Fetal Physiology, Growth and Programming

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Objectives

- Physiology of embryonic and fetal growth
- Landmarks of fetal development
- Fetal adaptation to unfavorable environment
- Barker Hypothesis: fetal origins of adult diseases
Early Pregnancy - Embryology

1. Ovulation
2. Fertilization
3. Zygote-cell division
4. Morula
5. Blastocyst (32-64 cells)
   - Trophoectoderm (outer)
   - **Inner cell mass**
   - Blastocele (liquid)
   - Zona Pellucida (“shell”)
6. Blastocyst “hatches”
7. Implantation
8. Decidualization

Day 6-7 after ovulation
3 weeks GA
Blastocyst
Early Pregnancy-Embryology

- Bilaminar embryonic disk
  - 4 weeks GA
    - Ectoderm and Endoderm
- Trilaminar embryonic disk
  1. Ectoderm
  2. Endoderm
  3. Mesoderm

5 weeks Gestation
3 layer embryonic disk → organogenesis

Internal Organs:
- GI tract
- Thyroid

Skin
Hair
Lens
Nervous system

Ectoderm
Mesoderm
Endoderm

Muscles
Skeleton
Heart
Vascular system
Urogenital System
Embryonic and Fetal Development

Embryonic age = gestational age – 2 weeks
Embryonic Development

CRL 6.8 mm
6w4d GA
4w4d embryonic age

Embryo can be seen by 5 weeks GA

8 weeks GA
CRL 20 mm
Fetal Growth and Development

By 8 to 10 weeks, the embryo has a human appearance. It is now called a FETUS.

GA: 10 weeks 1 day
CRL 33 mm
Fetal Growth and Development

Fetal Development:
- 10 weeks GA to term
- Growth and maturation of structures formed during the embryonic period
- Insults = abnormal growth

CRL 50 mm
GA 11 weeks 5 days
11-13 weeks
Fetal Development- Landmarks

• 8-12 weeks GA:
  CRL 6-7 cm
  – Centers of ossification appear
  – Fingers & toes are differentiated
  – External genitalia is male or female

• 13-16 weeks GA:
  CRL 12 cm - 110 g
  – Rapid growth (body>head)
  – Active ossification
Fetal Development

(a) 5 weeks. Limb buds, eyes, the heart, the liver, and rudiments of all other organs have started to develop in the embryo, which is only about 1 cm long.

(b) 14 weeks. Growth and development of the offspring, now called a fetus, continue during the second trimester. This fetus is about 6 cm long.

(c) 20 weeks. By the end of the second trimester (at 24 weeks), the fetus grows to about 30 cm in length.
Fetal Development-Landmarks

• 17-20 weeks: 300 g
  – Quickening
  – Cornification of skin: less transparent
  – Lanugo

• 21-24 weeks: 630 g
  – Weight gain - Fat deposition
  – Canalicular period of lung development nearly completed by 24 weeks.
Fetal Development-Landmarks

- 24-28 weeks: 1100 g
  - VIABLE
  - Eyelids open
- 32 weeks: 1500-1800 g
- 36 weeks: 2500g
- Term: 37-42 weeks – 3400 grams
Fetal Growth Curve

- Fat accumulation
  - 15% body weight
  - Rapid after 32 wks
    - 82 g fat per week

- Skeletal Mass
  - 25-50% body weight

- Fetal weight gain
  - 100-200g (4-8oz) per week in 3rd Trimester
Fetal Growth - Mechanisms

- **Hyperplasia**: Increase in cell number - cell division.
- **Hypertrophy**
  - Increase in cell size
  - Increase in cellular protein synthesis
  - Extracellular matrix protein synthesis
  - Increase in cell organelles
    - Mitochondria
    - Smooth and rough endoplasmic reticulum
- **Maturation**
  - Transition in protein content
Fetal Growth - Placental Role

• All maternal nutrients and fetal waste pass through the placenta.

