Maternal-Placental Syndromes

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Chief of Obstetrics and Maternal Fetal Medicine
Adverse Pregnancy Outcomes

Placental Cause

• **Definite**
  - Placenta previa/accreta (0.5%/0.2%)
  - Abnormal placental or cord morphology (velamentous, vasa previa)
  - Tumors (e.g. trophoblastic neoplasia, choriangioma)

• **Likely**
  - Twin to twin transfusion syndrome (0.1%)
  - Miscarriage (up to 20%)
  - Fetal death (0.1%)
  - Preeclampsia/gestational hypertension (6-8%/15%)
  - Fetal growth restriction (3-10%)
  - Abruption (1%)

• **Suspected**
  - Preterm birth (10-12%)
  - Oligohydramnios (up to 5%)
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Other Placental Conditions

• Gestational Diabetes
• Hyperemesis gravidarum
• Fatty liver of pregnancy
• Cholestasis of pregnancy
• Pruritic urticarial papules and plaques of pregnancy (PUPPP)
Placenta Previa

• Covers the internal os

• Risk factors
  – Advanced maternal age
  – Multiparity
  – Multiple gestation
  – Prior uterine surgery (CD, myomectomy, curettage)
  – Substance abuse (smoking, cocaine)
  – Abnormal placental development

• Delivery by cesarean

• Risks:
  – Bleeding (antepartum, intraoperative)
  – Fetal growth abnormalities
  – Preterm birth
  – Accreta
Placenta Accreta

- Morbidly adherent placenta (accreta, increta, percreta)
- Risk factors
  - Prior uterine surgery
  - Placenta previa
- Preterm delivery
- Morbidity and mortality
Abnormal Morphology

• Abnormalities
  – Succenturiate lobe
  – Circumvallate placenta
  – Velamentous cord insertion
  – Vasa previa

• Risks
  – Stillbirth
  – Fetal bleeding
  – Growth restriction
  – Cesarean delivery
Twin to Twin Transfusion Syndrome (TTTS)

- Monozygotic pregnancies
- Disequilibrium in fetal blood circulation
- Fluid overload in recipient
- Intravascular volume contraction in donor
- Risk of stillbirth, PTB, neurologic damage
## Pregnancy Loss

<table>
<thead>
<tr>
<th>Early pregnancy loss</th>
<th>Loss before 10 wk</th>
</tr>
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<tbody>
<tr>
<td>Fetal death</td>
<td>10 0/7–19 6/7 wk</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>At least 20 wk</td>
</tr>
</tbody>
</table>
Stillbirth

• About 1 in 160 pregnancies in the US
• About 26,000 per year
• Equal to number of deaths due to preterm birth
  PLUS the number of deaths due to SIDS
• Equal to the number of infant deaths
• Antepartum vs intrapartum
Stillbirth Hazard Among Singletons, 2001 - 2002

Willinger et al., Am J Obstet Gynecol 2009;201:469.e1-8

FIGURE
Stillbirth hazard among singletons, 2001–2002

Gestation (weeks)

Hazard of stillbirth per 1,000 ongoing pregnancies

- Non-Hispanic White
- Non-Hispanic Black
- Hispanic
Probable / Possible Cause of Death
Broad Categories

Percent

0 5 10 15 20 25 30 35

Obstetric  Placental  Fetal  Infection  Cord  Htn  Medical

SCRN; JAMA 2011;306:2459-68
Timing in Gestation of Stillbirths

Percent

<table>
<thead>
<tr>
<th>Weeks Gestation</th>
<th>Overall</th>
<th>Intrapartum</th>
<th>rtum</th>
</tr>
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<tbody>
<tr>
<td>20-24</td>
<td>80</td>
<td>70</td>
<td>50</td>
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<tr>
<td>25-28</td>
<td>20</td>
<td>10</td>
<td>5</td>
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<tr>
<td>29-32</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>33-36</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>37+</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

p < 0.0001

SCRN; JAMA 2011;306:2459-68
Probable / Possible Cause of Death by Timing of Death

