Preeclampsia is a placental disorder: lies, damn lies and medical science
PREECLAMPSIA: PATHOPHYSIOLOGY

- Defective spiral artery remodeling
- Systemic vasoconstriction and endothelial dysfunction
- Hypertension and end-organ damage
- Placental hypoperfusion
- I want a belly button!
- Curative treatment is delivery
- Diseased placenta releases proinflammatory proteins into maternal circulation
- Hemolysis elevated liver enzymes low platelets
- Proteinuria

HELLP!
Placental histology
Late-onset preeclampsia

Prevalence of vascular and villous lesions in PE

3x over-reporting of abnormal histology in PE when unblinded

Placental histology is neither sensitive nor specific for preeclampsia

Falco M et al. UOG 2017
Sebire N. UOG 2017
SGA in preeclampsia

Most (80%) of preeclampsia are late-onset

Term PE associated with both LGA and SGA birth (after exclusion of diabetes)

Important correlations

![Graph showing firearm-related death rate per 100,000 residents vs. guns per 100 residents. The graph includes data points for several countries, with a linear trend line and an R² value of 0.9231.](image)

\[ R^2 = 0.9231 \]
Spurious correlations

$r = 0.791$
$P < 0.0001$
PLEXIT
Cardiac performance

Placental function

Fetal demands

The placenta: Villain or victim?
Pre-pregnancy
### Association Between Prepregnancy Cardiovascular Function and Subsequent Preeclampsia or Fetal Growth Restriction

Fung L. Foo, Amita A. Mahendru, Giulia Masini, Abigail Fraser, Stefano Cacciatore, David A. MacIntyre, Carmel M. McEniery, Ian B. Wilkinson, Phillip R. Bennett, Christoph C. Lees

<table>
<thead>
<tr>
<th>Preconception Parameter</th>
<th>Normal pregnancy</th>
<th>FGR and preeclampsia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO, L/min</td>
<td>5.8 (1.0)</td>
<td>4.9 (0.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>CI, L/min per meter²</td>
<td>3.3 (0.6)</td>
<td>2.9 (0.6)</td>
<td>0.031</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>67.3 (10.3)</td>
<td>66.2 (10.4)</td>
<td>0.685</td>
</tr>
<tr>
<td>SV, mL</td>
<td>82.2 (14.5)</td>
<td>73.9 (14.6)</td>
<td>0.047</td>
</tr>
<tr>
<td>TPR,* dynes·sec·cm⁻⁵</td>
<td>1156.1 (776.2–1819.7)</td>
<td>1396.4 (891.3–1737.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>113.6 (10.5)</td>
<td>119.2 (10.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>66.2 (7.3)</td>
<td>67.0 (7.3)</td>
<td>0.158</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>82.3 (7.3)</td>
<td>87.1 (7.3)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**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 Factors Collaboration

**Childhood Adiposity, Adult Adiposity, and Cardiovascular Risk Factors**

Markus Juonala, M.D., Ph.D., Costan G. Magnusen, Ph.D.
Early pregnancy
Uterine Doppler and Trophoblast Function

Endothelial cell behaviour and apoptosis

Table II: Histological findings in products of conception from pregnancies with high- and low-resistance uterine artery blood flow examined in the late first trimester

<table>
<thead>
<tr>
<th></th>
<th>High-resistance (n = 17)</th>
<th>Low-resistance (n = 14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation site identified</td>
<td>12/17 (76%)</td>
<td>12/14 (86%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Endovascular trophoblast invasion present</td>
<td>8/13 (62%)</td>
<td>8/12 (67%)</td>
<td>0.79</td>
</tr>
<tr>
<td>No. of implantation site vessels per case</td>
<td>14 (±77)</td>
<td>15 (±92)</td>
<td>0.44</td>
</tr>
<tr>
<td>No. of implantation site vessels with endovascular trophoblast invasion</td>
<td>39/114 (34%)</td>
<td>70/143 (49%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Increased Apoptosis, Altered Oxygen Signaling,
and Antioxidant Defenses in First-Trimester
Pregnancies with High-Resistance Uterine Artery
Blood Flow

Decidual cell regulation of trophoblast is altered
impairment of decidual natural killer cell regulation of vascular
doppler are more sensitive to apoptotic
dehydrated endothelial cells from pregnancies with
high uterine artery
Elevated glucocorticoid metabolism in placental tissue from first trimester
pregnancies at increased risk of pre-eclampsia