• Placental mechanisms for fetal growth and survival:
  1. Efficient gas exchange
  2. Active transport of energy substrates
  3. Immunological tolerance
  4. Fetal acquisition of maternal immunity (IgG)
  5. Others
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
<th>Substances Exchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive diffusion</td>
<td>No energy required; high conc. to low conc. gradient</td>
<td>O2, CO2, NaCl, lipids, fat-soluble vitamins</td>
</tr>
<tr>
<td>Facilitated diffusion</td>
<td>Energy may be required; faster than gradient, “pump”</td>
<td>Glucose, other CHOs</td>
</tr>
<tr>
<td>Active transport</td>
<td>Energy required; occurs against concentration gradient; carrier molecules</td>
<td>Amino acids, H2O-soluble vitamins, Ca++, Fe++</td>
</tr>
<tr>
<td>Bulk flow</td>
<td>Transport based on hydrostatic or osmotic gradient</td>
<td>Water, dissolved electrolytes</td>
</tr>
<tr>
<td>Pinocytosis</td>
<td>Small vesicles pinch off on one side of placenta, go to other side, and release contents</td>
<td>IgG, serum proteins (IgM too large to cross)</td>
</tr>
<tr>
<td>Breaks</td>
<td>Villi break off and contents extruded into maternal circ.</td>
<td>Fetal Rh-positive cells</td>
</tr>
</tbody>
</table>
Fetal Growth – Placental Transport

- 2 most important substrates for fetal survival and growth
  - $O_2$ -- DIFFUSION
  - Glucose -- FACILITATED DIFFUSION

- Placental Barrier:
  - large molecules (Heparin, Insulin)
  - low lipid solubility

- Factors affecting placental transfer:
  - Vascular: maternal blood flow, umbilical blood flow, placental surface
  - Substrate:
    Concentration in maternal and fetal circulation
    Mechanism of transfer
Fetal Growth Determinants

- Maternal: utero-placental blood flow, nutrition
- Placental: large reserve. Also uses substrates
  * Fetal size correlates with placental size.
- Fetal:
  - Genome
  - Gender
  - IGF 1 and 2
  - Insulin
  - Glucocorticoids promote storage of glucose as glycogen in the liver.
- Other:
  - Epidermal growth factors
  - Thyroid hormones
Maternal-Fetal Circulation

- Decidual-placental interface
  - Transport mechanisms

- Placental circulation
  - Low resistance
  - High capacitance
  - Affected by uterine contractions

- Umbilical cord
  - Wharton’s jelly
  - 2 arteries from fetus carrying deoxygenated blood

- Fetus
  - Receives oxygenated blood and nutrients from umbilical vein
Fetal Oxygenation

• Fetus requires constant supply of $O_2$ because its stores are very small.
• The placenta itself uses 40-60% of $O_2$ and Glucose provided by the mother.
• $O_2$ and $CO_2$ diffuse across the placenta (driven by gradient).
# Fetal Oxygenation

Fetal PO$_2$ is lower than maternal, but O$_2$ content is similar: WHY???
Oxyhemoglobin dissociation curve in pregnancy

Factors shifting curve to right include ↑ 2,3-diphosphoglycerate, hypercapnea, acidosis, ↑ body temperature.

The end result favors oxygen delivery to the fetus.
Fetal Erythropoiesis

- Yolk sac, liver, bone marrow & spleen
  - 3rd wk
  - Term

- Nucleated RBCs
  - Immaturity (fetal RBC’s)
  - Stress response

- RBCs (Hb) carry O₂ needed for aerobic metabolism

- Fetal Hb (15-17g/dl) > Adult Hb (12g/dl)
- Fetal Hb has higher O₂ carrying capacity
Fetal vs. Adult Hemoglobin

- 2-3 DPG stabilizes adult deoxyHgb by binding to the exposed β-chains.
- Higher PO₂ needed to load adult Hb with O₂.
- Fetal Hgb is insensitive to 2-3 DPG so O₂ affinity is increased.
Ontogeny of Fetal Hgb

- Proportion of Hb F to Hb A changes between 26-40 weeks (regulated by fetal cortisol)
- Hb F decreases from 100% to 70% by birth
- Change in $\gamma$- to $\beta$-globin synthesis occurs in erythroid progenitor cells
- Important for fetal Hb disorders
  - Sickle cell anemia
  - Thalassemia
  - Hydrops fetalis (Hb Bart’s disease)
Fetal Environment

- Fetus inhabits uterine cavity
- Surrounded by amnion and chorionic membranes
- Bathed in amniotic fluid
  - inhales and swallows AF
  - urinates in amniotic fluid
- Connected to mother and placenta via an umbilical cord
- Can hear
- Can move
- Breathing movements
Fetal Behavior