Percent

- Placental: p < 0.0001
- Obstetric: P = 0.003
- Fetal: P < 0.001
- Infection: p = 0.007
- Medical
- Cord
- HTN

Source: SCRN; JAMA 2011;306:2459-68
Stillbirth Hazard Among Singletons, 2001 - 2002

Willinger et al., Am J Obstet Gynecol 2009;201:469.e1-8

FIGURE
Stillbirth hazard among singletons, 2001–2002

Preterm Labor

Hazard of stillbirth per 1,000 ongoing pregnancies

Gestation (weeks)
Preeclampsia

• Specific to human pregnancy
• Multi-organ disease
• Major cause of maternal and perinatal mortality
Hypertension in Pregnancy

Report of the American College of Obstetricians and Gynecologists’ Task Force on Hypertension in Pregnancy

Hypertension in Pregnancy was developed by the Task Force on Hypertension in Pregnancy: James M. Roberts, MD, Chair; Phyllis A. August, MD, MPH; George Bakris, MD; John R. Barton, MD; Ira M. Bernstein, MD; Maurice Druzin, MD; Robert R. Gaiser, MD; Joey P. Granger, PhD; Arun Jeyabalan, MD, MS; Donna D. Johnson, MD; S. Ananth Karumanchi, MD; Marshall Lindheimer, MD; Michelle Y. Owens, MD, MS; George R. Saade, MD; Baha M. Sibai, MD; Catherine Y. Spong, MD; Eleni Tsigas; and the American College of Obstetricians and Gynecologists’ staff: Gerald F. Joseph, MD; Nancy O’Reilly, MHS; Alyssa Politzer; Sarah Son, MPH; and Karina Ngaiza.

Obstet Gynecol 2013;122:1122-31
Pregnancy Related Hypertension

- Gestational hypertension
- Preeclampsia
  - Without severe features
  - With severe features
- Superimposed preeclampsia
- Eclampsia
**TABLE E-1. Diagnostic Criteria for Preeclampsia**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure</strong></td>
<td>• Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure</td>
<td>• Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy</td>
</tr>
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<td></td>
<td>• Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy</td>
<td>and</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>• Greater than or equal to 300 mg per 24-hour urine collection (or this amount extrapolated from a timed collection)</td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>• Protein/creatinine ratio greater than or equal to 0.3*</td>
<td>• Dipstick reading of 1 + (used only if other quantitative methods not available)</td>
</tr>
<tr>
<td></td>
<td>Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:</td>
<td></td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>• Platelet count less than 100,000/microliter</td>
<td></td>
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<td><strong>Renal insufficiency</strong></td>
<td>• Serum creatinine concentrations greater than 1.1 mg/dl or a doubling of the serum creatinine concentration in the absence of other renal disease</td>
<td></td>
</tr>
<tr>
<td><strong>Impaired liver function</strong></td>
<td>• Elevated blood concentrations of liver transaminases to twice normal concentration</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary edema</strong></td>
<td></td>
<td></td>
</tr>
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<td><strong>Cerebral or visual symptoms</strong></td>
<td></td>
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*Each measured as mg/dl.
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| **Pulmonary edema** |  
| **Cerebral or visual symptoms** |  

*Each measured as mg/dl.
Placentation & Preeclampsia

A  Normal placentation
   Maternal side
   Spiral artery
   Endovascular cytotrophoblast
   Cytotrophoblast
   Myometrium
   Intervillous space
   Anchoring villus
   Placental side

B  Abnormal placentation
   Maternal side
   Spiral artery
   Endothelium
   Arterial smooth muscle
   Macrophage
   Decidua
   NK cell
   Decidual villus
   Intervillous space
   Syncytiotrophoblast

C  Stages of preeclampsia
   STAGE 1
   First half of pregnancy
   Poor placentation
   STAGE 2
   Second half of pregnancy
   Oxidatively stressed placenta
   sFlt-1
   Syncytiotrophoblast debris/other factors
   Dysfunctional maternal endothelium
   Maternal systemic inflammatory response
   Clinical signs of pre-eclampsia

Redman et al. Science 2005;308:1592-4
Pathogenesis of Preeclampsia

Abnl trophoblast invasion

\[\downarrow\]

