Cutting the Cord: View from the Other Side

Placental Effects on the Fetus and Neonate

Lindsey Koele-Schmidt, MD
Pediatric Grand Rounds
May 15, 2015

Learning Objectives
At the end of this presentation, the participant will be able to:
1. Discuss the normal morphologic development of the placenta
2. Characterize the role of the placenta in gas exchange and oxygenation of the fetus
3. Identify the role of the placenta in the energy metabolism of the fetus
4. Identify the types of abnormal placentation
5. Discuss the benefits and controversies of delayed cord clamping

Why is the placenta important?
**Why is the placenta important?**

- Supplies fetus with nutrients
- Facilitates oxygen and gas exchange
- Protects the fetus

**IT’S ON THE BOARDS!!**

---

**The Placenta**

Two opposing functions during gestation
- Source of metabolic substances and nutrient sensor
- Protection against noxious external substances
  - Genital bacteria
  - Maternal immune system
  - Teratogens

---

**Early placenta formation**

Formation of Placenta and Extraembryonic Membranes
Placental Anatomy

Placental Perfusion

- Achieved by...
  - Increased maternal intravascular volume
  - Decreased maternal vascular tone

- Perfusion is decreased by maternal renal disease, HTN, collagen vascular disease, antiphospholipid antibody syndrome

Transplacental Transfer

- Simple diffusion
  - Passive, no energy required
  - $O_2$, $CO_2$, $H_2O$, Na, Cl, lipids, fat-soluble vitamins, most meds

- Facilitated diffusion
  - Compounds move with concentration gradient, no energy required
  - Glucose, cephalixin

- Active transport
  - Compounds move against concentration gradient, from maternal to fetal, energy required
  - Amino acids, Ca, Mag, Phos, Fe, iodide, water-soluble vitamins
Transplacental Transfer

- **Bulk flow**
  - Transfer by hydrostatic or osmotic gradient
  - H₂O, electrolytes
- **Pinocytosis**
  - Compounds engulfed in cell and transported across cell in vesicles
  - Immunoglobulin G
- **Breaks**
  - Placental membrane abnormalities
  - Maternal or fetal cells

Gas Exchange and Oxygenation

- Placental gas exchange is much less efficient than in the lungs
  - Minimum diffusion distance is larger (3.5 μm vs 0.5 μm)
  - Lower permeability of the blood-blood barrier (vs. blood-gas barrier in the lung)

Gas Exchange and Oxygenation

- Increasing oxygen needs of the fetus are met by...
  - Increased maternal blood flow to the placenta (20-fold increase)
  - Increased fetal blood supply to placenta
  - Fetal hemoglobin – higher oxygen affinity than maternal HbA
  - Higher Hb concentration in the fetus
  - The “Double Bohr Effect”

<table>
<thead>
<tr>
<th>CROSS the placenta</th>
<th>Do NOT CROSS the placenta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Billirubin</td>
<td>Biliverdin</td>
</tr>
<tr>
<td>Aspirin, coumadin</td>
<td>Heparin</td>
</tr>
<tr>
<td>Dilantin, valproate</td>
<td>Glucagon, insulin, GH</td>
</tr>
<tr>
<td>Small amounts of T₃, T₄</td>
<td>TSH</td>
</tr>
<tr>
<td>Alcohol, iodine</td>
<td>PPU</td>
</tr>
<tr>
<td>Maternal IgG</td>
<td>Maternal IgM</td>
</tr>
</tbody>
</table>
Maternal Vascular Pathology

- **Stenosis** → chronic uteroplacental underperfusion
- **Occlusion** → villous infarction
- **Rupture** due to ischemic-reperfusion injury or trauma → acute abruption

Placental Abruption

- Premature separation of a normally implanted placenta
- Associated with maternal HTN (most common), AMA, increased parity, cigarette/cocaine use, trauma
- 15-25% perinatal mortality
  - Increased risk of premature delivery, stillbirth, HIE

Placental Abruption

- Diffuse chorioamnionic hemosiderin deposition
- Most evidence suggests venous (vs arterial) hemorrhage
- Can be due to chronic peripheral separation
- Risk factors include trauma, decompression of the overdistended uterus, acute vascular changes due to cocaine

