Calcium in premature infants: basics and beyond

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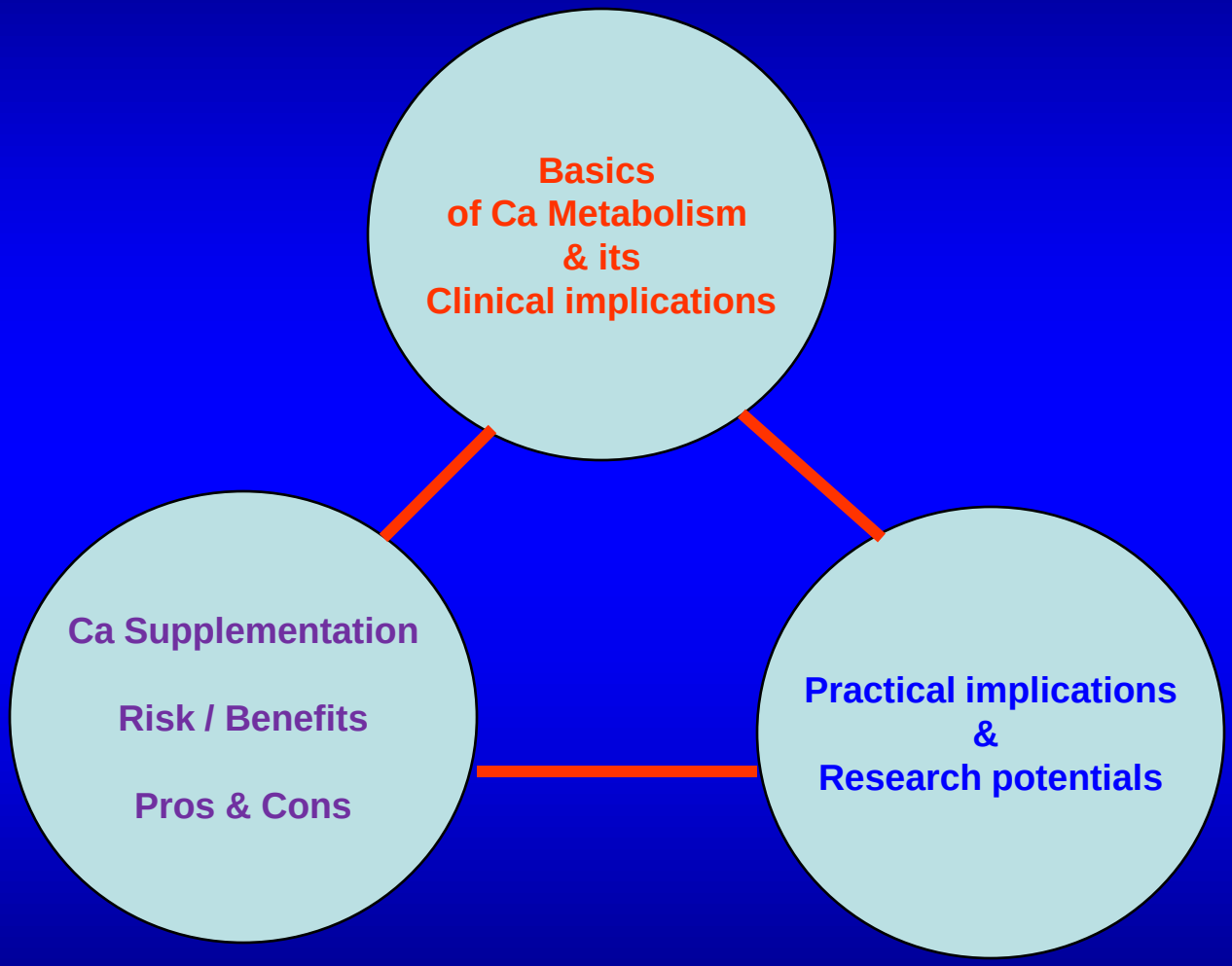
Presentation overview



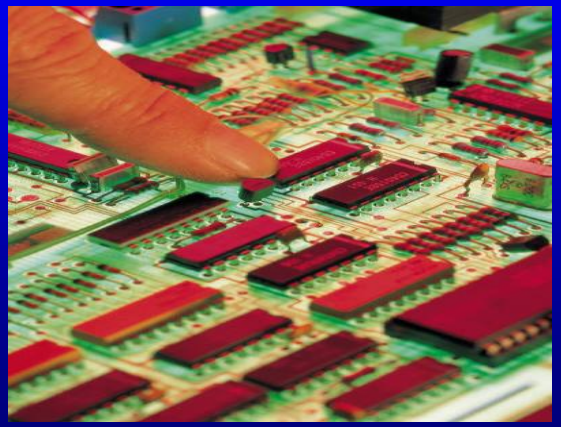
Metabolism

Ca metabolism (mother to fetus to newborn)
Homeostasis/Regulating factors
Clinical aspects