Reduced placental perfusion
Pathogenesis of Preeclampsia

Vascular dx → Abnl trophoblast invasion → Reduced placental perfusion
Pathogenesis of Preeclampsia

Vascular dx  \( \rightarrow \) Abnl trophoblast invasion  \( \rightarrow \) Reduced placental perfusion  \( \rightarrow \) Excessive trophoblast
Pathogenesis of Preeclampsia

Vascular dx  Abnl trophoblast invasion  Excessive trophoblast

↓

Relative reduced placental perfusion
Pathogenesis of Preeclampsia

Vascular dx → Abnormal trophoblast invasion → Excessive trophoblast

Relative reduced placental perfusion → Endothelial injury
Pathogenesis of Preeclampsia

Vascular dx        Abnl trophoblast invasion        Excessive trophoblast

Relative reduced placental perfusion

⇑⇓

Endothelial injury
Pathogenesis of Preeclampsia

Vascular dx  ➔ Abnl trophoblast invasion ➔ Relative reduced placental perfusion ➔ Endothelial injury ➔ Activation of coagulation

Excessive trophoblast ➔ Altered vascular permeability ➔ Vasospasm
Pathogenesis of Preeclampsia

Vascular dx  Abnl trophoblast invasion  Excessive trophoblast

Relative reduced placental perfusion

Endothelial injury

↑↓

Altered vascular permeability
Proteinuria

Edema

HTN

Vasospasm

Oliguria

Abruption Fetal distress

Seizures

DIC

PLT dysfcn

Elevated LFTs

Thrombocytopenia
Normal Pregnancy

Placental Perfusion → Placental Metabolic Need
Preeclampsia

Placental Perfusion

Placental Metabolic Need

Release Factors into Maternal Circulation

Endothelial Dysfunction

Blood Pressure Increase and Organ Damage
Placental Abruption

- Premature separation of the placenta
- Overlaps with other adverse pregnancy outcomes
- Major cause of maternal mortality and morbidity
- Diagnosis is clinical and imprecise
Fetal Growth Restriction Definitions

EFW < 10\textsuperscript{th} percentile
(10\% of population)

EFW > 2 SD below mean
(~ 3\textsuperscript{rd} percentile)

EFW or AC < 5\textsuperscript{th} percentile
(most clinically applicable)

Favored by ACOG
Fetal Growth Restriction

- Associated with perinatal mortality and morbidity
- Common reason for indicated preterm delivery
- Differentiate between small for gestational age (80%) and true growth restriction (20%)
- Intrinsic (20%) versus extrinsic (80%)
Preterm Birth

• Delivery between 16 and 36 6/7 weeks
• Classification
  – Spontaneous
    • With intact membranes
    • Following premature rupture of membranes
  – Non-spontaneous
## Causes of Preterm Birth

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Spontaneous preterm labor</td>
<td>31 – 50%</td>
</tr>
<tr>
<td>pPROM</td>
<td>6 – 40%</td>
</tr>
<tr>
<td>Multiples and complications</td>
<td>12 – 28%</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>12%</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td>2 – 4%</td>
</tr>
<tr>
<td>Antepartum hemorrhage</td>
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A United States National Reference for Fetal Growth
CUSTOMISED ANTENATAL GROWTH CHART

Mrs Small (DOB: 01/01/75)

Para 1 Pakistani
Maternal height: 150
Booking weight: 49
Body Mass Index: 21.8

37w 0d: 2500 g: Army

Gestation week

X = Fundal height  O = Estimated weight by scan

24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42

CUSTOMISED ANTENATAL GROWTH CHART

Mrs Large (DOB: 01/01/75)

Para 1 European
Maternal height: 177
Booking weight: 78
Body Mass Index: 24.9

37w 0d; 2500 g; Amy

X = Fundal height  O = Estimated weight by scan

Gestation week

<table>
<thead>
<tr>
<th></th>
<th>24</th>
<th>25</th>
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Fundal Height (cm) vs. Weight (g)
FGR and Prematurity
Standard Population Norms

