Preeclampsia: challenging the placental origins hypothesis
UtA Doppler and Endovascular Trophoblast Invasion
Early screening for PE

### History
- Maternal age (yr)
- BMI (Kg/m²)
- Racial origin
  - Black
  - Indian or Pakistani
  - Mixed
- Parous
- No previous PE
- Previous PE
- Maternal history of PE
- History of hypertension
- Ovulation drugs

### PIGF

- Normal PE

### Statistical Data
- 10,000 pregnancies
  - 6% Screen +ve
- 600 pregnancies
  - Early-PE 40/50
  - Late-PE 90/200

### Detection Rate
- 50% detection
“Maternal” Preeclampsia

80% of PE occurs at term with features that are inconsistent with the placental origins hypothesis.

‘Maternal’ PE or ‘heterogeniety’ are neither adequate nor actual explanations.
### Aetiology of Gestational Diabetes

**Disorder ONLY occurs in pregnancy**

<table>
<thead>
<tr>
<th>Effect</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Placenta</td>
<td>Required</td>
</tr>
<tr>
<td>Fetal growth</td>
<td>Compromised</td>
</tr>
<tr>
<td>Cured by</td>
<td>Birth</td>
</tr>
<tr>
<td>Maternal organ system</td>
<td>Compromised</td>
</tr>
<tr>
<td>Postpartum</td>
<td>Legacy effect</td>
</tr>
</tbody>
</table>
Numerous classic placental histological villous and vascular lesions described.

- Villous infarcts
- Villitis
- Villous hypoplasia
- Syncytial knots
- Vasculopathy
- Muscularisation
- Acute atherosclerosis
Association or Causation?
Placental Histology

Villous lesions 6-times more prevalent in preeclampsia

Falco M et al. UOG. (in press)
Placental histology is neither sensitive nor specific for preeclampsia.

<table>
<thead>
<tr>
<th>Placental histology findings</th>
<th>Diabetic placentas (n = 40)</th>
<th>Control placentas (n = 40)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villous immaturity</td>
<td>32 (80%)</td>
<td>19 (47.5%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Chorangiosis</td>
<td>16 (40%)</td>
<td>8 (20%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Infarction</td>
<td>7 (17.5%)</td>
<td>4 (10%)</td>
<td>0.33 (NS)</td>
</tr>
<tr>
<td>Villous fibrinoid necrosis</td>
<td>33 (82.5%)</td>
<td>21 (52.5%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Nucleated fetal red blood cells (NFRBC)</td>
<td>22 (55%)</td>
<td>11 (27.5%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ischemia</td>
<td>20 (50%)</td>
<td>12 (30%)</td>
<td>0.11 (NS)</td>
</tr>
</tbody>
</table>
Most cases of PE (80%) occur at term.
Most term PE cases (85%) are not SGA.
Term PE is also associated with LGA births.

**Norwegian registry**
80,000 pregnancies
3000 with PE

Preeclampsia
Epidemiology

The association between birthplace and mortality from cardiovascular causes among black and white residents of New York City

Jing Fang, M.D., Shantha Madhavan, Dr.P.H., and Michael H. Alderman, M.D.

Lifetime Risks of Cardiovascular Disease
Jarett D. Berry, M.D., Alan Dyer, Ph.D., Xuan Cai, M.S., Daniel B. Garside, B.S.,

C-Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction
The Emerging Risk Factor Collaboration*

Childhood Adiposity, Adult Adiposity, and Cardiovascular Risk Factors
Markus Jounjala, M.D., Ph.D., Costan G. Magnussen, Ph.D.,
1m Danish births linked to national prescription register
How does abdominal implantation of the placenta explain low UtA PI due to spiral artery conversion?