Supplementation

Pros/Cons of supplementation
- Why supplement
- What are the risk & benefits
- When to supplement
- How much

Research



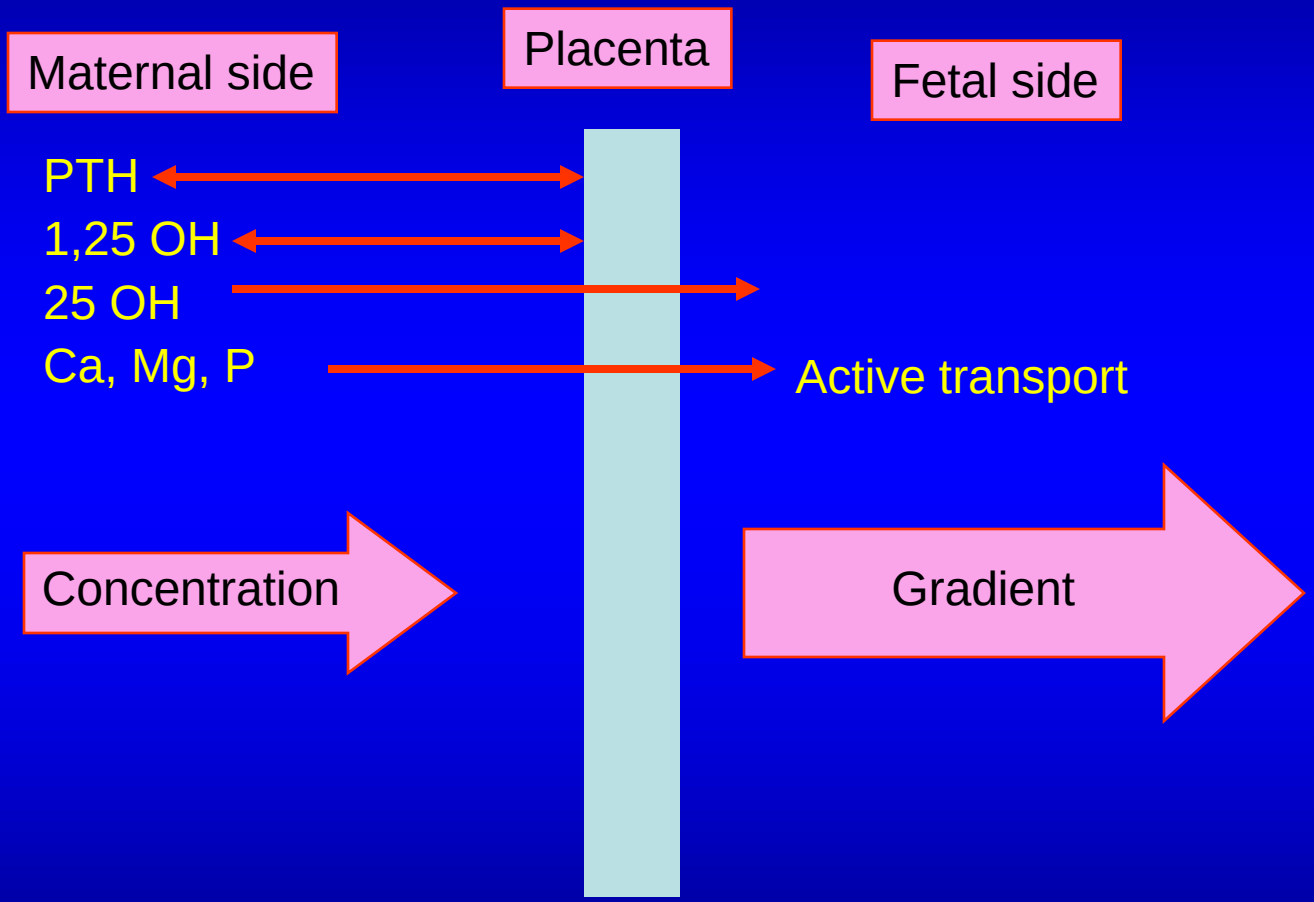
Practical implication
Future direction/ research potential

