FEEDING THE ILL NEONATE

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Objectives of the Talk

- Some physiological bases of nutrition during fetal life, parturition and in postnatal life.
- Feeding the neonate with acute pulmonary disease.
- Feeding the neonate with bronchopulmonary dysplasia.
- Feeding the neonate with congenital heart disease.
- Feeding the neonate with sepsis.
- Feeding the surgical neonate.

Postnatal changes in metabolism involve the transition from almost exclusive reliance on glucose energy production in the fetus to markedly increased use of fatty acids and ketone bodies for energy production in the neonate. In addition, glycogen is critical in order to maintain glucose homeostasis immediately after birth.

An increase in epinephrine, norepinephrine and glucagone and a decrease in insulin at birth promote mobilization of fatty acids and glycogen metabolism

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Glucose and the Fetus

- Glucose is the principal energy substrate for placenta and fetus
- Fetal life is characterized by constant glucose supply.
- Carbohydrate is transported to the fetus as glucose which is taken up from the maternal plasma by the GLUT 1 transporter and transported to the fetus by facilitative diffusion according to concentration-dependent kinetics.
- How to insure an adequate glucose supply:
  - *the maintenance of maternal glucose concentration by increasing rates of maternal glucose production*
  - *development of relative maternal glucose intolerance and insulin resistance*

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Nitrogen and the Fetus

- Transport of N to the fetus is 54nmol/day.
- Accumulation of about 400gm of protein by term.
- AA transport is
  - Not influenced by fluctuation of uterine or placental blood flow
  - Exceeds the amounts needed for nitrogen accretion
  - Via 2 major transporters
    - Na dependent transporter for taurine, glutamine, alanine, serine and glycine.
    - Na independent transporter for branched chain aa., lysine and arginine.
- Critical aa are not transported across the placenta but rather produced in the placenta e.g.: glutamate and aspartate.
- Placenta produce ammonia used by fetal liver for more ptn synt.

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Lipids and the Fetus

- No lipid utilization for energy production in fetal life.
- Placental lipid transfer to the fetus involves:
  - Direct transporter mediated transfer of certain FA.
  - Lipid uptake from lipoprotein, metabolic alterations in the placenta and release into the fetal plasma.

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Energy Stores in the Fetus and Newborn

Weeks	Wt (g)	Water (%)	Protein (%)	Lipid (%)	Energy (kcal)
24	690	86.6	8.8	0.1	19.5
26	880	86.8	9.2	1.5	123.6
28	1160	84.6	9.6	5	326.2
40	3450	74.0	12	15.3	3152.4
2 months	5450	71.4	11.4	25	9866

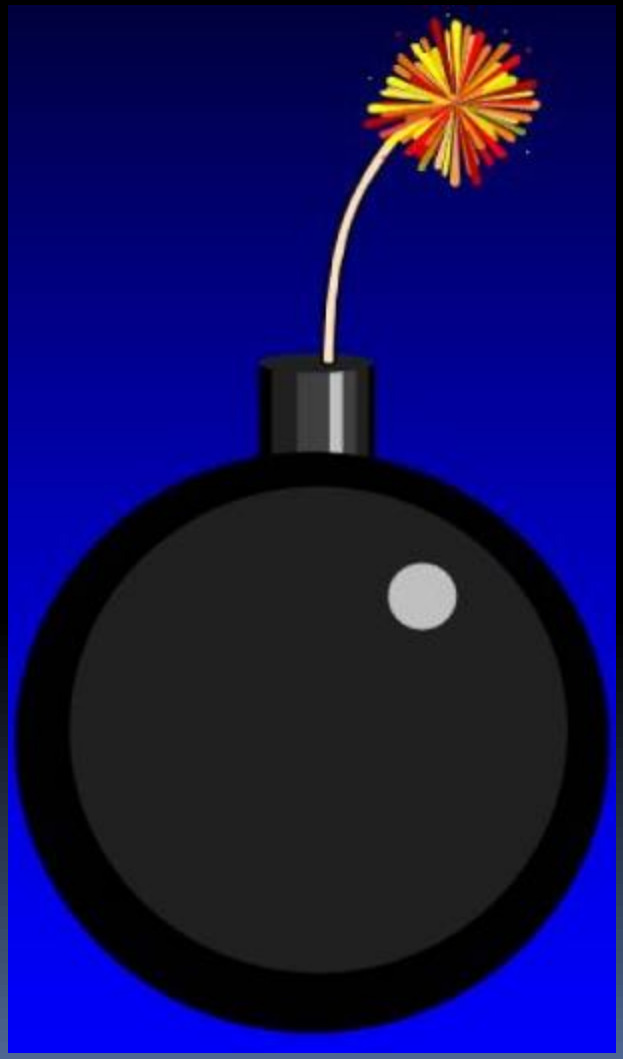
Ziegler, E. Growth, 1976

The Preterm Newborn:
A NUTRITIONAL EMERGENCY

Neonatal transition: From anabolic to catabolic

Glucose stores: **of only 200 kcal**

Catabolic: **net protein loss**



- **With IV glucose alone, he lose 1% body protein/day**
- **10% loss of protein stores = protein malnutrition**

Is early nutrition important?

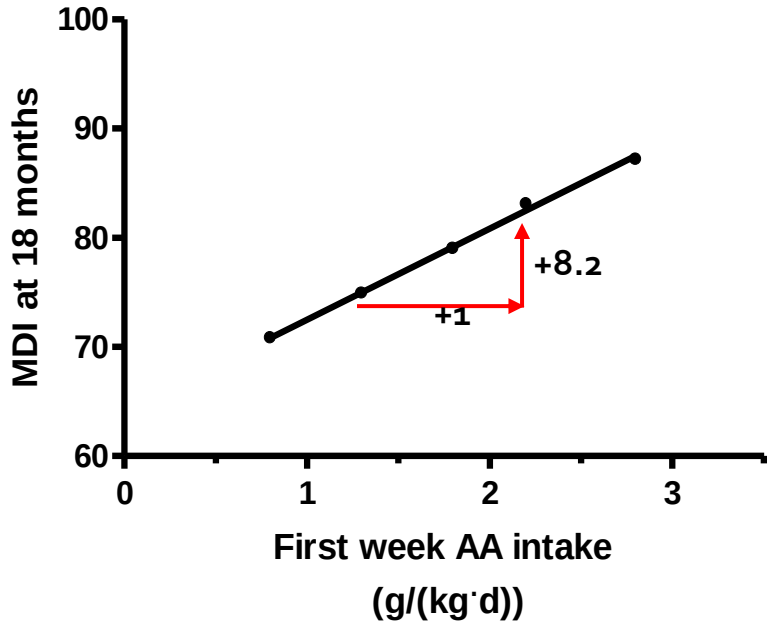
Early Nutrition Mediates the Influence of Severity of Illness on ELBW Infants.

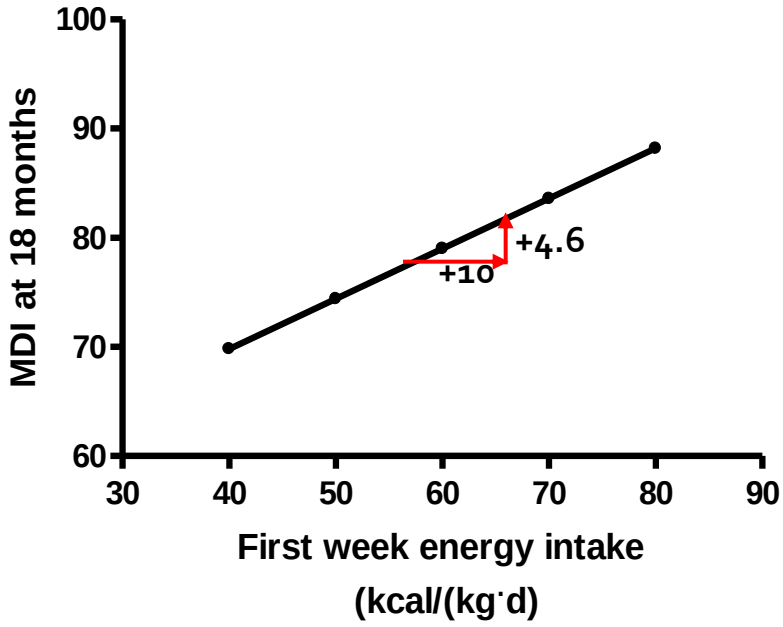
- 1366 participants in the NICHD Neonatal Research Network parenteral glutamine supplementation randomized controlled trial who were alive on day of life 7 were studied.
- Adjusted analyses demonstrated that the influence of critical illness on the risk of adverse outcomes was mediated by total daily energy intake during the first week of life.
- As total energy intake during the 1st 7days of life increased in critically ill infants , the Odds Ratio of adverse outcomes as NEC, BPD, LOS and NDI at 18-22wk of life decreased by approximately 2% for each 1 kcal/kg/d of total energy intake.

Ehrenkranz et al Pediatr Res 2011 Jun;69(6):522-9

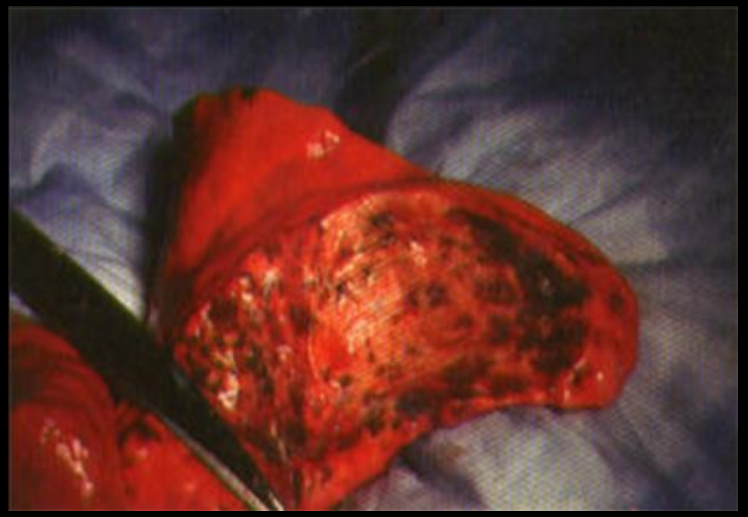
First week protein and energy intake and neurodevelopmental outcome at 18 months

- Retrospective study of 124 ELBW infants at 18 months CA

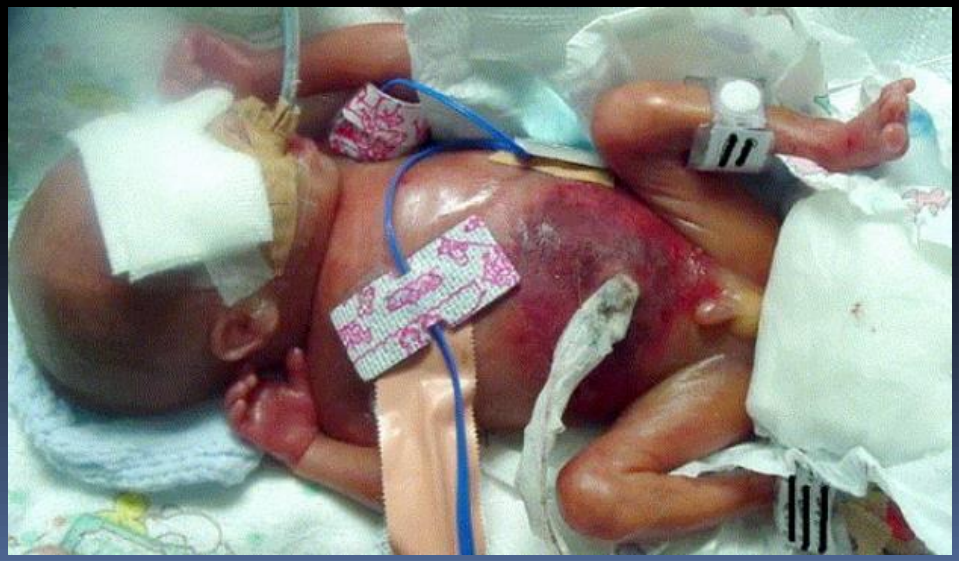




Stephens, B.E. Pediat. *2009*.



