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VIETNAM – FRANCE – ASIA – PACIFIC
CONFERENCE ON OBSTETRICS AND GYNECOLOGY
Ho Chi Minh City, May 19th - 20th, 2016

16th

Is Pre-eclampsia Predictable and Preventable?

Liona Poon

Clinical Associate Professor

MBBS MRCOG MD(Res)

香港中文大學醫學院

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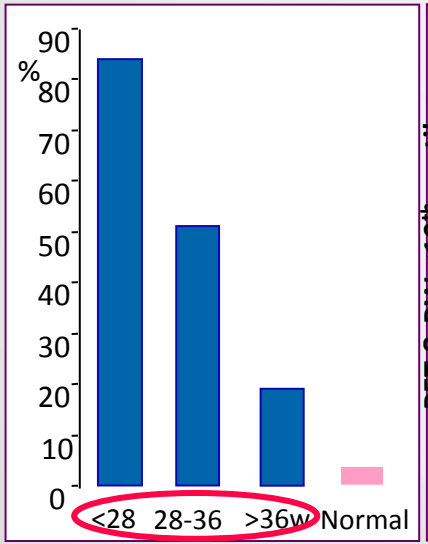
Preeclampsia

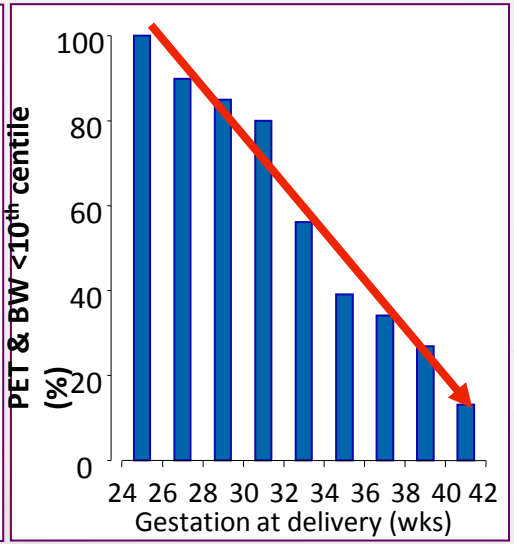
Preeclampsia: Prevalence <34w 0.3%, >34w 2.0%

Decidual arteriolopathy



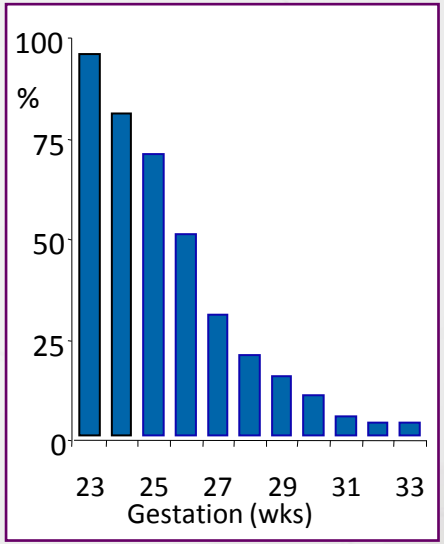
Moldenhauer et al, 2003

Fetal growth restriction

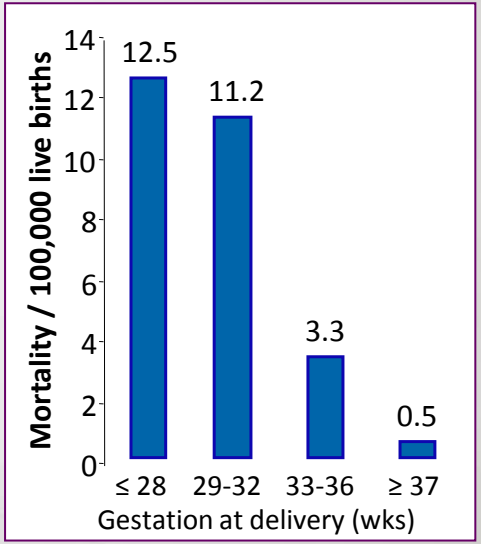


Yu 2007: n=30,775, PET 614 (2%)

Perinatal death



Maternal death



Mortality USA 1979-1992

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Prevention of PE

Low-dose aspirin

Prevention of pre-eclampsia by early antiplatelet therapy
Beaufils M, Uzan S, Donsimoni R, Colau JC, Lancet 1985; 1: 840-2.

- Randomized study
- 102 patients at high risk of PE and/or FGR
- Aspirin 150 mg and dipyridamole 300 mg / day from 12 weeks (group A) vs no treatment (group B)

- Preeclampsia: Group A n=0 vs. Group B n=6
- Fetal death or severe FGR: Group A n=0 vs. Group B n =9

- The treatment did not produce serious adverse effects
- Antiplatelet therapy given early in pregnancy to high-risk patients may protect against PE and FGR

Prevention of PE

Low-dose aspirin

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

Askie LM, Duley L, Henderson-Smart DJ, Stewart LA; PARIS collaborative group. Lancet 2007; 369: 1791-8.

- Meta-analysis of individual patient data from 32,217 women, recruited to 31 randomised trials of PE prevention.

Antiplatelet agents vs. control

- Relative risk of developing preeclampsia: 0.90 (95% CI 0.84-0.97)
- Relative risk of delivery before 34 weeks: 0.90 (95% CI 0.83-0.98)
- Relative risk of serious adverse outcome: 0.90 (95% CI 0.85-0.96)

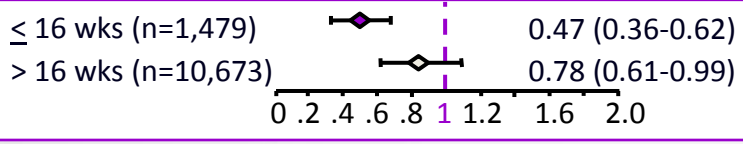
- Antiplatelet agents had no significant effect on the risk of bleeding events for either the women or their babies

Antiplatelet agents during pregnancy are associated with moderate reductions in risk:
of PE, birth <34 weeks and serious adverse outcome