Fetal Vascular Pathology

- Vessels within the cord are protected by Wharton’s jelly
- Vessels are at risk for injury due to:
  - decreased hydration of matrix (chronic uteroplacental underperfusion)
  - Excessive coiling → torsion-related kinking
  - Insertion of vessels into membranes (unprotected from trauma)

Fetal Vascular Pathology

- Thrombotic occlusion
  - Increased risk with inflammation (chorio), toxic damage (mec), stasis (fetal CHF), clotting, hyperviscosity, DM
  - Villi downstream from the occlusion are avascular
  - Increased risk for fetal disease – smaller fetal vascular bed, thromboembolic disease, consumptive coagulopathy
<table>
<thead>
<tr>
<th>Fetal Vascular Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased/stenosed villous arterioles</td>
</tr>
<tr>
<td>– Villous arterioles help to regulate placental resistance to fetal blood flow</td>
</tr>
<tr>
<td>– Decreased in trisomies</td>
</tr>
<tr>
<td>– Stenosed in severe IUGR</td>
</tr>
<tr>
<td>• Vessel rupture → massive subchorionic thrombosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fetal Vascular Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Leaky placental capillaries</td>
</tr>
<tr>
<td>– Leak fluid → villous edema</td>
</tr>
<tr>
<td>– Leak blood → villous stromal hemorrhage</td>
</tr>
<tr>
<td>• Both lesions associated with adverse outcomes in premature infants</td>
</tr>
<tr>
<td>• Rupture of capillaries</td>
</tr>
<tr>
<td>– Hypovolemia, fetal anemia, fetomaternal hemorrhage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection and Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute chorioamnionitis</td>
</tr>
<tr>
<td>– Most common cause of preterm labor</td>
</tr>
<tr>
<td>– Bacteria overwhelm normal host defenses or gain access to amniotic cavity after ROM</td>
</tr>
<tr>
<td>– Neutrophilic response involving the membranes and chorionic plate</td>
</tr>
<tr>
<td>• Subnecrotizing funisitis or chronic chorio → infants at increased risk for chronic lung disease (exposure to chronic inflammatory mediators)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection and Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Transplacental infections</td>
</tr>
<tr>
<td>– Acquired via breaks in the interhemal barrier</td>
</tr>
<tr>
<td>– HIV, Hep B, parvo, enteroviruses</td>
</tr>
<tr>
<td>• Intrapartum infections</td>
</tr>
<tr>
<td>– Acquired as fetus passes through birth canal</td>
</tr>
<tr>
<td>– Gonorrhea, Chlamydia</td>
</tr>
<tr>
<td>– GBS, E. coli</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection and Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neutrophilic exudates of villi and intervillous spaces</td>
</tr>
<tr>
<td>– Listeria</td>
</tr>
<tr>
<td>– Campylobacter</td>
</tr>
<tr>
<td>• Microabscesses on the umbilical cord</td>
</tr>
<tr>
<td>– Candida</td>
</tr>
<tr>
<td>• Generalized inflammation (panplacentitis)</td>
</tr>
<tr>
<td>– TORCH infections</td>
</tr>
<tr>
<td>– EBV, varicella</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormal Placentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>...</td>
</tr>
</tbody>
</table>
Placenta Previa

- Abnormal implantation of placenta near or over the internal cervical os
- Common finding during 2nd trimester, decreases with increasing GA
- Increased risk of premature delivery
- Increased risk of fetal anomalies by 2.5-fold, reason unclear

Abnormal Placental Adherance

- Accreta: placental villi attach to myometrium
- Increta: placental villi invade myometrium
- Percreta: placental villi penetrate through myometrium

Clinicopathologic Correlations

<table>
<thead>
<tr>
<th>Clinical Complication</th>
<th>Placental Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm Labor</td>
<td>Chorio</td>
</tr>
<tr>
<td></td>
<td>Abruption</td>
</tr>
<tr>
<td></td>
<td>Chronic uteroplacental underperfusion</td>
</tr>
<tr>
<td></td>
<td>Chronic uterine inflammation</td>
</tr>
<tr>
<td>IUGR</td>
<td>Chronic uteroplacental underperfusion</td>
</tr>
<tr>
<td></td>
<td>Villitis</td>
</tr>
<tr>
<td></td>
<td>Abruption</td>
</tr>
<tr>
<td></td>
<td>Fetal thrombotic vasculopathy</td>
</tr>
<tr>
<td>IUFD</td>
<td>Large placenta, delayed villous maturation</td>
</tr>
<tr>
<td></td>
<td>Fetomaternal hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Intervillous thrombi</td>
</tr>
</tbody>
</table>

