Vitamin D & Iron Dosing Guidelines
Ayman Khmour, MD

I have no actual or potential conflict of interest in relation to this program.

Objectives
- Review Ca metabolism
- Review Recent AAP Guidelines
- Review CMH Recommendations
- Discuss Recommendations for Fe Suppliments

Fetal blood calcium regulation
- PTH and PTHrP both contribute to blood calcium regulation.
- In the absence of PTHrP, the blood calcium falls to the maternal level.
- In the absence of parathyroids, the blood calcium falls well below the maternal calcium concentration.
- Absence of PTH, the blood calcium equals the maternal level.
- In the absence of both PTHrP and PTH, the blood calcium falls even farther than in the absence of the parathyroids.

Vitamin D

Breast Feeding and Ca
- Breast is a central regulator of skeletal demineralization during lactation.
- Suckling and prolactin inhibit GnRH, which inhibits LH and FSH.
- PTHrP production is release from breast controlled by several factors: suckling, prolactin, and Ca receptor.
- PTHrP enters bloodstream and combines with low estradiol levels to markedly upregulate bone resorption.
- Increased bone resorption releases Ca and PTHrP, which are then pumped into the breast milk.
- PTHrP passes into milk at high concentrations, Unknown if swallowed.
- PTHrP plays a role in regulating Ca physiology in neonate.
Vitamin D (Cholecalciferol)

- A steroid hormone
- Deficiency in children causes rickets
- In Adults causes osteomalacia.

Vitamin D metabolism

- 2 forms of vitamin D:
  - Active form: 1,25-dihydroxycholecalciferol, D2 (ergocalciferol, synthesized by plants)
  - D3 (cholecalciferol, synthesized by mammals).
- Synthesis in the skin
  - Main source for humans
  - UV-B in 290 to 315 nm converts 7-dehydrocholesterol into previtamin D3
  - Previtamin D3 further transformed into vitamin D3
- Binds to vitamin D-binding protein

Vitamin D Functions

- Beyond bone integrity and Ca homeostasis
- Increases activity of NK cells, phagocytic activity of macrophages
- Polymorphisms of vitamin D receptor (VDR) gene associated with increased risk of breast cancer
- Low levels associated with increased risk of peripheral artery disease
- Prevention of certain disease states
  - Infection
  - Autoimmune diseases (multiple sclerosis, RA)
  - Some forms of cancer (breast, ovarian, colorectal, prostate)
  - Type 2 diabetes
- Vitamin D supplements in infancy and early childhood may decrease the incidence of type 1 diabetes mellitus
Dietary Supplements

- Limited in most diets
  - fatty fish and certain fish oils
  - liver
  - fat from aquatic mammals
  - egg yolks of chickens fed vitamin D

- Measuring concentration of 1,25-OH2-D instead of 25-OH-D for assessment of vitamin D status can lead to erroneous conclusions
  - 1,25-OH2-D concentrations: normal or even elevated vitamin D deficiency
  - result of secondary hyperparathyroidism

AAP Statement: November 2008

- Replace 2003 clinical report:
  - recommended a daily intake of 200 IU/day of vit D for all infants (Beginning first 2 months after birth), children, and adolescents.
- The new recommended daily intake of vit D is 400 IU/day for all infants, children, and adolescents beginning in first few days of life

Vitamin D Deficiency

- Rickets: preventable with adequate nutritional intake of vitamin D
- Cases of rickets due to low vitamin D intake and decreased exposure to sunlight reported
  - exclusively breastfed infants and infants with darker skin
- Not limited to infancy and early childhood
  - Cases of rickets caused by nutritional vit D deficiency reported in adolescents.

Rickets

- Peak incidence between 3 and 18 months of age.
- Deficiency occurs months before obvious on exam
- May present with hypocalcemic seizures, FTT, lethargy, irritability, and a predisposition to respiratory infections

Rickets

- 2 types of presentations.
  1. Symptomatic hypocalcemia (including seizures)
     - In periods of rapid growth increased metabolic demands,
  2. more chronic disease, with rickets and/or decreased bone mineralization and either normocalcemia or asymptomatic hypocalcemia
Sun Light Exposure and Vitamin D

- Full-body exposure during summer months for 10 to 15 minutes in adult with lighter pigmentation:
  - 10,000 and 20,000 IU of vitamin D3 within 24 hours
  - 5 to 10 times more exposure with darker pigmentation

Sun Light Exposure and Vitamin D

- Amount of UV exposure available for synthesis of vit D depends on many factors:
  - time spent outdoors.
  - amount of skin pigmentation
  - body mass,
  - degree of latitude,
  - season,
  - the amount of cloud cover,
  - extent of air pollution,
  - amount of skin exposed,
  - extent of UV protection.

Sun Light Exposure and Vitamin D

- Skin pigmentation: most important factor
- Difficult to determine what is adequate sunshine exposure for any given infant or child
- Limited UV light exposure recommended by the CDC and AAP
  - infants younger than 6 months should be kept out of direct sunlight.