Metabolism

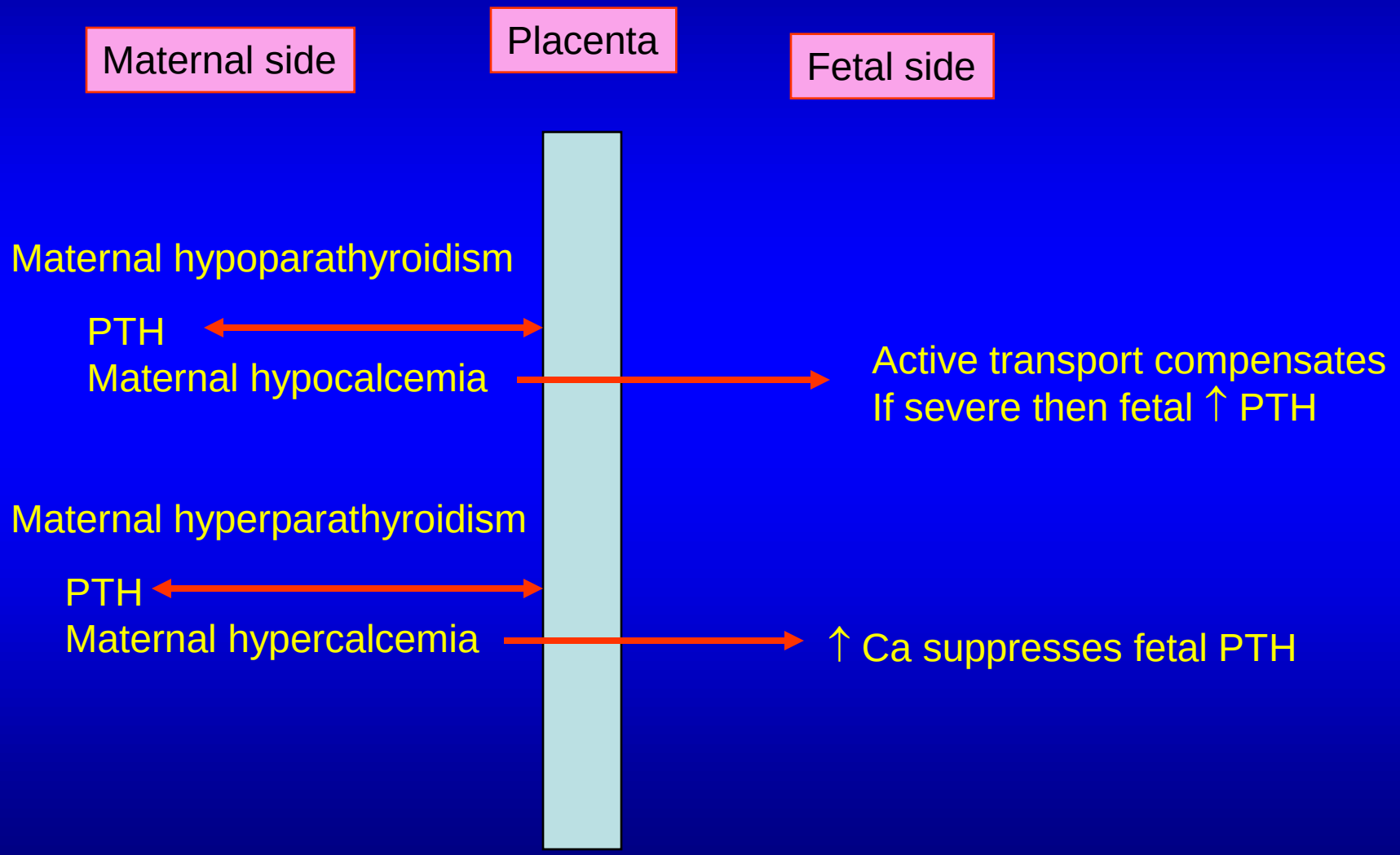
- Maternal
  - -↑ PTHrp & ↑ 1,25 OH, ↑ Ca from GIT
- Placental
  - - Active transport
- Fetal
  - -↑ Ca suppresses fetal PTH
- Neonatal
  - -Transition, Ca ↓ ↑ PTH
- Postnatal
  - - Stabilization (early / late hypocalcemia)

PTHrp : Parathyroid related hormones

Transport across placenta



Maternal - Fetal, Ca - PTH transplacental patho-physiology



Regulation

Ca, P, Mg metabolism – interrelated

Vitamin D : Activation – Calcidiol (liver), Calcitriol (kidney)

