The third trimester is a time of rapid brain growth and development which continues on through the first year.

- Cortical neurons are generated in the periventricular germinal matrix.
- Almost all neurons have actually been generated by 25 weeks.

Neurological

- Neurons then migrate out towards the surface of the cortex, branch out, and form synapses.
- By 32-34 weeks, focus of development shifts to the cortex
- Germinal matrix tissues themselves undergo involution.
Neurological: Hemorrhage

At 24-28 weeks, the supportive structures around the germinal matrix are still very fragile, making the baby vulnerable to hemorrhage into the ventricles.

Neurological

The autonomic control of cerebral blood flow is poorly developed in the preemie, allowing fluctuations in cerebral blood flow which can lead to bleeding and/or ischemia.

Intraventricular Hemorrhage (IVH)

- Risk Factors:
  - <34 weeks
  - <1500 grams
  - “unstable”
- Incidence:
  - Has decreased over the past 20 years to about 10-20% of VLBW babies in most NICUs. (Down from over 50%)

Intraventricular Hemorrhage (IVH)

- Clinical Presentation:
  -Ranges from catastrophic (least common) to silent (most common)
- Risk period: first 3-4 days of life
- Diagnosis:
  - Cranial Ultrasound at 1 week of age detects 95% of all IVH.
Intraventricular Hemorrhage (IVH)

- **Management**
  - Serial ultrasounds
  - CSF taps or drainage for progressive hydrocephalus
  - Ventricular-peritoneal shunt

- **Prognosis**
  - Neurodevelopmental outcome of preemies with grade I or II hemorrhage similar to comparable babies with no hemorrhage.
  - Some increased risk in visual motor integration skills.

Intraventricular Hemorrhage (IVH)

- 30-40% of those with moderate (Grade III) bleeds have major neurologic sequelae (higher with periventricular infarct or PVL)
- “Major” neurologic sequelae
  - Blindness
  - Deafness
  - Cerebral Palsy
  - Severe mental retardation

Periventricular Leukomalacia (PVL)

- Necrosis of white matter in a characteristic distribution dorsal and lateral to the lateral ventricles. It is the primary ischemic lesion of the premature infant.
- Currently the major form of brain injury in preterm infants.
Periventricular Leukomalacia

- Risk Factors
  - Prematurity – 23-32 weeks
  - Postnatal illness – hypoxia, ischemia, inflammation

Periventricular Leukomalacia (PVL)

Pathophysiology
- Pressure passive cerebral circulation
- Rapidly growing cerebral white matter has high metabolic needs
- Periventricular vascular anatomic factors
- Low blood flow leading to necrosis, hemorrhage, and cysts
- Initial insult plus damage to process of myelinization

Periventricular Leukomalacia (PVL)

Clinical Presentation
- Generally silent, picked up on ultrasound. Delay before evident on ultrasound.

Prognosis
- Major long term sequela is spastic diplegia, especially affecting legs.
- High risk for developmental problems.
Diffuse Cellular PVL

- MRI can detect diffuse PVL on cellular level.
- May play a role in intellectual deficit.

Neuroprotective Strategies:

- Stable BP and oxygenation
- Maintain good glucose levels
- Avoid rapid infusion of bicarb
- Avoid low pCO2 levels
- Gentle handling, developmental support

Retinopathy of Prematurity (ROP)

- ROP describes an abnormality of growth and development of the retina of the premature infant.
- Untreated, it may progress to retinal detachment and blindness.
- In the US, approximately 500 to 700 infants lose their vision due to ROP each year.
- Additionally, 4500 infants will develop complications of ROP including myopia, strabismus, and late-onset retinal detachment/blindness.

Normal Retinal Development

- The retina begins to develop at the 16th week of gestation.
- Blood vessels grow out of the optic disc and slowly advance outward.
- The retina is not completely vascularized until 36 to 40 weeks gestation.
- Preterm infant has immature formation of antioxidant enzymes and free radical scavengers.

