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University of California, San Diego

Update of Pathophysiology of Preeclampsia for Clinicians
Pathophysiology of Preeclampsia: Objectives

- Highlight historical antecedents
- Define pathological nature of the disease
- Update knowledge of placental origin
- Review physiology of maternal illness
- Discuss role of circulating factors
- Update patho-directed interventions
Consultant for Alere, Inc.
Historical Antecedents: Eclampsia

2200 BC – Egypt
- Third Papyrus
- Tongue biting at birth
- Olive oil treatment

400 BC - Greece
- Hippocrates
- Seizure in labor are fatal
- Eclampsia = brilliant light

Middle Ages
- Midwifery care
- Fetus won’t survive fits
- Toxic humors => phlebotomy, blistering, starvation, purges
Recognition of “Pre-eclampsia”

- **Key observations**
  - 1797 – Edema (Demanet)
  - 1842 – Proteinuria (Lever)
  - 1847 – Hypertension (Vaquez and Nobelcourt)

- **Syndrome of “pre-eclampsia”**
  - Linked to morbidity and mortality
  - Etiologies: nephritis, urea, proteinemia, bacteria, fetal debris or waste
  - Treatments: salt restriction, diuresis, phlebotomy, diet, lavage, colonic irrigation
20th Century: Preeclampsia as Toxemia

- Slow progress
- Few interventions
- Ambiguous, conflicting guidelines
What is Preeclampsia?

What is not Preeclampsia?
Classification of Preeclampsia

ACOG 2012

Hypertension
- Average DBP ≥ 90

Proteinuria
- 300 mg per 24° collection
- 30 mg/mmol in random sample

Severe Criteria
- Cerebral or visual disturbances, including seizures
- Epigastric or RUQ pain
- Pulmonary edema or cyanosis
- BP ≥ 160, or ≥ 110
- ≥ 5 gms/24°, or 3+ dipstick x 2
- Thrombocytopenia
- Impaired liver function
- Oliguria
- Fetal growth restriction

SOGC 2008

Hypertension
- Average DBP ≥ 90

Proteinuria
- 300 mg per 24° collection
- 30 mg/mmol in random sample

and

≥ 1 adverse condition
- Headache, visual disturbance, abdominal or RUQ pain, nausea vomiting, chest pain or dyspnea
- Eclampsia, severe hypertension, pulmonary edema or abruption
- Elevated AST, ALT or LDH, plts < 100 or albumin < 20 g/L
- Oligohydramnios, IUGR, umbilical artery Doppler or IUFD

Severe Criteria
- Severe hypertension (≥160/110), heavy proteinuria (≥ 3 gm/24°, onset < 34 weeks’, of ≥ 1 adverse condition present
What really is Preeclampsia?

- Preeclampsia is a “maternal” syndrome
  - Recognized by clinical endpoints
- Preeclampsia is a two-stage disease
  - Placental contribution
  - Maternal response
- Preeclampsia is a disturbance of endothelial function
  - Multiple pathogenic insults
- Preeclampsia is more than just hypertension
Stage I: Placental Origins

- **Normal placentation**
  - Deep trophoblast invasion
  - Remodeling of spiral artery
  - Endovascular replacement
  - Controlled, sequential perfusion

- **Pathological placentation**
  - Shallow trophoblast invasion
  - Limited arterial remodeling
  - Failed endovascular invasion
  - Over, or underperfusion of placenta
Stage I: Spiral Artery Remodeling

- **Extravillous trophoblast**
  - Invade interstitially/endothelially
  - Plug spiral arteries
  - Remodel extracellular matrix
  - Induce EC and VSMC apoptosis

- **Fibrinoid**
  - Deposited by EVT

- **Extracellular matrix**

- **Decidual natural killer cell**
  - Regulate EVT invasion
  - Prime vessel for remodelling
  - Induce VSMC disorganisation/loss

- **Decidual macrophage**
  - Regulate EVT invasion
  - Accumulate around spiral arteries
  - Phagocytose dead cells

- **Endothelial cell**
  - Interact with EVT
  - Temporarily lost from vessel

- **VSMC**
  - Lost from vessel
  - De-differentiate/migrate
  - Undergo apoptosis
  - Loss of vessel contractility

Update 1: Multiple causes of placental defect

- Impaired cell interaction
  - Failed trophoblast integrin switching
  - Immune dysregulation
  - Decidual inflammation
  - Inhibitory micro RNAs
- Focal ischemia
  - Impaired vasculogenesis
  - Oxidative stress
  - Thrombophilia
- Common pathways for adverse outcomes
  - Preeclampsia, IUGR, fetal loss, abruption, preterm labor
Update 2: Maternal decidual natural killer cells (dNK) are key mediators of implantation

- Predominant lymphocyte in decidua
  - Highly active
    - Chemokines, angiogenic growth factors, proteinases
    - Induce spiral arteriole remodeling
    - Enhance trophoblast invasion and differentiation
    - Suppress immune rejection
- dNK cells reduced (8-fold) in preeclampsia*

