Vitamin D in Pregnancy – Supplementation or Not?

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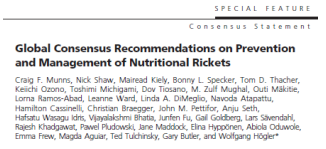
Disclosures

- Consultant for Sanofi
- Research grants from
  - BioCeuticals

Outline

- Case of nutritional rickets
- Vitamin D and calcium in pregnancy
- Nutritional rickets
- Prevention and Treatment of Nutritional Rickets


SPECIAL FEATURE
Consensus Statement

Global Consensus Recommendations on Prevention and Management of Nutritional Rickets

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Munns et al *JCEM* 2016; 101(2)

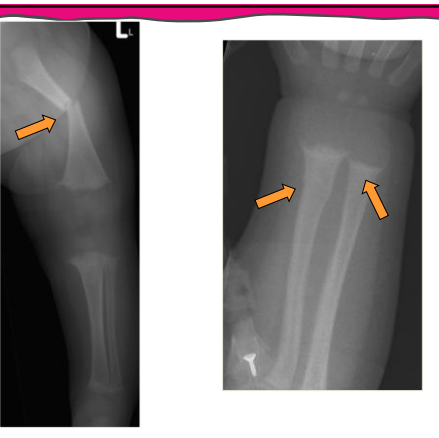
Case

- 3 month old female
- Irritable
- Painful leg and bruise
- No history of trauma

- Term, LSCS, Birth Weight 2490 g
- Mother not supplemented with vitamin D during pregnancy
- Breast fed
- Non-consanguineous Pakistani parents
- Mother wears traditional modest clothing

Examination

- Painful left leg
- Irritable
- Rachitic rosary, flaring wrists
- Poor weight gain
- Systemic examination otherwise normal



Further Investigation

- Calcium 1.59 mmol/L (2.10-2.65)
- Phosphorus 0.80 mmol/L (1.20-2.10)
- Magnesium 0.72 mmol/L (0.71-0.96)
- Alk-phos 1453 U/L (160-400)
- 25-(OH)vit D <12 nmol/L (>50)
- PTH 62.9 pmol/L (1.0-7.0)

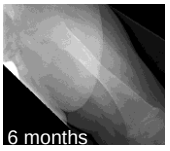
Mother

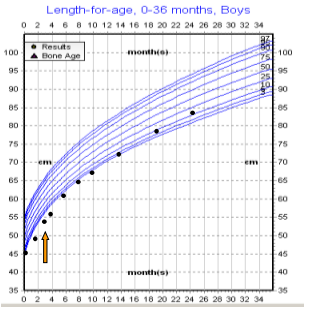
- 25 (OH) vit D 12 nmol/L
- Calcium 2.40 mmol/L

Treatment

- Calcitriol 60 nanograms/kg/day
- Oral calcium 100 mg/kg/day
- Discharge when calcium >2.00 mmol/L
- Cholecalciferol 2000 IU daily for 3 months
- Calcium 150 mg bd
- Maintenance vitamin D 400 IU daily
- Treat mother
  - Cholecalciferol 5000 IU daily 3 months
  - Calcium 600 mg bd

Follow-up





Calcium and Vitamin D in Pregnancy and Lactation

- Increased demands on calcium homeostasis with pregnancy and lactation
  - Foetal skeletal mineralisation
  - Calcium for breast milk

Pregnancy

- Term foetal skeletal has about 30 g of calcium
- 80% of this is accrued in the last trimester
- Calcium comes from a doubling of maternal intestinal calcium absorption
  - Mediated by 1,25-(OH)D (calcitriol)
  - ?Prolactin or placental lactogen
- Mild increase in maternal bone turnover from 12 weeks gestation
- Pregnancy does not lead to any significant reduction in maternal BMD or risk of developing osteoporosis in later life

Sowers. *J Bone Miner Res 1996;11*

Lactation

- 210 mg of calcium lost in breast milk daily
- Comes from demineralisation of maternal skeleton
  - PTHrP (breast) and fall in oestradiol levels
- Fall in BMC of 3 – 10% after 2 – 6 months of lactation at trabecular sites (spine, hip and distal radius)
- Fall in BMC correlated with amount of calcium in breast milk
- Supplementation with high-dose calcium does not prevent BMC loss

Laskey et al. *Am J Clin Nutr* 1998;67

Kalkwarf et al. *N Engl J Med* 1997;337

Lactation

- After weaning there is regaining of BMC
- Lactation does not appear to be a risk factor for subsequent osteoporotic fractures

Sowers. *J Bone Miner Res 1996;11*

Vitamin D in Pregnancy and Lactation

- Maternal vitamin D levels do not change throughout pregnancy or lactation

	Recommended Daily Allowance (RDA)	Upper Level Intake
14 – 18 year old	600 IU daily	4000 IU daily
>18 year old	600 IU daily	4000 IU daily

- RDA is the dose that will keep 97.5% of the population >50 nmol/L

OIM. Dietary reference intakes for calcium and vitamin D. The National Academies Press; 2011
Munns et al *JCEM* 2016; 101(2)

