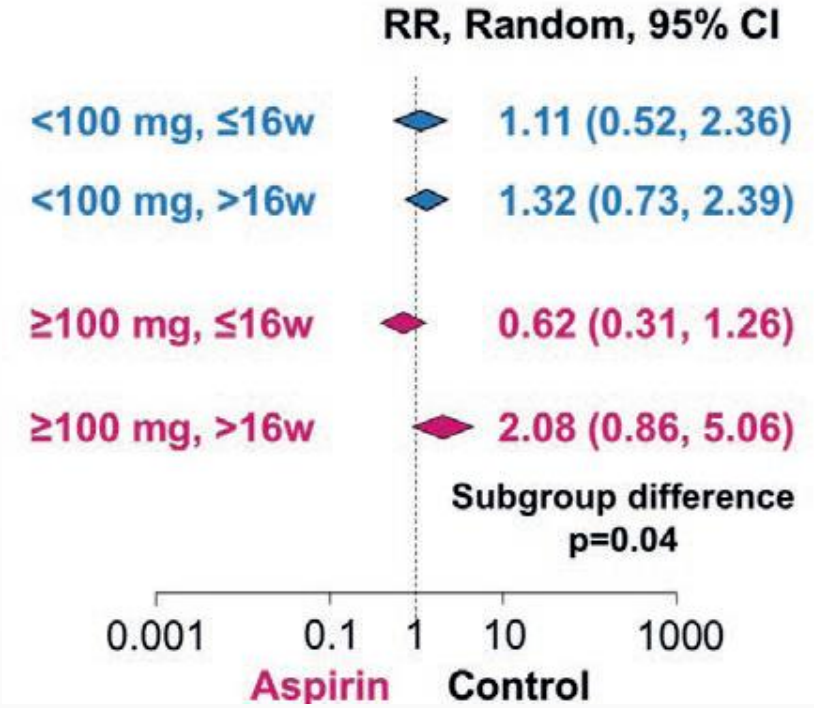
No significant effect on the incidence of term preeclampsia

High Compliance: 71% patients took >90% tablets

Aspirine effect in prevention of PE independent of type of maternal risk factor **unless Chronic Hypertension** *(Poon, AJOG 2017; 217)*

Prevention of Preeclampsia

Side Effects of High Dose Aspirin: Placental Abruptio & Antepartum hemorrhage



AJOG American Journal of Obstetrics & Gynecology

Roberge S, Bujold E, Nicolaides KH. Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage. Am J Obstet Gynecol. 2018; pii: S0002-9378(17)32812-0

Meta-Analisys: 20 studies, 12585 participants

- Aspirin <100 mg/day, given either < or >16w, does not increase the rate of abruption
- **Aspirin > 100mg/day start <16w reduce the risk of abruption whereas if start after 16 weeks increase the risk**

Rationale: Major causes of abruption is impaired placentation

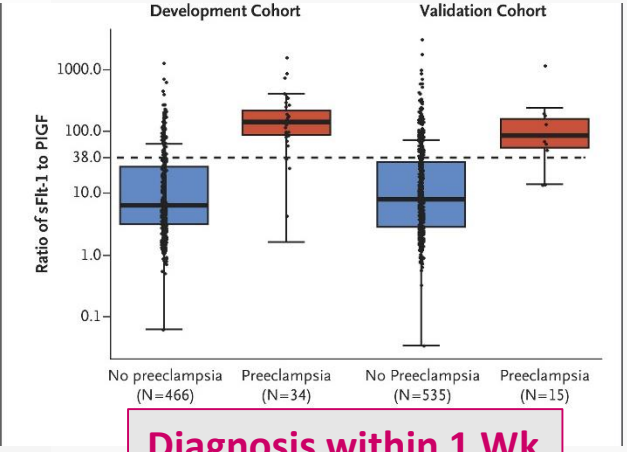
Aspirin started early could prevent abnormal placentation and reduce the rate of abruption

High Dose Aspirin started late in established impaired placentation increase hemorrhagic risk

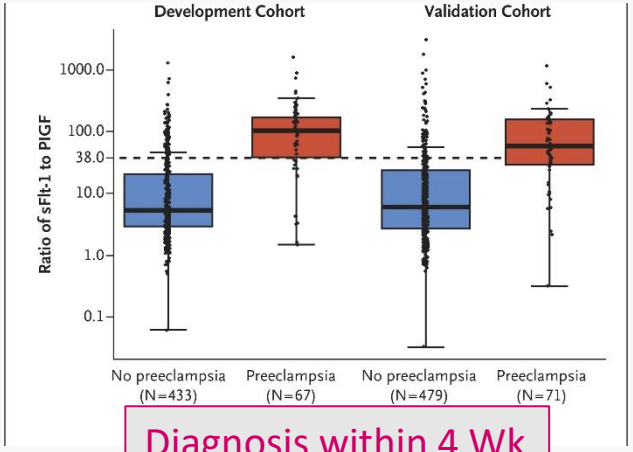
Preeclampsia Predictivity in 2° trimester

sFlt-1 to PlGF Ratio

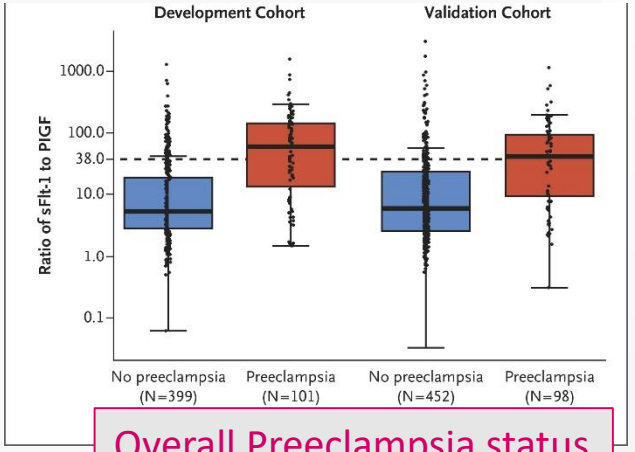
- Index of antiangiogenic activity, that reflects changes in the balance between sFlt-1 & PlGF obviously seen in PE
- **High risk women –sFlt-1/PlGF Ratio higher** at **22-26 weeks** highly predictive of **early onset PE** (<34weeks) **Prediction Rate: about 89%**
- **Twin pregnancies** are associated with 2-3 fold increased risk for PE.
  - sFlt-1 PlGF ratio were twice as high as in singleton