Increased Apoptosis in First Trimester Extravillous
Trophoblasts from Pregnan at Higher Risk of
Developing Pre-eclampsia

Decidual Natural Killer Cell Interactions with
Trophoblasts Are Impaired in Pregnan at Higher Risk of
Increased Risk of Pre-eclampsia

Increased Apoptosis in First Trimester Extravillous
Trophoblasts from Pregnan at Higher Risk of
Developing Pre-eclampsia

Alison E. Wallace, Amanda J. Host, Guy S. Whiteley, and Judith E. Cartwright

Kerin Leslie, "Guy S. Whiteley", "Ronan Horan", "Eoin De Chenu", "Sandra Ashton", "Ken Ling", "Baskaran Thilaganathan", and
Judith E. Cartwright
Late pregnancy
39 studies
3082 patients
Paradoxical drop in cardiac output at term

Cardiac output and related haemodynamics during pregnancy: a series of meta-analyses
Victoria L Meah,1 John R Cockcroft,2 Karianne Backx,1 Rob Shave,1 Eric J Stöhr1
Left ventricular mass

Relative wall thickness

- >2.0: Concentric remodeling
- <2.0: Normal

- Concentric Hypertrophy
- Eccentric Hypertrophy

Absent
Present
LV mass increase
40% in pregnancy (9 months)
25% in elite athletes (24 months)
Term Pregnancy
25% trabeculations

Reversible De Novo Left Ventricular Trabeculations in Pregnant Women: Implications for the Diagnosis of Left Ventricular Noncompaction in Low-Risk Populations
Sabilla Gati, Michael Papadakis, Nikolaos D. Papanikolaou, Abbas Zaidi, Nabeel Sheikh, Matthew Reed, Rajan Sharma, Baskaran Thilaganathan and Sanjay Sharma

Circulation. 2014;130:475-483; originally published online July 8, 2014;
Impaired myocardial relaxation

Impaired myocardial contraction (+relaxation)

Chamber diastolic dysfunction

Chamber systolic (+diastolic) dysfunction

Melchiorre K et al. Hypertension 2016

Asymptomatic diastolic dysfunction in 10-15% of women at term

Shortness of breath
Swelling of feet & legs
Chronic lack of energy
Difficulty sleeping at night due to breathing problems
Increased urination at night
Confusion and/or impaired memory
Cardiac function in preeclampsia
Remodelling in preeclampsia

LVM increases by 71% and RWT by 46% more in preeclampsia than during a normotensive pregnancy

De Haas et al. UOG 2018
Meta-analysis of 48 studies
Myocardial function in preeclampsia

Melchiorre K et al. Circulation 2014:130:703-14
Maternal cardiac dysfunction

- **FGR and Preeclampsia**
  - De Haas et al. UOG 2018
  - Meta-analysis (48 studies)

- **Pregnancy**

- **Systematic review (36 studies)**
Post-partum
Cardiac function one year after preeclampsia

- Impaired myocardial relaxation persisted in term and preterm PE
- Impaired myocardial contractility persisted in preterm PE

Impaired LV myocardial relaxation

<table>
<thead>
<tr>
<th></th>
<th>Preterm PE</th>
<th>Term PE</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>85</td>
<td>64</td>
<td>28</td>
</tr>
<tr>
<td>Postpartum</td>
<td>74*</td>
<td>46*</td>
<td>13</td>
</tr>
</tbody>
</table>

*=p<0.0001 versus postpartum controls

Prevalence %

Hypertension 2011;57:85
Hypertension 2011;58:709
Circulation 2014;130:475
<table>
<thead>
<tr>
<th></th>
<th>GDM</th>
<th>HDP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>New onset abnormal glucose &gt;20wks</td>
<td>New onset abnormal BP &gt;20wks</td>
</tr>
<tr>
<td><strong>Predisposing factors</strong></td>
<td>Same as for type 2 diabetes mellitus</td>
<td>Same as for cardiovascular disease</td>
</tr>
<tr>
<td><strong>Screening test</strong></td>
<td>GTT (measures pancreatic function)</td>
<td>BP and Uterine Doppler (measures cardiac function)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>High glucose levels</td>
<td>High BP levels</td>
</tr>
<tr>
<td><strong>Pre-pregnancy disease</strong></td>
<td>More severe pregnancy phenotype</td>
<td>More severe pregnancy phenotype</td>
</tr>
<tr>
<td><strong>‘Cure’</strong></td>
<td>Birth</td>
<td>Birth</td>
</tr>
<tr>
<td><strong>Maternal Long-term</strong></td>
<td>50% risk of diabetes in 10 years</td>
<td>30% risk of hypertension in 10 years</td>
</tr>
</tbody>
</table>