Nutrition During Disease



Acute Pulmonary Disease

- Acute pulmonary disease not only is the most common admission diagnosis in the neonatal intensive care unit (NICU), but it is the most common severe illness of the neonate.
- It encompasses respiratory distress syndrome (hyaline membrane disease), pneumonia, meconium aspiration syndrome, and other disease states, such as congenital diaphragmatic hernia and acute respiratory distress syndrome due to sepsis.
- Several studies in adults, children, and infants have demonstrated that acute pulmonary disease increases oxygen consumption, thus increasing energy requirements.

Nutrition and Neonatal Respiratory Problems

- It is more complicated in neonates than in adults:
  - Provide energy intake to cover energy expenditure.
  - Avoid nutrition that increases respiratory demands.
  - Meet the superadded caloric needs for growth.

Van Aerde JE, Narvey M, Neonatal Nutrition and Metabolism, 2nd Ed, 2005

Energy Intake Dilemmas in Ventilated Neonates

- Infants need sufficient energy intake to be able to wean from the ventilator
- However, excessive energy intake may result in $\Uparrow pCO_2$. In infants with underlying lung disease this may prevent weaning from the ventilator

Nutrition and Neonatal Respiratory Problems
Animal Studies

- In term of lung development:
  - Nutrition should provide for body growth in length since lung size, alveolarization and total alveolar surface area are dependent on the length or stature.
  - Nutrition deprivation even for short period interfere with surfactant metabolism.
  - Early postnatal period appears to be the most critical for beneficial nutritional effects on lung development

Nutrition and Neonatal Respiratory Muscles

- During starvation, energy utilization and protein synthesis in the visceral organs are maintained by skeletal muscle break down including respiratory muscles leading to their atrophy.
- ***Only*** the minority of muscle fibres of the preterm diaphragm appear to be fatigue resistant as those of the adults increasing the risk of repiratory failure in preterm infants.

Nutrition and Ventilatory Drive

- A ⇓ in apneas of prematurity has been observed in infants on Amino Acids + Glucose versus Glucose alone
- High carbohydrate intake produces ⇑ carbon dioxide production (VCO_2) which in turn results in ⇑ in minute ventilation
- Oxygen consumption (VO_2) and (VCO_2) correlate with energy intake but not with protein intake

Nutrition, Proteins and the Lung

- Negative protein balance is frequent with RD
- Undernutrition have the following deleterious effects:
  - Respiratory muscle strength and function can be compromised
  - Alteration of the lung response to
    - Barotrauma
    - Hyperoxia
    - Infection
  - Exacerbation of pulmonary structural and biochemical immaturity
  - Poor protein status leads to low oncotic pressure exacerbating pulmonary edema

Nutrition and Acute Pulmonary diseases

- **Energy I :**
  - Infants who have respiratory distress syndrome have a range of estimated resting energy expenditure of 40 to 60 kcal/kg per day, with caloric needs directly proportional to the severity of the illness.
  - Objectives and phases of illness (initial insulin resistant vs later)
  - Ventilated Preterm Neonates:
    - Sedation and mechanical ventilation ⇓ EE
    - May need as little as 40-50 kcals/kg/d energy to avoid catabolism
  - For non-ventilated neonates with lung disease, those on CPAP or those in ventilation modes using some patient assistance:
    - Energy requirement not as predictable, may be quite high
    - Measuring EE is difficult

Nutrition and Acute Pulmonary diseases

- **Energy II :**
  - Exceeding maximal glucose oxidative capacity(GOC)results in:
  - Glucose $\Rightarrow$ fat: energy inefficient
  - Adverse effects:
    - $\Uparrow$ energy expenditure
    - $\Uparrow$ oxygen consumption
    - $\Uparrow$ carbon dioxide production
  - High rates of carbohydrate delivery (12.5 mg/kg /m) increase carbon dioxide production because this nutrient had a high respiratory quotient (RQ) (1.0) when completely oxidized that is even higher (1.0) when excess glucose is used for fat production.
  - The risk associated with an increased rate of carbon dioxide production in the infant who has respiratory disease is to raise minute ventilation needs, increasing the work of breathing or exposure to barotrauma in infants who are receiving mechanical ventilation.
  - Initiate glucose infusion at a GIR of 4-6mg/kg/min = 9g/kg/d
  - Advancing the glucose administration is done by 2g/kg/d
  - The max GOC is estimated to be 12-13 mg/kg/min = 18 g/kg/d

Nutrition and Acute Pulmonary diseases

- **Energy III :**
  - Lipids are an excellent source of energy because they are calorically dense. They have a lower RQ (0.7) and, therefore, create less carbon dioxide when metabolized.
  - This may confer an advantage to a nn on mechanical ventilation.
  - However, lipid emulsions have been shown to have a direct effect on pulmonary function by impairing gas exchange. This has been attributed to the production of vasoactive metabolites, which uncouples hypoxic vasoconstriction and increases ventilation/perfusion mismatching. Infusing the lipid solution over at least 16 hours during a 24-hour period may decrease this effect.
  - Despite being associated with problems such as hypoxia and pulmonary hypertension (which generally occur at substantially higher rates of infusion than currently recommended), early initiation of lipids seems prudent because significant growth failure is associated with severe lung disease.

Nutrition and Acute Pulmonary diseases

- **Energy IV :**
  - The initial objectives in beginning lipid infusions is to prevent essential fatty acid deficiency, resume growth, and facilitate the transition to enteral feedings.
  - How to start and how to increase?
  - Addition of carnitine
  - Role of MCT
  - Energy expenditure increases with worsening acute pulmonary disease.
  - A balanced delivery of energy from carbohydrates and lipids (rather than exclusively one or the other) is indicated.

Nutrition and Acute Pulmonary diseases

- **Proteins :**
  - Daily protein loss is 1.2-1.4g/kg/day
  - Daily in utero protein accrition is 2.1g/kg/day
  - A total of 3.5(1.4+2.1)g/kg/day is needed to keep the preterm on track with the expected in utero accretion rates
  - No need for gradual increment of protein intake or increment related to the degree of RD.

Nutrition and Acute Pulmonary diseases

- **Minerals:**
  - Disorders of calcium, phosphorus, and magnesium metabolism are common in acute pulmonary disease.
  - Hypocalcemia, hypophosphatemia, and hypomagnesemia each can affect optimal respiratory and cardiac function.
  - Transient neonatal hypocalcemia is exacerbated by acute respiratory disease and, when severe, can cause tetany and cardiac arrhythmias.
  - Hypophosphatemia and hypomagnesemia cause muscle weakness, lethargy, and poor respiratory effort.
  - Hypermagnesemia can lead to apneas
  - Monitoring Ca, Ph, Mg, and alkaline phosphatase levels is important in assessing nutrient delivery, remembering that calcium levels always will be maintained at the expense of bone.

Nutrition and Acute Pulmonary diseases

- **Vitamins :**
  - Infants who are at high risk for BPD and have low vitamin A levels may benefit from vit supplementation during the time of acute pulmonary disease.
  - The recommended dose is at least 2,000 U (IM)every other day.
  - The goal is to achieve a serum retinol level of greater than 20 mcg/dL.

Brochopulmonary dysplasia

Nutrition and Bronchopulmonary Dysplasia

- BPD has been defined as an "oxygen radical disease of prematurity"
- Oxidative processes, especially of lipids and proteins, contribute to the development of BPD
- Postnatal growth failure and poor nutrient stores in the ELBW infant ⇓ the ability to counter oxidative stress
- Nutritional support in the ELBW infants is critical for prevention, amelioration and recovery from BPD
- There are currently no evidence-based guidelines for nutritional management in BPD
- However, specific nutrients likely have a role in prevention, treatment and catch-up growth

Nutrition and Bronchopulmonary Dysplasia

- **Energy l :**
  - 25% higher resting energy expenditure
  - 10-15% increase in total caloric needs
- Much of this is related to their pulmonary status(persistant airway inflammation secondary to lung injury) and increased work of breathing, with a correlation between degree of respiratory compromise and oxygen consumption.
- In infants with BPD, energy expenditure increases by 0.7 kcal//kg/d per breath *Meer DEK et al Eur J Pediatr 56:299-304, 1997*
- Energy requirements for growth generally are in the range of 130 to 150 kcal/kg per day.
- Options to meet this increased metabolic demand are aimed at decreasing the work of breathing, increasing the caloric intake, or both.
- Optimization of methylxanthines and diuretics and adequate nutrition may facilitate weaning the infant from mechanical ventilation.

Nutrition and Bronchopulmonary Dysplasia

- **Energy II :**
  - Fat is a good nutritional adjuvant for infants who have compromised lung function (as BPD), because of both its high caloric density and its low RQ.
  - Fat should not provide more than 60% of the total calories.