Diagnosis within 1 Wk



Diagnosis within 4 Wk



Overall Preeclampsia status

Preeclampsia Predictivity in 2° trimester

sFlt-1 to PlGF Ratio: Cut Off >38, Prognosis

A single cut-off point for the sFlt-1:PlGF ratio, **independent of the weeks of gestation**, was validated for ruling out PE, eclampsia, and the HELLP syndrome **within 1 week** after assessment of the ratio

Observed PPV value for PE < 1week of the sFlt-1:PlGF ratio was 36.7%

- **Proteinuria** and **measurement of blood pressure** reported PPV of only 20% in detecting PE-related adverse outcomes

sFlt-1:PlGF ratio cutoff point of 38 or lower also had value in predicting the **absence of fetal** (Stillbirth; Delivery <34w; Placental abruption; RDS) **or maternal (**cerebral hemorrhage or thrombosis) **outcomes** within 1 week

Harald Zeisler, M.D.et al: Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia; January 7, 2016 N Engl J Med 2016; 374:13-22

Prediction of Preeclampsia

II Trimester (19-24w) III trimester (30-37w) Risk Reassessment

Please record the following information and then press Calculate.

Pregnancy type

Singleton or twins

Pregnancy dating

Gestational age — weeks — days

Examination date — dd-mm-yyyy

Maternal characteristics

Date of birth — dd-mm-yyyy

Height — cm — ft — in

Weight — kg — lbs

Racial origin

Smoking during pregnancy — Yes / No

Mother of the patient had PE — Yes / No

Conception method

Medical history

Chronic hypertension — Yes / No

Diabetes type I — Yes / No

Diabetes type II — Yes / No

Systemic lupus erythematosus — Yes / No

Anti-phospholipid syndrome — Yes / No

Obstetric history

Nulliparous (no previous pregnancies at ≥24 weeks)

Parous (at least one pregnancy at ≥24 weeks)

Biophysical measurements

Mean arterial pressure — mmHg

Mean uterine artery PI

Date of measurement — dd-mm-yyyy

Biochemical measurements

Includes serum PLGF — No / MoM / Raw data

Includes serum sFLT-1 — No / MoM / Raw data

Calculate risk

FMF Risk calculator

Cut-off:

1:150

HighRisk group:

II trimester

Reassessment of Risk

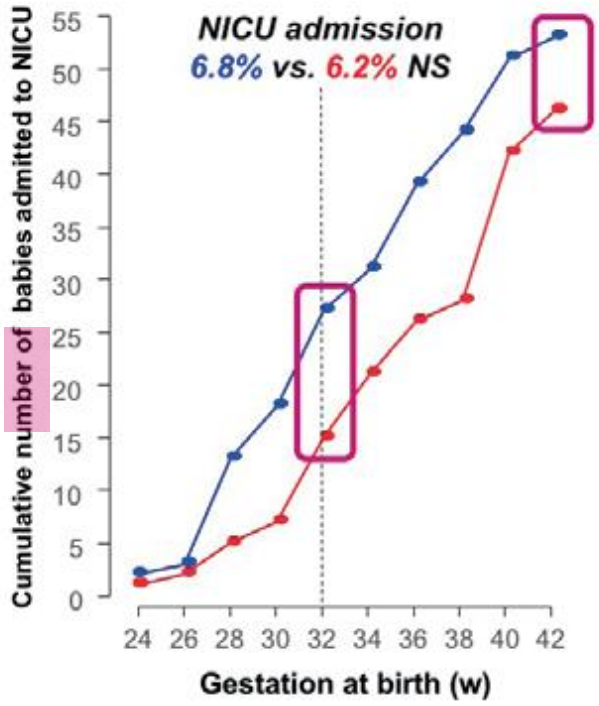
II trimester

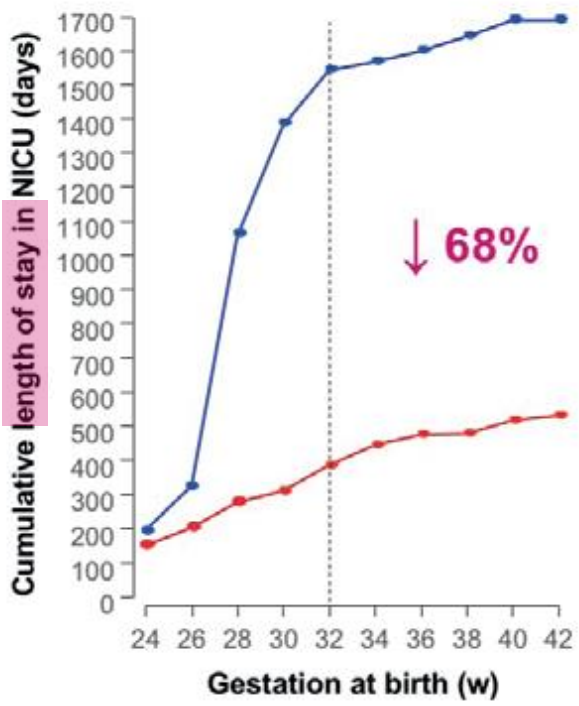
Prediction PE/FGR within 1 week

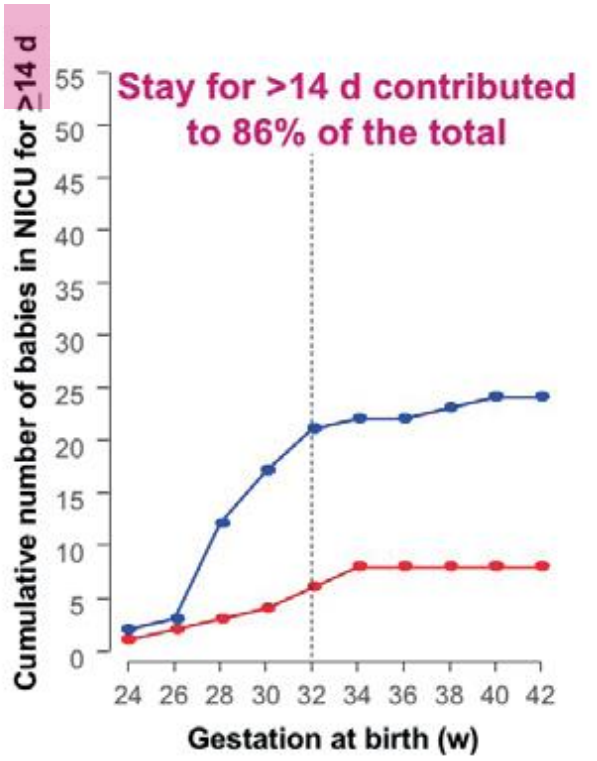
Management

Prevention of Preeclampsia

ASPRE trial: Rate of admission to the Neonatal intensive Care Unit







Total Number of admission in NICU: NS differences in Aspirin treated versus placebo

- Rate of admission of Preterm Babies <32w significantly lower in the aspirin group

Total Length of stay in NICU: 83% arises from Preterm Babies <32w

- Significant 68% reduction in the OVERALL and LONG (>14d) length of stay in NICU for Aspirin group

Wright *et al*. Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. Am J Obstet Gynecol 2018, doi: 10.1016/j.ajog.2018.02.014.

Preeclampsia Prevention

Diet and Supplements

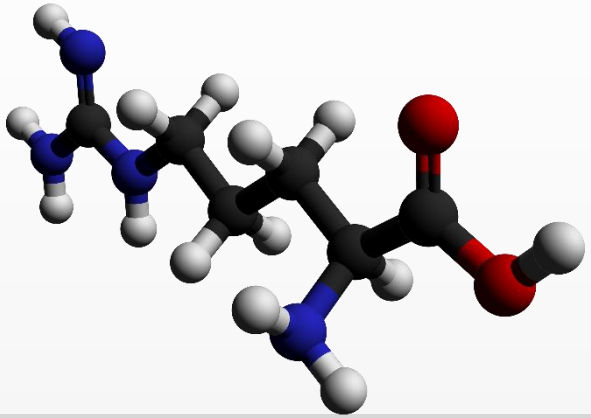
Nitric Oxide Donor

Rationale

- Preeclamptic women may be deficient in nitric oxide (Vasodilation and Inhibits platelet aggregation)

Nitric oxide donors

- Glyceryl trinitrate did not prevent PE
- *Cochrane SR, 2007*



Arginine

Substrate for synthesis of nitric oxide

Reduction in PE (RR: 0.34, 95% CI: 0.21-0.55)

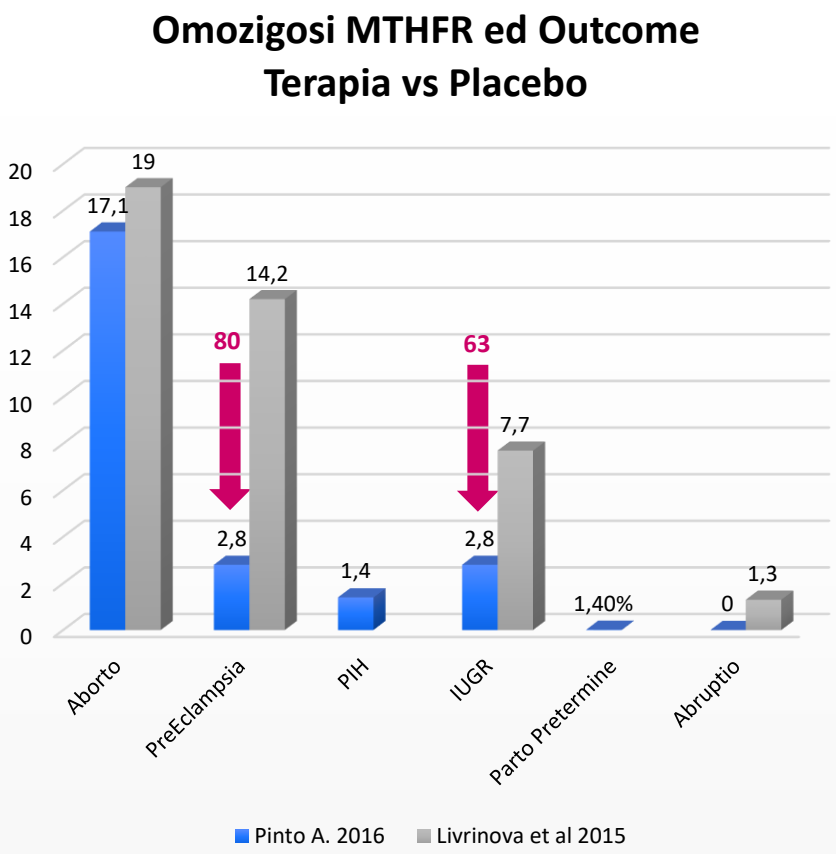
PTL (RR: 0.48 and 95% CI: 0.28 to 0.81).

Dorniak-Wall et al, MA, 2014

Germain AM: evidence supporting a beneficial role for long term L-arginine supplementation in high-risk pregnancies. Hypertension 2004;44:e1)

Prevenzione di Preeclampsia

MTHFR 677 t/t; PE Screening + M.Folato 15 mg + ASA 150 mg NG 5 mg + L Arg



Vesna Livrinova et al. *Factor V Leiden, Prothrombin* and *MTHFR* Mutation in Patients with Preeclamsia, Intrauterine Growth Restriction and Placental Abruption. Maced J Med Sci. 2015 Dec 15; 3(4): 590–594

Studio su 651 gravidanze

MTHFR Omozigote Mutato: 114/651 17,5%

- 15mg MTHF ante-gravidico
- **Associazioni con Trombofilia acquisita:** 18,5%
  - Deficit Prot S/C, AT III, IperHCY

Screening Preeclampsia: 12-14s

- Cut-Off 1:150:
- ASA 150 mg
- **Resistenza Arteria Uterina Elevata** 18,5%
  - Per Uterina PI > 1,35 a 24s e >2,35 a 13s
  - Nitroglicerina TD 5 mg + L-Arginina 3000mg
    - : da 14 o 24s a 34s 61%