<table>
<thead>
<tr>
<th>PERCENTILE STANDARD NORMS</th>
<th>PRETERM N = 44</th>
<th>TERM N = 44</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5&lt;sup&gt;th&lt;/sup&gt;</td>
<td>3 (6.8)</td>
<td>1 (2.3)</td>
<td>0.366</td>
</tr>
<tr>
<td>&lt;10&lt;sup&gt;th&lt;/sup&gt;</td>
<td>5 (11.4)</td>
<td>2 (4.5)</td>
<td>0.272</td>
</tr>
</tbody>
</table>
FGR and Prematurity
Individualized Growth Potential

<table>
<thead>
<tr>
<th>PERCENTILE</th>
<th>G.R.O.W.</th>
<th>PRETERM N = 44</th>
<th>TERM N = 44</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5&lt;sup&gt;th&lt;/sup&gt;</td>
<td>10 (22.7)</td>
<td>2 (4.5)</td>
<td>0.008</td>
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<tr>
<td>&lt;10&lt;sup&gt;th&lt;/sup&gt;</td>
<td>13 (29.5)</td>
<td>2 (4.5)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Fetal growth and onset of delivery: A nationwide population-based study of preterm infants

Nils-Halvdan Morken, MD, a,c Karin Källen, PhD, b Bo Jacobsson, MD, PhD c,d

Table III Odds ratio, with 95% CI, for SD classes ( <-3, -3 to -2.1, -2 to -1.1, 1to1.9, and 2 to 2.9) versus appropriate for gestational age (-1 SD to 0.99 SD) among infants born after spontaneous preterm labor, compared with term infants (born spontaneously after at least 37 completed weeks of pregnancy)*

<table>
<thead>
<tr>
<th>SD classes</th>
<th>&lt; 28 wks (95% CI)</th>
<th>28-31 wks (95% CI)</th>
<th>32-33 wks (95% CI)</th>
<th>34-36 wks (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;-3</td>
<td>9.3 (6.2-13.8)</td>
<td>13.3 (10.3-17.2)</td>
<td>5.9 (4.4-7.9)</td>
<td>3.1 (2.6-3.6)</td>
</tr>
<tr>
<td>-3 to -2.1</td>
<td>2.6 (2.0-3.3)</td>
<td>3.2 (2.7-3.8)</td>
<td>1.9 (1.6-2.2)</td>
<td>1.2 (1.1-1.3)</td>
</tr>
<tr>
<td>-2 to -1.1</td>
<td>1.8 (1.6-2.1)</td>
<td>2.0 (1.8-2.2)</td>
<td>1.3 (1.2-1.5)</td>
<td>1.0 (1.0-1.0)</td>
</tr>
<tr>
<td>1 to 1.9</td>
<td>0.6 (0.5-0.7)</td>
<td>0.5 (0.5-0.6)</td>
<td>0.7 (0.7-0.8)</td>
<td>1.1 (1.1-1.2)</td>
</tr>
<tr>
<td>2 to 2.9</td>
<td>0.4 (0.2-0.7)</td>
<td>0.4 (0.2-0.6)</td>
<td>0.8 (0.6-1.0)</td>
<td>1.6 (1.5-1.7)</td>
</tr>
</tbody>
</table>

Unifying Theory of Placental Conditions

• Co-occurrence of the various conditions
• Overlap in risk factors
• Occurrence of one condition increases risk for all conditions in future pregnancies
Unifying Theory of Placental Conditions

- **Implantation**
  - Structure Location
    - Abnormal placentation
      - Early loss
        - Adequate
          - Gestational hypertension
            - Adequate
              - Fetal growth restriction
            - Inadequate
              - Preterm birth
            - Excessive
              - Preeclampsia
        - Inadequate
          - Fetal compensation
            - Preterm birth
          - Stillbirth
Tip of the Iceberg

Adverse Pregnancy Outcomes
Tip of the Iceberg

Adverse Pregnancy Outcomes

Long Term Outcomes
Tip of the Iceberg

Adverse Pregnancy Outcomes

Offspring

Mother
Tip of the Iceberg

Adverse Pregnancy Outcomes

Offspring

Directly Related
Neuromotor dysfunction
Broncho-pulmonary dysplasia
Retinopathy of prematurity
Tip of the Iceberg

