The Placenta – More than a Conduit

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Fetal Growth and Development

Fetal Programming

Trophoblast Invasion/Uteroplacental Blood Flow

Maternal Substrates

Maternal Hormones

Maternal metabolism

Peptide/Steroid Hormones Production/Metabolism

Fetal placental blood flow

Oxygen

Angiogenic Factors

Nutrient Transport

Metabolism

Fetal GROWTH AND DEVELOPMENT

FETAL PROGRAMMING

Uterus

Placenta

Fetus

Immune Barrier

Nutrient Transport

Carbon Dioxide

FETAL GROWTH AND DEVELOPMENT

FETAL PROGRAMMING
Maternal-Placental-Fetal Unit

Mother

External Environment

Intrauterine Environment

Placenta

Fetus
Why is Monitoring Placental Health Important?

- **Acute**
  - Placental and fetal health at different stages of gestation
  - Monitoring fetal growth and development
- **Chronic**
  - Role of placenta in fetal programming of disease in adult life
  - Relationship of placental disease to future maternal cardiovascular health
Adult Disease

Cardiovascular
Diabetes (Insulin resistance/Metabolic syndrome)
Obesity
Stroke
Osteoporosis
Obstructive Airway Disease
Cancer
Disordered HPAA axis
Behavioral abnormalities
<table>
<thead>
<tr>
<th>Hormones and growth factors produced by the human placenta</th>
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<tbody>
<tr>
<td>Estrogens</td>
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<tr>
<td>Progesterone</td>
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<td>Inhibin/activin</td>
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<td>Nitric Oxide</td>
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<tr>
<td>Chorionic gonadotropin</td>
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<tr>
<td>GnRH</td>
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<td>Placental growth hormone</td>
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<td>Placental lactogen</td>
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<td>IGF-1</td>
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<td>IGF-2</td>
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<td>Growth hormone-releasing factor</td>
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<tr>
<td>Somatostatin</td>
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<tr>
<td>PIGF, sFlt1, sEndoglin</td>
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<td>Corticotropin-releasing hormone</td>
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<td>Thyrotropin-releasing hormone</td>
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<td>Leptin</td>
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<td>VEGF</td>
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<td>Atrial naturetic hormone</td>
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<td>Encephalins</td>
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<tr>
<td>Serotonin</td>
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<tr>
<td>Erythropoietin</td>
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<td>Prorenin</td>
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<td>Relaxin</td>
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<td>PTHrP</td>
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<td>1,25 dihydroxyvitamin D3</td>
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Trophoblast Populations in Placental Villi

[Image of histological sections showing ST and CT cells]
How does the placenta contribute to alterations in fetal development?

- Passive: e.g. Exposure to altered levels of nutrients, EDC’s and transfer
- Physical: Altered vascular resistance (heart)
- Functional: Effect of adverse intrauterine environment e.g. oxidative stress
- Molecular: Altered expression of nutrient transporters, receptors, synthesis of steroids and peptides regulating maternal metabolism and fetal growth and development eg hPL, serotonin
- Genetic: Imprinted genes
- Epigenetic: Environmental influences on placental (and fetal) gene expression and function
Placental Vascular Impedance and Fetal Heart Development

- Changes in placental vascular impedance impact fetal cardiovascular loading
- Heart fitness is determined by hemodynamic, growth factor and oxygen/nutrient cues before birth.
- All are influenced if not regulated by the placenta
Confounders/Adverse Environments

• Fetal Sex
• Ethnicity
• Environmental influences
  – Obesity, Nutrient composition and level
  – Inappropriate exposure to developmental signals e.g. glucocorticoids
  – Medical conditions (GDM, PE, ART)
  – Oxygenation, oxidative stress, smoking
  – Immune status, infection
  – EDC’s, Xenobiotics
  – Stress (maternal/fetal)
Evidence for Fetal and Placental Sexual Dimorphism

- Male fetuses larger but have more adverse outcomes: preterm birth, PPROM, placenta previa, PE, lagging lung development, macrosomia, late stillbirths.
- Differences in fetal programming of metabolic syndrome based on sex of fetus.
- Differences in placental gene expression, immune genes expressed at higher level in female placenta (JAK1, IL2RB, Clusterin, LTBP, CXCL1, IL1RL1, TNFR)
- Responds to maternal inflammatory status in sex specific manner
- microRNA expression different in males vs females in normal pregnancy
Critical periods during placental development