- **Aborto 1° Trimestre: *NS*** 17,2%
  - PAI-1 4G/4G: 33,3%
  - Ipotiroidismo secondario: 16,6%

Peripheral Vascular Resistance TVR

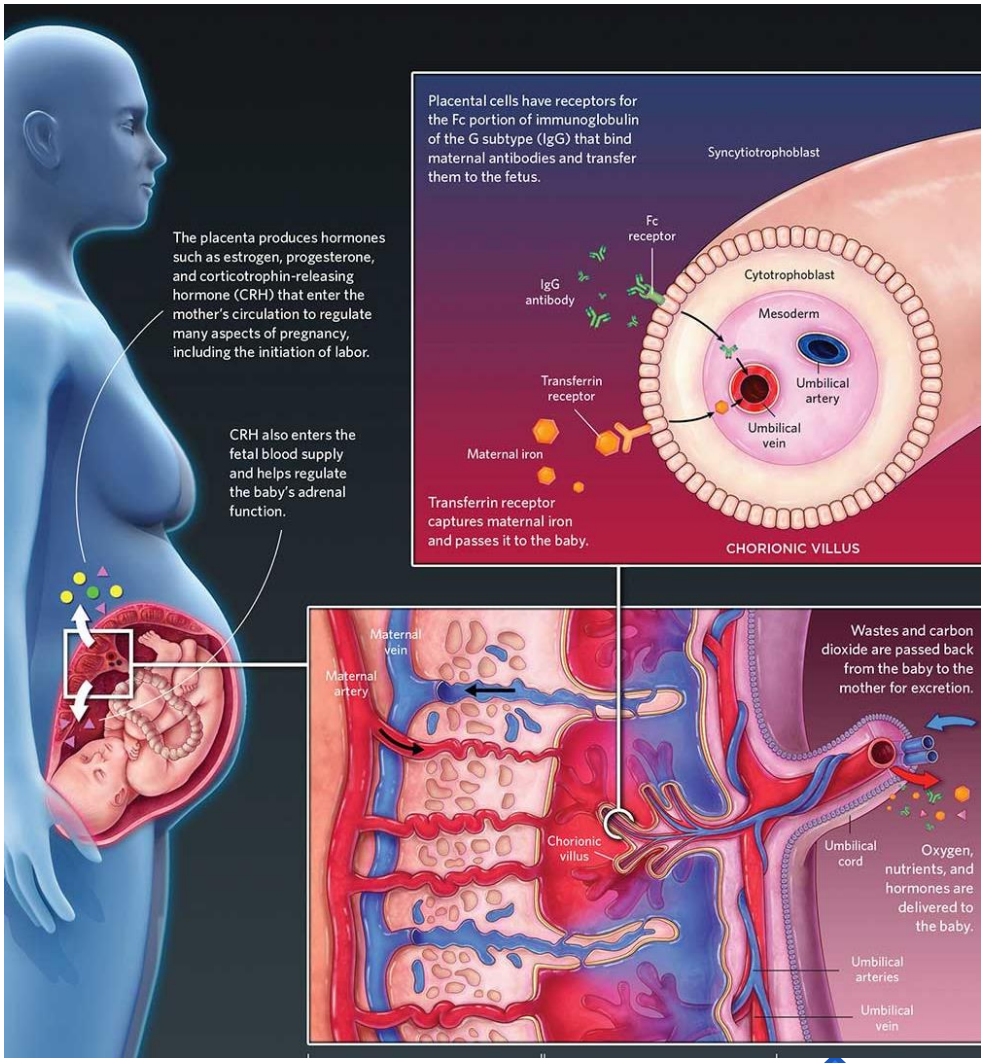
Placental Perfusion

Normal Pregnancy

- Reduction of PVR
  - Trophoblastic Invasion
    - Uterine Arteries Resistance Reduction

PVR in high Risk Pregnancy

1. Predictive factor of abnormal placentation
2. FGR fetus management
   - Hemodynamic maternal factor correction

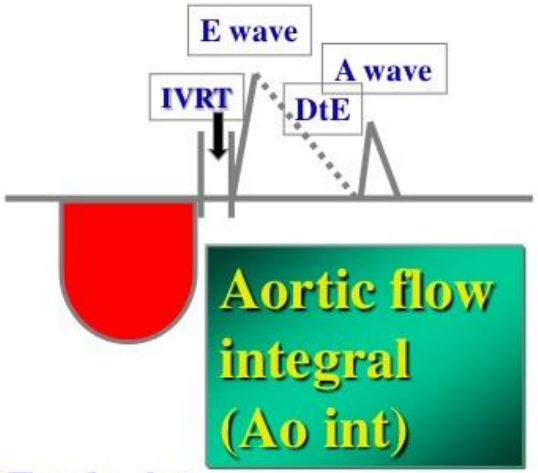


NORMAL PREGNANCY: PVR ↓ **FGR: PVR** ↑

Peripheral Vascular Resistance PVR

Calculation

Echocardiography



Stroke volume (SV)=Area LVOT x Ao int

Cardiac output (CO)=SV x heart rate

Calculation of Total Vascular Resistance:

PVR = (MAP/CO) × 80 *(MAP: mmHg -CO: L/min)*

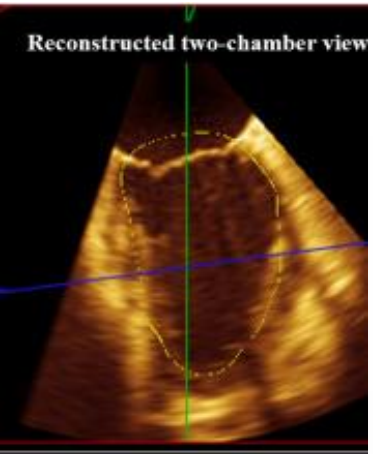
Non-Invasive BioReactance technology to calculate Stroke Volume