Kalafat & Thilaganathan. Curr Opin O&G. 2017
Longitudinal study
15 nullips, 15 multips
Started pre-pregnancy
9 time points
270 echocardiograms

“Pre-conditioning”

Clapp AF. Am J Cardiol. 1997 (n=30)
Turan OM et al. UOG. 2008 (n=4689)
Ling HZ et al. AmJOG. 2109 (n=1574)
Longitudinal study
829 nullips, 632 multips
113 prev PE+/-SGA

“Multipara have the optimal haemodynamic response to pregnancy”

Ling HZ et al. AmJOG. 2109 (n=1574)
Increase in PE risk explained by inter-pregnancy interval
IVF and ovum donation

26,696 IVF/ICSI
999,804 controls

PE risk conferred by ovum donation, not IVF

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OD vs. IVF/ICSI Adjusted OR (95% CI)</th>
<th>OD vs. spontaneous conception Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caesarean section</td>
<td>2.37 (1.93–2.92)</td>
<td>2.37 (1.93–2.91)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>3.05 (2.23–4.16)</td>
<td>2.84 (2.10–3.84)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>1.04 (0.46–2.38)</td>
<td>0.96 (0.43–2.18)</td>
</tr>
</tbody>
</table>

High risks of maternal and perinatal complications in singletons born after oocyte donation

SARAH NEJDET¹, CHRISTINA BERGH¹, KARIN KÄLLÉN², ULLA-BRITT WENNERHOLM³ & ANN THURIN-KJELLBERG¹
33% reduction in PE

Immediate effects (minutes)
Vasconstriction – nicotine

Short-term effects (hours/days)
Hypotension – carbon monoxide

Wei J et al. Oncotarget 2015
Placenta or heart: Does it really matter?
Conventional risk assessment

Risks treated as equal
Modest risk elevation
Interaction of factors
Risk elevation only

Low Risk
☐ No known risk factors

Increased Risk: one or more of the following:
Maternal Risk Factors
☐ Maternal age >40 years
☐ Ongoing smoker (at booking)
☐ Drug misuse
Previous Pregnancy History
☐ Previous SGA baby (<10th centile)
☐ Previous stillbirth
Maternal Medical History
☐ Chronic hypertension
☐ Diabetes
☐ Renal impairment
☐ Antiphospholipid syndrome
Unsuitable for monitoring by fundal height- e.g.
☐ Large fibroids
☐ BMI >35

Current Pregnancy Complications
Early Pregnancy
☐ FAPP-A <0.415 MoM
☐ Fetal echogenic bowel
Late Pregnancy
☐ Severe pregnancy induced hypertension or pre-eclampsia (=PIH and proteinuria)
☐ Unexplained antepartum haemorrhage

High false +ve rate (60%)
Low detection (40%)
Aspirin prescription (15%)
Aspirin compliance (?)
ASPRE screening

Rolnik D et al. NEJM 2018
Kalafat E et al. UOG 2018
Khalil A et al. BJOG 2008
Maternal ophthalmic and radial artery Doppler at 11-13 weeks is as good as uterine Doppler in prediction of preeclampsia.
Placental surface 12-15m2
Capillary surface 6000-7000m2
(x500 higher surface area)

PIGF protein produced equally by endothelium of most organs

http://biogps.org/#goto=genereport&id=5228
# ASPRE screening
## Implementation at StGeorges

## 11-14wk scan - FMF Algorithm (History, UtA Doppler, MAP, PAPP-A)

<table>
<thead>
<tr>
<th></th>
<th>2017-2018 Routine care</th>
<th>2019 ASPRE screen</th>
<th>↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies</td>
<td>8110</td>
<td>3260</td>
<td>40%</td>
</tr>
<tr>
<td>Preterm PE (&lt;37wks)</td>
<td>61 (0.75%)</td>
<td>15 (0.46%)</td>
<td>40%</td>
</tr>
<tr>
<td>Term PE (&gt;37wks)</td>
<td>167 (2.1%)</td>
<td>50 (1.5%)</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Potential therapies:** Aspirin, Calcium, Statins, Metformin
Diagnosis and prognosis
Diagnosis