Update 3: Angiogenesis is essential for placental development

- VEGF family

Update 4: Abnormal angiogenesis in placenta precedes preeclampsia

Serum Placenta Growth Factor
11 to 14 weeks

Control  Early PE  Late PE  Gest Htn

PIGF (MoM)

* *

sEnd

sFlt-1

PIGF


Update 5: Thrombophilia not strongly associated with preeclampsia

- Low risk of preeclampsia in unaffected carriers

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>N</th>
<th>Incidence of preeclampsia</th>
<th>Odd Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Carriers</td>
<td>Noncarriers</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>21,833</td>
<td>3.8%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Factor II Variant</td>
<td>14,254</td>
<td>3.5%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>N</th>
<th>Odd Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticardiolipin antibody</td>
<td>6751</td>
<td>1.78 (0.39-8.16)</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>4657</td>
<td>5.17 (0.60-44.56)</td>
</tr>
</tbody>
</table>


- Thrombophilia probably not cause of preeclampsia
  - Aggravates existing placental defects
Stage II: The Maternal Syndrome

- Hypertension
- Proteinuria
- Edema
- Seizure
- Thrombocytopenia
- Liver injury
- Pulmonary edema
Stage II: The Maternal Syndrome

- Hypertension
- Proteinuria
- Edema
- Seizure
- Thrombocytopenia
- Liver injury
- Pulmonary edema

Healthy endothelium

Activated endothelium

Preeclampsia: An endothelial cell disorder

James M. Roberts, MD, Robert N. Taylor, MD, PhD, Thomas J. Musci, MD, George M. Rodgers, MD, PhD, Carl A. Hubel, PhD, and Margaret K. McLaughlin, PhD

San Francisco, California (AM J Obstet Gynecol 1989;161:1200-4.)
What factors induce maternal endothelial dysfunction in preeclampsia?

Candidate “toxin” should be:

- Produced by placenta
- Invariably present in disease
- Precede clinical manifestations
- Rapidly cleared after delivery
- Unique to pregnancy
- Modulate endothelial function
  - Endothelial dysfunction is the key
## Proposed Pathogenic Factors of the Maternal Syndrome of Preeclampsia

- Oxidative stress, lipid hydroperoxides
- Placental trophoblast debris
- Inflammatory cytokines (TNF-a, IL-6)
- Activated neutrophils, monocytes and platelets
- Inflammatory prostaglandins (thromboxane)
- Inhibitors of nitric oxide synthase (ADMA)
- Agonistic anti-angiotensin receptor autoantibodies
- Endothelin-1
- Anti-angiogenic growth factors (sFlt-1, sEnd)
Update 6: Imbalance of circulating placental angiogenic factors causes the syndrome of preeclampsia

Soluble Flt-1 (sVEGF R1)

Is elevated in women diagnosed with preeclampsia.

- Rises slowly through normal pregnancy
- Is elevated in women destined to develop preeclampsia
- Is 3-fold higher in women with preeclampsia

Placental Growth Factor (PIGF)

- Rises then falls in normal pregnancy
- Lower in women destined to develop preeclampsia
- Significantly decreased at time of diagnosis of preeclampsia

Update 7: Oxidative stress contributes to endothelial dysfunction, but antioxidants do not prevent preeclampsia

Trial of Antioxidants (vitamin C and E) to prevent preeclampsia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Antioxidants (N=4993)</th>
<th>Placebo (N=4976)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>358 (7.2)</td>
<td>332 (6.7)</td>
<td>1.07 (0.93-1.24)</td>
</tr>
<tr>
<td>Mild</td>
<td>212 (4.2)</td>
<td>191 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>134 (2.7)</td>
<td>129 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Eclampsia</td>
<td>10 (0.2)</td>
<td>4 (0.1)</td>
<td></td>
</tr>
<tr>
<td>BW &lt; 3%</td>
<td>133 (27)</td>
<td>132 (2.7)</td>
<td>1.00 (0.79-1.27)</td>
</tr>
<tr>
<td>Fetal loss</td>
<td>113 (2.3)</td>
<td>122 (2.5)</td>
<td>0.92 (0.72-1.19)</td>
</tr>
</tbody>
</table>

## Update 8: Low dose aspirin initiated before 16 weeks demonstrates greater risk reduction

Meta-analysis of low dose aspirin for the prevention of adverse perinatal outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Initiated (wks)</th>
<th>N</th>
<th>Treat (%)</th>
<th>Con (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preeclampsia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 16</td>
<td>1479</td>
<td>7.6</td>
<td>17.9</td>
<td>0.47</td>
<td>(0.36-0.62)</td>
</tr>
<tr>
<td>&gt; 16</td>
<td>10673</td>
<td>7.5</td>
<td>8.4</td>
<td>0.78</td>
<td>(0.61-0.99)</td>
</tr>
<tr>
<td><strong>Severe preeclampsia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 16</td>
<td>649</td>
<td>1.5</td>
<td>12.3</td>
<td>0.18</td>
<td>(0.08-0.41)</td>
</tr>
<tr>
<td>&gt; 16</td>
<td>1494</td>
<td>3.3</td>
<td>5.5</td>
<td>0.65</td>
<td>(0.40-1.07)</td>
</tr>
<tr>
<td><strong>Perinatal death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 16</td>
<td>1308</td>
<td>1.1</td>
<td>4.0</td>
<td>0.41</td>
<td>(0.19-0.92)</td>
</tr>
<tr>
<td>&gt; 16</td>
<td>9557</td>
<td>2.6</td>
<td>3.0</td>
<td>0.93</td>
<td>(0.73-1.19)</td>
</tr>
</tbody>
</table>