Causes of Poor Growth in BPD

- Fluid restriction
- Long-term parenteral feedings
- Enteral feeding intolerance
- Gastroesophageal reflux (GER)
- Steroids
- Increased energy expenditure

Nutrition and Bronchopulmonary Dysplasia

- **Protein :**
  - Patients with BPD have lower somatic muscle stores.
  - Atrophy and fatigue of respiratory muscles may lead to atelectasis and extubation failure.
  - Using dexamethasone is associated with markedly increasing protein breakdown

Nutrition and Bronchopulmonary Dysplasia

- **Minerals and Trace Elements:**
  - Infants with BPD often are receiving diuretics
  - Diuretics commonly used increase urinary Na, K, Cl, Ca losses.
  - Diuretic use may increase sodium need to as high as 12 mEq/kg per day.
  - Similarly, the potassium requirement, will rise to 7 to 10 mEq/kg per day under diuretic pressure.
  - Severe hypochloremia has been associated with sudden infant death in those who have BPD.
  - Because the primary deficit is of chloride, sodium and potassium must be repleted as sodium chloride and potassium chloride.
  - Calcium losses result from both diuretics and glucocorticoid intake, and while the normal rate of Ca accretion in last trimester is 150-180 mg/kg/day the preterm baby with BPD and receiving furosemide is in need of 200-225 mg/kg/day.
  - The iron dilemma
  - Selineum:Cochrane Rev, 2003: doesn't ⇓ BPD, ROP or survival but may reduce number of episodes of sepsis

Nutrition and Bronchopulmonary Dysplasia

- **Vitamins: Vitamin A**
  - Vitamin A is a biologic antioxidant
  - Vitamin A influences epithelial growth, differentiation, and repair.
  - Keep serum retinol concentrations higher than 20 mcg/dl.
  - Vit A deficiency also affects
    - T-cell proliferation
    - phagocytic immunomodulatory activity of polymorphonuclear leukocytes.
  - **Cochrane Rev, 2002: Vit A supplementation in VLBW infants associated with:**
    - **Reduced death or oxygen requirements at one month of age**
    - **Reduced oxygen needs at 36 weeks of age**
    - **May also ⇓ incidence of ROP and nosocomial sepsis**
    - **Greatest effect of benefit at 36 weeks was in those <1000g at birth**
  - Give Vit A 2000 IU IM every other day to reduce the risk of BPD.

Nutrition and Bronchopulmonary Dysplasia

- **Vitamins: Vitamin E**
- Vitamin A is a biologic antioxidant that protects the polyunsaturated fatty acids of cell membranes from peroxidation.
  - Vitamin E deficiency compromises:.
    - Cellular immunity
    - Humoral immunity
    - Antimicrobiol phagocytic function
  - Vitamin E deficiency is associated with severe hemolytic anemia made worse by iron therapy.
  - No proof for a role of Vit E in BPD, ROP, IVH.
  - Supplement with 50-75 IU/d

Congenital Heart Disease

Nutrition and Congenital Heart Disease

- **Energy Needs:**
- Infants who have CHD, particularly with an element of congestive heart failure, have higher resting and total energy expenditures
- High metabolic demands are needed by
  - Myocardium
  - Muscles of respiration
  - Hematopietic system
- Difficulty in meeting nutritional needs in postoperative period according to:
  - Type of surgery curative vs palliative
  - Respiratory compromise
  - Renal failure
  - Catecholamine use.
  - Delayed gastric emptying
  - Fatigability with feeding
  - Vomiting and malabsorption
- Diet should be high in calory and calorically dense. Supplement standard formula with carbohydrate(glucose polymers) or lipids (oils)
- Continuous enteral feedings are more beneficial than intermittent bolus.

Nutrition and Congenital Heart Disease

- **Protein**
  - Substantial proteins need after cardiac surgery as the patient is catabolic
  - Provide 2.5 g/kg/day in the immediate postoperative period with rapid increment to reach 3.5 g/kg/day.
  - Along with calory dense formula concurrent increasing protein intake is essential to avoid suboptimal growth.with proteins constituting 8-10% of the infant's diet.

Nutrition and Congenital Heart Disease

- **Minerals**
  - The use of diuretics to treat CHD can compromise Na, K, Cl, Ph,.
  - Abnormalities of potassium can result in fatal arrythmias.
  - Transient but significant hypocalcemia in the immediate pre- and postoperative period.
  - Adequate phosphorus must be delivered to support generation of adenosine triphosphate for optimal myocardial functions.
  - Iron requirements are high because of the expanded red cell mass in cyanotic congenital heart disease. Monitoring of iron status should be by serum ferritin, TIBC and indices

Nutrition and Congenital Heart Disease

- **Vitamins**
  - Congestive heart failure decreases intestinal absorption fats and fat soluble vitamins.
  - Cardiac surgery could be complicated by traumatic chylothorax leading to more reduction in fat soluble vitamins.
  - Water –soluble forms of vitamin A and E can be used when there is a question of fat malabsorption.

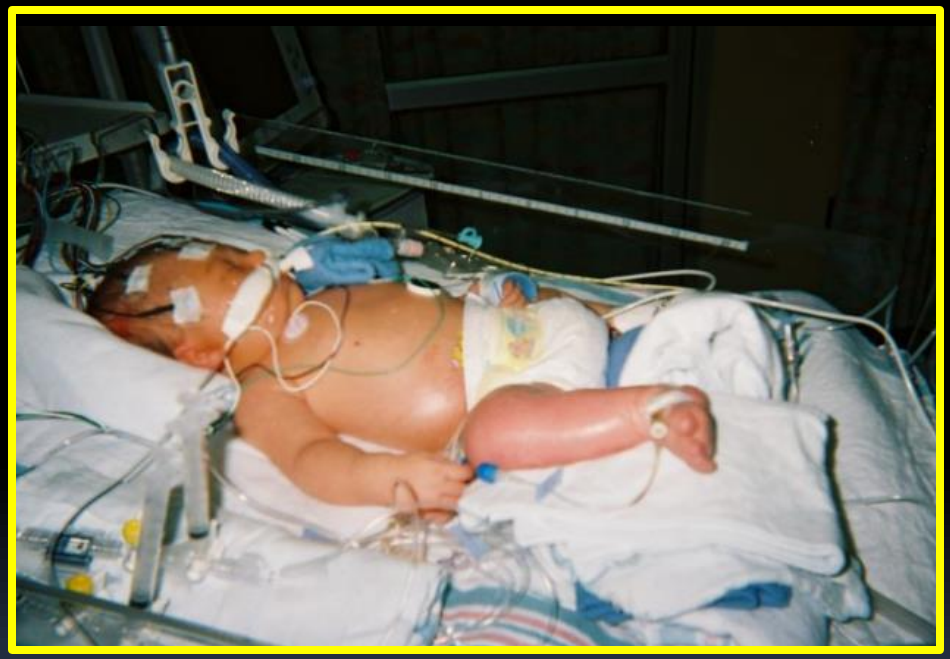
Sepsis

Nutrition and Sepsis

- **Energy needs:**
  - Hypermetabolic state with marked catabolic response with profound changes in energy and protein metabolism
  - Energy requirements in these neonates were elevated in proportion to the degree of septic illness.
  - The septic neonates required higher energy delivery during the acute phase of their illness than similarly ill nonseptic infants.
  - A goal of at least 6o kcal/kg per day seems prudent to meet the energy requirements during the acute phase of illness.

Nutrition and Sepsis

- **Protein:**
  - Sepsis alters protein requirements.
  - Muscle catabolism is enhanced.
  - Some infants remained in negative nitrogen balance for as long as 10 days after the sepsis began.
  - This will favor further sepsis and growth delay.



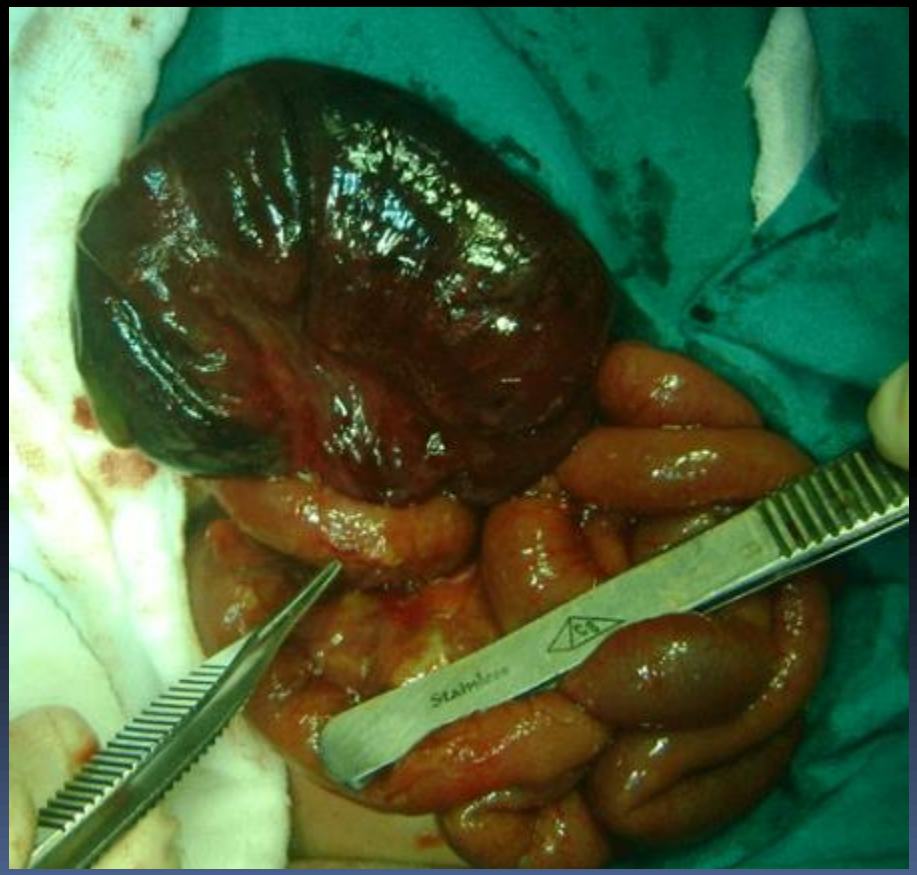
Nutrition and Sepsis

- **Minerals:**
  - No direct effect of sepsis on mineral homeostasis.
  - Significant fluid shifts occur and volume support is frequently needed.
  - Close attention to serum electrolytes and minerals is necessary.
  - Iron therapy should be avoided.

Nutrition and Sepsis

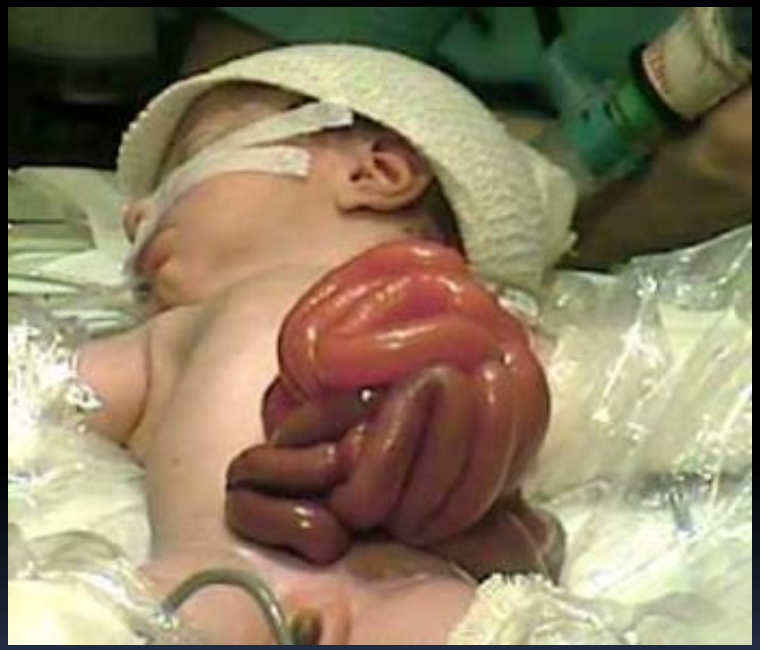
- **Vitamins:**
  - Excess Vit E may impair the bactericidal capacity of WBCs and increase risk of infections.
  - Antibiotic use reduce bacterial colonization of the gut decreasing Vit K production.
  - Vit K 1mg more than twice weekly should be given.