- Behavioral States
- Gross and small body movements
- Breathing movements (1-2 hr/day)
- REM Sleep
- Heart rate variability and accelerations
Fetal Activity

- Neuromotor activities develop and disappear in sequence
- First to appear / last to disappear under stress
  - Fetal tone—cortex @ 7.5-8.5 wks
  - Fetal movement—cortex nuclei @ 9 wks
  - Fetal breathing—pontine and medulla @ 20-21 wks
- Last to appear / first to disappear under stress
  - Heart rate reactivity—posterior hypothalamus and medulla @ 28-32 wks
- Amniotic Fluid—reflects renal perfusion
Fetal Heart Rate Control

- **Sympathetic vs. Parasympathetic Nervous System**
- **Chemoreceptors**
  - Sense decrease in pH
  - Results in increase HR to increase O2
- **Baroreceptors**
  - Sense BP or stretch of BV
  - Aortic arch and carotid body
  - Vagal response
  - Results in decrease HR
  - Results in vasodilatation to decrease BP
Fetal GI Tract

- Fetus able to swallow amniotic fluid by 20 weeks
- Full GI function by 28 weeks
- Meconium passage
  - Products of GI mucosa
  - Unabsorbed amniotic fluid
  - Seldom passed before 34 weeks
- Parasympathetic stimulation
  - Meconium release
- Aspiration of meconium is toxic to alveolar cells
  - Potentially fatal pneumonitis
Amniotic Fluid Dynamics

- Volume increases from 250ml @ 16 wks to 800ml @ 32 wks.

- First trimester—transudate

- Second trimester—lung liquid and urine
  - Smaller component from flow across membranes

- Third trimester—
  - 300-400ml/day lung fluid
  - 400-1200ml/day urine—depending on renal perfusion

- Less urine output = less fluid / more urine = more fluid

- Less swallowing = more fluid
Fetal Lung Maturation

(1) Pseudoglandular (5-17wks)

(2) Canalicular (16-25 wks)

(3) Terminal Sac (24-32 wks)

(4) Alveolar (32wks to 8yo)
Fetal Lung Maturation

- Glucocorticoids
- Thyroid hormone
- TRH
- Prolactin
- EGF

Antenatal maternal glucocorticoid prophylaxis for women at risk for preterm delivery
Definitions of Fetal Size

IUGR  AGA  LGA
Intrauterine Growth Restriction

- Birthweight $<10^{th}$, $5^{th}$ or 3rd percentile for gestational age (in practice: EFW)
- Increased risk of stillbirth
- Increased risk of intrapartum death or perinatal asphyxia
- Increased risk of neonatal death or other neonatal complications
Etiologies of IUGR

- Fetal
- Maternal
- Placental

Environmental Stress
- Nutrition
- Hypoxia
- Psychological
- Increased cortisol

Often difficult to separate these 2 contributions to IUGR
Fetal Etiologies

- Intrauterine infection - <10% IUGR
  - HSV, CMV, Rubella, Toxoplasmosis

- Chromosomal
- Genetic Syndromes
- Congenital Malformations

- Epigenetic effects—chromatin remodeling and environmental exposure
Maternal Etiologies

- Maternal vascular disease
- Maternal hypoxia
- Maternal thrombophilia
- Poor nutrition
- Maternal drug or tobacco use
- Advanced maternal age
Maternal Vascular Disease

• Diabetes
• Collagen vascular diseases
• Chronic Hypertension (HTN)
• Preeclampsia
  ▪ Failure of trophoblastic invasion into spiral arterioles by 20-22 wks
  ▪ Intimal thickening, fibrinoid degeneration
  ▪ Poor placental perfusion
  ▪ Fetal heart pumping against resistance
Placental Abnormalities
Placental Pathology

Normal placenta

Infarction and fibrosis
Placental Pathology

Normal Villi
Note numerous blood vessels for perfusion

IUGR Placenta
Infarction and fibrosis with lack of blood vessels and thickened villi
Clinical Diagnosis

• Symphysis fundal height (SFH)

• Serial Ultrasound
  ▪ Growth: change in size over time
  ▪ Decreased interval growth or no growth.
  ▪ Individual parameters
  ▪ EFW %
IUGR vs. SGA

- Human variation vs. Pathologically Small
- Symmetric or asymmetric?
- Review Dating
Fetal response to ↓Utero-placental flow