Endothelial Cell Function in Health

- Vasorelaxation
  - Blood pressure
- Permeability
  - Filtering
- Coagulation
  - Thrombosis
- Adhesiveness
  - Platelet and monocyte
- Proliferation
  - Smooth muscle

Stillmann I, 2009
Endothelial Control of Blood Pressure

Ang II → Ang I

ACE

Angiotensin

IL-1

epinephrine

AVP

thrombin

neutrophil

serotonin

acetylcholine

histamine

platelets

ET-B

ET-1

PIGF

ET-B

Flt-1

BK

ACE

Endothelium

Endothelin-1

Cyclo-oxygenase

PGH₂

Prostacyclin

[Ca²⁺]ᵢ

Contraction

Relaxation

Smooth Muscle

AT₁-R

ETₐ

ETₐ

TX-R

TX-R

L-arginine

eNOS

Nitric Oxide

cGMP

[Ca²⁺]ᵢ

Acetylcholine

serotonin

ADP

thrombin

shear stress

cAMP

K⁺
Proposed Mechanisms of Hypertension in Preeclampsia

- Increased sensitivity to Ang II and catecholamines
- Increased circulating and local endothelin-1
- Increased thromboxane; decreased prostacyclin
- Decreased NO production; increased NO clearance
- Increased sympathetic tone
Update 10: Antiangiogenic blockade by sFlt-1 also leads to hypertension

Proteinuria in preeclampsia


Update 10: Proteinuria of preeclampsia is caused by anti-angiogenic effect on endothelium

- Anti-angiogenic state
  - Blocks podocyte signaling
  - Disturbs capillary fenestrae
  - Induces endotheliosis
- Proteinuria
  - Loss of size and charge filter
  - Glycocalyx injury
  - Bland albuminuria
    - Few casts
- Similar phenotype in
  - Liver venules
  - Blood brain capillaries
Preeclampsia
A Linear Model

Stage I
- Predispositions
  - Genetic
  - Environmental
  - Nutritional
  - Immunological

- Decidua-Trophoblast
  - VEGF, IGF, and TGF-β
  - Altered Integrin switching
    - α6β1 to α5β1 and α1β1
  - Deficient dNK cell function

- Deficient trophoblast invasion
  - Shallow
  - Failed endovascular remodeling
  - Poor immunodulation
  - Thrombosis

- Placental injury / stress
  - Ischemia
  - Oxidative stress
  - Overgrowth / undergrowth
  - Apoptosis

Stage II
- Circulating toxin
  - Antiangiogenic Factor
  - Placental debris
  - Cytokines
  - Free radicals

- End-organ injury
  - Seizures / scotomata
  - Proteinuria
  - Hepatic injury
  - Stroke
  - IUGR / Abruption

- Hypertension
- Vasospasm
- Capillary leak
- DIC

- Vasopressors
  - ET-1, Ang I & II, TxA

- Cell Adhesion Molecules
  - VCAM, ICAM, e-selectin

- Platelet and monocyte activity

- Endothelial dysfunction
  - Decreased NO, EDHPF
  - Lost Refractoriness
  - Oxidative stress

- Placental injury / stress
  - Ischemia
  - Oxidative stress
  - Overgrowth / undergrowth
  - Apoptosis
End

- Thank you!
PET and HELLP are similar in many ways
- PE is about 10x more frequent than HELLP
- Onset of HELLP more rapid
- Both share typical placental lesions
  - But release of placental factors differs in quantity and timing
    - Earlier fall in PP13
    - Earlier and higher rise in sEnd

Greater inflammatory component in HELLP
- CRP, TNF-a, IL-6 higher
- WBC higher in HELLP
- Greater complement activation
- Greater release of multimeric wWF
  - Which leads to more platelet-vessel adhesion
Update 12: AT1R autoantibodies augment endothelial dysfunction

- AT1 AA prevalent in PET
- Titers correlate with severity of Dz
  - AA action detectable up to 18 mos after delivery
- Source
  - Ischemia in placenta induces AA in RUPP rat (Lamarca B, Hypertension, 2008)
  - The specific stimulus for the production of the AT1 AA is unknown
    - Structural similarity to Parvo B12 VP2 protein.
- Mechanism
  - Bivalent IgG may bind and dimerize the AT1R which leads to its sustained activation
- Treatment with Ang T1 antagonist (losartan) attenuates htn in RUPP model