Surgery



Nutrition and Surgery

- **Energy:**
  - If physiologically stable with adequate analgesia no apparent increase in energy requirement.
  - Acute underlying illness have expected rise in energy requirements seen with non surgical acute illness.
  - Lipid peroxidation is increased in proportion to stress.
  - A balanced mixed fuel(CHA &lipids) should be used



Nutrition and Surgery

- **Protein:**
  - Elective surgery causes a small reduction in nitrogen balance.
  - Postoperative fentanyl appears to suppress the catabolic response to surgery.
  - Infants with CDH or gastroschisis receiving 2.5g/kg/day with fentanyl on postoperative day 1 has positive nitrogen balance.

Nutrition and Surgery

- **Mineral:**
  - Surgery has no known specific effect on electrolytes, trace elements and vitamins.
  - Therapies associated with postoperative management such as diuretics and citrated blood products can affect mineral homeostasis.

Take Home Message
Nutritional Golden First Hours

1. Metabolic and nutritional requirements do not stop with birth.
2. Intravenous feeding is always indicated when normal metabolic and nutritional needs are not met by normal enteral feeding.

3. Hours, not days, are the longest periods infants should be allowed to not receive nutrition, IV or PO.
4. The metabolic and nutrient requirements of the newborn are equal to or greater than those of the fetus.

5. Proteins are well tolerated immediately after birth and no need for gradual increment of their dose.
6. Glucose administration needs to be increased gradually.
7. Calories should be provided from a mixture of glucose and lipids.

THANK YOU

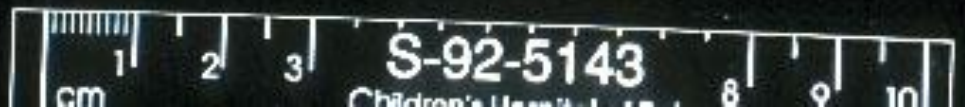
Sepsis

- **Protein:**
  - Sepsis alters protein requirements more acutely by its effect oncytokine-mediated muscle

    catabolism. .

Cholestatic Liver Diseases

- α-1 Anti-trypsin Deficiency
- Alagille Syndrome
- Progressive Familial Intrahepatic Cholestasis
- Defects of Bile Acid Metabolism
- Biliary Atresia
- Parenteral Nutrition Induced Liver Disease



Risk Factors

- Liver immaturity: prematurity, LBW, IUGR
- Inflammatory mediators: number of septic episodes.
- Long-term TPN.
- Short bowel syndrome.
- Prolonged duration of NPO
- Intestinal dysmotility.
- Overfeeding(Hyperalimentation)

Neonatal Cholestasis

Episodes of desaturation and hypoxia may occur in infants with bronchopulmonary dysplasia on mechanical ventilation

- They result from:
  - Decreased respiratory drive
  - Altered pulmonary mechanics
  - Excessive stimulation
  - Bronchospasm
  - Forced exhalation efforts.
- Forced exhalation efforts due to infant agitation may cause atelectasis and recurrent hypoxic episodes.
- Hyperoxia may overwhelm the neonate's relatively deficient antioxidant defenses worsening BPD.

JPEN J Parenter Enteral Nutr. 2012 January; 36(1_suppl): 81S–94S

- Intravenous lipid emulsions are an integral part of the parenteral nutrition regimen in preterm neonates. A substantial body of evidence indicates that a well-balanced fatty acid supply during the neonatal period is a crucial factor influencing outcome criteria such as growth, visual development, and cognitive development. In this study, a lipid emulsion containing fish oil, olive oil, medium-chain triglycerides, and soybean oil was found to be well tolerated in preterm infants, and n-3 long-chain polyunsaturated fatty acids (LC-PUFAs) were significantly increased. The higher availability of n-3 LC-PUFAs with this lipid might be considered advantageous with regard to their postulated role in ensuring adequate brain and retinal development in preterm infants and the postulated anti-inflammatory and immunomodulatory role.

- *Background*: For premature neonates needing parenteral nutrition (PN), a balanced lipid supply is crucial. The authors hypothesized that a lipid emulsion containing medium-chain triglycerides (MCTs) and soybean, olive, and fish oils would be as safe and well tolerated as a soybean emulsion while beneficially influencing the fatty acid profile.

- Preterm neonates, having missed the crucial period of intrauterine nutrient accretion and storage, possess only limited energy and fat reserves.[1,2] When enteral feeding is not tolerated or insufficient to meet the requirements, parenteral nutrition (PN) must be instituted shortly after birth.[2] Intravenous lipid emulsions are an integral part of the PN regimen in neonates.[2-4] A substantial body of evidence indicates that a well-balanced fatty acid supply during the neonatal period is a crucial factor influencing outcome criteria such as growth, visual development, and cognitive development

- Yet, most commonly used soybean oil–based lipid emulsions contain high amounts of linoleic acid (LA; C18:2 n-6) relative to α-linolenic acid (α-LNA; C18:3 n-3) but low amounts of arachidonic acid (AA; C20:4 n-6) and no n-3 long-chain polyunsaturated fatty acids (LC-PUFAs) such as eicosapentaenoic acid (EPA; C20:5 n-3) and docosahexaenoic acid (DHA C22:6 n-3). The need for more appropriate lipid emulsions in pediatric and neonatal care, however, has been recognized.[7] In enteral feeding studies, LC-PUFAs have been shown to positively influence neurological and mental development in both preterm and term infants.[8-10] It has been demonstrated that feeding preterm infants formulas containing DHA and AA enhances growth and improves mental and psychomotor development scores as well as visual acuity.[8,11] EPA functions as a precursor for the LC–fatty acid synthesized in the retina.[12] Consequently, it has been postulated that LC-PUFAs are important for growth and development of preterm and term infants.[5]

- In the present prospective, double-blind, randomized, parallel, controlled study, the safety, tolerability, and efficacy of a test lipid emulsion (SMOFlipid 20%; Fresenius Kabi, Bad Homburg, Germany) were evaluated in premature neonates as compared to a conventional soybean oil emulsion. The emulsion under investigation contains a physical mixture of 4 different lipid sources: soybean oil providing LA and α-LNA for essential fatty acid supply; olive oil rich in monounsaturated fatty acids (MUFAs), which are less susceptible to lipid peroxidation than PUFAs; medium-chain triglycerides (MCTs) showing a faster metabolic clearance than long-chain triglycerides; and fish oil for the supply of n-3 LC-PUFA EPA and DHA.[13-17]

- Soybean oil–based lipid emulsions contain high amounts of γ-tocopherol but relatively low amounts of α-tocopherol, the main lipophilic antioxidant. In some older studies, infusion of soybean- or safflower–based lipid emulsions has been associated with an increased production of peroxidative intermediates and, therefore, an aggravated risk of oxidative stress.[38,39] Oxidative stress, representing a common mediator of the inflammatory process, has been associated with hepatocellular injury in preterm infants on PN.[40] In previous studies evaluating the test emulsion in preterm infants and children, parameters of lipid peroxidation did not differ between treatment groups, but vitamin E status and total antioxidant potential were significantly improved with the provision of adequate amounts of vitamin E as compared to controls receiving a soybean oil emulsion.[24,37,41] Unfortunately, measurements of vitamin E status and lipid peroxidation were not within the scope of the present investigation. However, with regard to the previous finding, it was assumed also in the present trial that the provision of increased amounts of α-tocopherol with the test emulsion may have contributed to protecting the liver against PN-induced peroxidative damage. Eventually, the partial replacement of soybean oil with fish oil in the new lipid emulsion resulted in a lower phytosterol intake in the infants receiving the test emulsion. It has repeatedly been suggested that phytosterols may represent a further contributing factor to the pathogenesis of PN-related cholestasis.[30,42-44] Phytosterol concentrations have been shown to be particularly high in plant oil–based lipid emulsions, whereas fish oil emulsions are free from phytosterols.[35]

NEONATAL PHYSIOLOGY

Neonates must develop a homeostatic balance between energy requirements and the supply of substrates as they move from the constant glucose supply of fetal life to the normal intermittent variations in the availability of glucose and other fuels that characterize the absorptive and postabsorptive states. The development of this homeostasis is dependent on substrate availability and maturation of hormonal, neuronal, and enzymatic systems and is influenced by gestational age, health status, and intake.

Transitional Events

Metabolic transition is characterized by a shift from the anabolic-dominant fetal state to the catabolic state of the neonate. This transition is influenced by genetic, environmental, and endocrine factors as well as by major alterations in energy metabolism within the mitochondria. Changes in metabolism with birth are regulated by the expression of specific genes and gene products that alter the activity of various enzymes.[26] The ability of the fetus to use glucose anaerobically and to readily metabolize lactate may be important in maintaining homeostasis during the stresses of labor and delivery. The fetus prepares for this transition during the last weeks of gestation by increasing fuel storage in the form of glycogen and lipids. Glycogen is critical in order to maintain glucose homeostasis immediately after birth, whereas the fat stores, through lipolysis of fatty acids and ketone bodies, serve as an alternate energy source.[149] Postnatal changes in metabolism involve the transition from the almost exclusive reliance on glucose for energy production in the fetus to markedly increased use of fatty acid oxidation and ketone body use for energy production in the neonate. An increase in epinephrine, norepinephrine, and glucagon and a decrease in insulin at birth promote mobilization of fatty acids and glycogen metabolism.[76]

Carbohydrate Metabolism

Birth results in the loss of the maternal glucose source. As a result, neonatal blood glucose normally falls after birth, reaching a nadir at 60 minutes after birth (Figure 16-10).[76] These values then rise and stabilize at levels of 50 to 60 mg/dL (2.8 to 3.3 mmol/L) by 2 to 4 hours after birth.[74] The glucose nadir and timing of the nadir are related to maternal glucose infusion during the intrapartum period.[76] Steady-state hepatic release of glucose at 4 to 6 mg/kg/min is seen by 2 to 4 hours in term infants.[74,76] The basis for the fall in blood glucose is summarized in Table 16-5.

