Screening for Pre-eclampsia
SASUOG 2010

Ermos Nicolaou
Maternal & Fetal Medicine Unit
University of the Witwatersrand
Pre-eclampsia

“Hypertensive disease of pregnancy" remains a leading cause of direct maternal mortality and morbidity worldwide

• Hypertension and/or proteinuria is the leading single identifiable risk factor in pregnancy associated with stillbirth (one in five stillbirths in otherwise viable babies)

• Pre-eclampsia is strongly associated with fetal growth restriction, low birth weight, preterm delivery, respiratory distress syndrome, and admission to neonatal intensive care

• Worldwide, each year, more than four million women will develop pre-eclampsia.
• Approximately 100,000 women will have eclamptic convulsions.
• Over 90% occur in developing countries.
• 2% of women with pre-eclampsia will develop eclampsia.

• By conservative estimates, these disorders are responsible for 76,000 maternal and 500,000 infant deaths each year.

RCOG: Pre-eclampsia - study group consensus statement
Preeclampsia Foundation
Pre-eclampsia is a *multisystemic* syndrome usually recognised by

1. new onset hypertension and proteinuria appearing in the second half of pregnancy.
2. Clinicians should be aware that pre-eclampsia may occasionally occur with hypertension in the absence of proteinuria (and proteinuria without hypertension)
3. but with other features such as eclampsia, renal impairment, thrombocytopenia, liver dysfunction or fetal compromise.

RCOG: Pre-eclampsia - study group consensus statement
EPICure Study: Outcome at 30 months

# Improved Survival: 80’s to 90’s: 500-999

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Gestational Age (wks)</td>
<td>25.8</td>
<td>25.5</td>
</tr>
<tr>
<td>Birth Weight (grams)</td>
<td>761</td>
<td>756</td>
</tr>
<tr>
<td>Antenatal Steroids (%)</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>Caesarian Section (%)</td>
<td>32</td>
<td>45</td>
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<tr>
<td>Assisted Ventilation (%)</td>
<td>81</td>
<td>89</td>
</tr>
<tr>
<td>Surfactant (%)</td>
<td>1</td>
<td>68</td>
</tr>
<tr>
<td>Survival at 20 months (%)</td>
<td>49</td>
<td>67</td>
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</tbody>
</table>

For every 100 infants born weighing 500-999, there were 18 additional survivors- 7 normal and 11 impaired. (Pediatrics 2005)
The Small Fetus

**Definition**

- Abdominal circumference < 5th centile for gestation (US)
- 80% of such fetuses are **constitutionally small**, with no increased perinatal death or morbidity
- 15% are **growth restricted** due to reduced placental perfusion and "utero-placental insufficiency"
- 5% are growth restricted due to **low growth potential** (abnormal small)
IUGR or AGA?

When both the anomaly scan and umbilical artery waveforms are normal, the small fetus should be classified as a “normal small fetus”.

When the anomaly scan is abnormal and the waveforms are normal, the fetus is an “abnormal small fetus”.

When the anomaly scan is normal and Doppler waveforms are abnormal, there is IUGR.
Screening for pre-eclampsia

• The underlying mechanism for PE is thought to be impaired placentation, documented by the findings of
  1. abnormal blood flow in the uterine arteries and
  2. reduced maternal serum levels of placental products
The patient-specific risk of developing PE can be predicted by a combination of factors in the

- Maternal history
- Race
- High body mass index
- Prior or family history of PE

<table>
<thead>
<tr>
<th>Maternal history</th>
<th>LR</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>0.7</td>
</tr>
<tr>
<td>20-35</td>
<td>1.0</td>
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<tr>
<td>&gt;35</td>
<td>1.5</td>
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<tr>
<td>Body Mass Index</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>0.7</td>
</tr>
<tr>
<td>20-30</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;30</td>
<td>1.5</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.0</td>
</tr>
<tr>
<td>Black</td>
<td>1.5</td>
</tr>
<tr>
<td>Obstetric history</td>
<td></td>
</tr>
<tr>
<td>Nullipara</td>
<td>1.6</td>
</tr>
<tr>
<td>no PET</td>
<td>0.5</td>
</tr>
<tr>
<td>PET</td>
<td>4.0</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.6</td>
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</table>