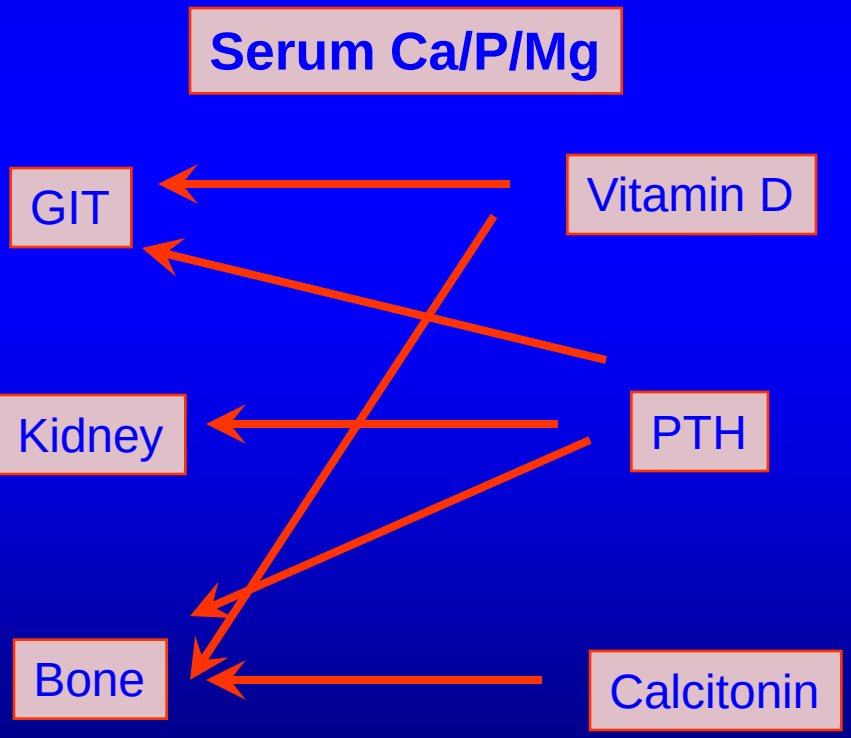
Hormones – PTH, Calcitonin

Remember ‘3’

Ca, P, Mg

GIT, Kidney, Bone

PTH, Vitamin D, Calcitonin



Minerals - Homeostasis

	GIT	Renal	Bone
Ca	~ 20-60%	reabsorb ~ 98%	↑ resorp with ↓ iCa
P	~ 70-90%	reabsorb ~ 90%	Cortisol/T4 ↑ release
PTH	↑ Ca / P	↓ **P**, ↑ Ca	Resorption (Vit D)
Vit D	↑ Ca / P	Conversion	PTH effect
Calcitonin	No effect	Ca / P excretion	↓ Bone resorption

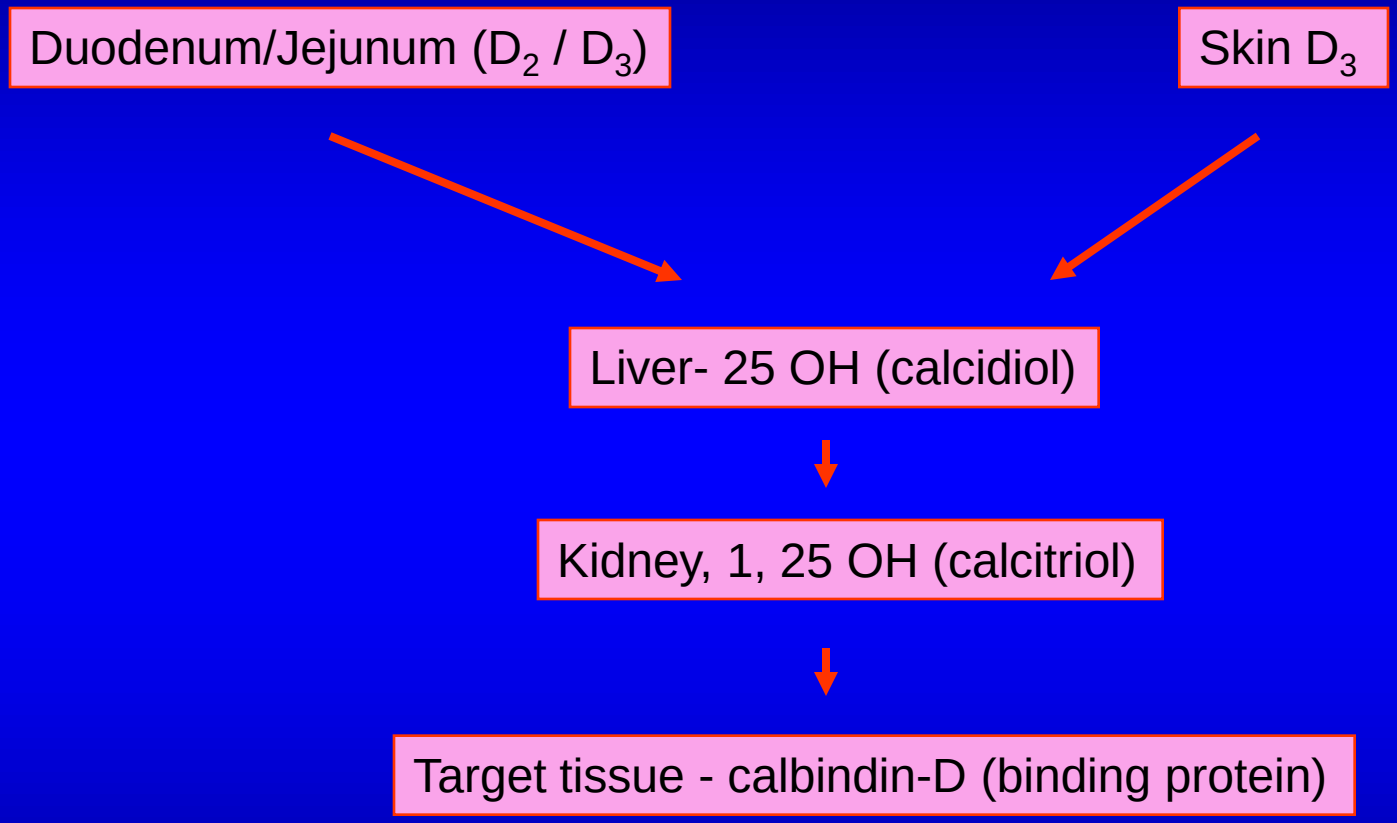
Regulating factors

- PTH - parathyroid gland
- Calcidiol (25 OH Vit D) – liver
- Calcitriol (1, 25 $(OH)_2$ Vit D – kidney
- Calcitonin – parafollicular cells
- Magnesium / Phosphorus
- Acid base status (0.1 change in pH changes iCa by 0.04 mmol/L)