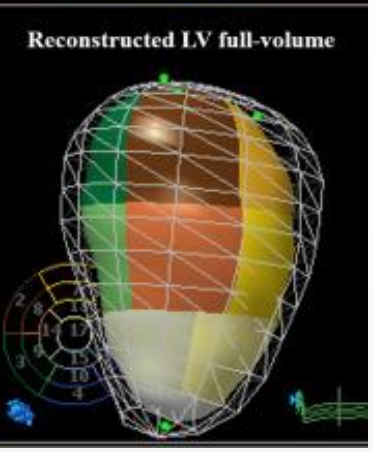
- Recording the relative phase shifts that occur when an alternating electrical current traverses the thorax

Stott D. et al: Ultrasound Obstet Gynecol 2018; 52: 359–364 Maternal hemodynamics in normal pregnancy and in pregnancy affected by pre-eclampsia

Cardiac Output & FGR

Cause of Low CO in FGR





Normal Pregnancy

Initial stimulus = reduction in peripheral resistance

Apoptotic trophoblast cause an **inflammatory response** in the maternal circulation

1. **Tachycardia**
2. **Upregulation of the renin–angiotensin system** and erythropoietin production
3. Lowering of the osmotic threshold for the secretion of ADH

- **Plasma volume thereby increases**, giving increased CO.
- **Early rise in CO** (peaking with a 40–50% increase at around 32w)

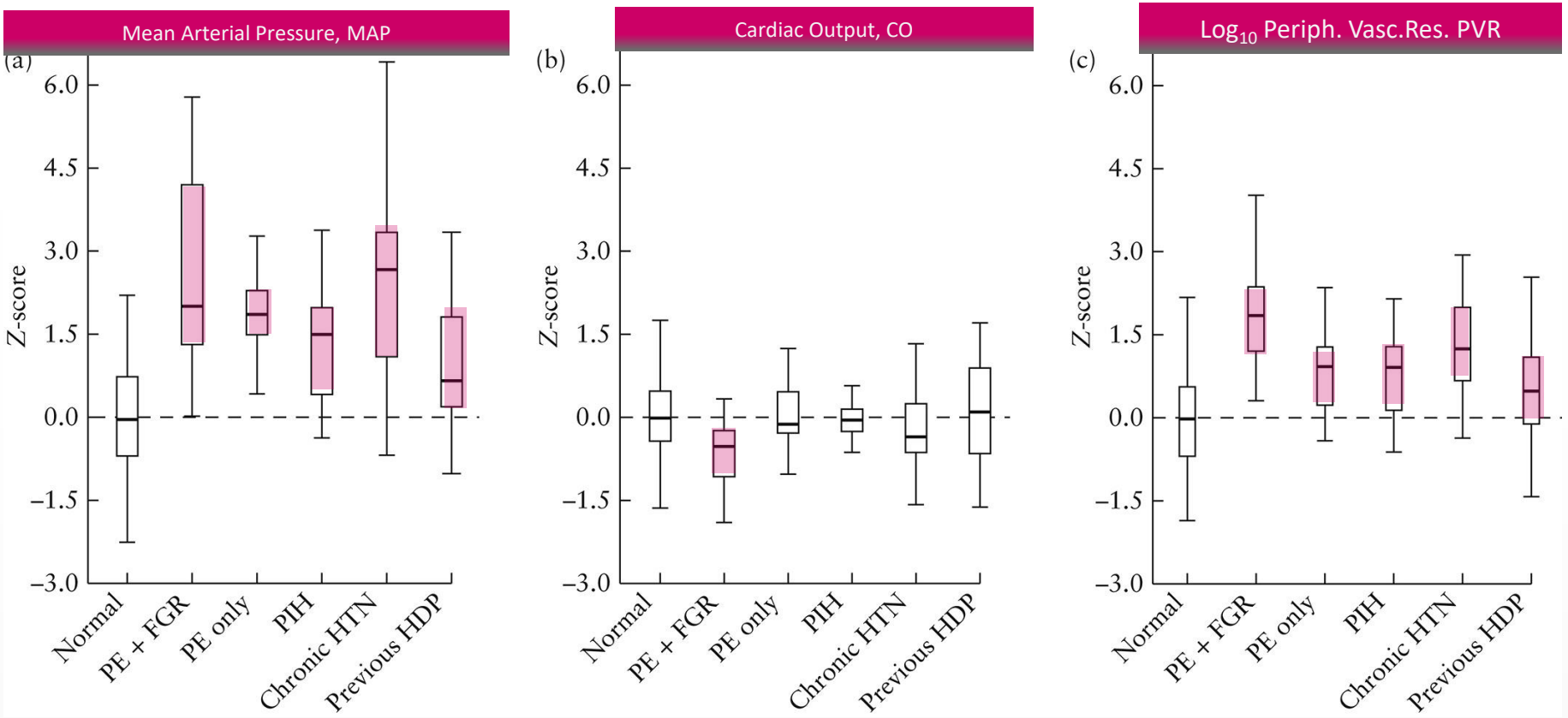
In FGR pregnancies

- Placental apoptosis and/or transfer to the maternal circulation may be impaired
- Maternal cardiovascular response to this stimulus is attenuated.

Stott D. et al: Ultrasound Obstet Gynecol 2018; 52: 359–364 Maternal hemodynamics in normal pregnancy and in pregnancy affected by pre-eclampsia

Maternal Hemodynamics

Preeclampsia +/- FGR Predictivity



Z-scores for **MAP and PVR were significantly higher in all subgroups** of high-risk pregnancies than in the normal-pregnancy

Z-score for **CO** was significantly lower only in the subgroup of women with **PE + FGR** than in all other subgroups

Stott D. et al: Ultrasound Obstet Gynecol 2018; 52: 359–364 Maternal hemodynamics in normal pregnancy and in pregnancy affected by pre-eclampsia

Cardiac Output in First Trimester & FGR

Literature Review

Stott D, et al: Maternal demographics and hemodynamics for the prediction of fetal growth restriction at booking, in pregnancies at high risk for placental insufficiency. **Acta Obstet GynecolScand 2016**; 95: 329–338.

