FETAL-PLACENTAL CIRCULATION

Irina Burd, MD, PhD
Maternal-Fetal Medicine
Placenta

- Umbilical vessels
  - 2 arteries
  - 1 vein
Placenta

- Placenta plays a key role in pregnancy, mediating exchanges between mother and fetus and maternal tolerance of feto-paternal antigens.
- In some species, it also produces hormones that ensure the maintenance of gestation and fetal well-being.
Gas exchange at placenta

- Passive diffusion
- Hemoglobin characteristics
Transport of oxygen
Oxygen dissociation curve

- Decrease in temperature increases Oxyhaemoglobin (
- Increase in pH decreases Oxyhaemoglobin (%)
- Decrease in CO₂ increases Oxyhaemoglobin (%)
- Decrease in 2, 3 DPG increases Oxyhaemoglobin (%)
- Increase in temperature decreases Oxyhaemoglobin (%)
- Increase in pH decreases Oxyhaemoglobin (%)
- Increase in CO₂ increases Oxyhaemoglobin (%)
- Increase in 2, 3 DPG decreases Oxyhaemoglobin (%)

Oxyhaemoglobin (%) vs. PO₂ (kPa)
Role of fetal hemoglobin

- Increased affinity for oxygen
Environment Special:
The oceans—why 70% of our planet is in danger

The Facebook Movie:
The secret history of social networking

How the first nine months shape the rest of your life
The new science of fetal origins
BY ANNIE MURPHY PAUL
Barker Hypothesis

- David Barker, M.D., Ph.D.,
- Professor of Clinical Epidemiology at the University of Southampton, UK and Professor in the Department of Cardiovascular Medicine at the Oregon Health and Science University, US.
- Twenty years ago, he showed for the first time that people who had low birth weight are at greater risk of developing coronary heart disease.
### Table 1 Current data on the association of assisted reproductive technology and Beckwith–Wiedemann syndrome and Angelman syndrome

<table>
<thead>
<tr>
<th>Citation</th>
<th>Type of study</th>
<th>Prevalence of IVF/ICSI in general population during study period</th>
<th>Prevalence of IVF or ICSI in study syndrome population</th>
<th>ART procedure(s)</th>
<th>No. of case(s) tested for imprinting defect</th>
<th>No. of case(s) with imprinting defect</th>
<th>Percentage of syndrome pts with imprinting abnormalities</th>
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*NR = not reported

**Note:** The prevalence of Angelman syndrome in the general population is 1/15,000, and the prevalence of Angelman syndrome with imprinting disorder in the general population is 1/30,000.
observed for all of the major perinatal outcomes and nearly all of the secondary outcomes. This consistency was observed despite varying study designs, patient populations, and IVF and obstetric protocols. Many have ascribed the higher rates of adverse outcomes to the effects of multiple gestations and the increased age and nulliparity of women who obtain IVF.

Our results refute this assertion in that we observed increased adverse outcomes even in studies of singleton gestations that controlled for 2 major confounders: maternal age and parity.

Absolute risks and risk differences are generally more useful in counseling patients than relative risks. However, summary absolute risk differences could not be estimated using these studies given that several studies either did not provide raw incidence data in the spontaneous group or provided incidence rates unadjusted for age and parity.

The absolute risks in the IVF group as a whole were clearly elevated as evidenced by the increased incidence of each outcome, ranging from 2.0% for perinatal mortality to 14.6% for SGA. These numbers can be used to approximate the absolute risk in IVF singletons as a group but are simple arithmetic averages and cannot be applied to individual patients. Furthermore, individualized risks based on age and parity would be clinically useful but were also not estimable from the data given.

A limitation of any meta-analysis, especially one based upon observational studies, is that biases in individual studies will be reflected in the summary statistics. The most likely source of bias in our meta-analysis is related to altered management of IVF pregnancies. Because IVF pregnancies are highly valued by patients and their doctors, these patients may be more likely to be hospitalized or to undergo labor induction or cesarean for minor complications, thus leading to iatrogenic increases in preterm delivery and LBW. Indeed, most studies reported higher rates of induced labor and elective cesarean.
Genomic imprinting

Certain genes are expressed in a monoallelic, parent-of-origin specific manner

Unmethylated CpG
Methylated CpG

Maternally-Expressed Imprinted Gene
Fetal Growth

- Grb10: adaptor molecule that negatively regulates fetal growth
- Functions downstream of EGFR and IGF1R
- Deletion of the maternal copy of Grb10 led to a 40% increase in fetal weight and a 30% increase in placental weight
- Our human data show differences in Grb10 methylation between ART and control placentas