Placental Lesions Associated With Cerebral Palsy and Neurologic Impairment Following Term Birth

- Retrospective comparison of placentas from term infant with neurologic impairment to those without impairment
- Placental lesions found to be associated with neurologic impairment
  - Severe chorio
  - Extensive avascular villi
  - Diffuse chorioamnionic hemosiderosis
**Placental Tumors**

- Hydatidiform mole – AKA Molar pregnancy – abnormal chorionic villi with trophoblastic proliferation and villous edema within the uterine cavity
  - Complete- 46XX, paternal origin, no fetus, often with medical complications
  - Partial- 69XXX/XXY/XY, nonviable fetus, medical complications rare
- Gestational trophoblastic disease
  - Invasive mole
  - Choriocarcinoma – highly malignant
- Chorioangioma - benign

**Umbilical Cord**

- Cord stump usually falls off within two weeks
- Keep stump clean and dry, avoid submersion in water
  - Application of chlorhexidine is recommended for home births in high mortality settings/underdeveloped countries

**Umbilical Cord**

- Velamentous insertion of the cord
  - Umbilical vessels are exposed in the membranes before they insert into the placental tissue
  - Frequent in twins, almost always in triplets
  - At risk for rupture and hemorrhage
- Vasa previa: umbilical vessels cross the internal os and are positioned ahead of the fetal presenting part

**Umbilical Cord**

- Umbilical granuloma – 1:500 newborns
  - Soft, pink tissue in center of umbilicus after cord falls off
  - Clear discharge
  - Treated with silver nitrate

**Umbilical Cord**

- Omphalitis – 1:200 newborns
  - Bacterial infection of stump and surrounding tissues
  - Tender, swollen, foul odor
  - Complications: necrotizing fasciitis, myonecrosis, sepsis, peritonitis
  - Treated with systemic antibiotics
Umbilical Cord

- Delayed separation
  - > 2 weeks of life
  - DDx: leukocyte adhesion defects, bacterial infections, anatomic anomalies of the urachus
- Single umbilical artery
  - 0.5-1% of infants
  - one of the most common malformations
  - 3-4x more common in twins
  - Need to assess for GU tract and cardiac anomalies

The Placenta as a Nutrient Sensor

Fetal growth restriction

- Reduced amount of certain amino acids
- Some are hypoglycemic and hypoxic in utero
- Limitations in nutrient and oxygen supply but exact mechanism still being investigated
  - O2 is small and lipophilic hence is subject to blood flow-limited transport
  - Reduction in placental blood flow contributes to fetal hypoxia
  - Transport of glucose and AA is limited by the barrier itself thus is less affected by changes in blood flow

Fetal overgrowth

- Factors other than maternal hyperglycemia may contribute to fetal overgrowth
- The placental response to metabolic disease may differ between study populations
- Current findings suggest that diabetes in pregnancy is associated with enhanced placental nutrient transfer

Theory: The placenta as a nutrient sensor

- The placenta may coordinate nutrient transport functions with maternal nutrient availability
- Alterations in placental transport may provide a mechanism to match fetal growth rate to a level that is similar to the amount of nutrients provided by the mother
The Placenta as a Filter: 
Effects of medications, drugs and environmental agents on the fetus/neonate

Maternal Exposures

Effects of Antenatal Steroids

- Betamethasone/Dexamethasone
  - Fetal: decreased movement (transient), decreased HR (transient), growth restriction (multiple courses)
  - Neonatal: risk of early-onset sepsis (multiple courses), smaller FOC
  - Betamethasone with greater reduction in risk of death than dex

- Prednisone
  - Doesn’t cross the placenta as well as dex/betamethasone
    - Concentration of active compound in the fetus is <10% of that in the mother
    - IUGR

Maternal Exposures

Neonatal effects of Maternal Tocolytics

- Indomethacin
  - Renal insufficiency
  - Pulmonary HTN
  - Ileal perforation
  - NEC
  - Fetal: oligohydramnios, premature PDA closure

- Magnesium
  - Decreased respiratory effort
  - Decreased peristalsis
  - Hypotonia
  - Hypotension