- A study of 126 **high-risk first-trimester** pregnancies found **reduced CO in gestations with FGR**

*Khaw A, Nicolaides KH et al; Maternal cardiac function and uterine artery Doppler at 11–14weeks in the prediction of pre-eclampsia in nulliparous women**. BJOG 2008; 115: 369–376.***

- **Screening study of 534 nulliparous pregnancies** reported **decreased CO at 11–13 weeks' gestation in those delivering small babies**

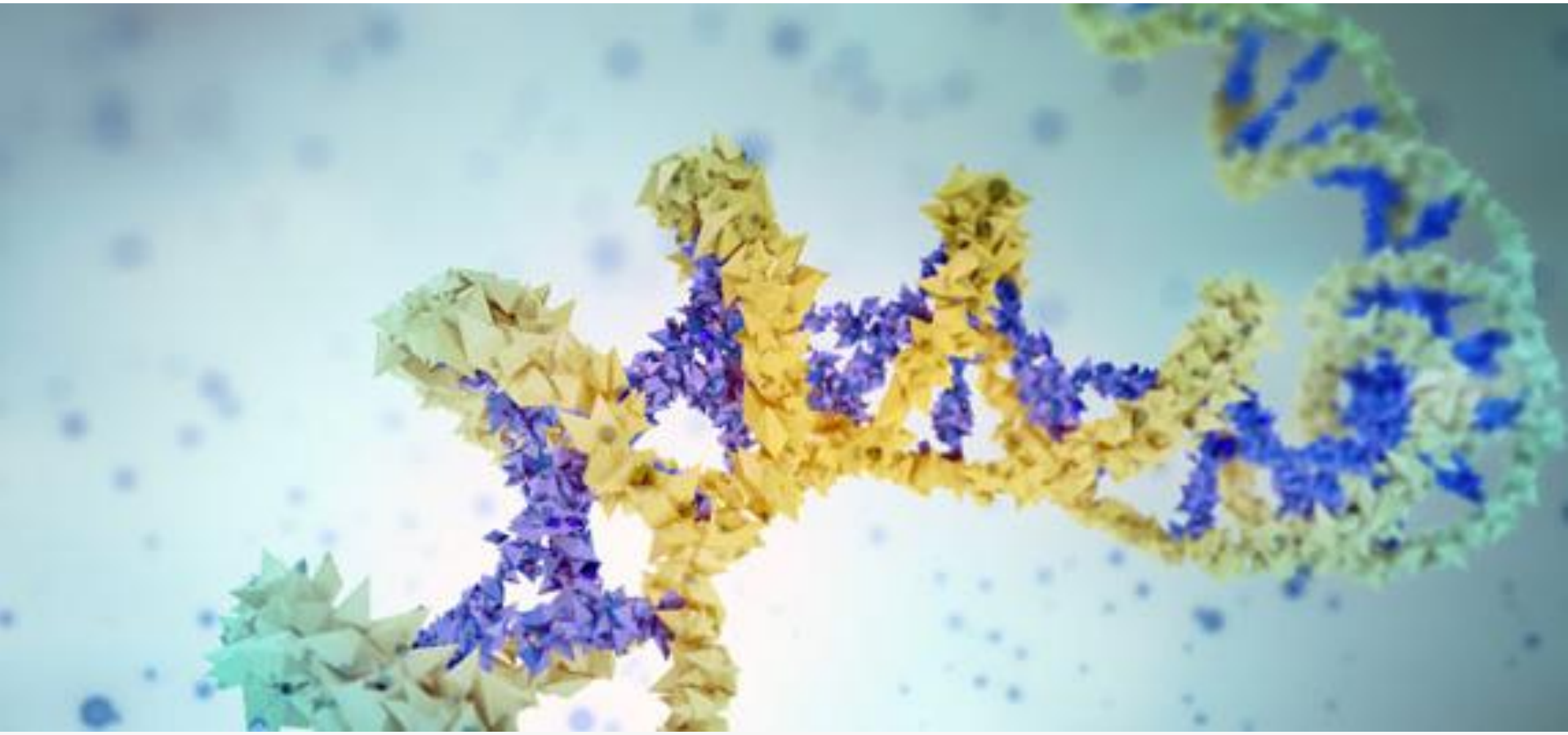
*Valensise H,et al. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease**. Hypertension 2008**; 52: 873–880.*

- 1345 normotensive **mid-trimester** women
- Early-PE being primarily placental in origin
- Late-PE being linked to maternal metabolic factors
  - **Early-PE group**, with a high FGR rate, CO was reduced
  - **Late-PE group,** with a lower FGR rate, CO was increased

Stott D. et al: Ultrasound Obstet Gynecol 2018; 52: 359–364 Maternal hemodynamics in normal pregnancy and in pregnancy affected by pre-eclampsia