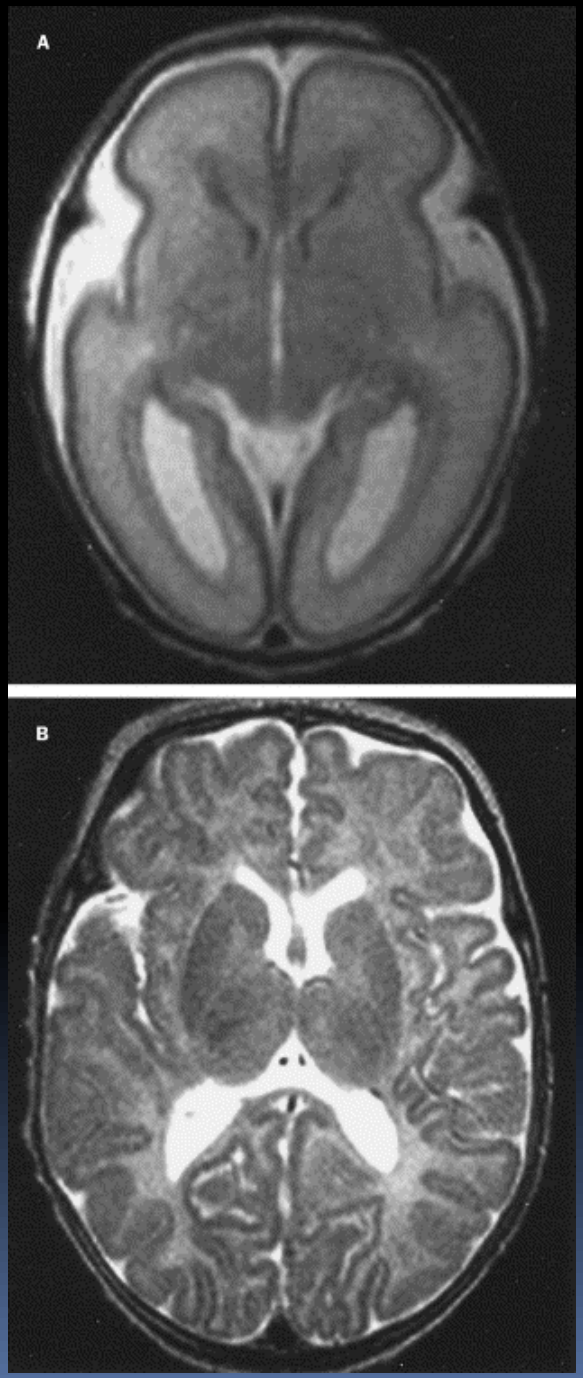
The newborn responds to the decrease in blood glucose in several ways. The rapid glycogenolysis (liberation of glucose from glycogen) after birth is stimulated by a fall in the insulin-to-glucagon ratio and sluggish

Our Approach to Early Aggressive Parenteral Nutrition

- The Very Preterm Newborn:
  - *A NUTRITIONAL EMERGENCY*
  - **Glucose stores of only 200 kcal**
  - ***Catabolic*: net protein loss**
    - **With IV glucose alone, lose 1% body protein/day**
    - **10% loss of protein stores = protein malnutrition**