Collins SL et al. Placenta 2011
Leslie K et al. Placenta 2012
Ophthalmic Artery Doppler

1st trimester ophthalmic artery Doppler is associated with PE

Kalafat E et al. Ultrasound Obstet Gynecol. (in press)
Gestational diabetes
Cardiac hypertrophy

Increase in LV mass

Elite athletes (2yrs) - 25%

Maternal Cardiovascular Function in Normal Pregnancy
Evidence of Maladaptation to Chronic Volume Overload
Karen Melchiorre, Rajan Sharma, Esma Khalil, Baskaran Thilaganathan


Altered cardiac geometry (RW1 > 0.42 and LVMI > 95 g/m²)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NPC (n=50)</th>
<th>T1 (n=109)</th>
<th>T2 (n=105)</th>
<th>T3 (n=102)</th>
<th>Term (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered cardiac geometry (RW1 &gt; 0.42 and LVMI &gt; 95 g/m²)</td>
<td>2% (1)</td>
<td>6.4% (7)</td>
<td>6.7% (7)</td>
<td>5.9% (6)</td>
<td>5.3% (5)</td>
</tr>
</tbody>
</table>

ASE/ESE criteria to diagnose concentric hypertrophy of LV
Cardiac remodelling

Term pregnancy
25% trabeculations

St George's
University of London

Circulation. 2014;130:475-483
Myocardial and ventricular function

Melchiorre K et al. Hypertension 2016

- Impaired relaxation
- Diastolic dysfunction

8 of 9 were NYHA class 4
Physiological Adaptation or Cardiac Dysfunction?

- Changes in cardiac indices consistent
- Expected response to volume load
- Magnitude of change unexpected:
- Cardiac signs correlate to symptoms

www.heart-failure.co.uk
Cardiovascular maladaptation

Preeclampsia

Pregnancy

NYHA 1:
- ↑ Contractility
- ↓ Relaxation
- ↓ Capillary density

NYHA 2-3:
- ↓ Contractility
- ↓ Relaxation
- ↓ Exercise
- → Cardiac output
- ↓ Fibrosis
- ↓ Metabolic switch

NYHA 4:
- ↑ Contractility
- ↓ Relaxation
- Ascites
- Pleural effusion
- Inflammation?
Cardiovascular dysfunction in preeclampsia

Melchiorre K et al. Circulation 2014:130:703-14
Cardiac Output

CI (L/min/m²)

Preterm PE

Term PE

Term

PP/NPC

Graph showing the relationship between body mass (kg) to the minus 1/4 power and the ratio of cardiac output ($Q_b$) to body mass ($M$) for various species, with the formula $Q_b/M = 200 M^{-1/4}$.
Cardiac Output versus insulin

Insulin Requirements during Pregnancy

- Normal
- Three times normal
- Two times normal

- Conception
- 10 weeks
- 12 weeks
- 20 weeks
- 24 weeks
- 28 weeks
- 30 weeks
- 36 weeks
- Delivery
Placental Growth Factor Regulates Cardiac Inflammation Through the Tissue Inhibitor of Metalloproteinases-3/Tumor Necrosis Factor-α-Converting Enzyme Axis

Crucial Role for Adaptive Cardiac Remodeling During Cardiac Pressure Overload

Daniela Carnevale, PhD; Giuseppe Cifelli, BSc*; Giada Mascio, BSc*; Michele Madonna, DVM; Mauro Sbragia, PhD; Cinzia Perrino, MD, PhD; Marta Grazia Persico, BSc†; Giacomo Frati, MD; Giuseppe Lenho, MD, PhD
Inadequate trophoblast invasion/development

Relative cardiac insufficiency (high fetoplacental demands)

Placental ‘stress’ response

Release of placental factors

Endothelial cell activation

Syndrome of preeclampsia

Term Preeclampsia

Dual cardiovascular AND placental aetiology of PE
Complex aetiology or unifying hypothesis?