Charalambous et al. 2010
Liu and Roth 1995
**Maternal copy Grb10**

-CH$_3$

H3K37ME3

Paternal Grb10

---

**Maternal expression**

---

**Paternal expression**

---

**NORMAL GROWTH**

---

**Maternal Grb10 Mutant**

---

No Maternal expression

---

Paternal expression only

---

**OVERGROWTH**

---

Maternal copy Grb10

-CH3

H3K37ME3

Paternal Grb10

Maternal expression

Paternal expression

NORMAL GROWTH

Following superovulation

Maternal copy Grb10

-CH3

H3K37ME3

Paternal Grb10

Excess Grb10

SMALL MOUSE & SMALL PLACENTA
Mouse Model

Control female mated with vasectomized male

Superovulated female mated with vasectomized male

Uterine horn

10 naturally conceived blastocysts

Sacrifice at E18.5
Five control (white bars) and eight SO dams (black bars) were sacrificed at E18.5.

Mainigi M A et al. Biol Reprod 2014;90:26
Placental expression of Grb10 was elevated in placentas obtained from SO recipients (black bar) compared to control recipients (white bar) though expression of other growth-related genes did not differ between the two groups (A–D).

Mainigi MA et al. Biol Reprod 2014;90:26
Placental development

Control

Superovulated recipient

Mainigi M A et al. Biol Reprod 2014;90:26
GRB10 expression primarily in the labyrinth zone of the placenta, with increased expression in the SO placenta.
Fetal erythrocytes

- Nucleated
  - Proportion decreases during gestation
  - Neonatal count is normally low
  - Elevated counts associated with hypoxia, infection, anemia
- Larger, more deformable than adult cells
  - Mean cell volume initially 180 fL, decreases to 105 fL
- Shorter life span (~90 days)
- Hemoglobin concentration increases
  - 12 g/dL in midpregnancy, increases to 18 g/dL at term
- Blood volume ~125 mL/kg at term
  - 35 to 40% in placenta
Fetal erythropoiesis

- Controlled by fetal erythropoietin
  - Maternal does not cross placenta
  - Hormone produced in liver then kidney
- Site of primary red cell production changes
  - Yolk sac
  - Liver
  - Bone marrow
Fetal erythropoiesis

- Circulation established
- Yolk sac
- First hepatic colonization
- Second hepatic colonization
- Bone marrow colonization

Days: 17, 19, 21, 23, 27, 30

Weeks: 10.5
Fetal hemoglobin

- Tetrameric protein
- 2 copies each of 2 protein chains
  - $\alpha$-like
  - $\beta$-like
- Multiple precursors made during fetal life
- Fetal hemoglobin has greater oxygen affinity
Fetal hemoglobin

Source: Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY; 

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Genetics: methylation

- No (or hypo-) methylation leads to persistence of fetal hemoglobin
  - Sickle cell anemia
    - Increased fetal hemoglobin level is beneficial later in life
  - Fetuses of diabetic mothers
From placenta back to heart

- Umbilical vein
  - 40% of total output

- Portal sinus (50%)

- Ductus venosus (50%)

- IVC
  - 2/3 of flow to heart
  - 1/3 is from DV
From placenta back to heart

- **Umbilical vein**
  - 40% of total output

- **Portal sinus (50%)**

- **Ductus venosus (50%)**

- **IVC**
  - 2/3 of flow to heart
  - 1/3 is from DV
From placenta back to heart

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  - 1/3 is from DV
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  - 40% of total output

- Portal sinus (50%)

- Ductus venosus (50%)

- IVC
  - 2/3 of flow to heart
  - 1/3 is from DV
In the heart

- Two shunts
In the heart

- Two shunts
  - Foramen ovale
In the heart

- Two shunts
  - Foramen ovale
  - Ductus arteriosus
In the heart

- Two shunts
  - Foramen ovale
  - Ductus arteriosus
- Preferential streaming
  - DV blood directed across FO
  - Highest oxygen saturation to brain
- Lungs bypassed
  - DA directs blood to rest of body
Anatomic Perspective
Cardiac defects

- Important cause of infant mortality
  - 5% of all deaths
  - 27% of deaths due to congenital anomaly