Cell Free DNA

Biochemical Predictors



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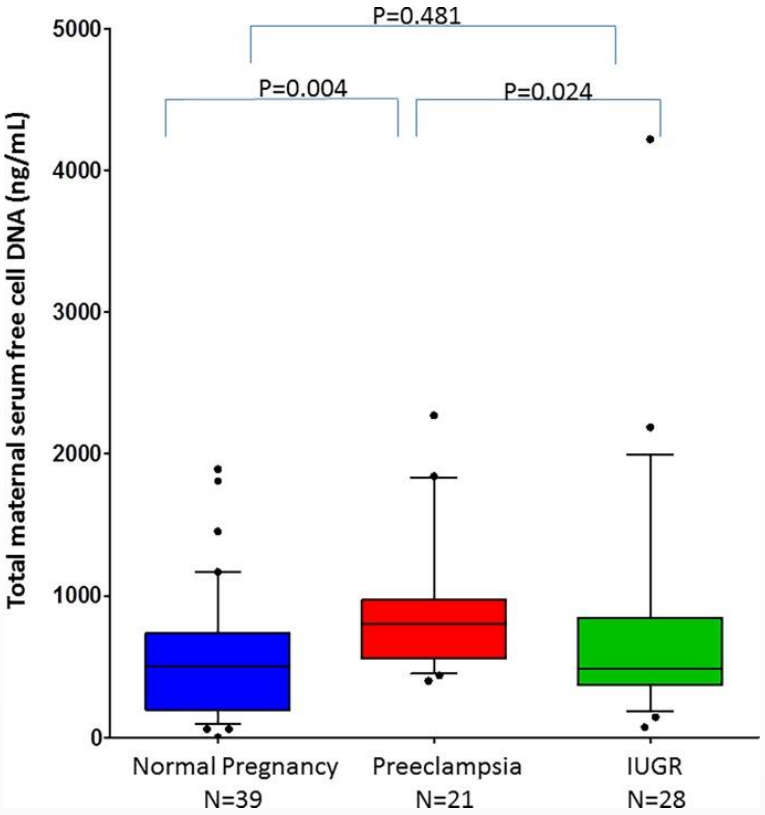
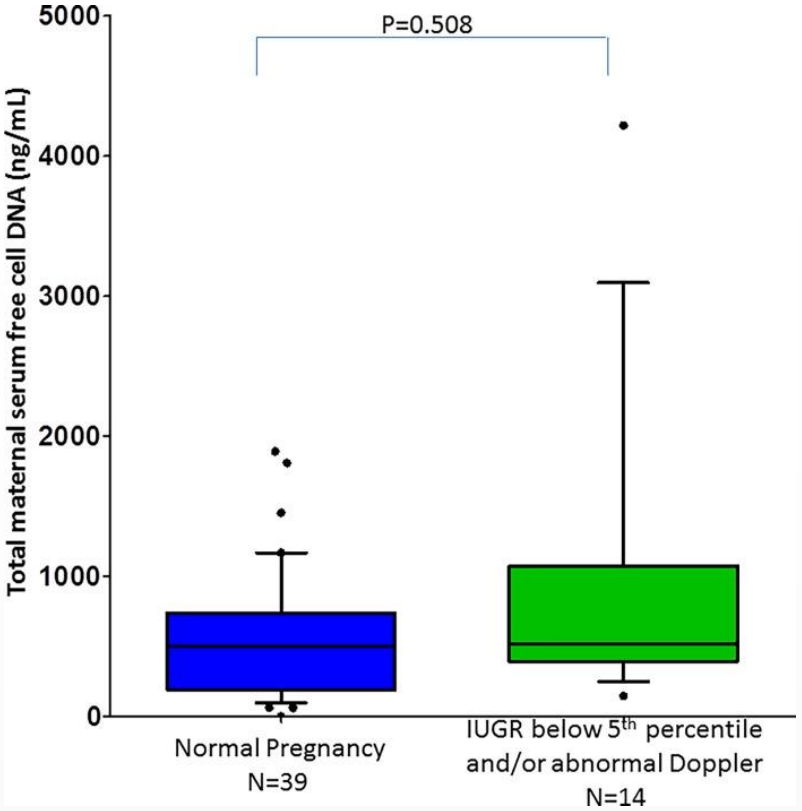
MATERNAL TOTAL cell-free DNA in preeclampsia and fetal growth restriction: Evidence of differences in maternal response to abnormal implantation.

Rafaeli-Yehudai T, et al: PLoS One. 2018 Jul 12;13(7)

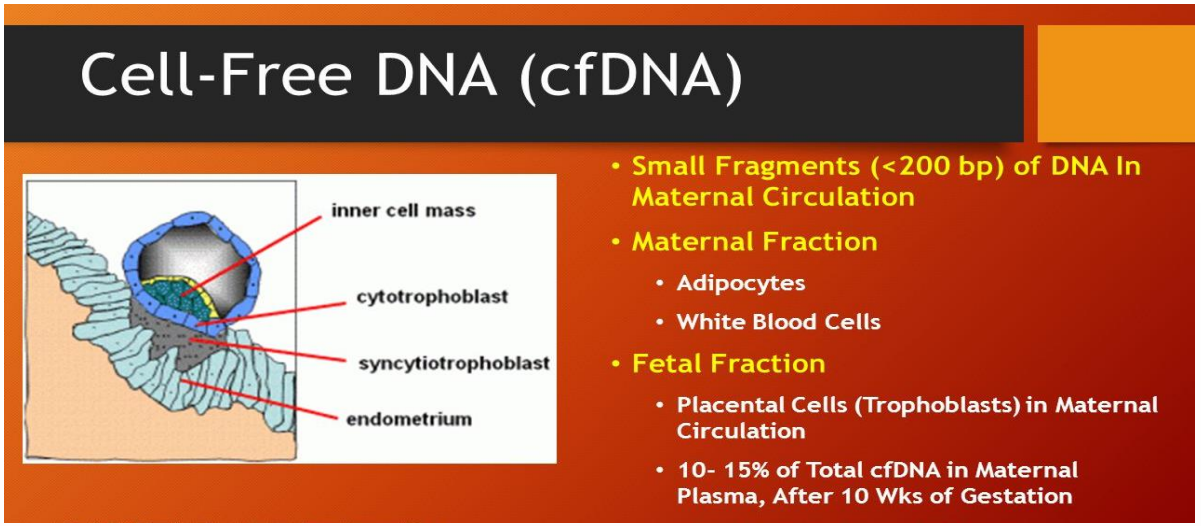




- **Preeclampsia is associated with significative (P=0,004) higher maternal serum t-cfDNA concentration than normal pregnancy or FGR.**
- Rationale: Increased systemic activation of the **maternal inflammation**, rather than placental
  - Placental ischemia, inflammatory nature of the vascular damage, reduced clearance of cfDNA from the maternal circulation
  - Not-significant change (P=0,508) in the maternal serum t-cfDNA in patients with placental-mediated FGR.

Low FETAL fraction of cell-free DNA predicts placental dysfunction and hypertensive disease in pregnancy.

Gerson KD et al: Pregnancy Hypertens. 2019 Apr;16:148-153.