- Redistribution of blood flow to essential organs (brain, heart, adrenals).
- Decreased perfusion of other organs including fetal kidneys.
- Result: oligohydramnios (↓urine output), less sub-cutaneous fat (asymmetric IUGR)
Amniotic Fluid Level Assessment

Oligohydramnios

Normal amniotic fluid
## IUGR Etiology

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<tr>
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<th>Symmetric</th>
<th>Asymmetric</th>
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<td>Early</td>
<td>Later</td>
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<td>Etiology</td>
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## IUGR - Etiology

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<tr>
<td>Onset</td>
<td>Early (&lt;24 weeks)</td>
<td>Later (&gt;24 weeks)</td>
</tr>
<tr>
<td>Etiology</td>
<td>Aneuploidy, Genetic syndromes, Congenital anomalies, Infections (TORCH), WRONG DATES!!!</td>
<td>Utero-placental insufficiency (UPI)</td>
</tr>
<tr>
<td>Amniotic fluid</td>
<td>Normal or increased</td>
<td>Decreased</td>
</tr>
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Constitutionally small baby: later onset, symmetric – Normal RATE of growth
Pathways to Uteroplacental Insufficiency

- Maternal Vascular Disease
- Other etiologies?
- Thrombophilia?

Decreased blood flow to uterus → Damaged Placenta → Increased placental resistance

Decreased blood flow to fetus (IUGR, Fetus) → Abnormal Umbilical Cord Dopplers
Umbilical Artery Dopplers

Measure placental resistance to flow
S/D ratio
What can we do?

• Monitor fetal well-being (NST, BPP, Doppler flow studies)
• Administer steroids
• Time delivery to minimize morbidity/mortality
Neonatal Complications of IUGR

- Birth asphyxia
- Meconium aspiration
- Hypoglycemia
- Hypocalcemia
- Hypothermia
- Hyponatremia
- Sepsis
- Pulmonary hemorrhage
- Polycythemia
- Hyperbilirubinemia
- Thrombocytopenia
- Malformations
- “Feeding Intolerance”
Pediatric Concerns

- Partial “catch-up” growth
- 75% achieve Ht and Wt >10th percentile in 8 years
- 36-50% poor school performance
- Attention deficit disorder, hyperactivity
This “new” concept has received much attention in the lay press.

“You are what your mother ate.”
The Barker Hypothesis

- In the 1980’s DJP Barker
- Birth records from the early 1900’s in England
- Correlation with Death Certificates
- Association between increased mortality from CAD in men and women with lower birth weights as newborns
- This observation has been confirmed in multiple cohorts from around the world
STANDARDIZED MORTALITY RATIOS FOR CHD <65 YEARS OF AGE BY BIRTHWEIGHT

DJP Barker, Lancet 1989
MEAN SBP IN 1228 MEN AND WOMEN AT AGE 60-71 YEARS BY BIRTHWEIGHT

Law CM et al, BMJ 1993
Possible signals – Animal studies

- Steroid administration – Stress
- Decreased uterine blood flow (Ut artery ligation experiments)
- Unbalanced nutrition
- Results in less nephrons, less beta cells, permanent alterations of appetite centers…HBP, Diabetes, Obesity
- Programming: fetus adjust their physiology to prepare for the outside world.
- Problem: discrepancy between in-utero “world” and ex-utero.
Barker Hypothesis Model

Maternal diet, body composition, utero-placental blood flow, placental transfer

Fetal demands > placental supply = fetal malnutrition

Brain-sparing
Impaired development of blood vessels, liver, kidneys, pancreas

Endocrine changes:
Decrease islet cells production of insulin

Stress: increase cortisol = reduced number of islet cells and nephrons

End result: hyperlipidemia, hypertension, central obesity, insulin resistance
Adult Concerns-Summary

• Fetal physiology has been reprogrammed
• Barker Hypothesis
  ▪ Hypertension
  ▪ Coronary artery disease
  ▪ Diabetes
  ▪ Stroke
  ▪ Obesity
  ▪ Hyperlipidemia
• All are primary care and public health issues that require future research, preventative care, and epidemiological follow-up
Fetal Physiology, Growth and Programming Summary

- Maternal, fetal, placental role for normal fetal growth and development.
- Mechanism of fetal growth and timing of insults determines type of IUGR.
- Fetal response to unfavorable environment.
- Barker hypothesis: fetal stress leads to adult diseases.
Thank you!