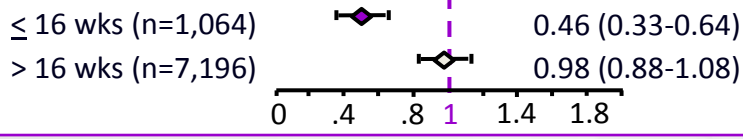
Prevention of PE

Low-dose aspirin

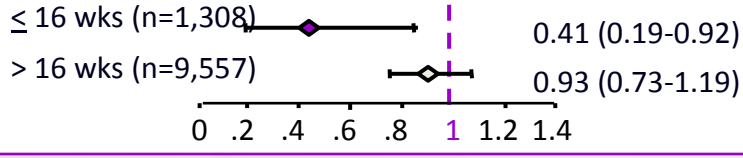
Preeclampsia



Fetal growth restriction

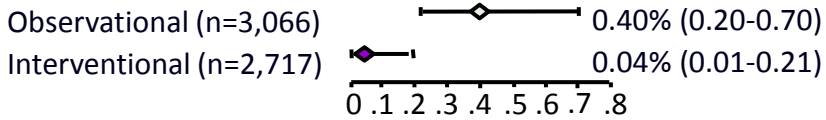


Perinatal death



Bujold *et al.,* 2010; Roberge *et al.,* 2013

Early preeclampsia



Park et al., 2015

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Prevention of PE, SGA, IUD

Low-dose aspirin

funded by EU FP7 ASPRE project

CU Medicine HONG KONG

Study design

DOSE:	**150 mg**	**Aspirin resistance: 30% at 81mg, 10% at 121 mg and 5% at 160 mg** Caron et al: J Obstet Gynaecol Can 2009;31:1022-7
START:	**12 weeks**	
FINISH:	**36 weeks**	**Avoid potential haemorrhage for neonate**
TIME:	**Bed time**	**RCT aspirin 100 mg vs placebo morning, afternoon, night** **Aspirin at night: lower incidence of composite of PE, FGR, PTB, IUD** Ayala DE, Ucieda R, Hermida RC: Chronobiol Int 2013; 30:260-279
OUTCOME:		**Preterm PE, FGR, IUD**
STUDY POPULATION:		High-risk group defined by FMF algorithm

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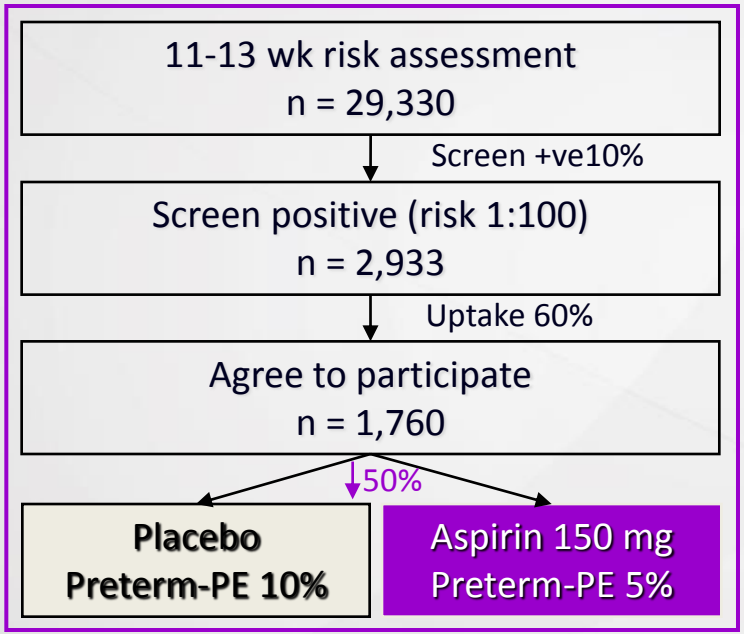
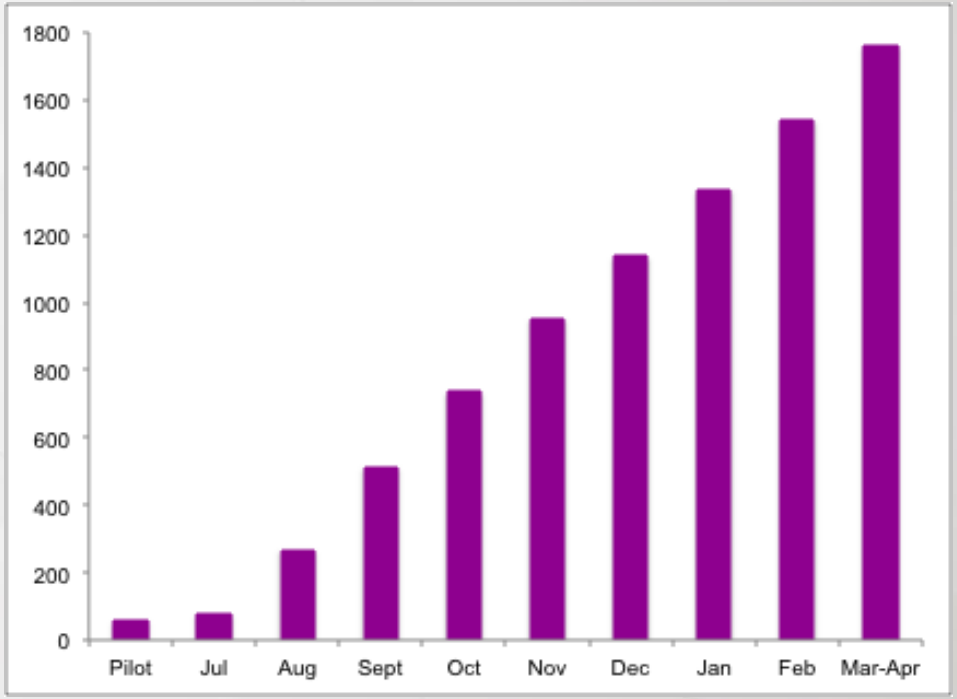
Prevention of PE

Low-dose aspirin



Primary outcome: **Preterm PE (<37w)**



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Prevention of PE

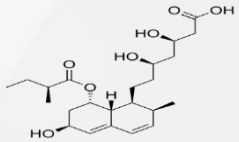
Pravastatin

PE shares biological & pathological similarities as well as risk factors with adult cardiovascular diseases

↓ cytokine-mediated release of sFlt-1 & sEng

↑ NO bioavailability
↑ VEGF & HO-1 expression

Pravastatin



HMG-CoA reductase inhibitor
"A class of lipid-lowering drug"

Mobilises endothelial progenitor cells that protect endothelium & reducing inflammatory & oxidative insults

A hydrophilic statin & poorly crosses the placenta
It has favourable safety & pharmacokinetic profiles

Ahmed A, Cudmore MJ. Can the biology of VEGF and heme oxygenases help solve preeclampsia? Biochem. Soc. Trans. 2009; 37:1237–42.
Brownfoot F, Tong S, Hannan N, Binder N, Walker S, Canon P, Hastie R, Onda K, Kaitu'u-Lino T. Effects of Pravastatin on Human Placenta, Endothelium, and Women With Severe Preeclampsia. Hypertension 2015 66:687-697