PTH

- Secreted by parathyroid gland
- Pre-pro-PTH cleaved to small active fragments
- Effects: ↑ Ca by ↑ bone resorption and ↑ renal absorption, ↑ 1, 25 OH which ↑ GIT absorption (net result ↑ serum Ca)
- PTH ↓ P by phosphaturic action (counter balance hyperphosphatemia resulted from bone resorption)
- Regulation : Serum iCa (↓ Ca ↑ PTH), Ca-sensing receptor at parathyroid gland, serum Mg (↓ Mg ↑ PTH)

Vitamin D



D_3 (cholecalciferol) - animal source, D_2 (ergocalciferol) - vegetable source

Vitamin D

Actions:

- GIT: ↑ Ca / P absorption
- Bone : mobilize Ca / P by ↑ osteoclastic activity
- Kidney : ↑ Ca reabsorption

Regulation:

- Counter regulation : PTH, ↓ Ca and ↓ P – ↑ 1, 25 OH
- 25 OH – loosely regulated, 1, 25 OH – tightly regulated
- Serum 25 OH = 12-40 ng/mL& 1,25 OH = 70-100 ng/mL

Supplementation:

- Human milk = 20-60 IU/L, 400 IU/L in formula
- Pretern formula = 500-1200 IU/L

Calcitonin

- Secreted from parafollicular cells – thyroid galnd
- Effects are independent of PTH & Vit D
- ↓ Osteoclastic activity, ↓ Ca / P release from the bone
- Calciuric & phosphaturic (↓ serum Ca / P)
- Regulation : ↑ Ca ↑ calcitonin

Calcium

- 99 % of calcium is in the bones
- 1% in serum = 50% ionized, 40% bound to albumin,
  10 % lactate, bicarbonate, citrate

Intestinal absorption (20-60%)

Renal re-absorption (98%)

- however in VLBW infants the urinary Ca / Cr ratio reaches 0.75 -1.32 (mean in first 6 months is 0.22) or even 1.80 with furosemide

Calcium…….contd

Diet : Milk ,diary products, fruits, vegetable, grains, nuts

Supplement : Ca-chloride, Ca-gluconate, Ca-carbonate, Ca-ascorbate

SI unit for serum calcium: 4 mg/dl = 1 mmol/L

1 mEq of calcium = 20 mg of elemental calcium*

1 mL of 10% calcium gluconate = 9.3 mg of elemental calcium (700 mOsm/L)

1 mL of 10% calcium chloride = 27 mg of elemental calcium (2040 mOsm/L)

* 1 mmol = atomic weight in mg

mg = (mEq x atomic weight)/ valence

mEq = (mg x valence)/ atomic weight

Causes of hypocalcemia in neonates

Early:

- Prematurity
- Maternal diabetes
- Perinatal asphyxia
- Maternal anticonvulsants

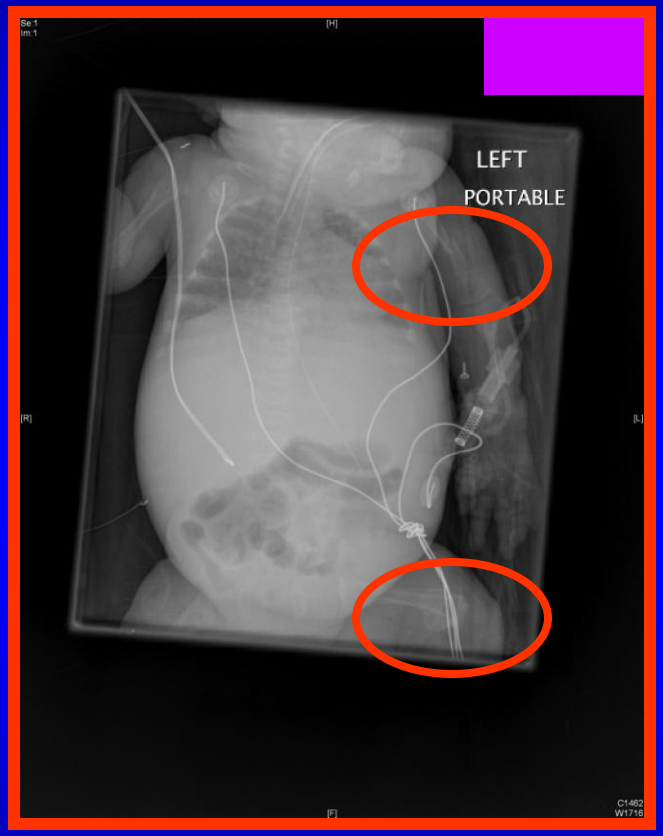
Late:

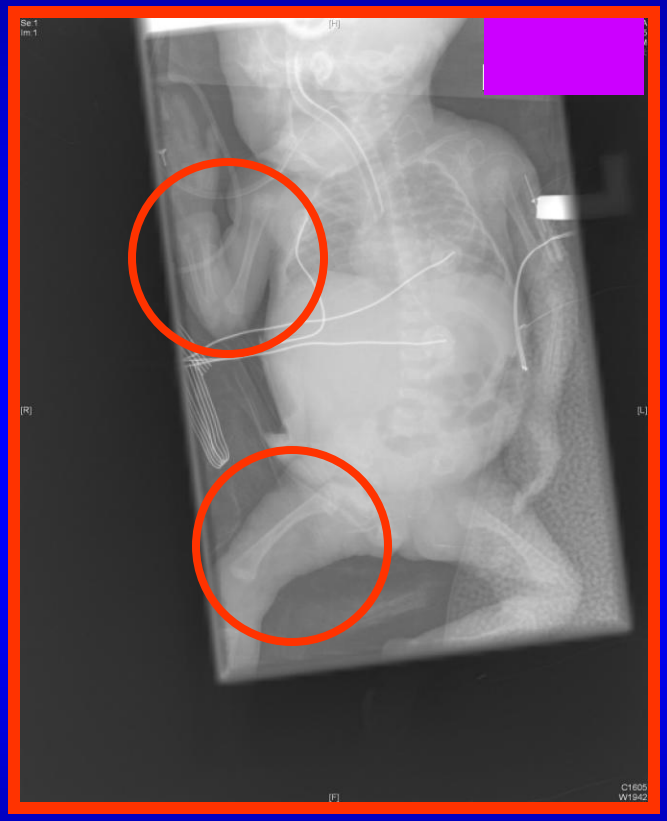
- Cow’s milk-based formula
- Hypomagnesemia
- Hypoparathyroidism
- Phototherapy
- Genetic conditions

Osteopenia of prematurity:

- Insufficient provision

Osteopenia of prematurity - OOP





Metabolic bone disease of prematurity (Osteopenia of prematurity – OOP)

- Insufficient provision (supplementation)
- Normal serum Ca (increased bone resorption)
- Decreased P (low supply, urinary excretion is NOT high)
- Increased alkaline phosphatase (isoenzyme)

} Variable

- Vitamin D / PTH (normal to high)
- Bone densitometry (DEXA) -specific / standard (not portable -feasibility??)

Full Text write up on OOP:

http:// www.geocities.com/medicos76/osteopeniaprematuridad.html

Power Point presentation on OOP:

http:// www.ttuhsc.edu/elpaso/som/pediatrics/neonatology/Presentations/OOP_files

Labs - interpretation

	Serum Ca	Serum P	Other
Osteopenia	N / ↓	↓ / N	↑ Alk Phos
Hyperparathyroidism	↑	↓	↑ PTH
Prim hypoparathyroidism	↓	↑	↓ PTH
Pseudo-hypo-parathyroid	↓	↑	↑ PTH *
Chronic renal failure	↓	↑	↑ PTH **
Malabsorption	↓	↓	Other deficiency

* Tissue resistance, ** low Ca causes feedback stimulation of PTH

Recap

- Calcium -maternal/fetal/neonatal
- Regulation - rule of 3

  (Ca, P, Mg /GIT, Renal, Bone / PTH, Vitamin D, Calcitonin)
- Briefly about: PTH, Vitamin D, Calcitonin
- About Calcium :

  (source, absorption, IV preparation, conversion factors)
- Causes of hypocalcemia in neonates
- Outline of osteopenia of prematurity

Pros & Cons of Calcium supplementation

- Risk / Benefit assessment
- Threshold / Cutoff
- Optimal time
- Appropriate dose
- Source (IV / Oral)

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Potential Benefits of Ca supplementation

- Replenishes stores
- Accomplishes physiological needs
  - Bone mineralization (prevents osteopenia)
  - Clotting
  - Cell membrane permeability
  - Neuromuscular excitability
  - Muscle contraction
  - Cellular signaling / messenger to hormones

Potential Risks of Ca supplementation

- Extravasation
  - IV burns
  - Skin necrosis
    - Neofax 2000 pg 168-70
- Osmolality changes
    - Venkataraman et al . J Pediatr Gastroenterol Nutr 1991;13: 134-8
- Associated Bradycardia
    - Venkataraman et al . Pediatrics 1985;76:543-50

Pros & Cons of Calcium supplementation

- Risk / Benefit assessment
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Threshold / Cutoff