Pathophysiology of ROP

- Initial hyperoxic injury
  - Elevated oxygen levels (oxygen saturations >95%) cause severe vasoconstriction and destruction of immature retinal vessels
  - The vasoconstriction severely inhibits blood flow to the retina (retinal ischemia)
  - By about 30-34 weeks gestation the ischemic retina attempts to restore its blood flow by releasing growth factors to stimulate new blood vessel growth (neovascularization)
  - This “catch-up” growth is abnormal and poorly controlled and may result in retinal detachment and blindness.
Pathophysiology of ROP

Hyperoxia (high O2 saturations)
Vessel constriction/destruction

Neovascularization (abnormal vessel growth)

ROP: Prevention
- Avoid **hyperoxia** (O2 sat >95%), especially in the first few weeks of life
- Avoid large **fluctuations** in oxygen saturations

Retinopathy of Prematurity (ROP): Screening Guidelines
- 30 weeks or less at birth
- <1500 grams at birth
- Consider screening if premature, 1500-1800 grams at birth, and unstable
- Start 4 to 6 weeks after birth at 31 to 33 weeks corrected gestational age.


Stages of ROP: Stage 4

Stage 4: Subtotal retinal detachment beginning at the ridge.
The retina is pulled anteriorly into the vitreous by the fibrovascular ridge.

http://www.ret.uchicago.edu/images/ROP10-25-0608.jpg
Laser Surgery

Laser photocoagulation/retinal ablation has been successfully used to prevent retinal detachment in threshold ROP.

Retinopathy of Prematurity (ROP) – Laser Treatment Guidelines

- Zone 1 ROP: any stage with plus disease
- Zone 1 ROP: stage 3 – no plus disease
- Zone II: stage 2 or 3 with plus disease

Emerging Therapy: Intravitreal Bevacizumab (Avastin)

- 2011 Study showed benefit for vision threatening ROP in Zone 1
- Anti-VEGF agent (vascular endothelial growth factor)

VON presentation Dec. 2011

Outcome

Mild ROP (Stage 2 or less) generally has a favorable outcome.

Severe ROP (Stage 3 and above) may progress to partial or total retinal detachment and blindness.

Infants with severe ROP are also at risk for severe myopia (near-sightedness) and strabismus/amblyopia.

Infants with severe ROP may have retinal scarring which can lead to late retinal detachments in adolescence or early adulthood.

Hematological: Anemia

- Acute (pathologic)
  - bruising, hemorrhage, or hemolysis
- Iatrogenic Anemia from lab testing
- Survival of premature infant’s red blood cells about 50% less than adult circulation time. (Adult cells last average of 120 days)

Transfusion Infant Protocol

- Puget Sound Blood Center Infant 0-4 month Protocol uses specimen of infant or cord blood for type and antibody screen. This screen is good until infant is 4 months old (when they begin to make significant antibody of their own) or leaves hospital.
**Transfusion**

**Assigned Aliquots**
- Pediatric Assigned Unit
- 1 Adult unit divided into 8 aliquots and kept for that baby.
- Reduces exposure to multiple donors
- All units leukoreduced and irradiated
- Good for 42 days from collection

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**Anemia of Prematurity**

**Physiologic**
- At birth, the infant is suddenly transferred from the relative hypoxia of the uterus to the oxygen rich environment of the outside atmosphere.
- Red cell production in the bone marrow virtually ceases and resumes activity when the infant is about 2 months old.
- In the preterm infant, this physiologic process can be prolonged and the hematocrit fall to a lower level.

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**Anemia of Prematurity**

**Management**
- Premature infants on breast milk only need supplemental iron once on full oral feedings to ensure they have iron when they begin reticulating.
- Consider transfusion if infant has hematocrit in low 20’s or teens, has apnea or oxygen needs, is not growing well, or has low reticulocyte count.
- Erythropoetin in limited situations
  - Works slowly
  - Needs adequate iron stores

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**Hematological: Hyperbilirubinemia**

- The preterm infant liver is immature and does not clear bilirubin as efficiently.
- Concern that immaturity of the blood/brain barrier makes preemie more vulnerable to bilirubin toxicity.