Timing of Teratogenic Exposure

Effects of Alcohol

- Most common teratogen
- Early exposure → more classic features
- Greater effect with binge drinking compared to smaller chronic intake
- Classic facial features: smooth philtrum, thin upper lip, short palpebral fissures
- VSD most common cardiac finding
- Microcephaly with avg IQ 63
Effects of Environmental Agents

• Mercury
  – Neurotoxic- cognitive and motor delays
  – Nephrotoxic- proximal tubules
  – Immunotoxic
• Pesticides
  – Anomalies including limb reductions, orofacial clefts, eye/GU/CNS/CV defects
  – Growth restriction
• Lead
  – Bone is major repository, turnover 25-30yrs
  – Increased risk for spontaneous abortion, premature delivery, neurologic problems

Delayed Cord Clamping

NRP 2010 Recommendation

“Delay in umbilical cord clamping for at least one minute is recommended for newborns not requiring resuscitation. There is insufficient evidence to support or refute a recommendation to delay cord clamping in babies requiring resuscitation.”

Trends in Cord Clamping

• For many centuries, cutting cord too soon was thought to be dangerous to mother and baby
• 1900 – introduction of cord clamps
• Trend toward earlier cord clamping, possibly in order to:
  – Reduce infection??
  – Preventing postpartum hemorrhage??
  – Align with increasing knowledge of neonatal resuscitation (APGAR scores)??

Current thoughts on Delayed Cord Clamping

• Pro
  – Higher hematocrit?
• Con
  – Polycythemia?
  – Hyperbilirubinemia?
  – Delay in resuscitation?

Delayed Cord Clamping in the Term Infant: Hematocrit/Anemia Outcomes

• 2013 Cochrane review –
  – Improved iron stores, less risk of anemia in 3-6mo who had received delayed cord clamping
• Hutton, meta-analysis in JAMA, 2007 –
  – Term infants with ≥ 2min of cord clamping
  – Increased hct, ferritin and iron stores at 2-6mo
  – Decreased risk of anemia at 2-6mo
Delayed Cord Clamping in the Term Infant: Hyperbilirubinemia Outcomes

- 2013 Cochrane review —
  - Increased risk of hyperbilirubinemia requiring phototherapy
- Hutton, meta-analysis in JAMA, 2007 —
  - No difference in bilirubin levels or need for phototherapy

Prep Question
You are called to the delivery room for a multigravida mother who is having a vaginal delivery at 30 wks. The obstetrician, covering for a colleague, does not know what medications the mother is taking. The father tells you that the mother is taking a medicine for a thyroid problem.

Of the following, the substance that BEST crosses the placenta is:

a. Iodide ion  
b. TSH  
c. Thyrotropin-releasing hormone  
d. T4  
e. T3

Prep Question
A physician colleague shows you a doppler flow ultrasound scan of a fetus and placenta taken at ~ 30wks. You review the ultrasound scan.

Doppler ultrasound reveals umbilical vessels (arrow showing umbilical vein [V]) inserting laterally and not directly into the placenta (P) central region, consistent with velamentous cord insertion.

Prep Question
You are called to the delivery room for a multigravida mother who is having a vaginal delivery at 30 wks. The obstetrician, covering for a colleague, does not know what medications the mother is taking. The father tells you that the mother is taking a medicine for a thyroid problem.

Of the following, the substance that BEST crosses the placenta is:

a. Iodide ion  
b. TSH  
c. Thyrotropin-releasing hormone  
d. T4  
e. T3

Prep Question
A physician colleague shows you a doppler flow ultrasound scan of a fetus and placenta taken at ~ 30wks. You review the ultrasound scan.

Of the following, the fetus:

a. is at risk for chronic intrauterine hypoxia-ischemia  
b. is at risk for meconium aspiration  
c. is at risk for perinatal hemorrhage  
d. is at risk for polyhydramnios  
e. should be electively delivered by C/S at 36wks
Prep Question

A physician colleague shows you a doppler flow ultrasound scan of a fetus and placenta taken at ~ 30wks. You review the ultrasound scan.

Of the following, the fetus:

a. is at risk for chronic intrauterine hypoxia-ischemia
b. is at risk for meconium aspiration
c. is at risk for perinatal hemorrhage
d. is at risk for polyhydramnios
e. should be electively delivered by C/S at 36wks

QUESTIONS??

References

- Neonatology Review. Brodsky, Martin. 2003