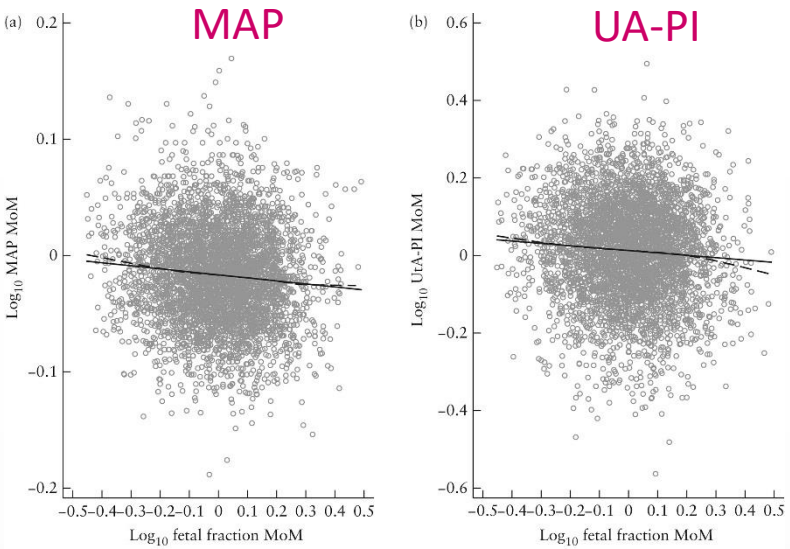
- Low fetal fraction
  - <25th percentile
- Indicators of placental compromise
  - hypertensive disease of pregnancy
  - intrauterine growth restriction
  - abruption, and oligohydramnios

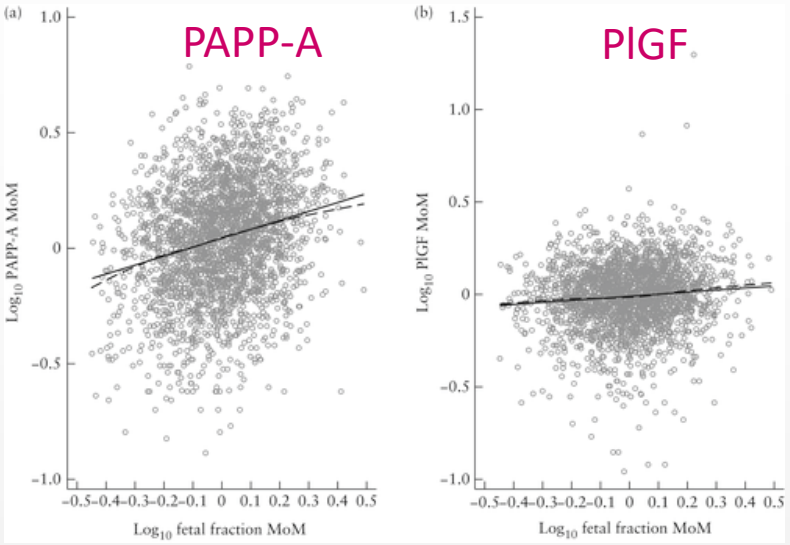
Low fetal fraction was associated with:

- Placental compromise (RR 1.6 [CI 1.1-2.2])
- Hypertensive disease of pregnancy (RR 1.6 [CI 1.003-2.6])
- Preeclampsia with severe features (RR 3.3 [CI 1.2-8.9])

Association between FETAL fraction on cell-free DNA testing and FIRST TRIMESTER MARKERS for pre-eclampsia

D. L. Rolnik et al; Ultrasound Obstet Gynecol. 2018 Dec;52(6):722-727





MAP et Uterine PI inverse correlation with fetal fraction MoM

MAP, Uterine PI

PAPP-A MoM and PlGF MoM had a significant positive association with fetal fraction MoM

PAPP-A, PlGF

mami
woman and fetal care

Association between FETAL fraction on cell-free DNA testing and first-trimester markers for pre-eclampsia

D. L. Rolnik et al; Ultrasound Obstet Gynecol. 2018 Dec;52(6):722-727

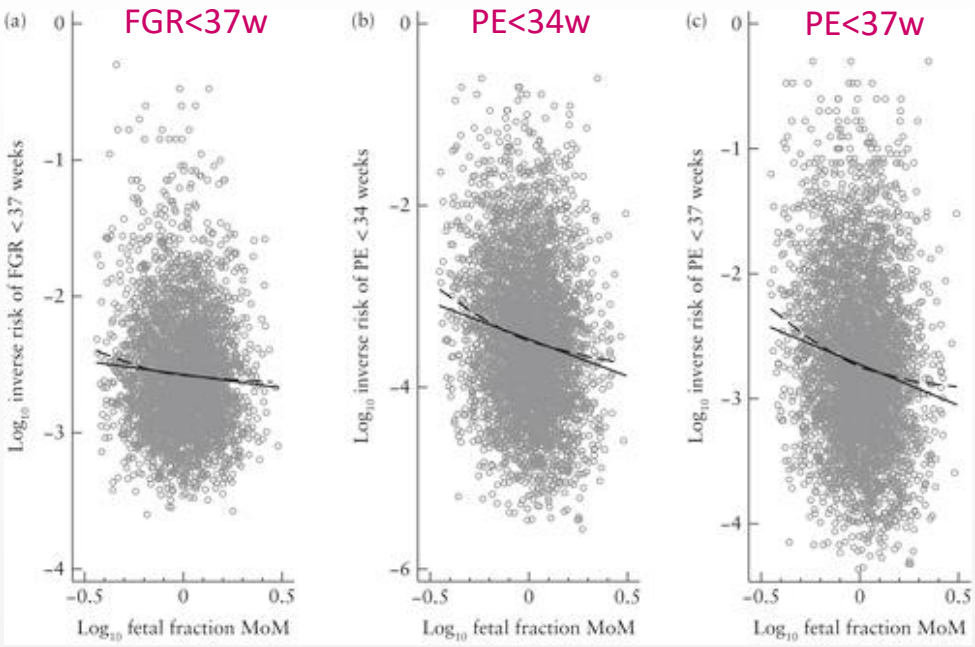
Fetal fraction increases with advancing gest. age, **decreases** in IVF pregnancies and with increased BMI

Release of cell-free fetal DNA would be related to:

- **Size of the placenta** and rate of **Trophoblastic Apoptosis**

Low FETAL fraction on cfDNA testing marker of **poor placental development** and **dysfunction**

- Significant correlation with first-trimester markers for PE and risks for PE and FGR.



Significant (all $P < 0.001$) negative correlation between fetal fraction MoM and inverse risks for:

- PE before 34 weeks
- PE before 37 weeks
- FGR before 37 weeks

Fetal fraction could potentially enhance first-trimester screening for PE, particularly when placental biochemistry is not performed.

Thank you

Questions and answers

Contact information

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