Neonatal medicine: Transition from intrauterine to extrauterine life
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Communicating in English
- Foreign visitor:
  - “So, how often do you have elections in China?”
- Chinese official, beaming happily:
  - “Evely molning!”

From intra- to extrauterine life
Dramatic events in the life of a human

- Conception
- Birth
- Death

From intra- to extrauterine life
Processes/functions
- Examples

- Energy metabolism
  - Cessation of glucose supply from mother
  - Initiation of lipolysis and gluconeogenesis

- General metabolism
  - Cessation of transplacental transport of waste products such as bilirubin
  - Induction of enzyme activities related to hepatic conjugation and clearance of bilirubin

- Respiration
  - End of respiration through placenta
  - Start of pulmonary respiration

- Circulation
  - Cessation of placental circulation
  - Step-up of pulmonary circulation
  - Closure of ductus arteriosus

- Energy metabolism
- General metabolism
- Hematologic transition
- Immunologic transition

- From fetal to adult hemoglobin
- Altered erythrocyte oxygen affinity
- In utero sterile environment
- Ex utero “all the world’s bugs”
From intra- to extrauterine life

Processes/functions
- Examples
• Thermal regulation
  - Fetal body temperature essentially maintained and regulated by maternal organism
  - “Radiator effect” of large body surface-to-volume ratio makes newborn vulnerable to hypothermia and necessitates initiation of thermogenesis

• Digestion
  - Enteral digestive enzymes and secretions largely dormant
  - Use of gut to receive nutrients, accompanied by induction of many enzymatic digestive processes

• Fluid balance
  - Accelerated reduction of extracellular water compartment
  - Shortly after birth intracellular water becomes largest fluid compartment

• Mineral/electrolyte balance
  - Cessation of active maternal-to-fetal transport of calcium
  - Mobilization of calcium stores

• Growth
  - Prenatal regulation through insulin, IGF1, and IGF2
  - Postnatal regulation through pituitary growth hormones

• Circadian rhythms
  - Diurnal rhythm found in fetus after 20 wk GA
  - Postnatal circadian rhythm takes 2-3 months to establish

• Gene activation
  - Many enzymes dormant in fetal life
  - Increased mRNA for many enzymes after birth

Lung development

A-C fetal lungs at 4 wks

D-E fetal lungs at 5 wks

Lung development

• Terminal airways at 24 wks gestation
  - Alveoli are few
  - Epithelium is cuboidal
  - Production of surfactant is low
  - Interstitium separates alveoli and capillaries
Lung development

- Terminal airways at term
  - 20-70 million alveoli are present
  - Surfactant is produced by type II pneumocytes
  - Close proximity alveoli-capillaries

- The neuromuscular control of breathing is established early
  - The fetus spends nearly 30% of its time in rapid, discoordinate panting associated with REM sleep
  - Near term up to 600 mL of amniotic fluid per day is inhaled through this activity - a lot of it is swallowed

Lung transition

- In utero lungs are fluid filled
- The alveoli are open and filled with fetal lung liquid
  - This liquid is produced by ultrafiltration of capillary blood and secretions from alveolar cells

- During passage through the birth canal the thoracic cage is compressed
  - Pressures can rise to 30-160 cm H₂O
  - This is accompanied by ejection of fluid from the trachea

- Recoil of the chest wall at delivery draws air into the airways
  - The pressure gradient generated during this process may be as high as 60-100 cm H₂O
  - Due to the tension inherent in the air-liquid interface, inflation with air requires more force than inflation with fluid

- During the next few breaths liquid in the airways is gradually replaced by air
  - Blood starts to enter the pulmonary circulation, filling the capillaries
Lung transition

- The air-liquid interface now being established in the alveoli generates a surface tension that would tend to collapse the lung were it not for the presence of surfactant in the alveolar lining.

Stimuli for breathing

- A multitude of stimuli meet the newborn during and after birth:
  - Cold
  - Hypoxia
  - Light
  - Acidosis
  - Noise
  - Hypercapnia
  - Gravity
  - Pain

Pulmonary adaptation

- Inadequate stimuli, e.g. Caesarean delivery without preceding labor, will often result in delayed clearance of lung fluid:
  - Pulmonary adaptation disturbance ("wet lung", "transient tachypnea of the newborn")

Circulatory adaptation

- The fetal circulation is characterized by
  - Low systemic vascular resistance
  - High pulmonary vascular resistance
- The post-natal circulation is characterized by
  - High systemic vascular resistance
  - Low pulmonary vascular resistance