- For term infants iCa < 1.10 mmol/L is taken as hypocalcemia*
- Data insufficient for premature infants
- Premature infants are at increased risk of hypocalcemia

  - Peak transfer 24-37 weeks
  - Low stores
  - High renal losses
    - (Urinary Ca/ Cr ratio 0.75-1.32, normal 0.22)
  - Low GIT absorption
  - Physiological hypoparathyroidism

* DeMarini S, Tsang RC. In : Fanaroff & Martin, 2002. pg 1376-92

Pros & Cons of Calcium supplementation

- Risk / Benefit assessment
- Threshold / Cutoff
- Optimal time
- Appropriate dose
- Source (IV / Oral)

Optimal time

- Soon after birth (add in maintenance IVF)
- Basing on symptoms
- Early : < 72 hrs (controversial)
- Late : > 72 hrs (in agreement)
- Institutional policies
- Basing on serial iCa values (potential)

Pros & Cons of Calcium supplementation

- Risk / Benefit assessment
- Threshold / Cutoff
- Optimal time
- Appropriate dose
- Source (IV / Oral)

Appropriate dose/ source

Target:

Intrauterine accretion rate (130 mg/kg/d)

Recommendation:

AAP = 60 mg/100 Kcal for first 6 months (Infants formula)
Preterm = 100-192 mg/100 Kcal (120-230 mg/kg/d)

TPN:

Ca : P ratio =1.3:1 or 1.7 :1
Ca = 60-90 mg/kg/d
P = 47-70 mg/kg/d

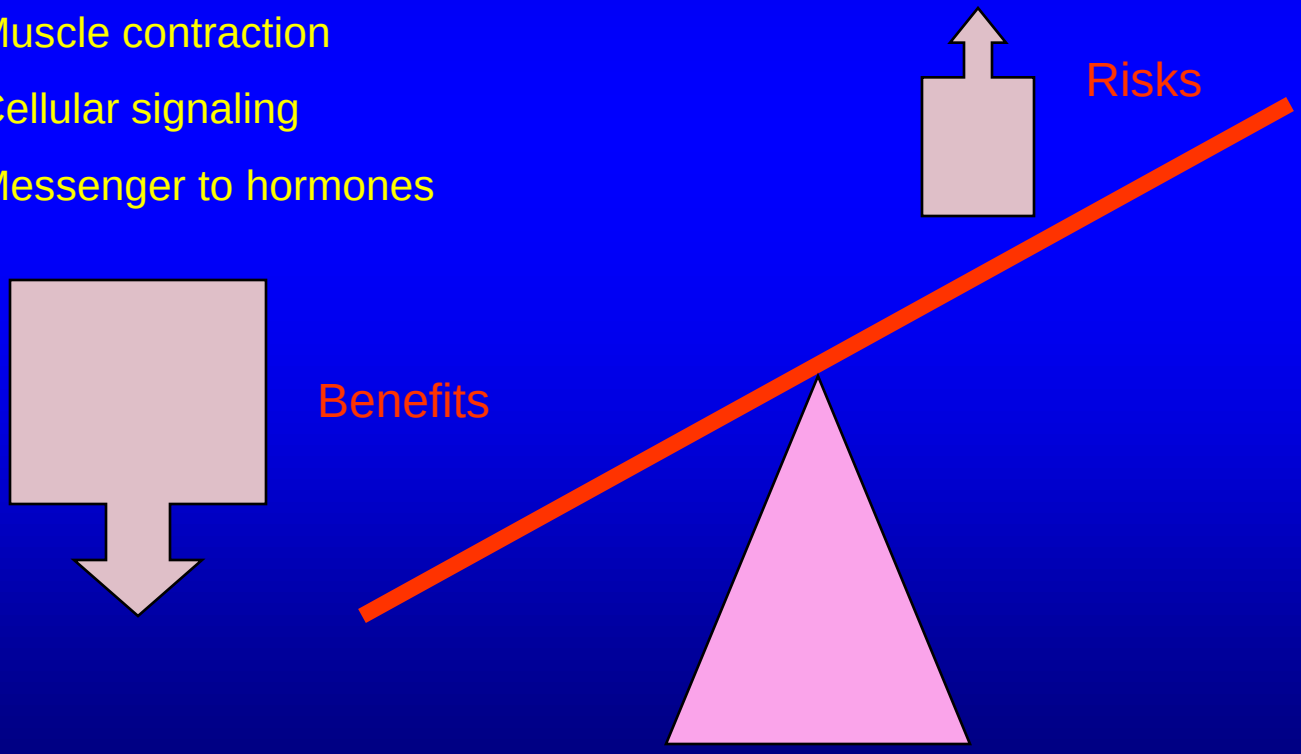
Feedings :

Ca in Human milk = 340 mg/L, Enfamil contains 527 mg/L

Risks vs benefits

- Bone mineralization (prevents osteopenia)
- Clotting
- Cell membrane permeability
- Neuromuscular excitability
- Muscle contraction
- Cellular signaling
- Messenger to hormones