- Implantation
- Trophoblast invasion
- Establishment of blood flow to the IVS
- Placental vascular development
  - Branching angiogenesis
  - Non-Branching angiogenesis
- Trophoblast differentiation and syncytium formation
- Exponential fetal growth

Gestation (weeks)
Effect of Time of “Insult” on Expression of Glucose and Amino Acid Transporters

- IDDM plus LGA gives increased Glut 1 in BM and increased system A aa transporter
- GDM plus LGA no change in Glut 1 in BM but increased system A
  (Consistent with hyperglycemia causing increased Glut 1 in the 1st trimester)
- System A increased in 3rd trimester not 1st trimester (Jansson)
- Glucocorticoids decrease expression and function of Glut transporters (Hahn)
Influences on Placental Amino Acid Transport

- Hypoxia decreases expression of system A in trophoblast
- In IUGR see decreased system A (no change in system Y+)
- In diabetes see increased system A
- Inverse relationship of system A in MVM and size at birth (Godfrey 1998)
- Inhibition of system A in rats causes IUGR
- IGF2po -/- mouse get IUGR but increased AA transport
Glucocorticoid Action and Metabolism

• $11\beta$HSD-2 in syncytiotrophoblast converts cortisol to cortisone (blocks exposure to maternal cortisol)
• $11\beta$HSD-2 increases with gestational age
• $11\beta$HSD-2 increases at time of oxygen switch (hypoxia decreases 11$\beta$HSD-2)
• Mutations in $11\beta$HSD-2 give IUGR
• Decreased $11\beta$HSD-2 with hypoxemia and PE
• Nutritional restriction causes decreased $11\beta$HSD-2
Obesity

• 52% of US women above 25 are overweight (BMI>25)
• 46% of these being obese (BMI>30)
• 12% morbidly obese (BMI>40)

• Obesity during pregnancy is linked to maternal complications and poor perinatal outcome PIH, Diabetes, Increased caesarean delivery and complications, Prematurity, Stillbirth, Macrosomia

• As adults the offspring show increased incidence of: obesity, insulin resistance, hypertension, cardiovascular disease.
Caution!

- Collection – C section
- Random sampling protocol
- Gestational age
- Medical conditions
- Sexual dimorphism
- Ethnicity
- Control for other associated conditions
  - e.g. SGA, LGA, PE
- Good clinical data
Effect of increasing maternal BMI on mitochondrial respiration

N=33 separate cultures from placentas of females (open circles) and males (closed circles).
(Mele et al 2013)
Reduction in ATP level and mitochondrial biogenesis in placentas of male and female with maternal obesity

Values are mean ± SEM. *, p<0.05 vs. LN group; #, p<0.05 vs. males within the same group of adiposity; n=6/gender/group. (Mele et al 2013)
Expression of placental mitochondrial complexes with increasing maternal adiposity

m, male; f, female *, p<0.05 vs. LN group, n=6/gender/group. (Mele et al 2013)
Effect of Maternal Obesity on Placental Mitochondrial Function

With increasing adiposity we have shown:

• Increased ROS generation
• Decreased mitochondrial respiration
• Decreased mitochondrial content
• Decreased ATP production and content
• Significant reduction in MtDNA copy number
• Decreased mitochondrial flexibility
Outcomes

• What is a good outcome?
  – Fetal size
  – Apgar
  – Development of offspring
  – Programming
What do we need to define the role of the placenta in programing?

- Animal models linking “insults/adverse environments” to placental function, fetal and neonatal outcome and beyond
- Mechanistic and interventional studies
- Human data with well defined maternal, fetal and neonatal phenotypes linked to accurate measures of placental function, both in vivo and ex vivo
- Methods for accurate assessment of placental structure/function
- Descriptions of placental structure/function on contemporary cohorts
Can we use the placenta as a diary of fetal exposures??
What can be measured in utero?

- Blood flows and resistance to flow.
- Peptide production, used as indices of:
  - Trophoblast invasion
  - Angiogenesis/antiangiogenesis
  - Regulation of metabolism
- Steroid secretion
- Inflammatory state
What can be measured post-delivery?

- Weight, Size, Shape, Surface area
- Histologic parameters, vascular and trophoblast
- Vascular reactivity and compliance
- Metabolic rate
- Function
  - transport,
  - Peptide synthesis,
  - steroid synthesis
- Content of metabolites, xenobiotics, metals
- Redox state
- Epigenome
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IFPA 2016: “Placenta – Back to the Basics”