Fetal circulation

- **In utero phase**
  - Pulmonary vascular resistance > systemic vascular resistance
  - RA and RV pressure > LA and LV pressure
  - >1/3 of oxygenated blood from placenta crosses through the foramen ovale to LA - LV and perfuses head/nose/upper trunk
  - Blood from SVC goes to RV - PA - ductus arteriosus - descending aorta, is mixed w/blood from RV = lower PO2 to the lower body
  - Only 8% of cardiac output perfuses the lungs

Circulatory adaptation

- **Immediate phase**
  - Occurs during the first 12-24 h after birth
  - Is responsible for the major part of reduction in pulmonary vascular resistance (PVR)
  - May be connected to production of vasodilating compounds (NO, prostacyclin, leukotrienes)
Circulatory adaptation

"Immediate phase"

- Air replaces fluid in lungs
- Mechanical distention of pulmonary vasculature results in rapid lowering of pulmonary vascular resistance
- Air in the alveoli increases oxygenation in pulmonary vessels, leading to further decrease of pulmonary vascular resistance

- In utero the placental vascular bed is a large low-resistance area
- When the umbilicus is cut this low-resistance vascular bed is immediately lost to the systemic circulation
- This results in a rapid increase in systemic vascular resistance

Circulatory adaptation

"Immediate phase"

Before birth
- RA - high pressure
- LA - low pressure
- Septum secundum
- Shunt
- Foramen ovale

After birth
- RA - lower pressure
- LA - higher pressure
- Septum secundum
- Septum primum

- This phase of transition is a vulnerable period
  - Several stimuli may cause shunt reversal
    - Asphyxia
    - Hypoxia
    - Infection
  - A fetal pattern of circulation may thus be reestablished
    - Persistent pulmonary hypertension of the newborn ("persistent fetal circulation")

Circulatory adaptation

"Final phase"

- Involves remodeling of pulmonary blood vessel musculature
- In the course of a few days vessel wall thickness is reduced in vessels of <250 um diameter
- In the course of a few months vessel wall thickness is reduced in vessels of 250-500 um diameter

Metabolic adaptation

Energy metabolism

- In utero the fetus receives a steady supply of glucose by active transport across the placenta
  - 4-6 mg/kg/min
- In late gestation ~50% of the glucose is converted to glycogen in liver and muscle, and to fat in liver and adipose tissue
  - Glucose storage is regulated by insulin and glucocorticoids
Metabolic adaptation

Energy metabolism

• When the cord is cut, blood glucose levels fall over the next 1-2 h
• This drop in blood glucose levels together with the surge in catecholamines induced by the stress of birth, stimulates important enzymes:
  – Hepatic phosphorylase is involved in glycogenolysis

Proteins

• Amino acids are transported across the placenta by
  – active transfer of essential AA
  – placental cytosolic synthesis of non-essential AA
• Some amino acids are essential to the fetus, but non-essential after birth
  – Due to immature enzyme systems

Lipids

• Supply of FFA to fetus occurs by
  – carrier-mediated transport
  – placental synthesis with release into the umbilical circulation
  – lipolysis of triglycerides, lipoproteins, or phospholipids from either maternal or fetal side

Metabolic adaptation

Lipids

• The activity of lipoprotein lipase is related to the degree of maturity
  – lower lipid-clearing ability in the premature infant
• High levels of FFA and glycerol soon after birth indicate onset of lipolysis and lipid oxidation
• Fatty acid oxidation increases significantly after birth

Bilirubin metabolism

• Bilirubin is the end product of heme catabolism
• Fetal erythrocytes have a shorter life-span than adult (35-90 vs 180 days)
  – More bilirubin is produced
• Some bilirubin is excreted into the fetal gut, but can then go no further
• Bilirubin from the fetus

Metabolic adaptation

Bilirubin metabolism

• After birth
  – Bilirubin production increases (8 mg/kg/d vs 4 mg/kg/d later)
  – Excretory capacity is low
    • Conjugating ability at <1% of adult
  – Bilirubin accumulates in serum, tissues and extra-cellular fluid, causing


Hematologic transition

- Fetal red cells contain hemoglobin F
  - Increased affinity for oxygen
    - Due to less binding of 2,3-diphosphoglycerate to HbF than HbA
- Production of red cells with adult type hemoglobin (HbA) starts late in gestation
- Production of HbF is switched off at birth

Hematologic transition

- Hemoglobin in the newborn is high
  - 16.5+/-.5 g/dL (mean +/-SD)
- After birth hemoglobin falls to a nadir
  - 11.4+/-.9 g/dL at 8-12 weeks
- This is due to
  - No longer need for high Hgb in high oxygen atmosphere
  - Decreased erythrocyte production
    - Decreased erythropoietin production
    - Short erythrocyte lifespan

Immunologic transition

- In utero the fetus is protected by the maternal organism
- The fetus is immunologically "naïve"
- Maternal antibodies are transferred to the fetus during the last part of pregnancy

Immunologic transition

- At birth the infant starts to be exposed to microorganisms
  - Pathogens
  - Commensals
- Skin/mucous membranes/large intestine are populated by microorganisms

Thermal regulation

- After birth body temperature may fall significantly
  - The infant has a large surface-to-volume ratio
  - The infant is wet
  - Radiation and evaporation cools the skin surface rapidly
- Thorough drying and then swaddling the newborn is necessary in order to prevent excessive heat loss!

