Central Role of the Placenta in Determining the Effect of Maternal Environment on Fetal Programming

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Pregnancy is the healthcare opportunity of two lifetimes
Top 10 Causes of Disease 1900 vs 2010

- Diphtheria, 40.3
- Senility, 50.2
- Cancer, 64.0
- Accidents, 72.3
- Nephropathies, 88.6
- Cerebrovascular disease, 106.9
- Heart disease, 137.4
- Gastrointestinal infections, 142.7
- Tuberculosis, 194.4
- Pneumonia or influenza, 202.2

- Suicide, 12.2
- Pneumonia or influenza, 16.2
- Nephropathies, 16.3
- Diabetes, 22.3
- Alzheimer's disease, 27.0
- Accidents, 38.2
- Cerebrovascular disease, 41.8
- Noninfectious airways diseases, 44.6

Fetal Programming
(Barker Hypothesis)
(Fetal Origins of Adult Disease)
(Developmental Origins of Health and Disease)

Life in utero determines the risk of development of disease in adult life
Birthweight and Coronary Heart Disease

Figure 2.1 Coronary heart disease death rates, expressed as standardised mortality ratios (SMR), in 10 141 men and 5585 women born in Hertfordshire, UK, according to birthweight. Derived from Osmond et al. (1993).
In-Utero Exposures or Adverse Environments

Under- or Over-nutrition, changes in diet
Inappropriate exposure to developmental signals
Inflammation, obesity
Infection/Immune status
Stress
Maternal medical condition – Diabetes, preeclampsia
Xenobiotics
Hypoxia/Oxygenation/Oxidative Stress/Redox State
Epigenetic (environmental) influences
Adult Disease linked to Fetal Programming

- Cardiovascular
- Diabetes (Insulin resistance/Metabolic syndrome)
- Obesity
- Stroke
- Osteoporosis
- Obstructive Airway Disease
- Cancer
- Disordered HPAA axis
- Behavioral abnormalities
Birthweight and Type 2 Diabetes

Figure 35.4  Odds ratios for type 2 diabetes among Taiwan schoolchildren according to birthweight: (a) adjusted for age and sex; (b) adjusted for the child's current BMI, socioeconomic status, family history of diabetes, and maternal gestational diabetes. From Wei et al. (2003). © 2003 American Diabetes Association. Reprinted with permission.
Maternal-Placental-Fetal Unit

Mother

External Environment

Intrauterine Environment

Placenta

Fetus
FETAL GROWTH AND DEVELOPMENT

FETAL PROGRAMMING

UTERUS

Trophoblast Invasion/ Uteroplacental Blood Flow

Maternal substrates

Maternal Hormones

Maternal metabolism

Peptide/Steroid Hormones Production/Metabolism

PLACENTA

Angiogenic Factors

Nutrient Transport

Fetal placental blood flow

FETUS

Oxygen

Immune Barrier

FETAL GROWTH AND DEVELOPMENT FETAL PROGRAMMING

Carbon Dioxide
## Placental Growth and Development Across Gestation

<table>
<thead>
<tr>
<th>Metric</th>
<th>6 weeks</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental Weight (g)</td>
<td>6</td>
<td>470</td>
</tr>
<tr>
<td>Fetal/Placental Weight Ratio</td>
<td>0.18</td>
<td>7.23</td>
</tr>
<tr>
<td>Villous volume occupied by vessels (%)</td>
<td>2.7</td>
<td>28.4</td>
</tr>
<tr>
<td>Trophoblast Surface area (m²)</td>
<td>0.08</td>
<td>12.5</td>
</tr>
<tr>
<td>Mean Trophoblast Thickness (µm)</td>
<td>18.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Maternofetal Diffusion Distance (µm)</td>
<td>55.9</td>
<td>4.8</td>
</tr>
</tbody>
</table>
Critical periods during placental development potentially related to fetal programming
Factors That May Result In An Adverse Intrauterine Environment and Affect Placental Health

- Immune status
- Infection
- Inflammation, obesity
- Maternal medical condition – Diabetes, preeclampsia
- Nutrient composition and level
- Xenobiotics
- Oxygenation/Oxidative Stress/Redox State
- Stress
- Physical Environment
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, nitrative stress
• Molecular: Altered expression of nutrient transporters, receptors, synthesis of steroids and peptides regulating maternal metabolism and fetal growth and development e.g. hPL, serotonin
• Genetic: Imprinted genes
• Epigenetic: Environmental influences on placental (and fetal) gene expression and function
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
Obesity

Obesity has become a major health problem in the US. In women of reproductive age:

- 56.7% are overweight (BMI >25)
- 30.2% are obese (BMI >30)

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.
Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

Obesity (BMI ≥30 kg/m²)

1994

2000

2013

Diabetes

1994

2000

2013

Increasing Weight of Men and Women

Americans get heavier.
Average weight of American men and women, 1960–2010

Source: CDC
Why Mitochondria?