Prevention of PE

Pravastatin

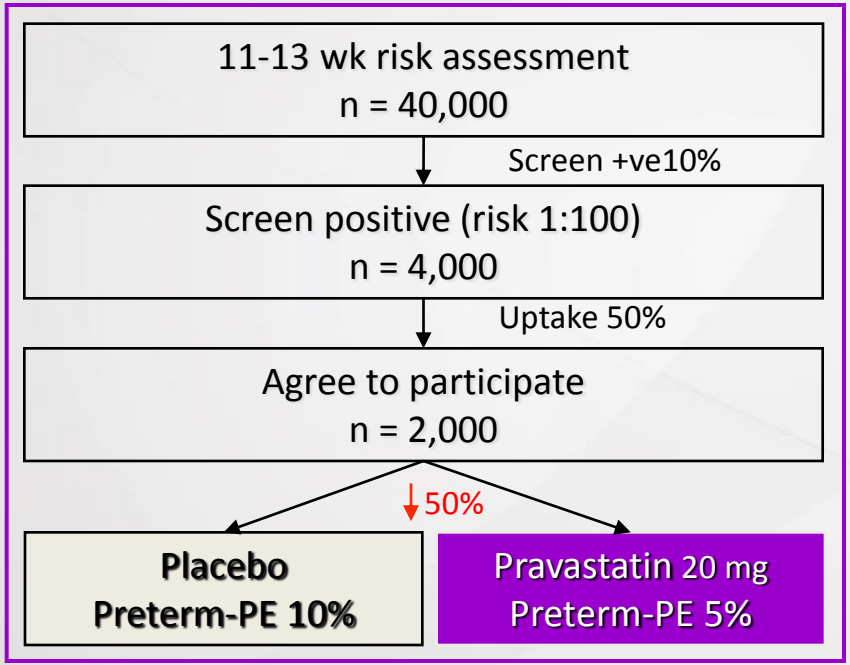
- Multicentre
- Double-blind RCT
- Aug 2012 to Feb 2014
- Pregnant women with prior severe early onset PE
- Randomised at 12-16 wk

Events	Placebo (n=10)	Pravastatin 10mg (n=11)*
Heartburn	3 (30)	4 (36)
MSK pain	1 (10)	4 (36)
Dizziness	2 (20)	3 (27)
Chest pain	0	2 (18)
Diarrhoea	1 (10)	2 (18)
Headache	3 (30)	2 (18)
Cough	1 (10)	2 (18)
Swelling	0	2 (18)
Nausea	1 (10)	1 (9)
Fever	2 (20)	1 (9)
Fatigue	0	1 (9)
Wheezing	0	1 (9)
Vomiting	1 (10)	0
Influenza-like symptoms	2 (20)	0
Preeclampsia	4 (40)	0

*one case of withdrawal

Prevention of PE

Pravastatin



Primary outcome:

Preterm PE (delivery <37 wks)

Secondary outcome:

- **Adverse outcome at <37 wks**
- **Adverse outcome at <34 wks**
- **Adverse outcome at ≥37 wks**
- **Composite neonatal morbidity**
- **Neonatal birthweight <3rd, 5th & 10th**
- **IUD or NND**
- **Spontaneous preterm delivery**

Start date: June 2016

Prediction of PE

- Determine prior risk (in Down's maternal age)
- Define the disease (in Down's T21)
- Identify and quantify biomarkers (in Down's NT, hCG, PAPP-A & PLGF expressed as MoMs)
- Propose models of screening and intervention (in Down's 1st trimester combined screening followed by cfDNA testing and CVS)

Prediction of PE

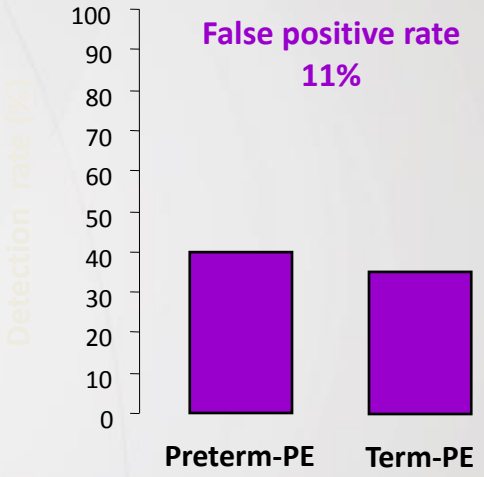
NICE guidelines 2010

High risk factors

- Hypertensive disease in a previous pregnancy
- Chronic renal disease
- Chronic hypertension
- Diabetes mellitus
- Autoimmune disease such as SLE or APS

Moderate risk factors

- First pregnancy
- Age ≥ 40 years
- Body mass index ≥ 35 kg/m^2
- Inter-pregnancy interval > 10 years
- Family history of preeclampsia



120,492 singleton pregnancies, including 2,704 (2.2%) with PE

Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. Am J Obstet Gynecol 2015; 213: 62.e1-10.

Prediction of PE

ACOG committee opinion 2015

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

Risk factors

- **Preeclampsia in a previous pregnancy**
- **Chronic renal disease**
- **Chronic hypertension**
- **Diabetes mellitus**
- **SLE or thrombophilia**
- **First pregnancy**
- **Age > 40 years**
- **Body mass index ≥ 30 kg/m²**
- **Conception by *in vitro* fertilization**
- **Family history of preeclampsia**

The best and only leader of the world

The best and only approach to screening for preeclampsia should be taking a detailed medical history to evaluate for risk factors. September 2015

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Prediction of PE

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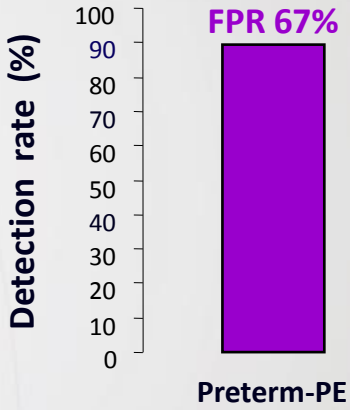

123,406 singleton pregnancies, including 2,748 (2.2%) with PE

Gallo D, Wright D, Casanova C, Campanero M, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and biomarkers at 19-24 weeks' gestation. Am J Obstet Gynecol 2015.