- Incidence
  - 5 to 8 per 1000

- Prenatal diagnosis important
  - Delivery planning
  - Positive impact on postnatal management
Maternal risk factors

- **Disease**
  - Congenital heart disease
  - Diabetes
  - Collagen vascular disease

- **Exposures**
  - Alcohol
  - Anticonvulsants
  - Lithium
  - Retinoic acid

- **Infections**
  - Rubella
  - CMV
  - Parvovirus
Fetal risk factors

- Chromosomal abnormality
- Extracardiac anomaly
  - Omphalocele
  - Esophageal atresia
  - Duodenal atresia
  - Increased nuchal translucency
Familial risk factors

- Family history of CHD
  - Siblings, parents

- Family history of syndromes a/w CHD
  - Tuberous sclerosis
  - Noonan syndrome
  - Holt-Oran syndrome
  - Chromosome 22q11 deletion
Embryology

- More complex than previously taught
  - Tube that bends and septates is “simplistic”
- Modular development
  - Ballooning
  - Looping
Increase in size

- Basic structures complete by 8 weeks
- Position and valves complete at 12 weeks
## Genetics of heart defects

<table>
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<tr>
<th>Cardiac anomaly</th>
<th>Overall aneuploid rate percent</th>
<th>T 21 percent</th>
<th>T 18 percent</th>
<th>T 13 percent</th>
<th>45X0 percent</th>
<th>Other percent</th>
<th>22q11 deletion</th>
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Tetralogy of Fallot

- Most common cyanotic CHD (0.2-0.5/1000)
  - 5-10% of CHD in newborns

- Four components
  - Right ventricular outflow tract obstruction (RVOTO)
  - Ventricular septal defect (VSD)
  - Overriding aorta
  - Right ventricular hyperplasia

- Genetics
  - Trisomy 21, 18, 13
  - Phenylketonuria
  - 22q11 deletion (10%)
Tetralogy of Fallot

AO = Aorta
PA = Pulmonary Artery
LA = Left Atrium
RA = Right Atrium
LV = Left Ventricle
RV = Right Ventricle

- Tricuspid Valve
- Pulmonary Valve
- Right Ventricular Outflow Obstruction
- Mitral Valve
- Aorta Shifted to Right
- Opening Between Ventricles

Oxygen-rich Blood
Oxygen-poor Blood
Mixed Blood
Atrioventricular septal defect

- AKA Endocardial cushion defect or A-V canal
- Central heart defect
  - Missing “crux” of heart
  - ASD
  - VSD
  - A-V valves
  - Conducting system
- Balanced or unbalanced ventricular physiology
- Associations
  - 0.11 – 0.36 per 1,000 live births
  - Trisomy 21 (40%)
Atrioventricular septal defect
Lung development

- **Anatomic development**
  - Formation of intrapulmonary fluid
  - Amniotic fluid
  - Breathing movements

- **Stages**
  - Pseudoglandular: 5 – 16 weeks
  - Canalicular: 16 – 24 weeks
  - Saccular: after 24 weeks
  - Alveolar: 36 weeks to after birth
embryonic period

- formation of major airways
- formation of bronchial tree and portions of respiratory parenchyma
- birth of the acinus

fetal period

- last generations of the lung periphery formed
- epithelial differentiation
- air-blood barrier formed
- expansion of air spaces
- surfactant detectable in amnionc fluid
- secondary septation

Organogenesis

Differentiation

alveolar

saccular

canalicular

pseudoglandular

embryonic

birth
Surfactant

- Produced by type II pneumocytes
- Surfactant lines alveoli
- Lowers surface tension
- Allows alveoli to expand

- Insufficient surfactant
  - Collapsed alveolus
  - Inadequate oxygen exchange

- Sufficient surfactant
  - Expanded alveolus
  - Adequate oxygen exchange
Clinical correlations

- Fetal anomalies may affect lung volume
  - Chest mass
  - Diaphragmatic hernia
  - Skeletal dysplasia with small ribs

- Lack of amniotic fluid (oliogo/anhydramnios)
  - Renal agenesis
  - Ruptured membranes

- Surfactant deficiency/dysfunction
  - Preterm
    - Corticosteroids
    - Fetal lung maturity testing
  - Diabetes
  - Meconium aspiration
Diaphragmatic hernia
Fetal cystic chest mass
Fetal skeletal dysplasia
Bilateral renal agenesis