Screen +ve 5%

Detection rate (%)
and the following measurements taken at 11-13 weeks:
- maternal blood pressure
- uterine artery pulsatility index (PI)
- maternal serum level of PAPP-A
- maternal serum level of PLGF

*Screening by this combined approach could identify about 90% of patients developing early-PE at a FPR of 5%*
In preeclampsia, excess placental soluble Flt-1 (VEGFR-1) binds circulating VEGF and PIGF and prevents their interaction with endothelial cell-surface receptors.
Impaired placentation

Pre-eclampsia
Fetal growth restriction
Fetal death

Good diastolic flow

Early diastolic notch
Poor diastolic flow

Preeclampsia: A renal perspective
S ANANTH, Kidney International
Vascular dysfunction in pre-eclampsia

The placenta is a two compartment nutrient, fluid and gas exchange organ:
- The maternal compartment is assessed by uterine artery Doppler
- The fetal compartment is assessed by umbilical artery Doppler

A Baschat, Doppler Ultrasound, FMF 2010
Umbilical Arteries

Abnormal villous vascular perfusion results in abnormal waveform in the umbilical arteries;
Depending on the degree of impaired vasculature:

- 30% impairment results in high pulsatility index
- 50% impairment results in absent end-diastolic velocity
- 70% impairment results in reversed end-diastolic velocity

The risk for hypoxemia / acidemia is proportional to the decrease in umbilical end-diastolic flow

A Baschat, Doppler Ultrasound, FMF 2010
Screening for pre-eclampsia at 11-13+6 wks

J. E. A. K. BAMFO, et al
Maternal cardiac function in fetal growth-restricted and non-growth-restricted small-for-gestational age pregnancies

K Spencer at al
First-trimester maternal serum PP-13, PAPP-A and second-trimester uterine artery Doppler pulsatility index as markers of pre-eclampsia
Screening for Pre-Eclampsia

Maternal history, uterine artery Doppler & serum biochemistry

Detection rate (%)

Screen +ve 5%

PET ≤33w

90%

80%

33%

K Nicolaides
Editorial: Some thoughts on the true value of ultrasound
*Ultrasound Obstet Gynecol* 2007; 30: 671–674
PAPP-A as a predictor of IUGR

Spencer, Nicolaides et al, 2006 – outcome of 55,000 pregnancies
PAPP-A as a predictor of PET

The value of Biochemical Screening in the 1st and 2nd Trimester
K Spenser, SASUOG, 2006
PAPP-A as a predictor of poor outcome

- Our series of 1236 patients (WITS) April 2008- April 2009
- 152 patients with low PAPP-A (normal karyotype)
Nicolaou E, Naidoo P, Bister S
PAPP-A as a predictor of poor pregnancy outcome
Mat & Fetal Med Unit, University of the Witwatersrand
PAPP-A as a predictor of poor pregnancy outcome
Mat & Fetal Med Unit, University of the Witwatersrand

Nicolaou E, Naidoo P, Bister S
Nicolaou E, Naidoo P, Bister S
PAPP-A as a predictor of poor pregnancy outcome
Mat & Fetal Med Unit, University of the Witwatersrand
Simon Glerup et al
Proteinase Inhibition by Proform of Eosinophil Major Basic Protein (pro-MBP) Is a Multistep Process of Intra- and Intermolecular Disulfide Rearrangements
Screening for Pre-Eclampsia

PP13 is a protein expressed only in the placenta. It is involved in gluing the placenta to the uterus, and in remodelling the maternal arteries to expand them.