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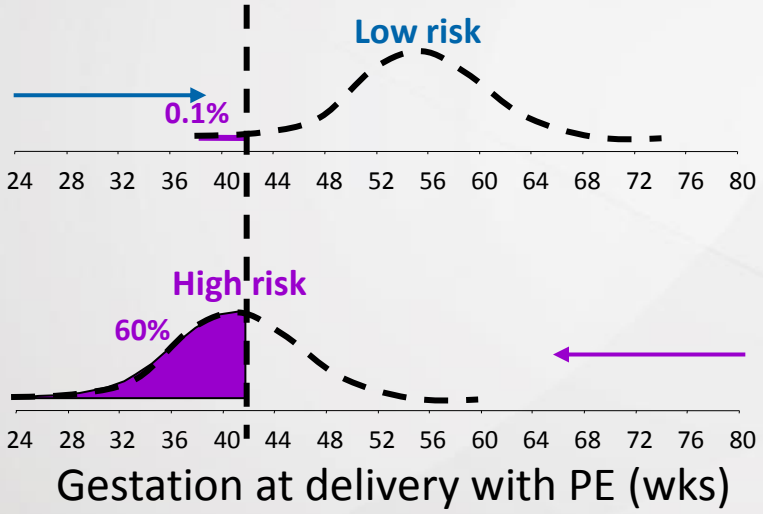
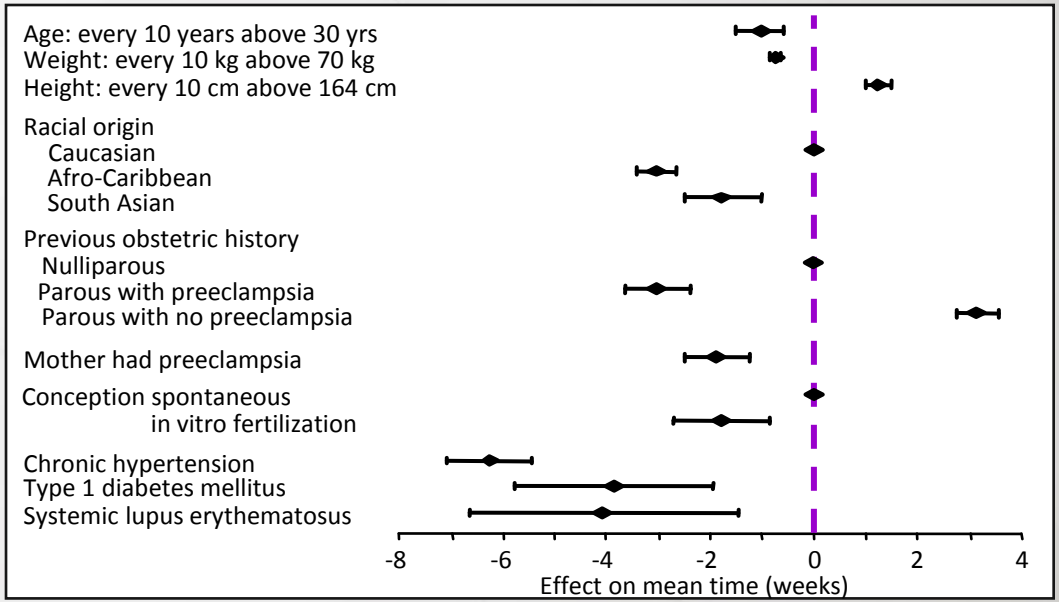
Prediction of PE

FMF algorithm: Prior risk





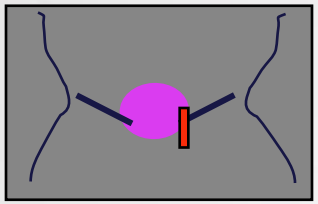
Prediction of PE

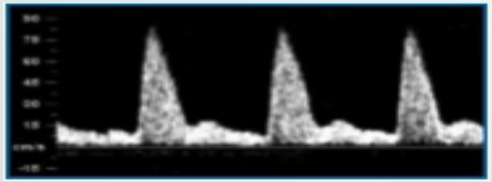
Mean arterial pressure

- Device: Automated (3BTO-A2, Microlife, Taipei, Taiwan), calibrated at regular intervals.
- Method: Women rested for 5 minutes, arms supported at the level of the heart.
- Cuff size: Small (<22 cm), normal (22-32 cm) or large (33-42 cm), depending on the mid-arm circumference.
- Both arms: Take average of two measurements in each arm.

Prediction of PE

Uterine artery PI





1st trimester – transabdominal ultrasound

-Obtain a sagittal section of the cervix and use colour Doppler

-Rotate the transducer from side to side to identify the uterine arteries at the level of the internal cervical os

Sampling gate: 2 mm to cover the whole vessel

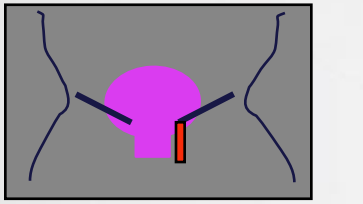
Angle of insonation: less than 30º

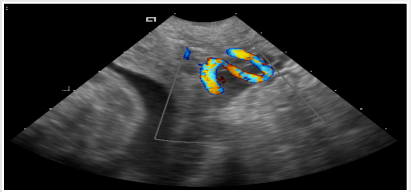
Peak systolic velocity: more than 60 cm/s

Mean PI: average PI (left + right / 2)

Prediction of PE

Uterine artery PI





2nd trimester – transvaginal ultrasound

-Place the women with empty bladder in the dorsal lithotomy position

-Place the probe into the left and right lateral fornix and use colour Doppler to identify the uterine arteries at the level of the internal cervical os

Sampling gate: 2 mm to cover the whole vessel

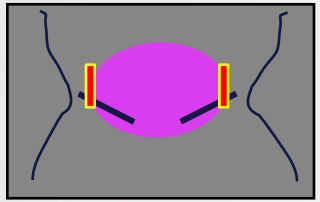
Angle of insonation: less than 30º

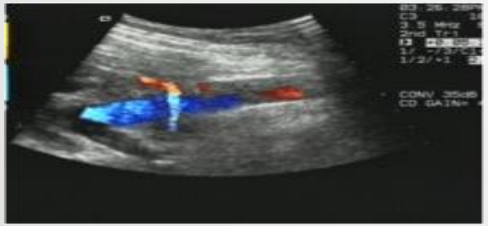
Peak systolic velocity: more than 60 cm/s

Mean PI: average PI (left + right / 2)

Prediction of PE

Uterine artery PI





2nd & 3rd trimester – transabdominal ultrasound

-Use colour Doppler to identify each uterine artery at the apparent crossover with the external iliac arteries