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**Hyperbilirubinemia**

- Preemies generally treated for hyperbilirubinemia at lower levels than term infants.
- Exact levels are controversial, but the 2004 AAP guidelines show that even the mildly premature infant is at increased risk.
Hyperbilirubinemia

- Late preterm infant at risk due to
  - immaturity of liver
  - immaturity of feeding skills
  - early discharge home without adequate understanding and supervision.

Fluids & Electrolytes

- Newborn babies have high total body water content
  
- Neonates have higher basic metabolic rate
  
- Newborn water requirements are 4-5 times greater

Immature Kidneys

- Newborns have a lower renal blood flow than adults
  - increases rapidly after birth in the term and older premature with postnatal shifts in blood flow
  - more slowly in the preterm less than 34-35 weeks. (Remember: mom was doing this!)
  
- Newborn has lower glomerular filtration rate; again, it doubles by two weeks of age, but increases more slowly in the younger preemie.
Renal
- Newborns have limited ability to concentrate urine, and prematures are even more limited in this regard. Lose salt and water in urine.
- Full complement of nephrons develops at around 35 weeks.
- Postnatal renal function is more related to postbirth age than gestational age; birth stimulates some maturation.

Renal: Preterm Problems
- Narrow margin of safety in calculating and administering fluids and electrolytes.
- Fluid and Electrolyte Problems: Vulnerable to overhydration, dehydration, hyper/hyponatremia, hypo/hyperkalemia.
- Buffering Capacity: The preterm infant is vulnerable to any event that causes acidosis or alkalosis. They do not retain bicarb well.

Renal: Preterm Problems
- Drug Clearance:
  - Prematurity and illness restrict a neonate’s ability to excrete certain drugs and increase risk of toxicity. Aminoglycosides in particular are timed with regard to gestational age and levels are followed.

Fluid & Electrolyte Management
- Fluid requirements
  - (May be much higher for the extremely low birthweight without humidity)
    - Day 1  80 cc/Kg/day
    - Day 2  80-100 cc/Kg/day
    - Day 3  100-120 cc/Kg/day
    - Day 4  120-150 cc/Kg/day
  - Adjust baseline for insensible water loss such as phototherapy, radiant warmer, surgical conditions, immature skin

Fluid & Electrolyte Management
- Electrolytes added once the baby voids
- Strict monitoring of intake and output until stable
- Monitor electrolytes, pH, and blood gases.

Gentamicin

<table>
<thead>
<tr>
<th>PMA (weeks)</th>
<th>Postnatal (days)</th>
<th>Dose (mg/kg)</th>
<th>Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤29</td>
<td>0 to 7</td>
<td>5</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>8 to 28</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>≥29</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>30 to 34</td>
<td>0 to 7</td>
<td>4.5</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>≥8</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>≥35</td>
<td>ALL</td>
<td>4</td>
<td>24</td>
</tr>
</tbody>
</table>

* or significant asphyxia, PDA, or treatment with indomethacin

Neofax 2011
**Fluids & Electrolytes**
- Fluid status is assessed based on I&O, daily weight, appearance, and electrolytes (mainly Na⁺)
- Normal electrolyte values:
  - Na⁺ 135-145
  - K 3.5-5.5
  - Cl 90-110

**Gastrointestinal/Nutritional**
- One way out of NICU: Grow, Baby, Grow!
- Immature GI tract function until 36-40 weeks limits digestion and absorption.
- GI motility is decreased in preterm infants
- Lower production of digestive and hepatic enzymes
- Maintaining Adequate Nutrition
  - Preterm infants are born without the reserves of fat, carbohydrate, vitamins and minerals which would have been transferred from their mothers during the latter part of pregnancy.

**Gastrointestinal/Nutritional**
- Maintaining Adequate Nutrition
  - Higher energy expenditure than in the womb
  - Caloric needs related to the disease processes
  - Developmentally, high caloric needs for growth.

**Growth & Nutrition**
- Many premature infants born on lower end of growth curve.
- With inadequate nutrition, they tend to fall even lower on the curve.
- Inadequate nutrition leads to growth failure and impaired neurocognitive development.
The Challenge of Catch-up Growth

Most VLBW infants regain birthweight by 2nd or 3rd week of life. The longer the time it takes to regain, the slower the catchup growth will be.