- Extravasation (IV burns, Skin necrosis)
- Osmolality changes
- Associated Bradycardia



Summary

Ca is actively transported across placenta

Postnatal drop in serum Ca may be physiological, however preterm infants are at increased risk of hypocalcemia

Ca homeostasis is complex (Mg, P, Vit D, PTH, Calcitonin)

Pros & Cons of Ca supplementation

Benefits outweigh the risks

Lets apply these facts to the practice

Exercise

Standard Neonatal TPN at a hospital pharmacy contains 13.8 mEq/L i.e. 276 mg/L of Calcium * (~ 28 mg / 100 mL)

Guess (calculate) how much of calcium supplementation a preterm infants gets per day in the standard TPN (13.8 mEq/L or 276 mg/L) in our unit.

DOL 2, Weight = 1 kg , Total fluid = 150 mL/kg/day (NPO)

The infants will get ~ 42 mg/kg/d { 28 mg (100 mL) + 14 mg (50 mL)} (or 0.276 mg / ml x 150 = 41.4 mg)

This calculated amount is low for the AAP recommended dose (60-90 mg/kg/d) or intrauterine accretion rate (130 mg/kg/d)

*** mg = mEq x atomic weight/ valance (mEq x 40/2)**

Exercise

Giving extra IV Ca:

Solution: Add 500 mg of Ca gluconate to 250 mL of D5 W and run it @ 2 ml/hr

Total calcium provided by this source:

250 mL contains 500 mg
1 mL = 2 mg
2ml/ hr = 48 mL (2 x 24)
48 (ml) x 2 (mg) = 96 mg (9.6 mg elemental Ca)

This is in addition to the Ca in HAL, if more Ca is needed double the strength of solution (1000 mg in 250 ml)

Risk for hypocalcemia & OOP

What is the actual incidence of hypocalcemia *(early)* and OOP *(late)* in our ELBW infants in context with relatively low Ca supplementation?

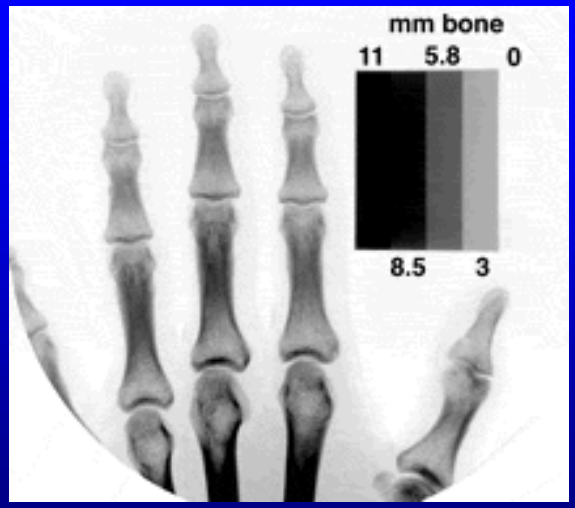
Sensitization : Do we look for it?

Catch:

iCa may be normal at the cost of increase bone demineralization
Fracture is a late sign of OOP
Laboratory indicators are non-specific for OOP
iCa is not an indicator of OOP

Limitations:

Non-availability (feasibility) of Dual Energy X-ray Absorptiometry (DEXA)* routinely



*DEXA: http://www.radiologyinfo.org/content/dexa.htm

Future directions

- We need to know the actual incidence of hypocalcemia (early-late, trend) in infants < 1000 grams*

Available tools:

- Numbers (enough cases ~ 50 / year)
- Technology :
  - iSTAT gives iCa with each blood gas analysis
  - Cerner system provides access to all these readings
- Motivated fellow (s) to search for the answer

* insufficient data on iCa for this weight group

Research prospect

Observational study :

- What is the distribution pattern (trend over time – first 2 weeks) of iCa among infants < 1000 grams?
- Taking 1.10 mmol/L as cutoff, what is the incidence of hypocalcemia in these infants?
- Do we have increased incidence of OOP (delayed linear growth – weekly charting, fractures – weekly x-ray, decreased bone density – DEXA?) with use of relatively low Ca containing TPN

Interventional study :

Randomized trial : Standard TPN (13.8 mEq/L-276 mg/L) versus
Customized TPN (20 mEq/L- 400 mg/L)*

** Based on NICU-net response from other national NICUs*

The End

Which of the following laboratory findings is most consistent with the diagnosis of osteopenia of prematurity

A) Normal Calcium, decreased Phosphate, increased Alkaline Phosphatase

B) Increased Calcium, decreased Phosphate , increased PTH

C) Decreased Calcium, increased Phosphate, decreased PTH

D) Decreased Calcium, increased Phosphate, increased PTH

E) Decreased Calcium, normal Phosphate, decreased Alkaline Phosphatase

B: hyperparathyroidism, C hypoparathyroidism,
D: pseudohypoparathyroidism, E : Unknown (distracter)

Thank you