Sun Light Exposure and Vitamin D

- Maternal vitamin D status essential during pregnancy
  - maternal well-being and fetal development.
  - Assessing maternal vitamin D status by measuring the 25-OH-D concentrations of pregnant women.
  - Supplementation if needed
    - ensure that her 25-OH-D levels are in a
  - Prenatal vitamins containing 400 IU of vitamin D3
    - Little effect on circulating maternal 25-OH-D concentration
      - especially during the winter months.

Vi D Supplementation During Lactation

- Vit D content of human milk related to lactating mother’s vitamin D status.
- Supplemented with 400 IU/day of vitamin D, result in Vit D content of BM 25 to 78 IU/L
- Exclusively BF infants with no supplemental vit D or adequate sunlight exposure: increased risk of vit D deficiency and/or rickets.
- Infants with darker pigmentation at greater risk
- Supplements of 1000 to 2000 IU of vitamin D per day to nursing mothers: little effect on BF infant’s

Pregnancy, Vit D and the Fetus

- Inadequacy of human milk in providing vitamin D
- 25-OH-D concentrations of 50 nmol/L can be maintained in exclusively breastfed infants with supplements of 400 IU/day of vitamin D
- Historic precedence of safety and prevention and treatment of rickets
Supplementation for Breast Feeding infants

- Supplement of 400 IU/day of vitamin D should begin within the first few days of life and continue throughout childhood.

- Any breastfeeding infant, whether being supplemented with formula, should be supplemented with 400 IU of vitamin D

- Unlikely that a breastfed infant would consume 1 L (1 qt) of formula per day – the amount that would supply 400 IU of vitamin D.

Formula-Fed Infants and Vitamin D Supplements

- All infant formulas sold in the United States must have minimum vitamin D concentration of 40 IU/100 kcal (258 IU/L of a 20 kcal/oz formula)

- Maximum vitamin D3 concentration of 100 IU/100 kcal (666 IU/L of a 20 kcal/oz formula)

- All formulas sold in the US have at least 400 IU/L of vitamin D3

- Because most formula-fed infants ingest nearly 1 L or 1 qt of formula per day after the first month of life, they will achieve a vitamin D intake of 400 IU/day.

Formula-Fed Infants and Vitamin D Supplements

- Infants receiving mixture of human milk and formula should get a vitamin D supplement of 400 IU/day to

- Any infant who receives 1 L or 1 qt of formula per day needs an alternative way to get 400 IU/day of vitamin D, such as through vitamin supplements

Forms of Vit D Supplements

- 2 forms:
  - vitamin D2 (ergocalciferol, plant derived)
  - vitamin D3 (cholecalciferol, fish derived).

- D3: greater efficacy in raising circulating 25-OH-D levels

- Vitamin D–only preparations are now available
  - Appropriate for BF infant with no need for multivitamin
  - The cost is minimal.

Oral Vitamin D Preparations Currently Available in the United States

CMH Vit D Recommendations

http://scope.cmh.internal/content/template.aspx?id=34642
Iron Metabolism
- Term infant contains ~75 mg/kg Fe compared to 40-50 mg/kg in adults
- 75% body Fe in hemoglobin & myoglobin, the remaining stored in ferritin
- Transferrin is Fe transport protein
- Transferrin & ferritin are influenced by body's need for Fe

Iron
- Cognitive development
- Cardiac & muscle function
- Growth
- Immunity
- Post-natal Erythropoiesis
- Anemia

Indications for Iron
- Preterm infants are born with very low Fe stores
- Hemoglobin nadir is reached earlier than term infant (1-3 months earlier)
- Erythropoiesis commences 4-8 weeks of life
- Iatrogenic losses

Recommendations
- AAP recommends 2-4 mg/kg/d Fe supplementation for VLBW infants no later than 2 months of age
- Maximum dose 15 mg/d
- Continued through first year of life

Too Much Iron?
- Very little day to day loss
- Fe absorption is not tightly regulated in preterm gut
- Absence of adequate protective mechanisms
- 85% circulating iron is recycled via red blood cell production
- Fe contributed by pRBC transfusions
Too Much Iron

- Tissue damage from free radical exposure, neonatal oxidative diseases
  - (ROP, CLD, PIVH, NEC have been postulated)
- Alteration among cell-mediated and humoral immunity
- High dose enteral iron competes with zinc and copper absorption necessary for growth

Iron Assessment

- Reticulocyte percentage
- Serum ferritin
- TIBC

Available Supplement

- Poly-vi-sol with Fe & Tri-vi-sol with Fe
  - 10 mg Fe
  - Infants <2.5 kg will receive >4mg/kg/d Fe
- Ferrous Sulfate
  - Standardized dosing based on weight
  - Maintains dose between 2-4 mg/kg/d