Goals for Growth:

- To approximate in utero growth of a normal fetus of the same postconceptual age

- Weight gain of 18 grams/kg/day

- Length: about .75 cm per week

- Head circumference: about .5 cm per week

Parenteral nutrition now started within 24 hours of birth

Trend is to start enteral nutrition earlier than in the past and be more aggressive in enteral feeding advancement.
**Recommended Protein Intake**

<table>
<thead>
<tr>
<th>Weight</th>
<th>g/Kg/day</th>
<th>g/100 kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000 gm</td>
<td>4.0-4.5</td>
<td>3.6-4.1</td>
</tr>
<tr>
<td>1000-1800 gm</td>
<td>3.5-4.0</td>
<td>3.2-3.6</td>
</tr>
</tbody>
</table>

European Society for Pediatric Gastroenterology, Hepatology and Nutrition 2010

**Options for Feeding**

1. Preterm human milk
2. Premature formula or fortified breastmilk
3. Fortification beyond the 24 calories
4. Post-premature formula
5. Extremely low birthweight babies

**Selecting appropriate feeding:**

- **Preterm Human Milk** is specially suited to the preterm infant’s higher protein and calorie needs for the first two to four weeks.

**Fortification:**

- Many preemies need fortification beyond the 24 calories in premature formulas in order to achieve adequate weight gain.
- Various ways to do this depend on:
  - Baby’s clinical situation
  - Hospital formula contract
  - Local availability of products after DC.

- Call nutritionist at Level III center for questions.

**Post-premature formula**

- If the infant is formula feeding, both formula companies make 22-calorie formulas that are higher in protein, vitamins and minerals than standard formula, but not as rich as premature formulas.
ELBW Infants

- The extremely low birthweight infant (ELBW, < 1000 grams) poses a challenge for bone mineralization, and some of these babies have been found to have fractures later if exclusively breastfed. Nutritionists recommend some fortification for them through the first year of life.

Gastrointestinal/Nutritional: Feeding Intolerance

- May be mild and respond to nursing measures or serious and require medical intervention.

Feeding Intolerance

- Signs and Symptoms:
  - Residuals: Current thinking is to tolerate up to 50% of previous feed if no associated GI symptoms.
  - Emesis
  - Abdominal distension
  - Diarrhea
  - Increased apnea and/or bradycardia

The Fear: NEC

Necrotizing Enterocolitis

- NEC is an idiopathic disorder characterized by inflammation and necrosis of the mucosal layers of the gastrointestinal tract.
- Any part of the bowel can be affected, but most often the distal ileum and proximal colon are involved.
### Necrotizing Enterocolitis (NEC)

**What causes NEC?**
- We still do not know for sure. The etiology has been debated and researched for many years.
- Some ischemic or hypoxic insult to gut?
- Bacteria involved
- Indomethacin?

### Necrotizing Enterocolitis (NEC)

**Who is at risk for NEC?**
- Prematurity is the greatest risk factor.
- Smaller babies born weighing less than 1500 grams make up 70% of cases, but it can happen to a term infant
- 90-95% have been fed

### Necrotizing Enterocolitis (NEC)

**Signs and Symptoms**
- Feeding Intolerance
  - Abdominal Distension
  - Visible Loops of Bowel
  - Blood in Stool
  - Gastric Residuals
  - Vomiting

### Necrotizing Enterocolitis (NEC)

**Signs and Symptoms**
- General systemic signs
  - Lethargy
  - Apnea/bradycardia
  - Temperature instability
  - Hypotension/hypoperfusion

### Necrotizing Enterocolitis (NEC)

**Diagnostic Tests**
- X-Ray
  - Dilated bowel loops with thickened walls due to local edema
  - Pneumatosis intestinalis occurs when gas-forming bacteria invade the intestinal wall (diagnostic of NEC)
  - Pneumoperitoneum occurs with bowel perforation

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### Necrotizing Enterocolitis (NEC)