Adverse Pregnancy Outcomes

Offspring

Directly Related
Neuromotor dysfunction
Broncho-pulmonary dysplasia
Retinopathy of prematurity

Developmental Programming
Cardiovascular disease
Metabolic dysfunction
Neurobehavioral
Tip of the Iceberg

Adverse Pregnancy Outcomes

Mother

Directly Related

Stroke
Renal failure
Operative morbidity
Tip of the Iceberg

Adverse Pregnancy Outcomes

Mother

Directly Related
- Stroke
- Renal failure
- Operative morbidity

Maternal Programming
- Cardiovascular disease
- Metabolic dysfunction
Placental Programming
Barker & Thornburg Placenta 2013;34:841-845

Development of the placenta and cord ➔ Disease

Process
- Spiral artery invasion
- Spiral artery unplugging
- Surface growth
- Polarized surface growth
- Compensatory enlargement
- Cotyledon development
- Cord development

Phenotype
- Weight
- Weight/birthweight
- Surface length
- Surface breadth
- Surface area
- Length – breadth
- Thickness
- Cotyledon number
- Cord length

Disease
- Coronary heart disease
- Chronic heart failure
- Sudden cardiac death
- Hypertension
- Rheumatic heart disease
- Type 2 diabetes
- Overweight
- Osteoporosis
- Asthma
- Lung cancer
- Colorectal cancer
- Hodgkin’s Lymphoma
- Premature death
Tip of the Iceberg

Adverse Pregnancy Outcomes

Mother

Directly Related
Stroke
Renal failure
Operative morbidity

Maternal Programming
Cardiovascular disease
Metabolic dysfunction
Microparticles/Microchimerism
Microparticles

Medical conditions associated with increased circulating MPs [14,17,18]

<table>
<thead>
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<th>Ischaemic heart disease</th>
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<td>Cerebrovascular events</td>
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<td>Metabolic syndrome</td>
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<td>Diabetes</td>
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<td>Heparin induced thrombocytopenia</td>
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<td>Antiphospholipid antibody syndrome</td>
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<td>Thrombotic thrombocytopenic purpura</td>
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<td>Sickle cell disease</td>
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Microparticles
Knight et al. BJOG 1998;105:632-40

STBM (ng protein/ml plasma)

Pre-eclampsia  Normal Pregnant  Non-pregnant

STBM (ng protein/ml plasma)

Uterine  Peripheral  Uterine  Peripheral

Pre-eclamptic  Normal Control
Challenges

• Evidence of placental involvement indirect
Multiple markers of abnormal placentation

- **Biochemical**
  - PAPP-A, AFP, Inhibin A, sFlt-1, PIGF etc
- **Ultrasonic**
  - Utero-placental Doppler flow velocimetry (uterine and umbilical)
  - Placental appearance (echolucencies and calcification)
  - Placental size (depth and volume [3D])
- **Other modalities**
  - MRI (structure, flow and metabolism [MRI spectroscopy])
- **Indirect assessment**
  - Through assessment of fetal growth
Challenges

• Evidence of placental involvement indirect
• Likely abnormality starts early
• Research in OB is heuristic (similarity, familiarity, availability)
• Too much hubris in the field
• Likely wrong in many assumptions
• We may have strayed too far
• Many interaction and compensations
Stage 1
- Reduced Placental Perfusion
- Abnormal vascular remodeling of spiral arteries
- Release of toxic factors

Abnormal Lipid Metabolism

Reduced HDL
Predominance of small, dense LDL cholesterol

Hypertriglyceridemia
Insulin resistance
Hyperinsulinemia
Hypertriglyceridemia

Endocrine Dysfunction

Stage 2
- Maternal Endothelial Damage → VASOSPASM

Inflammatory cytokines → + endothelial damage

Increased production of free radicals and lipid peroxides → + endothelial cell damage

Fetal Effects

Stage 1
- Reduced Placental Perfusion
- Abnormal vascular remodeling of spiral arteries
- Release of toxic factors

Inflammation

Oxidative Stress