• Metabolic homeostasis is largely dependent on mitochondria, the “powerhouse” of the cell.

• Changes in mitochondrial activity, induced by genetic and environmental factors such as nutrition, age, hormones, hypoxia, and exercise, may have a great impact on cell differentiation, proliferation and survival.

• Mitochondrial dysfunction seen with insulin resistance, diabetes and obesity in skeletal muscle, liver, adipose tissue, heart and pancreas which contributes to the pathogenesis of metabolic disorders.

• Mitochondria use oxygen but are the major source of ROS under physiologic conditions leading to oxidative stress which compromises mitochondrial function via damage to mitochondrial and cellular DNA, proteins and lipids leading to mitochondrial dysfunction.
Mitochondria: not just part of cellular energy metabolism

Functions associated with mitochondria:
- reactive oxygen species generation
- apoptosis
- steroid synthesis
- $\text{Ca}^{2+}$ homeostasis
- protein targeting and translocation
- amino acid transporters and carrier proteins for metabolic processes
- heat production
Trophoblast Populations in Placental Villi

First trimester

Term
Seahorse XF 24

Cutaway graphic of a single probe and wall
Effect of increasing maternal BMI on mitochondrial respiration

N=33 separate cultures from placentas of females (open circles) and males (closed circles).

Expression of placental mitochondrial complexes with increasing maternal adiposity

m, male; f, female *, p<0.05 vs. LN group, n=6/gender/group.

Gestational Diabetes

- GDM is a common, asymptomatic metabolic disorder of pregnancy, manifest by maternal impaired glucose tolerance from the late second trimester of pregnancy onwards.
- Incidence 6-7% in USA, varies by ethnicity
- Adverse outcomes:
  - Preeclampsia
  - Hydramnios
  - Macrosomia and large for gestational age infant
  - Fetal organomegaly (hepatomegaly, cardiomegaly)
  - Stillbirth
  - Maternal and infant birth trauma
  - Operative delivery
  - Perinatal mortality
  - Neonatal respiratory problems and metabolic complications (hypoglycemia, hyperbilirubinemia, hypocalcemia, erythremia)

+ Fetal programming
Expression of Mitochondrial Complexes in Placental Villous Tissue with GDM

CTRL  A1GDM  A2GDM

Complex I  Complex II  Complex III
Complex IV  Complex V  Actin

N= 6 in each group, values are mean± SEM, *p<0.05 vs CTRL, a p<0.05 vs A1GDM

Conclusions/Directions

• Mitochondrial respiration compromised by increasing maternal adiposity and by A2 GDM
• But all these pregnancies went to term with good outcomes!!
• However there may be a cost in later life for offspring and mother!
• Does compromised mitochondrial respiration matter?
• Is there sufficient placental reserve?
• What happens if there is additional insult or reserve is exceeded?
• Could this be associated with stillbirth??
Stillbirth

- **WHO definition:**
  - “fetal death late in pregnancy”
  - 2.6 million per annum (98% in LMIC)

- **USA:**
  - Death later than 20 weeks
    - (6.2/1000 live births and fetal deaths)
  - Early stillbirth 20-27 weeks (3.2/1000)
  - Late stillbirth >28 weeks (3.0/1000)
    - 50% at term

- **Disparity:**
  - White 1/202
  - Hispanic 1/183
  - African American 1/87
Gestational Age and Causes of Stillbirth

- Probable or possible cause only found in 76.2% of cases
  - (500 women, 512 neonates)

- Between 24 and 27 weeks of gestation causes were infection (19%), abruption (14%), and fetal anomalies (14%)

- After 28 weeks of gestation, the most frequent cause of stillbirth was unexplained fetal loss, including stillbirths associated with growth restriction and placental abruption.
  - 2/3 unexplained fetal deaths occurred after 35 weeks
  - rate >40 weeks was 2x more than <40 weeks

Stillbirth Collaborative Research Network Writing Group
Hazard (risk) of stillbirth for singleton births without congenital anomalies by gestational age, 2001-2002


(n= 5.5 million births)
Risk of Stillbirth by Gestational Period and BMI

(n=2.9 million births, 9030 stillbirths
Washington and Texas)

Relationship of Placental Function to Fetal Demand
What do we need to define the role of the placenta in fetal programming?

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