25 wk

term



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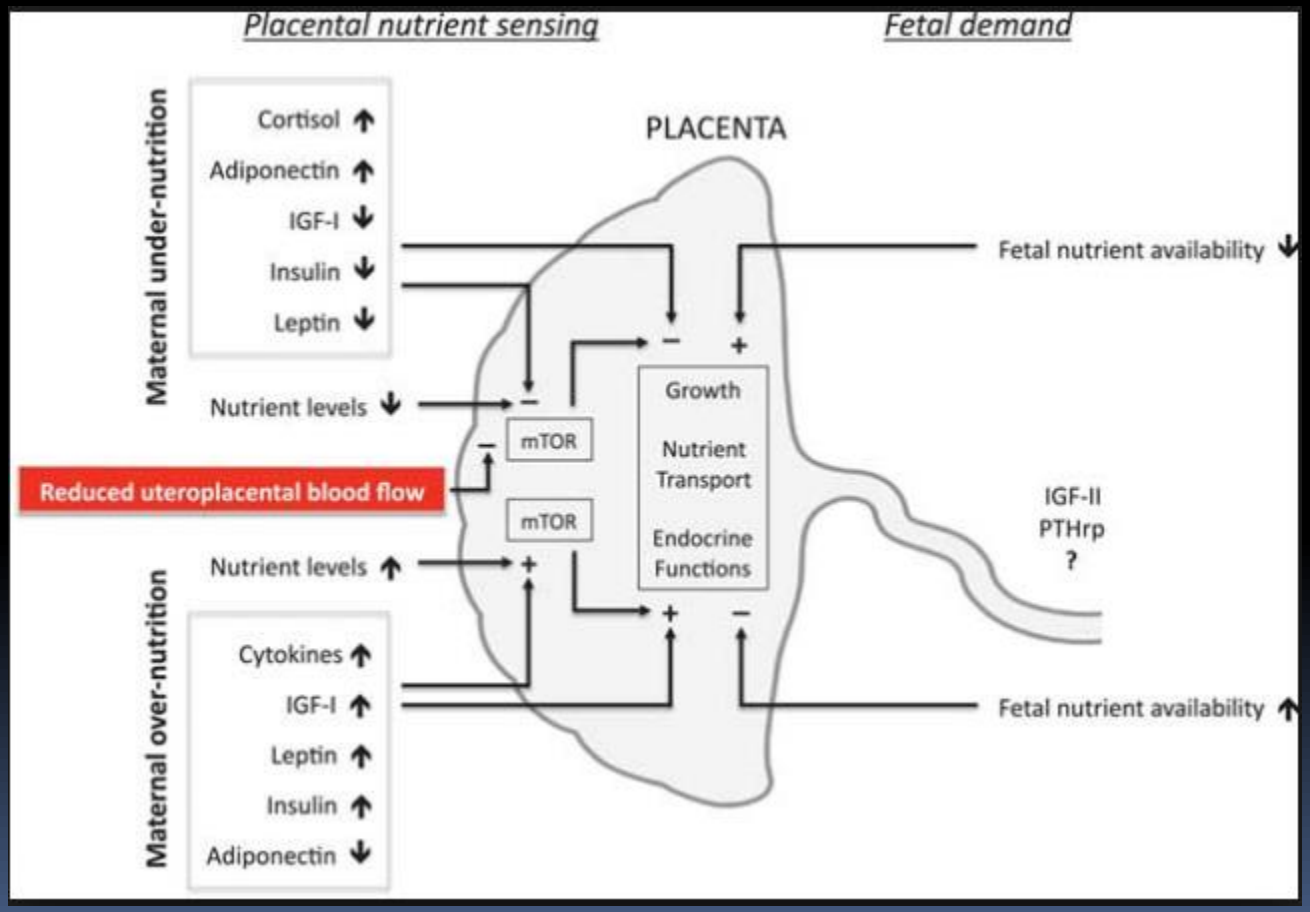
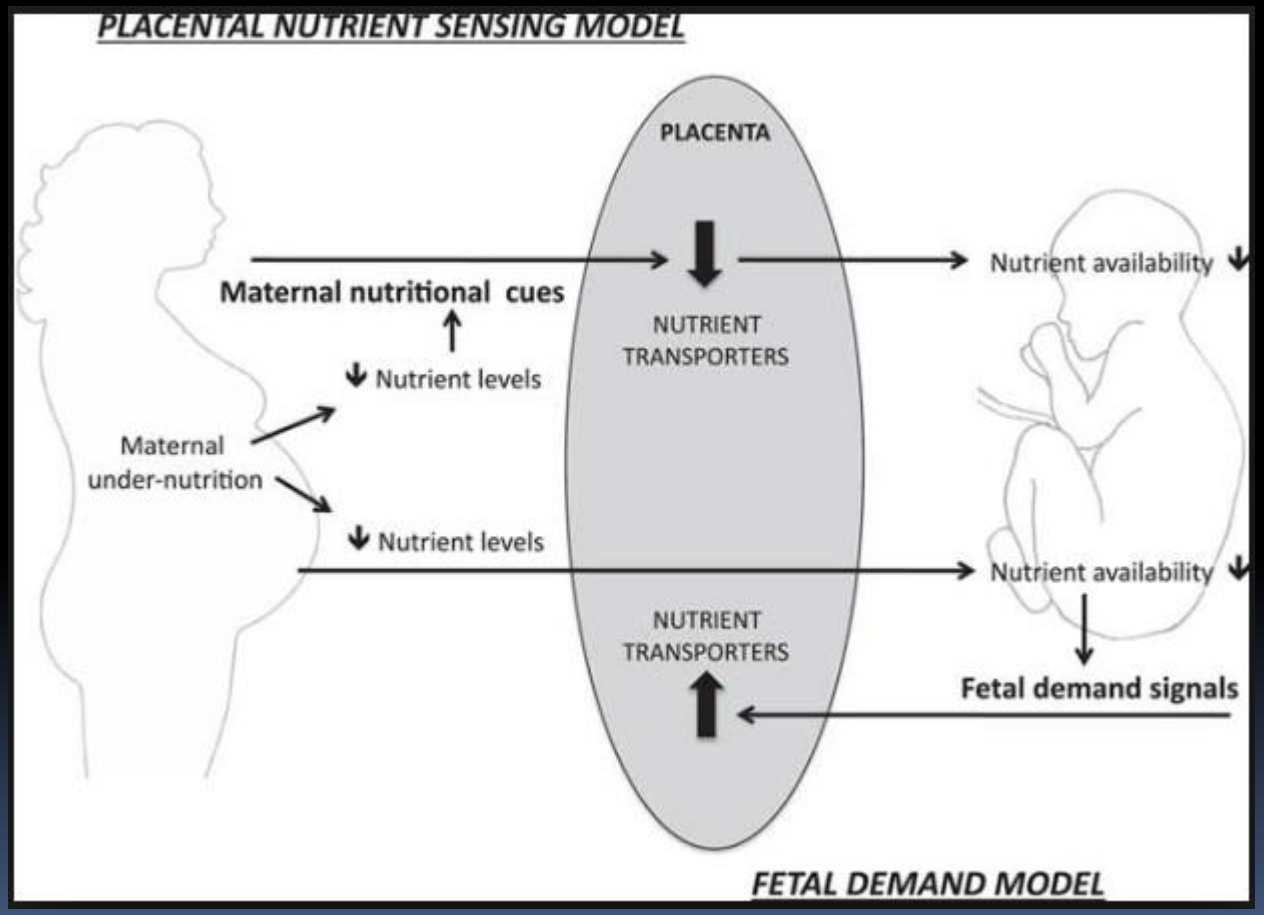
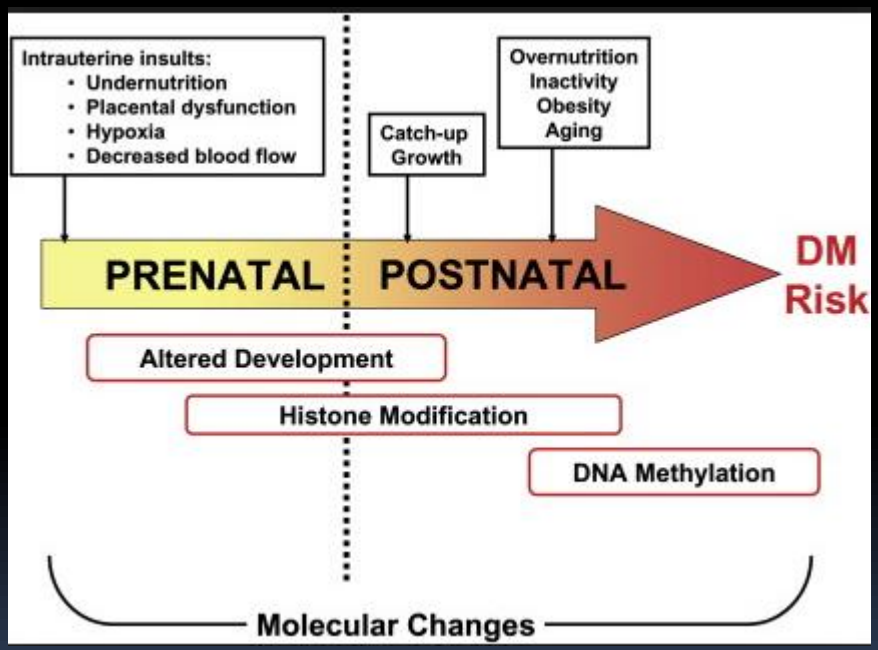
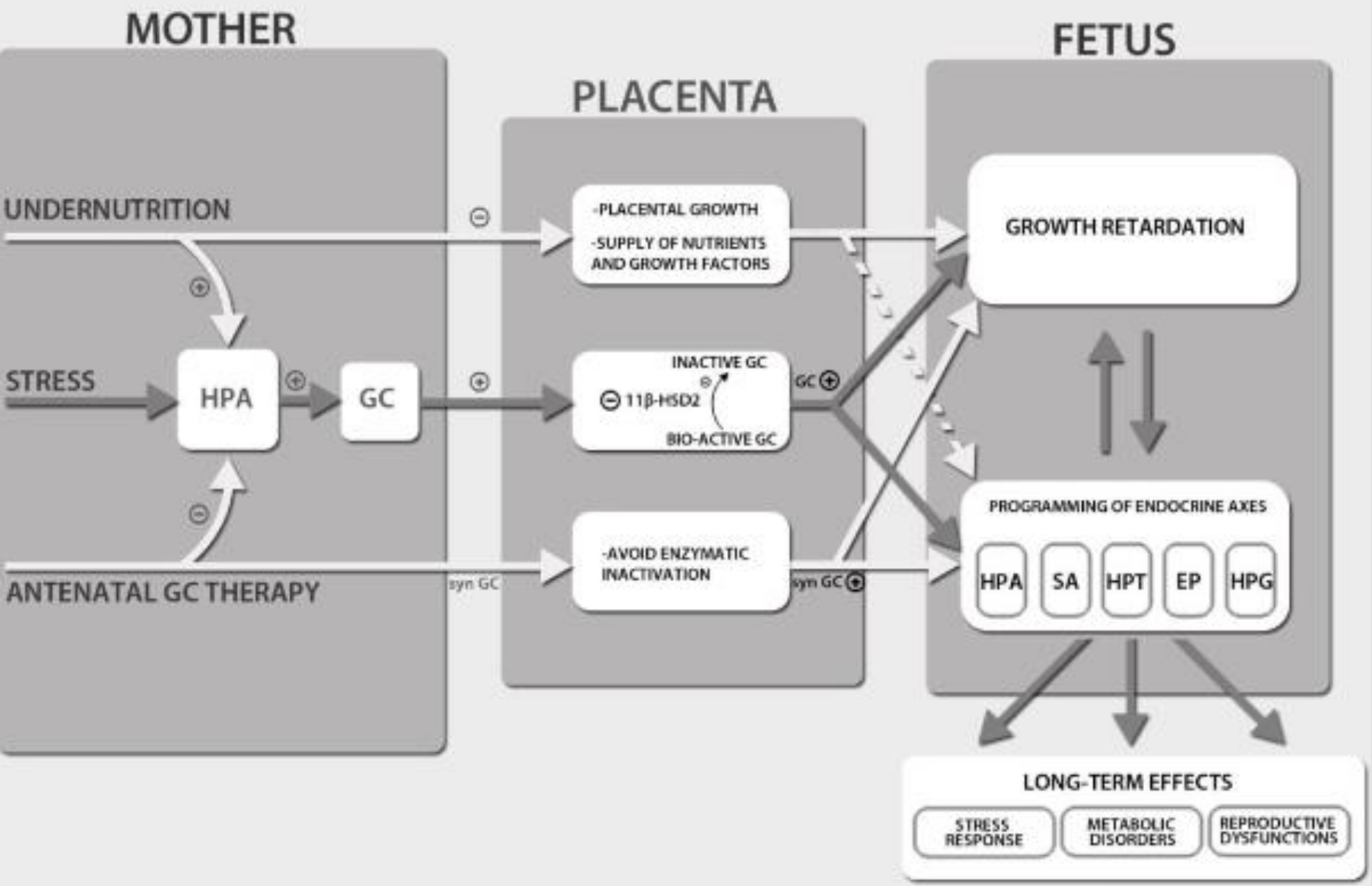
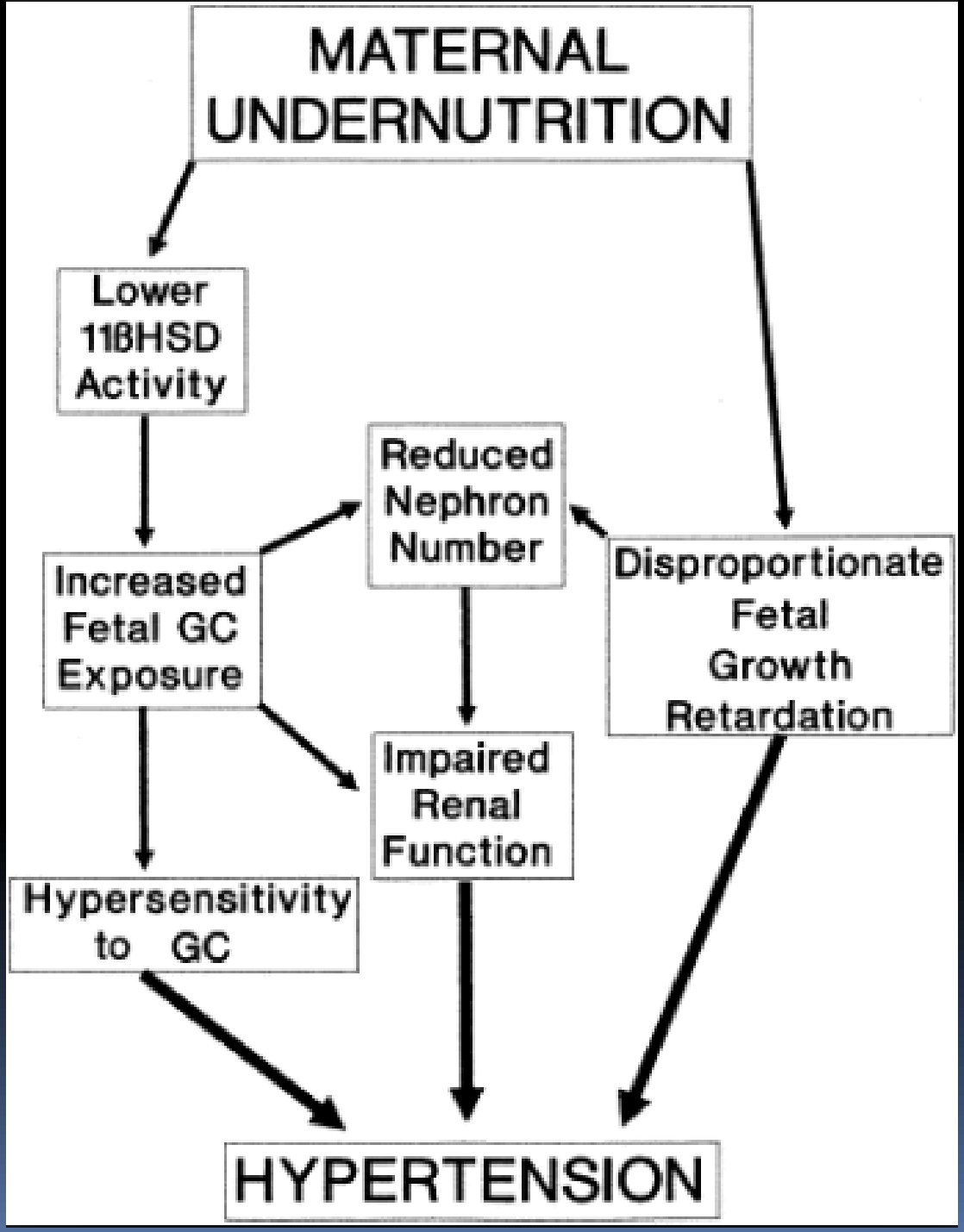
- The task for the practitioner is to customize nutritional delivery to fit the specific infant's needs.
- Understanding the nutritional requirements of healthy term and preterm infants forms a basis for assessing the effects of disease processes on nutrient needs

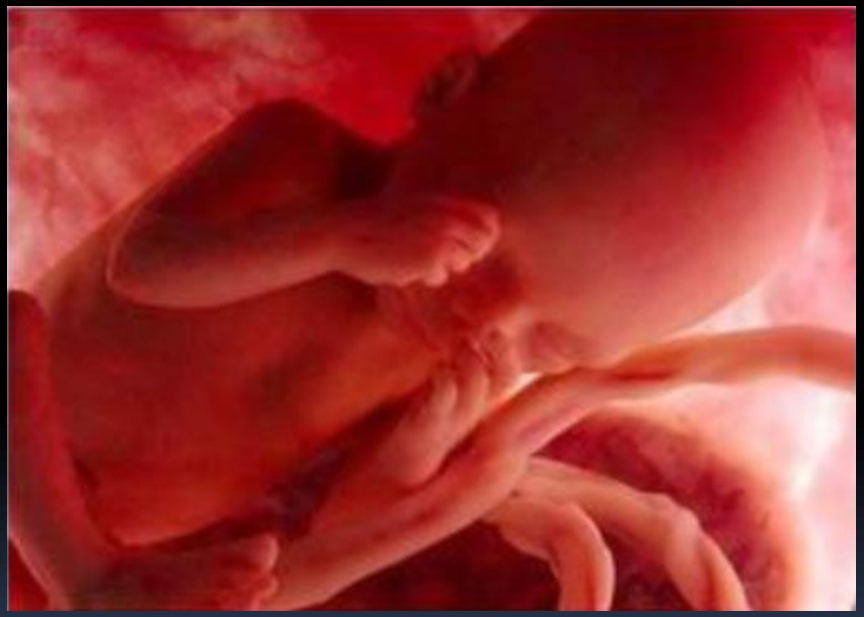

Placental nutrient sensing
Fetal demand
Maternal under-nutrition
Cortisol
Adiponectin
IGF-I
Insulin
Leptin
PLACENTA
Fetal nutrient availability
Nutrient levels
mTOR
mTOR
Growth
Nutrient Transport
Endocrine Functions
Reduced uteroplacental blood flow
IGF-II
PTHrp
?
Nutrient levels
Maternal over-nutrition
Cytokines
IGF-I
Leptin
Insulin
Adiponectin
Fetal nutrient availability