**Can move very fast!** Any of these signs warrant a careful look for others!
Necrotizing Enterocolitis (NEC)

**Diagnostic Tests**
- Blood culture
- CBC
- electrolytes

**Medical Management**
- NPO for bowel rest (often for 7-10 days)
- Gastric decompression
- Antibiotics
- Serial X-Rays
- Careful monitoring of blood glucose levels

**Surgical Management**
- Resection of necrotic bowel
- Creation of a stoma if necessary
- Drain
Necrotizing Enterocolitis (NEC)

- Prevention
  - Prevent prematurity
  - Careful infection control, as NEC does occur in clusters
  - Encourage pumping and breastfeeding, as antibodies in breast milk provide some protection.
Progression to Oral Feeding

- Evidence Based Approaches:
  - Breast Only
  - Step-wise
  - Cue-Based – current trend

- A consistent institutional guideline helps parents, nurses, and babies

Bottle feeding usually plays a role in getting a preemie to full oral feeding so they can go home, especially if mother cannot be in the hospital round the clock. Also important because of need for continued fortification.

Nipple Feeding: What makes it hard for a premie?

- weaker muscle tone
- lack flexion
- absent or reduced sucking pads
- few opportunities for positive oral sensation
- absent or immature reflexes
- limited energy stores

Nipple Feeding: Enhancing Success

- quiet environment
- watch for appropriate infant state
- time
- frequent burping/pacing
- flow/nipple choice
- positioning - support flexion
- Good breastfeeding support and a plan for the transition home

Techniques that Take the Initiative Away from the Baby

- Twisting/turning the bottle
- Moving nipple up/down
- Moving nipple in/out of baby’s mouth
- Massaging chin or stimulating the face
Discharge/Followup Issues

Remember: Day of discharge almost as stressful as admission. Don’t leave teaching til last day!!

Discharge/Followup Issues

Do you have a followup pediatrician?!

Infant safety & CPR class

Immunizations, on same schedule as term infants

Discharge/Followup Issues

ROP Exams

Communication about follow-up extremely important

Discharge/Followup Issues

Car Seat Test recommended by AAP for infants born at less than 37 weeks gestational age or 2500 grams

Car Seat Test – 2009 AAP Revised Guidelines

- 90 – 120 min or duration of travel time
- Advise parents to use car seat for travel only
- Advises monitoring in car bed if that is used
- Crash protection of car seats better documented than that of car beds
- Advises considering retesting before transition to car seat from bed
- Avoid similar upright equipment like swings, infant seat, carriers until baby is larger

Discharge/Followup Issues

“Back to Sleep” unless otherwise ordered

- Bed flat before baby goes home
- No sheepskins or fluffy bedding
- BUT, they need play time on their tummy while they are awake!

Pediatrics Vol 123, #5, May 2009
Discharge/Followup Issues

- Susceptibility to RSV
  - Teach parents to wash hands and protect baby from smoke and people with colds.

Hearing Screen:
All babies who have been in intensive care are at increased risk.

- Make sure they get their hearing screen before discharge
- Increased incidence of both sensorineural and conductive hearing loss
- Hearing loss occurs both in the newborn period and during the first year

Discharge/Followup Issues

- Synagis Criteria – 2009 revisions
  - Less than 2 years old:
    - Requiring medical therapy for chronic lung disease or significant congenital heart disease
  - Less than 1 year old:
    - Born at or before 28 weeks gestation
    - Congenital airway anomaly or neuromuscular disease
  - Less than 6 months old at start of season
    - Born before 32 weeks gestation
    - 32-35 weeks (“less than 35 weeks”) at birth with risk factors: daycare or siblings under 5 years old – Synagis only for first 3 months

Discharge/Followup Issues

- High Risk Followup Clinic
  - VLBW (<1250 grams)
  - 30 weeks gestational age or less
  - Bronchopulmonary dysplasia/significant mechanical ventilation
  - CNS complications: IVH, PVL, seizures, meningitis
  - Prenatal drug exposure

Discharge/Followup Issues

- Feeding Plan / Growth Monitoring

  - See gaining and growing website:
    - http://depts.washington.edu/growing

You’ve done your job! Let go and rest!