Thermal regulation

- The term newborn can regulate body temperature by
  - Sweating
  - Increasing metabolic rate
    - Non-shivering thermogenesis
      - Triiodothyronine stimulates thermogenin which converts proton energy to heat
  - This mechanism may be ineffective in
    - Hypoxia
    - Nutritional depletion
**Digestive tract**
- The fetus swallows amniotic fluid from week 11-12 of gestation
- Non-nutritive sucking appears at 18-24 weeks
- By term the fetus swallows up to 500 mL of amniotic fluid per day

**Digestive tract**
- By term, sucking movements are followed by
  - Swallowing
  - Esophageal peristalsis
  - Relaxation of the lower esophageal sphincter
  - Relaxation of the gastric fundus

**Digestive tract**
- Coordination of breathing, sucking, and swallowing is a complex process
  - Failure at this is probably the most common reason why many borderline premature (34-36 weeks GA) infants remain in hospital vs going home

**Digestive tract**
- At birth the large intestine is filled with meconium, a very tenacious/sticky material containing:
  - Intestinal secretions
  - Dead mucosal cells
  - Bile and pancreatic juices
  - Bilirubin
  - Mucous, blood, lanugo, and vernix
  - 70-80% water

**Digestive tract**
- The fetus makes little demand on its gastrointestinal tract
- The situation changes dramatically at birth
  - Demand for enteral intake of nutrients necessitates rapid maturation of the alimentary tract

**Fluid balance**
- Total body water is divided into
  - Intracellular water
    - Plasma volume
    - Interstitial fluid
  - Extracellular water
  - Distribution of body water in a term infant

(From Bell & Ols: Fluid and electrolyte management, 1994)
**Fluid balance**

- Water constitutes 94% of the body in early fetal life.
- Total body water gradually decreases and is 78% of the body at term.
- Extracellular water decreases.
- Intracellular water increases.
- In the first days of life fluid loss > fluid intake.

(From Friis-Hansen: Changes in body water compartments during growth, 1957)

**Insensible water loss (IWL)** occurs by:
- Evaporation from skin (70%)
- Moisture in expired air (30%)

IWL starts at birth.
IWL is inversely proportional to body weight and gestational age.

(From Costarino et al: Controversies in fluid and electrolyte therapy for the premature infant, 1985)

**Electrolyte balance**

- Na+ is the dominant ion in extracellular fluid (ECF).
- When extracellular water is lost rapidly, Na+ concentration in ECF will increase.
- Hypermaturemia is common in extremely premature infants.

(From Bell EF, Oh W: Fluid and electrolyte management, 1994.)

**Renal function**

- At birth the kidney replaces the placenta at the major homeostatic organ for maintenance of fluid and electrolyte homeostasis.
- Renal blood flow increases rapidly.
- The glomerular filtration rate rises quickly and doubles by 2 weeks of age.

(From Bell EF, Oh W: Fluid and electrolyte management, 1994.)

**Electrolyte balance**

- Calcium is actively transported to the fetus by the placenta.
  - During the last trimester Ca stores quadruple.
- At birth the constant supply of Ca is interrupted.
  - S-Ca falls during the first hours after birth (S-niCa from 1.45 mmol/L at birth to 1.33 mmol/L at 2 h and 1.23 mmol/L at 24 h)

**Renal function**

- Most aspects of renal function are immature at birth - more so in the premature infant.
  - Glomerular and tubular functions increase with age.
  - The maximal concentration ability is less than in adults.
  - Newborns have less ability to handle a water load.
Growth

- Prenatal growth is dependent on insulin and insulin-like growth factors
- Postnatal growth is mainly regulated through pituitary growth hormones

Circadian rhythms

- Diurnal rhythms are found in the fetus from the 20th week of gestation
  - It is not clear how they are regulated
- Postnatally it takes 2-3 months before circadian rhythms of sleep and wakefulness and the concomitant hormonal variations are established

Gene activation

- Labor affects the mRNA coding for a number of enzymes
  - Tyrosine hydroxylase
  - Dopamine-\(\beta\)-hydroxylase
- mRNA for substance P increases several fold in the nucleus tractus solitarius during the first days of life
  - Substance P is involved in respiratory drive through peripheral chemoreceptors