The New England Journal of Medicine

Predictive Value of the sFlt-1:PIGF Ratio in Women with Suspected Preeclampsia
Use of PlGF permitted earlier delivery and improved maternal outcomes
Elevated Soluble Fms-Like Tyrosine Kinase-1 and Placental-Like Growth Factor Levels Are Associated With Development and Mortality Risk in Heart Failure

Muhammad Hammadah, MD; Vasiliki V. Georgiopoulou, MD, MPH, PhD;
Prognosis

Assessment of the fullPIERS Risk Prediction Model in Women With Early-Onset Preeclampsia

U. Vivian Ukah, Beth Payne, Jennifer A. Hutcheon, J. Mark Ansermino, Wessel Ganzvoort, Shakila Thangaratinam, Laura A. Magee, Peter von Dadelszen

1388 preeclampsia cases
7.3% adverse maternal outcome
Table 3. Schemes of Oral Antihypertensive Medication in Mild-to-Moderate Hypertension in Pregnancy (SBP between 140 and 159 mm Hg or DBP between 90 and 109 mm Hg)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Oral Dose</th>
<th>Intervals</th>
<th>Maximum Total Dose/Die</th>
<th>Maternal Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>100 to 400 mg</td>
<td>2 to 4 times daily</td>
<td>1200 mg/d</td>
<td>Headache</td>
</tr>
<tr>
<td>Alfametildopa</td>
<td>250 to 500 mg</td>
<td>2 to 4 times daily</td>
<td>2000 mg/d</td>
<td>Maternal sedation, elevated liver function enzymes, depression</td>
</tr>
<tr>
<td>Intermediate-acting nifedipine</td>
<td>10 to 20 mg</td>
<td>2 to 3 times daily</td>
<td>Maximum 120 mg/d</td>
<td>Headache</td>
</tr>
<tr>
<td>Long-acting Nifedipine</td>
<td>20 to 60 mg</td>
<td>1 time daily</td>
<td>Maximum 120 mg/d</td>
<td>Headache</td>
</tr>
</tbody>
</table>

In the absence of comorbidities, whether BP targets should be high normotension (85 mm Hg DBP) or nonsevere hypertension (105 mm Hg DBP) is not standardized. Data from the Cochrane Database Systematic Review on Antihypertensive drug therapy for mild-to-moderate hypertension during pregnancy (2007), unless otherwise stated. The illustrated schemes of treatments are recommended by the Society of Obstetricians and Gynecologists of Canada (SOGC guidelines, 2008), American College of Obstetricians and Gynecologists (ACOG guidelines, 2012), and UK National Institute of Clinical Excellence (NICE guidelines, 2011) with minimal differences. In particular, for ACOG 2012, the maximum total dose/die for labetalol is 2000 mg and for alfametildopa is 3000 mg/die. BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

Cardiovascular Management in Pregnancy

Cardiovascular Implications in Preeclampsia
An Overview

Karen Melchiorre, MD, PhD; Rajan Sharma, MD, MRCP; Rasky Thilaganathan, MD, PhD, FRCOG

(Circulation. 2014;130:703-714.)
Tissue oxygen delivery

\[ \text{Blood pressure (BP)} = \text{Cardiac output (CO)} \times \text{Systemic vascular resistance (SVR)} \]

Cardiovascular Implications in Preeclampsia
An Overview
Karen Melchiorre, MD, PhD; Rajan Sharma, MD, MRCP; Rauky Thilagathan, MD, FRD, FRCOG

(Circulation. 2014;130:703-714.)
All three drugs achieved the primary outcome within 12hrs

Nifedipine and labetalol achieved outcome within 3hrs

Nifedipine resulted in:
- More maternal blood Tx
- Increased NICU admissions x2
- Increased RDS x4
- Increased SGA x2
Cardiovascular legacy
Chronic hypertension after PE

1m Danish births linked to national prescription register

Ida Brehens et al. BMJ 2017
Maternal health

Cerebrovascular morbidity

Chronic kidney disease

Cardiovascular morbidity

Cardiovascular-Placental axis

Feto-placental demands

Fetal growth restriction

Hypertension
Proteinuria
Cerebral oedema
Liver dysfunction

SF/It1
PIGF

Excessive demand
Fetal macrosomia
Twin pregnancy
Prolonged pregnancy
Excessive weight gain

Poor cardiac reserve
Maternal age
Obesity
Ethnicity
Diabetes
Auto-immune disease
Chronic hypertension
Chronic kidney disease
First they ignore you. Then they laugh at you. Then they fight you. Then you win.

Mahatma Gandhi