Impaired placentation

Cardiovascular dysfunction

FGR

PE (SGA-type) Mainly preterm

PE (AGA/LGA) Mainly at term
Preeclampsia: getting to the heart of the matter.
Thilaganathan B, UOG, Jan 2017
Effect of parity

- Weight gain greatest in 1st pregnancy
- Reduced fecundity after preterm PE
- Protective effect of pregnancy

McDonald-Wallis et al. AmJOG
Skjaerven R et al. BMJ 2012
Melchiorre K et al. Circulation 2014
Clapp JF et al. Am J Cardiol 1997

 Nullipara
 Multipara
Basky Thilaganathan

cfDNA: a case-based presentation
Assessing Risk
Combined NT and biochemistry

- False positive rate of 3%
- Detection rate of about 75%

Invasive prenatal tests

Cicero et al., 2001

Fetal cfDNA

- Originates from trophoblast
- Detectable from 5 weeks
- 5-10% of total cell-free DNA
- Cleared immediately after birth

10 mL blood sample is collected from the expectant mother.

Fully automated DNA extraction is carried out on the QIAsymphony®.

Library preparation using the NGS Sciclone®. Sample quantitation is done with LabChip® GX Touch.

Sample prepared for downstream sequencing using the ION Chef™ and then analyzed on the ION Proton™ systems.

Automated data analysis with the IONA® Software.

3 Days
Assume 10% of cfDNA is fetal

Need to distinguish 21 copies from 20 copies (5% difference)
Meta-analysis of NIPT

Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis

M. M. GIL*, M. S. QUEZADA*, R. REVELLO*, R. AKHILEKAR*† and K. H. NICOLAIDES*†

Table 2 Studies reporting on the application of cell-free DNA analysis of maternal blood in screening for trisomy 21 in singleton pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>GA (weeks)</th>
<th>Total (n)</th>
<th>Detection (n, 95% CI)</th>
<th>Non-trisomy 21 Total (n)</th>
<th>False positive (n, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiu (2011)</td>
<td>MPSS</td>
<td>13 (—)</td>
<td>86</td>
<td>86 (100, 95.8–100)</td>
<td>146</td>
<td>3 (2.05, 0.43–5.89)</td>
</tr>
<tr>
<td>Ehrlich (2011)</td>
<td>MPSS</td>
<td>16 (8–36)</td>
<td>39</td>
<td>39 (100, 91.0–100)</td>
<td>410</td>
<td>1 (0.24, 0.01–1.35)</td>
</tr>
<tr>
<td>Palomaki (2011)</td>
<td>MPSS</td>
<td>15 (8–21)</td>
<td>212</td>
<td>209 (98.6, 95.9–99.7)</td>
<td>1471</td>
<td>3 (0.20, 0.04–0.60)</td>
</tr>
<tr>
<td>Schnett (2011)</td>
<td>MPSS</td>
<td>15 (10–28)</td>
<td>13</td>
<td>13 (100, 75.3–100)</td>
<td>34</td>
<td>0 (0.00, 0.00–10.28)</td>
</tr>
<tr>
<td>Ashoor (2012)</td>
<td>CSS</td>
<td>12 (11–13)</td>
<td>50</td>
<td>50 (100, 92.9–100)</td>
<td>347</td>
<td>0 (0.00, 0.00–1.06)</td>
</tr>
<tr>
<td>Bianchi (2012)</td>
<td>MPSS</td>
<td>15 (10–23)</td>
<td>89</td>
<td>89 (100, 95.9–100)</td>
<td>404</td>
<td>0 (0.00, 0.00–0.91)</td>
</tr>
<tr>
<td>Jiang (2012)</td>
<td>MPSS</td>
<td>— (10–36)</td>
<td>11</td>
<td>16 (100, 79.4–100)</td>
<td>887</td>
<td>0 (0.00, 0.00–0.42)</td>
</tr>
<tr>
<td>Lau (2012)</td>
<td>MPSS</td>
<td>12 (11–18)</td>
<td>11</td>
<td>11 (100, 71.5–100)</td>
<td>97</td>
<td>0 (0.00, 0.00–3.73)</td>
</tr>
<tr>
<td>Nicolaides (2012)</td>
<td>CSS</td>
<td>12 (11–13)</td>
<td>8</td>
<td>8 (100, 63.1–100)</td>
<td>1941</td>
<td>0 (0.00, 0.00–0.19)</td>
</tr>
<tr>
<td>Norton (2012)</td>
<td>CSS</td>
<td>16 (9–38)</td>
<td>81</td>
<td>81 (100, 95.6–100)</td>
<td>2888</td>
<td>1 (0.04, 0.00–0.19)</td>
</tr>
<tr>
<td>Sparks (2012)</td>
<td>CSS</td>
<td>18 (11–36)</td>
<td>36</td>
<td>36 (100, 90.3–100)</td>
<td>131</td>
<td>0 (0.00, 0.00–2.78)</td>
</tr>
<tr>
<td>Guex (2013)</td>
<td>MPSS</td>
<td>17 (11–14)</td>
<td>30</td>
<td>30 (100, 88.4–100)</td>
<td>146</td>
<td>0 (0.00, 0.00–2.50)</td>
</tr>
<tr>
<td>Liang (2013)</td>
<td>MPSS</td>
<td>16 (11–39)</td>
<td>31</td>
<td>39 (100, 91.0–100)</td>
<td>367</td>
<td>0 (0.00, 0.00–1.00)</td>
</tr>
<tr>
<td>Nicolaides (2013)</td>
<td>SNP</td>
<td>13 (10–13)</td>
<td>25</td>
<td>25 (100, 86.3–100)</td>
<td>204</td>
<td>0 (0.00, 0.00–1.79)</td>
</tr>
<tr>
<td>Song (2013)</td>
<td>MPSS</td>
<td>11 (11–21)</td>
<td>35</td>
<td>8 (100, 63.1–100)</td>
<td>1733</td>
<td>0 (0.00, 0.00–0.21)</td>
</tr>
<tr>
<td>Verweij (2013)</td>
<td>CSS</td>
<td>14 (10–28)</td>
<td>18</td>
<td>17 (94.4, 72.7–99.9)</td>
<td>486</td>
<td>0 (0.00, 0.00–0.76)</td>
</tr>
<tr>
<td>Bianchi (2014)</td>
<td>MPSS</td>
<td>17 (8–39)</td>
<td>5</td>
<td>5 (100, 47.8–100)</td>
<td>1947</td>
<td>6 (0.31, 0.11–0.67)</td>
</tr>
<tr>
<td>Comas (2014)</td>
<td>CSS/SNP</td>
<td>14 (9–23)</td>
<td>4</td>
<td>4 (100, 39.8–100)</td>
<td>311</td>
<td>0 (0.00, 0.00–1.18)</td>
</tr>
<tr>
<td>Pergament (2014)</td>
<td>SNP</td>
<td>14 (7–40)</td>
<td>53</td>
<td>58 (100, 93.8–100)</td>
<td>905</td>
<td>0 (0.00, 0.00–0.41)</td>
</tr>
<tr>
<td>Porrecco (2014)</td>
<td>MPSS</td>
<td>17 (9–37)</td>
<td>137</td>
<td>137 (100, 97.3–100)</td>
<td>3185</td>
<td>3 (0.09, 0.02–0.28)</td>
</tr>
<tr>
<td>Shaw (2014)</td>
<td>MPSS</td>
<td>&gt; 12</td>
<td>11</td>
<td>11 (100, 71.5–100)</td>
<td>184</td>
<td>0 (0.00, 0.00–1.98)</td>
</tr>
<tr>
<td>Stumm (2014)</td>
<td>MPSS</td>
<td>15 (11–32)</td>
<td>41</td>
<td>40 (97.6, 87.2–99.9)</td>
<td>430</td>
<td>0 (0.00, 0.00–0.85)</td>
</tr>
<tr>
<td>Quezada (2015)</td>
<td>CSS</td>
<td>10 (10–11)</td>
<td>32</td>
<td>32 (100, 89.1–100)</td>
<td>2753</td>
<td>1 (0.04, 0.00–0.20)</td>
</tr>
<tr>
<td>Song (2015)</td>
<td>MPSS</td>
<td>9 (8–12)</td>
<td>2</td>
<td>2 (100, 15.8–100)</td>
<td>201</td>
<td>0 (0.00, 0.00–1.82)</td>
</tr>
</tbody>
</table>