First-trimester maternal serum PP-13, PAPP-A and second-trimester uterine artery Doppler pulsatility index as markers of pre-eclampsia
Screening for Pre-Eclampsia

R Romero et al, Am J Obstet Gynecol, 2008, 199(2); 122e1-122e11
First Trimester Maternal Serum PP13 in the Risk Assessment for Preeclampsia
### Screening for Pre-Eclampsia

**Early-onset pre-eclampsia screening in 1st trimester**

<table>
<thead>
<tr>
<th>DR% at 5% FPR</th>
<th>History</th>
<th>MAP ↑</th>
<th>uA Doppler abnormal</th>
<th>PAPP-A ↓</th>
<th>PIGF ↓</th>
<th>PP13 ↓</th>
<th>Inhibin-A</th>
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<td>33</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yu et al., <em>Am J Obstet Gynecol.</em> 2005</td>
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<td></td>
<td>Poon et al., <em>Ultrasound Obs Gyn,</em> 2008</td>
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<td>Poon et al., <em>Ultrasound Obs Gyn,</em> 2008</td>
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<td>✓</td>
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<td>Wortelboer et al., analysis by Prof Cuckle (publication submitted to BJOG)</td>
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<td>Poon et al., <em>Hypertension</em> 2008</td>
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<tr>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Audibert et al. Abstract at SMFM 2010</td>
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<td>93</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Poon et al., <em>Hypertension May</em> 2009</td>
</tr>
</tbody>
</table>

*) at 4% FPR
### Prevention of PET / FGR

**Aspirin 150 mg / day for abnormal Doppler at 23 wks**

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<thead>
<tr>
<th>DRUG</th>
<th>Aspirin</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>280</td>
<td>280</td>
</tr>
<tr>
<td>• Pre-eclampsia</td>
<td>18%</td>
<td>19%</td>
</tr>
<tr>
<td>• FGR &lt;5th Centile</td>
<td>22%</td>
<td>24%</td>
</tr>
<tr>
<td>• Abruption</td>
<td>4%</td>
<td>2%</td>
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</table>

Yu et al 2003

**Vitamin C 1000 mg / day & Vitamin E 400 IU / day**

<table>
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<tr>
<th>DRUG</th>
<th>Vitamins</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>935</td>
<td>942</td>
</tr>
<tr>
<td>• Pre-eclampsia</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>• Antihypertensives</td>
<td>4.6%*</td>
<td>2.8%</td>
</tr>
<tr>
<td>• FGR (&lt;10th centile)</td>
<td>8.7%</td>
<td>9.9%</td>
</tr>
<tr>
<td>• Baby deaths</td>
<td>1.3%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Rumbold et al 2006

**Low-risk (nulliparous) women**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Vitamins</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>1199</td>
<td>1205</td>
</tr>
<tr>
<td>• Pre-eclampsia</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>• Antihypertensives</td>
<td>7%*</td>
<td>3%</td>
</tr>
<tr>
<td>• FGR (BW&lt;2.5Kg)</td>
<td>28%*</td>
<td>24%</td>
</tr>
<tr>
<td>• Baby deaths</td>
<td>4%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Poston et al 2006

**High-risk women**

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<td>1.8%</td>
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Rumbold et al 2006
Preeclampsia and its complications are as common today as they were more than 30 years ago. This is mainly because of our

• Failure to understand adequately the patho-physiology of the condition

• Failure (so-far) to develop adequate methods of screening to identify the patients at high risk.

• Failure to develop effective strategies for their prevention, and

• Failure to develop adequate treatment strategies
Proposed screening for Preeclampsia

Universal 1\textsuperscript{st} trimester screening
(NT, PAPP-A & free beta HCG, UA-PI, BP)

- Normal test: Review at 20 weeks
- Increased NT, low PAPP-A
- Normal NT, low PAPP-A, UA PI
- High BP, Hx of PET

Fetal anomaly scan, Cx length, Dopplers
Consider karyotyping

If karyotype normal
Low dose Aspirin
review at 20 weeks
monitor BP, Doppler

Low dose Aspirin, monitor BP, Doppler
Low dose Aspirin, monitor BP, Doppler