Sampling gate: 2 mm to cover the whole vessel

Angle of insonation: less than 30º

Peak systolic velocity: more than 60 cm/s

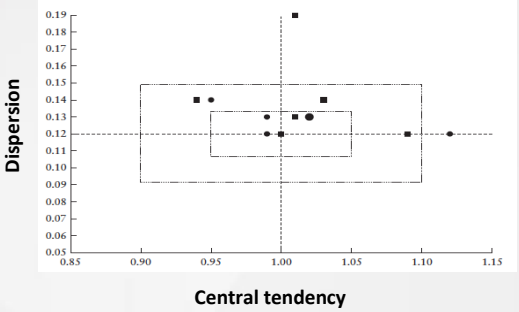
Mean PI: average PI (left + right / 2)

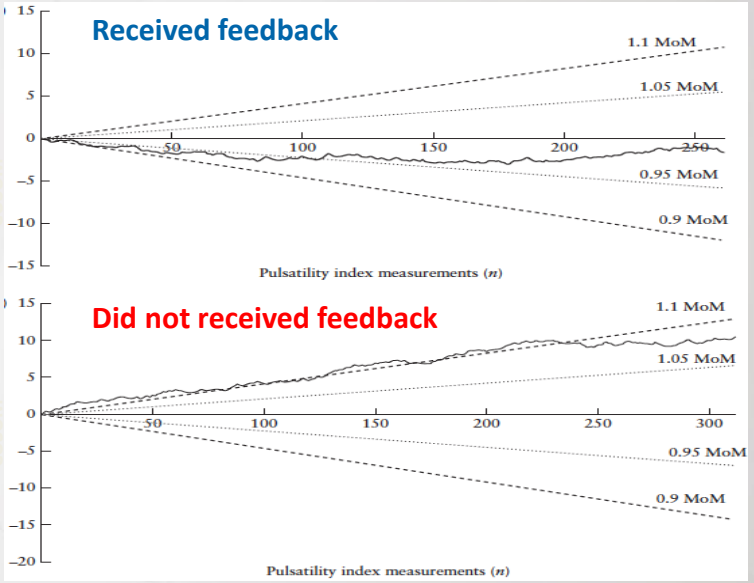
Prediction of PE

Quality standards

N=2519 singleton pregnancies
12 sonographers
6 received feedback
6 did not receive feedback

SPR: 4.3% vs 6.8%
Ideal central tendency & dispersion:
83% vs 58%





CUSUM & target graphs are effective method of audit of 1st trimester uterine artery PI.

Feedback to operators resulted in improved measurement performance, which will ultimately improve screening accuracy.

The Fetal Medicine Foundation

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Quality of measurements

MAP | UTPI | PLGF | PAPP-A | SFLT

Uterine artery pulsatility index (UTPI)

- The measured UTPI is influenced by gestational age, maternal age, weight, racial origin and history of PE in the previous pregnancy.
- To assess the quality of your measurements you need to upload an excel file providing data for each patient. For instructions on how the excel file should be formatted, please click here.
- The application will use these data to calculate the MoM values for each case. It will then assess the results and highlight whether your values are within or outside acceptable limits. The distribution of your measurements, adjusted for maternal factors, will be presented in a graph of UTPI against gestational age.
- If your results are outside acceptable limits, you will need to review your technique for measuring UTPI.

To view an example of a report with good measurements click here.
To view an example of a report with bad measurements click here.

Data file Select file

Submit

Prediction of PE

Quality report

BIAS - difference between the mean of your measurements & the expected.

SPREAD - difference of SD of the distribution of your measurements & the expected.

TREND - whether your measurements follow the normal pattern of change with gestation.

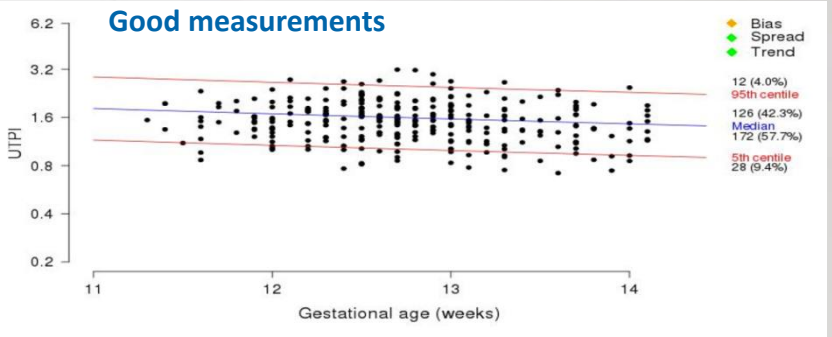
If the indicator is GREEN, your measurements are satisfactory.

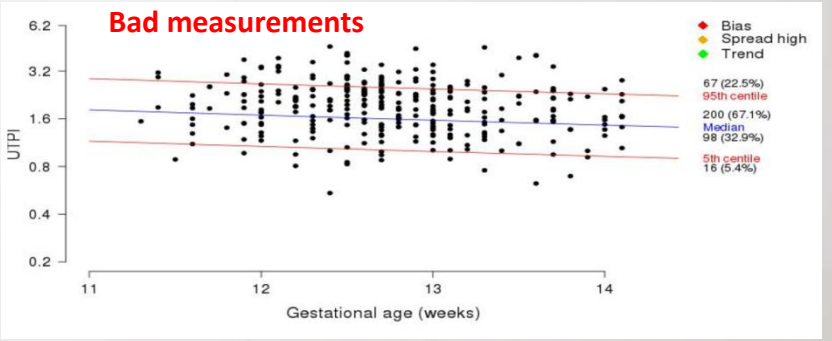
- Please continue to audit your results at regular intervals.

If the indicator is ORANGE, your measurements are within acceptable limits, but they need to improve.

If the indicator is RED, your measurements are outside acceptable limits.

- Please review the protocol for taking correct measurements & submit the results from your next 30 examinations for a new audit.