Pooled analysis (%) (95% CI)
- Fixed effects model
- Random effects model
- Cochran’s Q
- I² statistic (%) (95% CI)
- Egger bias

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>Non-trisomy 21</td>
</tr>
<tr>
<td>99.2 (98.5–99.6)</td>
<td>0.09 (0.05–0.13)</td>
</tr>
</tbody>
</table>
Q1

Does the a-priori T21 risk matter when using NIPT?
Prior Risks

Maternal age
Gestational age
Previous Trisomy

Test risk
For T21, T18, T13

NT βhCG PAPP-A
Q2

Can we trust a very low-risk result in a 42yr old?
Apparent commercial justification for NOT measuring FF:

- Unnecessary (0.5% x 1:700 = 1:140,000 risk of T21)
- Costly (laboratory and bioinformatics)
- Unreliable (various methods of FF estimation)
If we measure fetal fraction, the test fails more often.
Results with fetal fraction of 4% and 12% are equally reliable.
Q5

How do we compromise between cfDNA failure rates and test accuracy?
### Optimising test performance

Use correct a-priori risk

Dynamic FF integrated into risk

<table>
<thead>
<tr>
<th>FF (%)</th>
<th>Detection Rate</th>
<th>False Positive Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MA + cf DNA</td>
<td>CT + cf DNA</td>
</tr>
<tr>
<td>0.1%</td>
<td>37%</td>
<td>86%</td>
</tr>
<tr>
<td>1%</td>
<td>44%</td>
<td>87%</td>
</tr>
<tr>
<td>2%</td>
<td>62%</td>
<td>90%</td>
</tr>
<tr>
<td>3%</td>
<td>78%</td>
<td>94%</td>
</tr>
<tr>
<td>4%</td>
<td>88%</td>
<td>96%</td>
</tr>
<tr>
<td>5%</td>
<td>94%</td>
<td>98%</td>
</tr>
<tr>
<td>6%</td>
<td>97%</td>
<td>99%</td>
</tr>
<tr>
<td>7%</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>8%</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>≥9%</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>
Are cfDNA test results easier for women to understand?
Prospective NIPT trial

Nicolaides K et al. Ultrasound Obstet Gynecol. 2013 (in press)
Would you offer cfDNA tests to woman with a CT risk of 1:1500 and mild ventriculomegaly?
Additional value of prenatal genomic array testing in fetuses with isolated structural ultrasound abnormalities and a normal karyotype: a systematic review of the literature

M. C. DE WIT*, M. I. SREBNIAK†#, L. C. P. GOVAERTS†, D. VAN OPSTAL†, R. J. H. GALJAARD† and A. T. J. I. GO*
Q8

What should I do with a high-risk cfDNA result in a 20yr old woman with normal NT?
Positive SAFE result

In high-risk patients:
- Offer invasive test (amnio or CVS)
- Fetal anomalies or NT >3.5mm
  - Offer invasive test (amnio or CVS)

In low-risk patients:
- Offer ultrasound scan in FMU
- Normal ultrasound
  - Offer amnio (placental mosaicism*)
How about twin pregnancy and fetal sexing on cfDNA?
Twin pregnancy
FP rate of 1:500 (0.2%)
Sensitivity of 95%
Best available screen

Fetal sexing
FP rate of 1:250 (0.4%)
OAPR of 20%
IONA test: X-depletion

Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis

M. M. GIL*, M. S. QUEZADA*, R. REVELLO*, R. AKOLEKAR*† and K. H. NICOLAIDES*†
Q10

Should we check for fetal microdeletions on cfDNA?
22q11 microdeletions
1:4000 births
Variable expressivity
Screening criteria met?

Testing efficiency
FP rate of 1:200 (0.5%)
OAPR about 20%
Sensitivity unknown

Opinion
Cell-free DNA testing for 22q11.2 deletion syndrome: appraising the viability, effectiveness and appropriateness of screening
Implementing the SAFE test in the NHS

Thank you