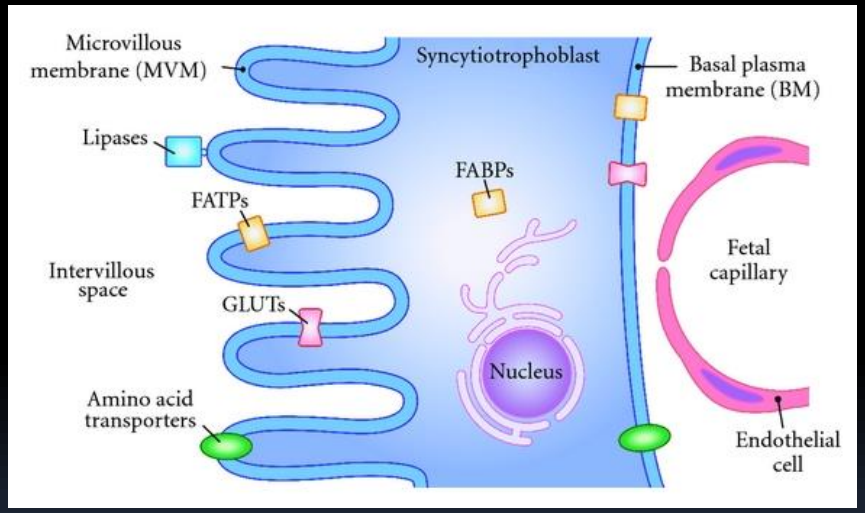

PLACENTAL NUTRIENT SENSING MODEL
PLACENTA
Maternal nutritional cues
NUTRIENT TRANSPORTERS
Nutrient availability
Nutrient levels
Maternal under-nutrition
Nutrient levels
Nutrient availability
NUTRIENT TRANSPORTERS
Fetal demand signals
FETAL DEMAND MODEL

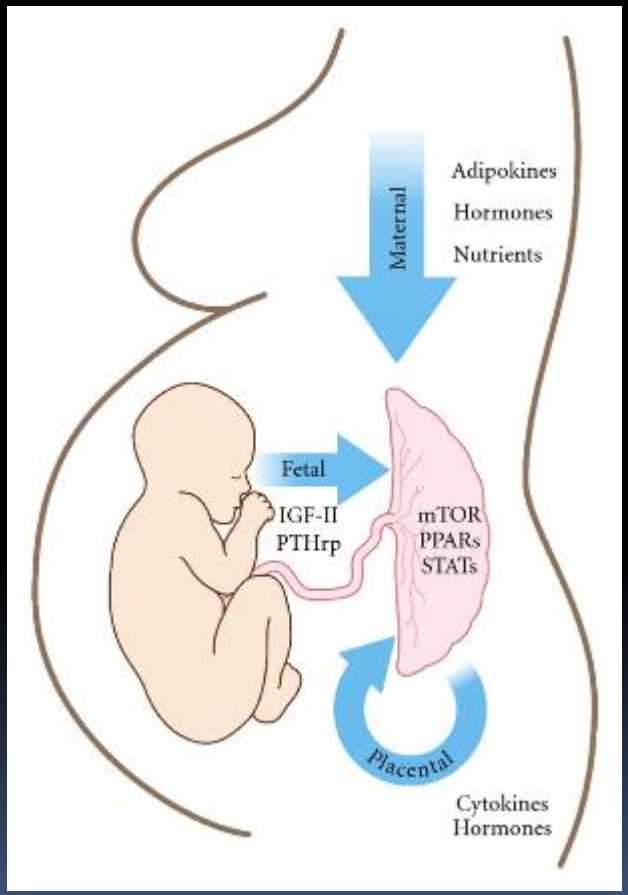

Intrauterine insults:
• Undernutrition
• Placental dysfunction
• Hypoxia
• Decreased blood flow
Catch-up Growth
Overnutrition
Inactivity
Obesity
Aging
PRENATAL
POSTNATAL
DM Risk
Altered Development
Histone Modification
DNA Methylation
Molecular Changes

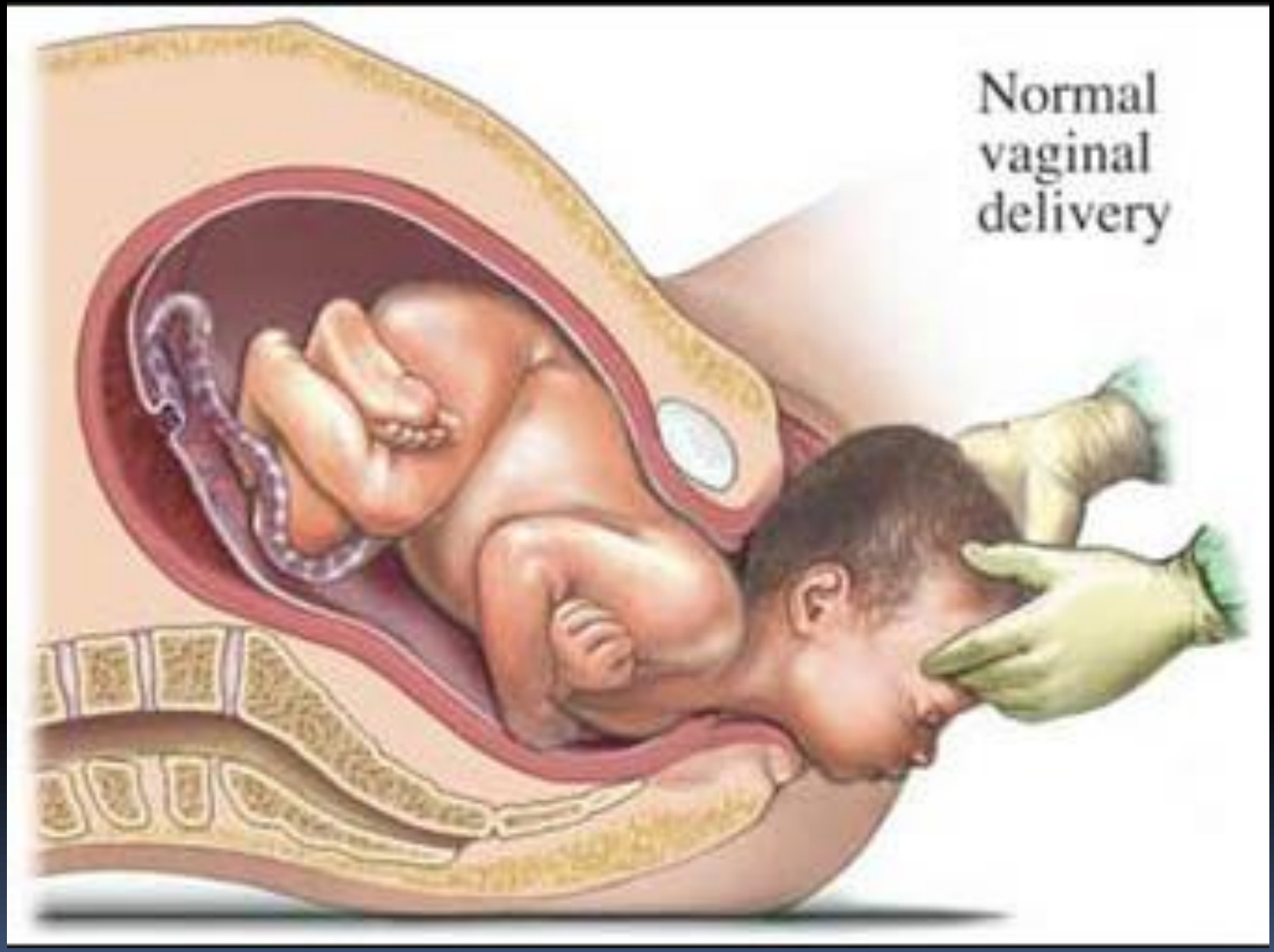

MOTHER
PLACENTA
FETUS
UNDERNUTRITION
STRESS
HPA
GC
ANTENATAL GC THERAPY
-PLACENTAL GROWTH
-SUPPLY OF NUTRIENTS AND GROWTH FACTORS
INACTIVE GC
11β-HSD2
BIO-ACTIVE GC
-AVOID ENZYMATIC INACTIVATION
syn GC
GC
syn GC
GROWTH RETARDATION
PROGRAMMING OF ENDOCRINE AXES
HPA
SA
HPT
EP
HPG
LONG-TERM EFFECTS
STRESS RESPONSE
METABOLIC DISORDERS
REPRODUCTIVE DYSFUNCTIONS


MATERNAL UNDERNUTRITION
Lower 11βHSD Activity
Reduced Nephron Number
Disproportionate Fetal Growth Retardation
Increased Fetal GC Exposure
Impaired Renal Function
Hypersensitivity to GC
HYPERTENSION




Microvillous membrane (MVM)
Syncytiotrophoblast
Basal plasma membrane (BM)
Lipases
FABPs
FATPs
Fetal capillary
Intervillous space
GLUTs
Nucleus
Amino acid transporters
Endothelial cell


Maternal
Adipokines
Hormones
Nutrients
Fetal
IGF-II
PTHrp
mTOR
PPARs
STATs
Placental
Cytokines
Hormones


Normal
vaginal
delivery

of nitrogen to the fetus of 54 nmol/day and a total accumulation of about 400 g of protein by term.[9,53,87] Amino acid transport is not significantly affected by fluctuations in uterine or placental blood flow.[53] Transport is via either sodium-dependent (for amino acids such as taurine, glutamine, alanine, serine, glycine, and glutamate) or sodium-independent (for branched-chain amino acids, lysine, arginine) receptor systems.[53]