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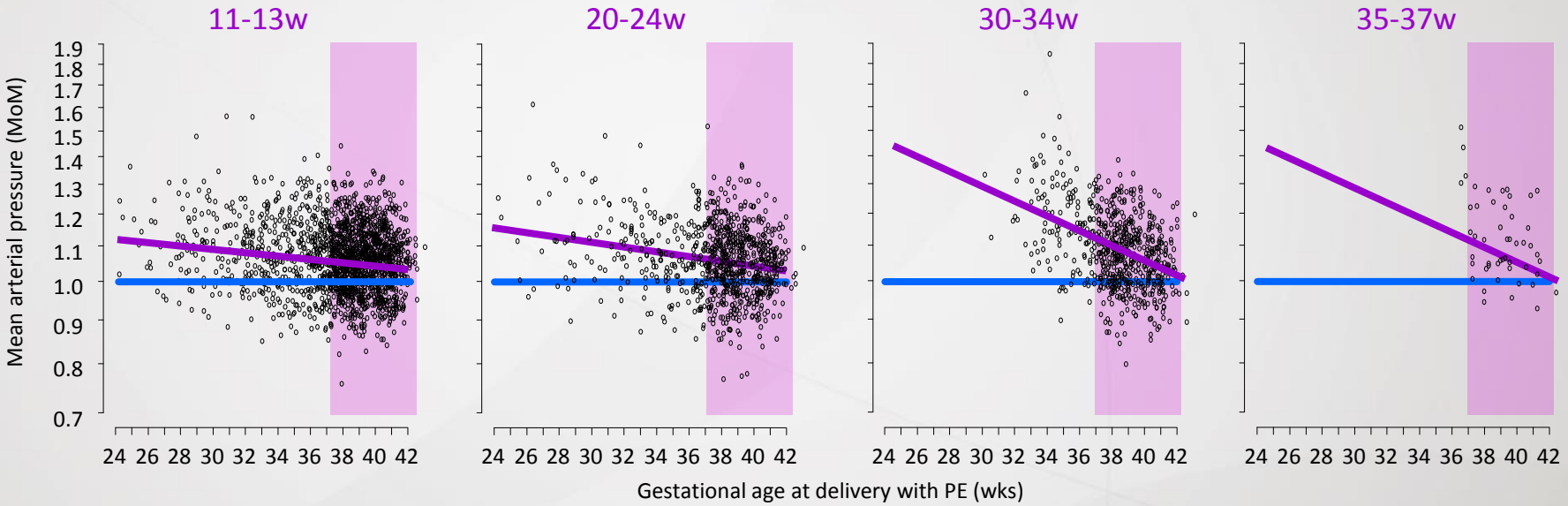
Prediction of PE

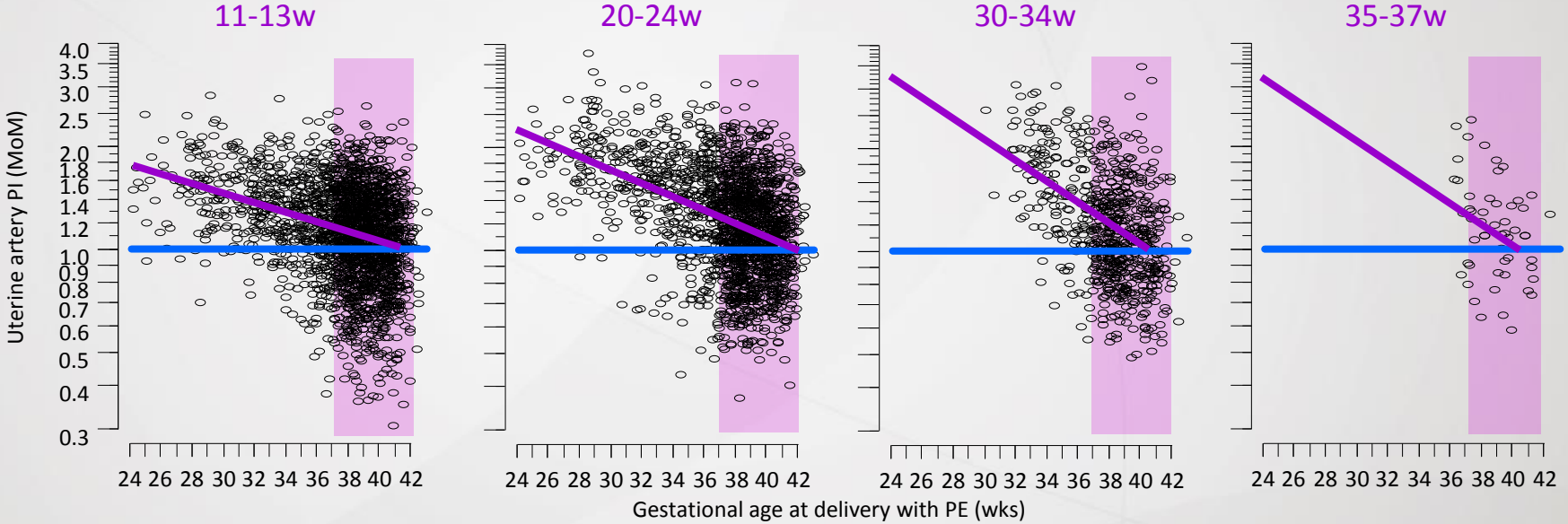
Mean arterial pressure



Tayyar et al: Mean arterial pressure at 12, 22, 32 and 36 weeks' gestation in screening for preeclampsia. Ultrasound Obstet Gynecol 2015

Prediction of PE

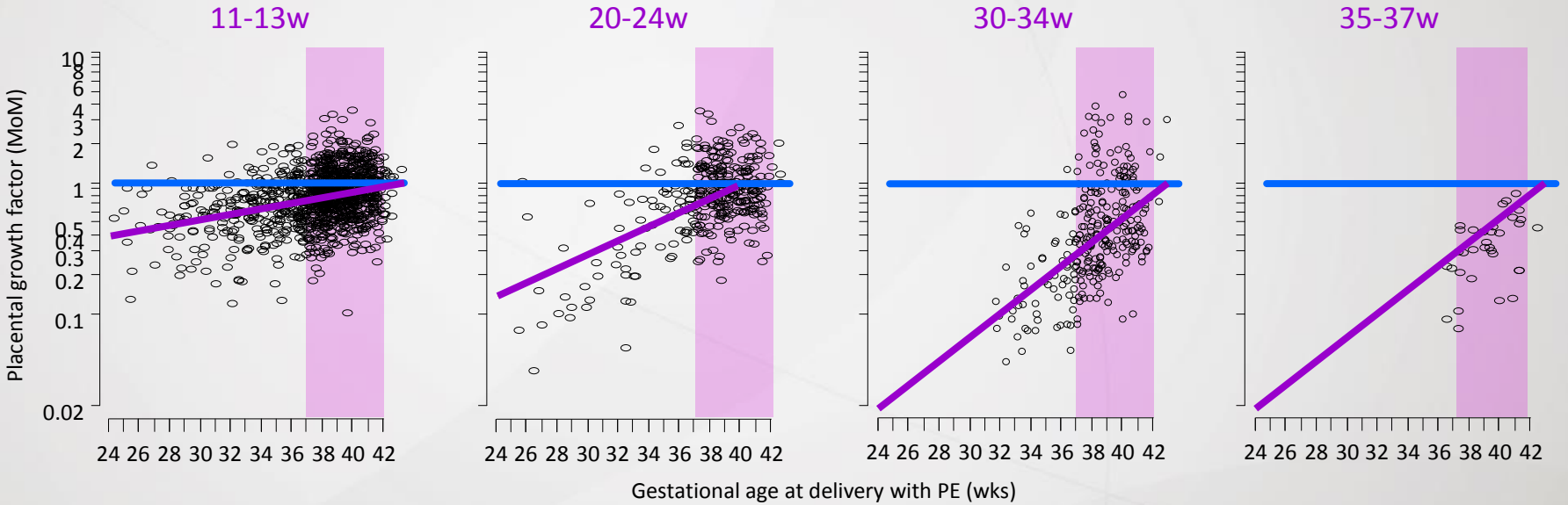
Uterine artery PI



O' Gorman et al: Uterine artery pulsatility index at 12, 22, 32 and 36 weeks' gestation in screening for preeclampsia. Ultrasound Obstet Gynecol 2015

Prediction of PE

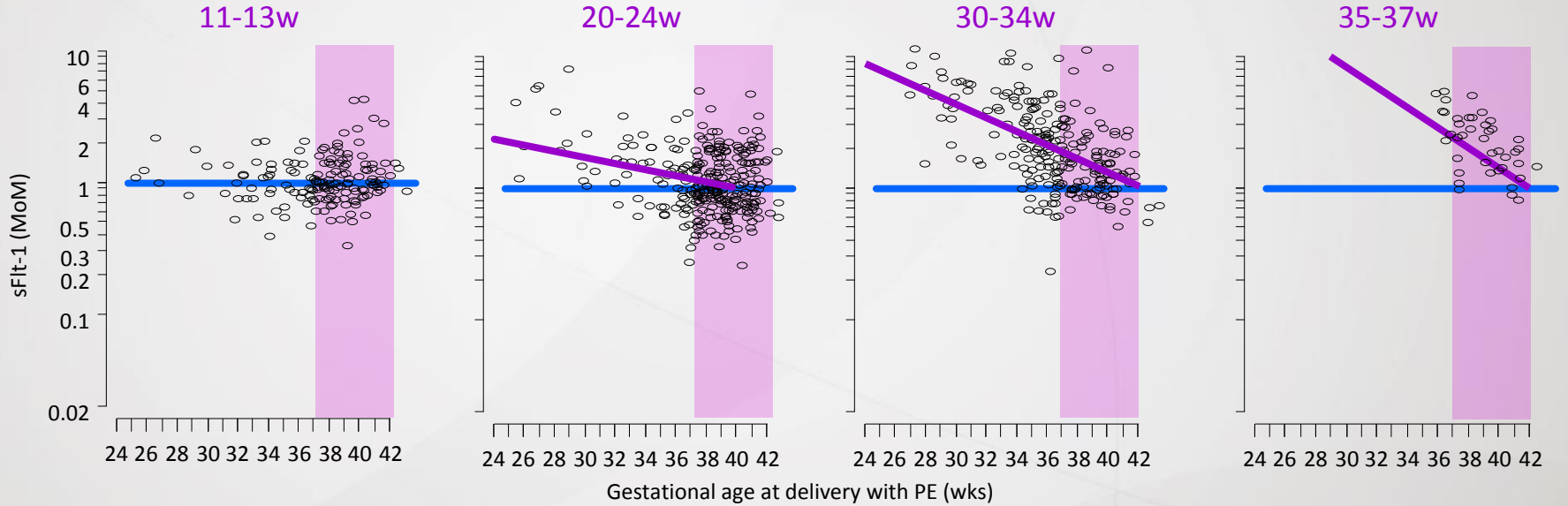
Placental growth factor



Tsiakkas et al: Serum placental growth factor at 12, 22, 32 and 36 weeks' gestation in screening for preeclampsia. Ultrasound Obstet Gynecol 2015

Prediction of PE

sFLT-1: soluble fms-like tyrosine kinase-1



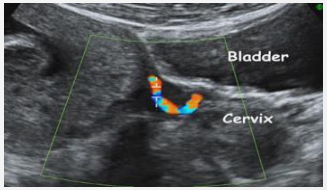
Tsiakkas et al: Serum soluble fms-like tyrosine kinase-1 at 12, 22, 32 and 36 weeks' gestation in screening for preeclampsia. Ultrasound Obstet Gynecol 2015

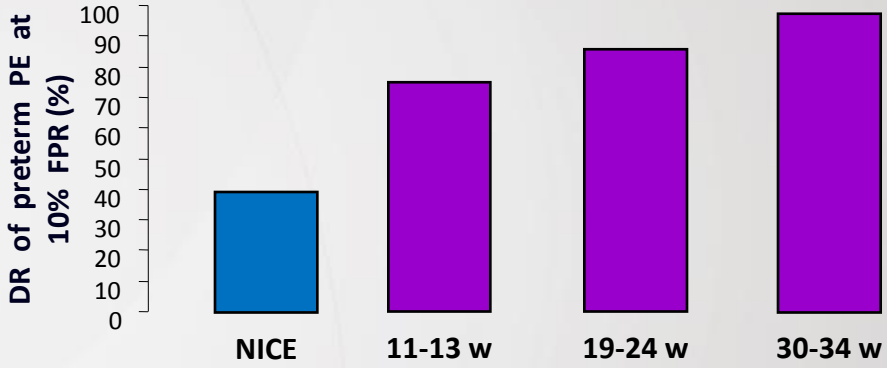
Prediction of PE

FMF algorithm: Bayes theorem

Maternal risk factors

- Age: every 10 years above 30 yrs
- 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
- Systemic lupus erythematosus



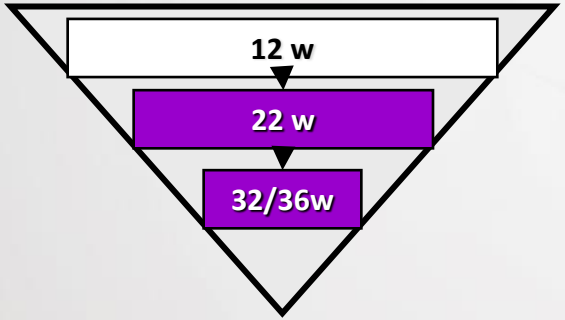


Method of screening: maternal factors plus biomarkers	DR at FPR 10%	
	PE <37w	PE ≥37w
12 w: MAP, UTPI, PLGF	75	47
22 w: MAP, UTPI, PLGF	85	46
32 w: MAP, UTPI, PLGF, sFLT-1	99	66
36 w: MAP, sFLT-1		82

- O' Gorman et al: Screening for PE at 11-13 w. Am J Obstet Gynecol 2015.
- Gallo et al: Screening for PE at 19-24 w. Am J Obstet Gynecol 2015.
- Tsiakas et al: Screening for PE at 30-34 w. Am J Obstet Gynecol 2015.
- Andrietti et al: Screening for PE at 35-37 w. Ultrasound Obstet Gynecol 2015.