Placental transport proteins regulate amino acid transfer. Amino acids are supplied to the fetus in greater amounts than are needed for nitrogen accretion. The fetus uses the carbon from excess amino acids for oxidation and to make nonessential amino acids.[50,53] Some

critical amino acids are not transferred across the placenta directly but are, rather, produced in the placenta. For example, glutamate, which is needed for neurotransmitters and brain development, is not transferred from mother to fetus. Instead glutamine is transferred from the mother to the placenta, where it is used to produce glutamate. Similarly asparagine is used by the placenta to produce aspartate, another neurotransmitter. Both glutamate and aspartate are toxic, so by transferring precursors, the placenta can produce only the amounts that are needed by the fetus.[49,50] The placenta also produces ammonia, which is used by the fetal liver for additional protein synthesis.[49,50]

The exchange of nutrients between placenta and fetus involves three major mechanisms: (1) direct placental transfer of nutrients from the maternal to the fetal plasma; (2) placental metabolism and consumption of nutrients; (3) placental metabolism of nutrient substrates to alternate substrate forms. Carbohydrate is transported to the fetus as glucose which is taken up from the maternal plasma by the GLUT 1 transporter and transported to the fetus by facilitative diffusion according to concentration-dependent kinetics. Protein is transported to the fetus as amino acids by specific amino acid transporter proteins. Placental lipid transport to the fetus involves direct transporter mediated transfer of certain fatty acids as well as lipid uptake from lipoproteins, metabolic alteration in the placenta, and release into the fetal plasma. Placental size, architecture, developmental and pathological processes, and interaction with the fetus cooperate with transport and metabolic mechanisms to affect placental-fetal nutrient exchange

- Glucose is the principal energy substrate for the placenta and the fetus and is essential for normal fetal metabolism and growth. Not surprisingly, therefore, its supply to these tissues is regulated by a relatively complex set of mechanisms that tend to keep its metabolism relatively constant. The first point in this regulation is the maintenance of maternal glucose concentration by increasing rates of maternal glucose production and development of relative maternal glucose intolerance and insulin resistance. The second point is the transfer of maternal glucose to the fetus by the placenta, which is buffered by placental glucose utilization. The third point is the production of insulin by the developing fetal pancreas, which enhances glucose utilization among the insulin-sensitive tissues (skeletal muscle, liver, heart, adipose tissue) that increase in mass and thus glucose need during late gestation. Glucose uptake into fetal tissues is regulated by glucose transporters that increase or decrease in response to both acute and chronic changes in fetal glucose concentration and conditions of intrauterine growth restriction. At the same time, signal transduction protein regulators of amino acid synthesis into protein are down-regulated, emphasizing that IUGR presents a mixed phenotype, with increased propensity to take up energy substrates, such as glucose, and diminished capacity for protein synthesis and growth.

- Initial phase: insulin resistant phase.
- Subsequent phase: tissue growth
- **In infants with BPD, energy expenditure increases by 0.7 kcal//kg/d per breath** Meer DEK et al *Eur J Pediatr* 56:299-304, 1997

- High rates of carbohydrate delivery (12.5 mg/kg /m) increase carbon dioxide production because this nutrient had a high respiratory quotient (RQ) (1.0) when completely oxidized that is even higher (.1.0) when excess glucose is used for fat production.
- The risk associated with an increased rate of carbon dioxide production in the infant who has respiratory disease is to raise minute ventilation needs, increasing the work of breathing or exposure to barotrauma in infants who are receiving mechanical ventilation.

Nutritional Management in BPD

Brunton JA, Saigal A, Atkinson SA. J Pediatr 133;340, 1998

- Few studies in the post-steroid era
- Brunton et al with 1st study showing ability to attain catch up growth in patients with BPD
  - Blinded trial, 60 preterm infants with BPD
  - Randomized to Isocaloric formulas from 37 weeks to 3 months corrected age :
    - Standard Formula (SF) or
    - Enriched Formula (EF): same calories as SF but enriched with protein and minerals
  - Follow-up at 1 month and 3 months corrected age

Randomized Trial of High Energy vs High Energy Nutrient Enriched Formula Post Discharge in Infants with BPD

Brunton JA, Saigal S, Atkinson SA. J Pediatr;133:340, 1998

Nutrient (per L)	Standard Formula	Enriched Formula	% increase
Energy (kcal)	900	900	0
Protein (g)	15	23	53
Pro:Energy (g/kcal)	4.0	6.1	53
Calcium (mmol)	10	25	250
Phosphorus (mmol)	9	20	220
Sodium (mmol)	6.5	17.6	270
Iron (umol)	27	44	163
Potassium (mmol)	14.3	24.9	174

Growth and Nutrient Retention

	STANDARD FORMULA (SF)	ENRICHED FORMULA (EF)
Weight (g/kg/d)	11.9 ± 2.9	10.8 ± 3.0
Net Protein Accretion (g/kg/d)	1.51 ± 0.41	2.21 ± 0.17*
Calcium Balance (mmol/kg/d)	0.95 ± 0.25	2.52 ± 0.78*
Zinc Balance (mmol/kg/d	-0.51 ± 7.5	6.30 ± 7.0**
Phosphorus Balance (mmol/kg/d)	1.20 ± 0.18	2.39 ± 0.54*
Nitrogen Balance (mg/kg/d)	262 ± 48	365 ± 34*

Values are mean ± SD * $p < 0.05$, ** $p < 0.01$

EF vs SF Study Conclusions

- At 3 months corrected age, the Enriched Formula group had significantly greater:
  - Length, lean mass and radial bone mineral content
  - Male infants had greater whole body mineral content
  - Faster "Catch-up"growth
  - 6 of 13 infants fed Standard Formula had a negative zinc balance, suggesting a possible zinc deficiency contributing to the lower lean mass accretion in the Standard Formula group

- The initial objectives in beginning lipid infusions is to prevent essential fatty acid deficiency, resume growth, and facilitate the transition to enteral feedings.
- How to start and how to increase?
- Addition of carnitine
- Role of MCT
- Energy expenditure increases with worsening acute pulmonary disease.
- A balanced delivery of energy from carbohydrates and lipids (rather than exclusively one or the other) is indicated.

Protein

- Negative protein balance is frequent with RD
- Undernutrition have the following deleterious effects
  - Respiratory muscle strength and function can be compromised
  - Alteration of the lung response to
    - Barotrauma
    - Hyperoxia
    - Infection
  - Exacerbation of pulmonary structural and biochemical immaturity
  - Poor protein status leads to low oncotic pressure exacerbating pulmonary edema
- Daily protein loss is 1.2-1.4g/kg/day
- Daily in utero protein accrition is 2.1g/kg/day
- A total of 3.5(1.4+2.1)g/kg/day is needed to keep the preterm on track with the expected in utero accretion rates
- No need for gradual increment of protein intake or increment related to the degree of RD

Guidelines for nutritional management of infants with BPD

Atkinson SA, Nutrition for Premature infants with BPD.
In *Neonatal Nutrition and Metabolism*, 2nd Ed, 2005

Early neonatal life (in hospital), consider:

-Vitamin A: given intramuscularly at 5000 IU 3 times per week for 4 weeks; given orally at 5000 IU once enteral feedings are established

-Vitamin E: up to 4-5 mg/day will maintain normal serum alpha-tocopherol (available from >150 mL of mother's milk or premature infant formula or the stand dose of parenteral or enteral multivitamin preparations)

-Fluid restriction: If fluid intake is restricted to < 150 mL/kg/d, then provide high nutrient density feedings as tolerated.

Stable and growing period (pre/post-hospital discharge to at least 3 months CA or longer):

-Target intake of nutrients in the following amounts:

Protein: ≥ 3.0 g/kg/d	Phosphorus: 3 mmol/kg/d
Energy: 120-130 kcal/kg/d	Zinc: 20 μmol/kg/d
Calcium: 4 mmol/kg/d	Vitamin D: 400-800 IU/d

-Fluid restriction: If fluid intake is restricted modular nutrient sources (lipid, carbohydrate and protein) may need to be added to breast milk or preterm formulas or other nutrient-enriched enteral nutrition products

Nutrition for Premature Infants with Bronchopulmonary Dysplasia (BPD)

Atkinson SA, *Neonatal Nutrition and Metabolism, 2nd Ed*, 2005

- BPD has been defined as an "oxygen radical disease of prematurity"
- Oxidative processes, especially of lipids and proteins, contribute to the development of BPD
- Postnatal growth failure and poor nutrient stores in the ELBW infant ⇓ the ability to counter oxidative stress

Nutrition for Premature Infants with BPD

- Nutritional support in the ELBW infants is critical for prevention, amelioration and recovery from BPD
- There are currently no evidence-based guidelines for nutritional management in BPD
- However, specific nutrients likely have a role in prevention, treatment and catch-up growth

Nutritional Antioxidants

- Vitamin E
  - Proposed free radial scavenger to prevent BPD and ROP
  - Trials in humans and baboons showed no benefit in prevention of BPD
  - Meta analysis: no clinical benefit at intakes above that which maintains normal α-tocopherol concentrations (10-30 mg/L)

Nutritional Antioxidants

- N-acetylcysteine (NAC)
  - Precursor of glutathione (GSH)
  - GSH neutralizes hydrogen peroxide
  - Single large trial in Scandinavia
    - 391 infants
    - IV NAC x 6 days early in life
    - No benefit in prevention of BPD or oxygen requirement

Nutritional Antioxidants

- Selenium
  - Component of glutathione peroxidase, an endogenous antioxidant
  - Plasma concentration used as measure of antioxidant status.
  - Single study: early low selenium concentration was not associated with development of BPD
  - Low plasma selenium at 28 days associated with ⇑ respiratory morbidity if <1500g
  - Cochrane Rev, 2003: doesn't ⇓ BPD, ROP or survival but may reduce number of episodes of sepsis

Nutrients to Prevent Lung Disease

- Inositol
  - 6-carbon sugar alcohol present as phosphatidylinositol in tissues and cell membranes
  - Proposed mechanism: ⇑ synthesis and secretion of surfactant
  - High concentration in preterm breast milk
  - Supplementation in neonates: ⇑ phosphatidylcholine / sphingomyelin ratio in surfactant
  - Cochrane Review (studies, small):
    - ⇓ in "death or BPD combined", IVH II/IV, Severe ROP
    - No effect on BPD alone at 28 days (positive trend)
    - More studies needed to clarify the role of inositol

Nutrients to Prevent Lung Disease

- Vitamin A
  - Proposed mechanism: stimulant for lung re-epithelialization after barotrauma or oxygen-induced lung injury
  - Stores in ELBW infants low at birth
  - Cochrane Rev, 2002: Vit A supplementation in VLBW infants associated with:
    - Reduced death or oxygen requirements at one month of age
    - Reduced oxygen needs at 36 weeks of age
    - May also ⇓ incidence of ROP and nosocomial sepsis
    - Greatest effect of benefit at 36 weeks was in those <1000g at birth
  - However, this appears to require multiple doses of IM Vitamin A over a prolonged period
  - Each unit needs to balance "modest benefits" vs repeated IM therapy
  - More studies need to be done on optimal dosing