Prediction of PE

Combined test at 22, 32 & 32w



Assessment at 22 w (n=100,000)
PE<32w n=198, PE 32-36w 440, PE ≥37w 1,562

Low-risk (85%), 85,000

Moderate-risk (10%), 10,000
Including 91% of PE 32-36w

High-risk (5%), 5,000
Including 98% of PE<32w

Follow-up 24-32 w

Assessment at 32 w (n=13,000)
15,000 minus 2,000 that have already delivered

High-risk (5%), n=650-4900
Including 89%of PE 32-36w

Follow-up 32-36w

Assessment at 36 w (n=95,000)
100,000 minus 5,000 that have already delivered

No further scan

High-risk (10%), n=9,500
Including 84% of PE ≥37w

Follow-up / delivery 38 w

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Training & Certification

- Certificates of competence
  - Nuchal translucency scan
  - Nasal bone
  - Ductus venosus flow
  - Tricuspid flow
  - Preeclampsia screening
  - The 18-23 weeks scan
  - Fetal Doppler ultrasound
  - Cervical assessment
  - Fetal echocardiography
  - Invasive procedures
- FMF fellowships
- Diploma in fetal medicine

Holders of the FMF certificate in preeclampsia screening

To view the list of sonographers who have obtained the certificate of competence in preeclampsia screening please click here.

Preeclampsia screening

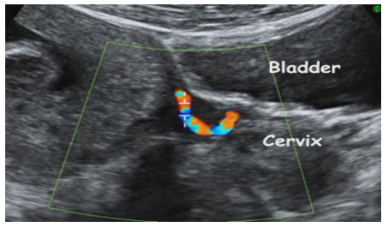
To visit the new FMF calculator for estimation of risk of preeclampsia please click here.

Certificates of competence

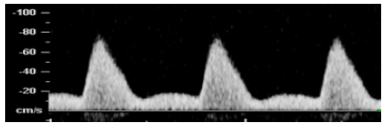
Preeclampsia screening

Preeclampsia (PE) is an important cause of maternal and perinatal mortality and morbidity. Consequently, a major challenge in modern obstetrics is early identification of pregnancies at high-risk of preterm PE and undertaking of the necessary measures to improve placentation and reduce the prevalence of the disease. There is now evidence that a combination of maternal demographic characteristics, including medical and obstetric history, uterine artery pulsatility index (PI), mean arterial pressure (MAP) and maternal serum pregnancy associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) at 11-13 weeks' gestation can identify a high proportion of pregnancies at high-risk for PE. Such early identification of the high-risk group for PE is important because the risk may be substantially reduced by the prophylactic use of low-dose aspirin starting from 11-13 weeks.

Color Doppler of uterine arteries



Uterine artery waveform



Requirements for certification

The requirements for obtaining the FMF certificate of competence in preeclampsia screening are:

1. Attendance of the internet based course on preeclampsia screening (available at the end of ~~April~~ July).
2. Submission of 3 images demonstrating color flow mapping and waveforms of the uterine artery at 11-13 weeks.

Protocol for measurement of the uterine artery PI

- The gestational age must be between 11 weeks and 13 weeks and six days.
- Sagittal section of the uterus must be obtained and the cervical canal and internal cervical os identified. Subsequently, the transducer must be gently tilted from side to side and then colour flow mapping should be used to identify each uterine artery along the side of the cervix and uterus at the level of the internal os.
- Pulsed wave Doppler should be used with the sampling gate set at 2 mm to cover the whole vessel and ensuring that the angle of insonation is less than 30°. When three similar consecutive waveforms are obtained the PI must be measured and the mean PI of the left and right arteries be calculated.

Assessment of risk for preeclampsia (PE)

Maternal factors

Maternal characteristics

Date of birth	26-06-1979
Height	162 cm / 5 ft 4 in
Weight	55 kg / 121 lbs
Racial origin	Afro-Caribbean
Conception method	Spontaneous
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)

Method of pregnancy dating (select one of the methods below)

▸ **Fetal crown-rump length (43-84mm)**

Crown-rump length: 65 mm

▸ Fetal head circumference (158-226mm)

▸ Manual (any gestation)

Gestational age	12.8 weeks
Date of measurement	15-11-2015

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	MAP (mmHg)	Mean UTPI
15-11-2015 GA: 12.8 w	55 kg 121 lbs	97.08	2

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	PLGF (MoM)	PAPP-A (MoM)	SFLT (MoM)
15-11-2015 GA: 12.8 w	55 kg 121 lbs	0.5	1.2	

Calculate risk

Preeclampsia risk assessment: First trimester

Date: 15-11-2015
Gestational age: 12 weeks plus 6 days (Measured at 15-11-2015)

Maternal factors

Maternal characteristics

Date of birth: 1979-06-26
Height: 162 cm
Weight: 55 kg
Racial origin: Afro-Caribbean
Method of conception: Spontaneous
Family history of PE: Yes

Medical history

Chronic hypertension: Yes
Diabetes type I: No
Diabetes type II: No
Systemic lupus erytheromatosus: No
Anti-phospholipid syndrome: No

Obstetric history

Nulliparous (no previous pregnancies ≥24 weeks)

Biophysical measurements

Date of measurement	Weight	MAP	Mean UTPI
15-11-2015	55 kg	97.08 mmHg (1 MoM)	2 (1.18 MoM)

Biochemical measurements

Date of measurement	Weight	PLGF	PAPP-A
15-11-2015	55 kg	0.5 MoM	1.2 MoM

Preeclampsia risk from history only

< 32 weeks: 4 % **1 in 25**
< 37 weeks: 16 % **1 in 6**
≥ 37 weeks: 28 % **1 in 4**

Preeclampsia risk from history plus MAP, UTPI, PLGF, PAPP-A

< 32 weeks: 5.2 % **1 in 20**
< 37 weeks: 25 % **1 in 4**
≥ 37 weeks: 36 % **1 in 3**