Vitamin D Deficiency (<50nmol/L) and Pregnancy

25OHD level	Westmead	Campbelltown	Adelaide	ACT	Shepparton	Brisbane
>50 nmol/L	59%	55%	26%	65%	74%	91%
25 – 49 nmol/L	32%	34%	42%	31%	21%	6%
<25 nmol/L	9%	12%	32%	4%	5%	3%

Lau et al. *MJA 2011*;194(7)
Perampalam et al. *ANZJOG* 2011;51
Thomas et al. *BMJ* 2011;2
Teale et al. *ANZOG* 2010;50
McLeod et al. *MJA* 2011;195(7)

Classical Features of Vitamin D Deficiency During Pregnancy

- Worsening of hypocalcaemia
- Osteomalacia
- Limb / bone pain
- Myopathy / myalgia
- Obstetric problems during labor

Kovacs. *Endocrinol Metab Clin N Am* 2011;40

What are the Typical Features and Biochemistry of Vitamin D Deficiency in Pregnancy?

- Asymptomatic
- 25 OHD <50 nmol/L

Neonatal Calcium and Vitamin D

- In utero foetal calcium = maternal calcium
- Unless mother hypocalcaemic, foetal development normal

- Neonatal vitamin D is 75% of maternal vitamin D
- Little vitamin D in breast milk – 25 IU/L
- Half life of vitamin D about 8 weeks
- Un-supplemented neonate can quickly become vitamin D deficient

Countries with Reports on Nutritional Rickets

North America	South America	Europe	Asia	Africa/Middle East
Canada	Argentina	Algeria	India	Ethiopia
U.S.	Chile	Denmark	Bangladesh	Kenya
	Columbia	Finland	China	Nigeria
		France	Indonesia	Sudan
		Netherlands	Israel	S. Africa
		Norway	Japan	Saudi Arabia
		Spain	Kuwait	Yemen
		Sweden	Lebanon	
		U.K.	Mongolia	
		Germany	New Zealand	
			Vietnam	
			Australia	

Incidence

- Nutritional Rickets:
  - 2.9, 4.9, 7.5, and 24 per 100,000 children in Canada, Australia, UK, and the USA, respectively
- Hypocalcaemic seizures due to Vitamin D deficiency in the UK:
  - 3.49 per 1 Million children (age 0-15)
- Vitamin D and/or calcium deficiency:
  - Worldwide, widespread

Munns et al JCEM 2016; 101(2)

The 3 primary causes rickets and osteomalacia

- Lack of Mineral Supply (Calcium, Phosphporus)
  - Calcium deficiency rickets
  - Hypophosphataemic rickets

- Lack of the Mineral Supplier (Vitamin D)
  - Vitamin D deficiency
  - Vitamin D resistance

- Lack of Mineral Deposition (TNSALP)
  - Hypophosphatasia

Vitamin D, Calcium and Nutritional Rickets

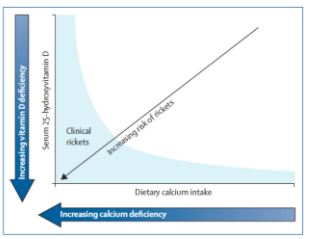


Figure: Vitamin D and dietary calcium deficiency—detrimental to bone in combination

Högler W, Munns CF Lancet Glob Health. 2016 Apr;4(4):e229-30.

What is the definition of vitamin D deficiency?

Classified by serum 25OHD level

	Serum 25OHD
Sufficiency	> 50 nmol/L
Insufficiency	30-50 nmol/L
Deficiency	<30 nmol/L

1+++

Strong recommendation
High quality evidence

Functional outcomes of this definition

- Depend on balance between dietary calcium intake and 25OHD level
- Majority of children asymptomatic and detected through screening
- Osteomalacia and rickets most significant outcome
- Biochemical results and bone density are associated outcomes

No indication for routine screening for vitamin D deficiency

Munns et al JCEM 2016; 101(2)

Risk Factors for Vitamin D Deficiency

- Reduced intake or synthesis of vitamin D
  - Maternal vitamin D deficiency
  - Prolonged exclusive breast feeding (>6 months)
  - Darker skin colour
  - Limited sun exposure
    - Disability
    - Clothing
    - Sunscreen
- Abnormal gut function / malabsorption
  - Small bowel: Coeliac disease
  - Pancreatic insufficiency: Cystic fibrosis
  - Biliary obstruction
- Reduced synthesis / increased degradation / sequestration
  - Chronic liver disease
  - Medication: antiepileptic, glucocorticoids
  - Obesity

Munns et al *MJA* 2006; 185(5)
Adams et al. *JCEM* 2009;95(2)

Definition of dietary calcium deficiency

- For infants 0-6 and 6-12 months of age, the adequate calcium intake is 200 and 260mg/day, respectively. **(1+++)**
- For children > 12 months of age
  - Dietary calcium intake of <300mg/day increases the risk of rickets independent of serum 25OHD levels. **(1++O)**
  - **Classified by dietary calcium intake**: **(1++O)**

	Daily calcium intake
Sufficiency	>500mg
Insufficiency	300 – 500mg
Deficiency	<300mg

Assessment: Dietary questionnaire specific to the diet of country/ region

Munns et al JCEM 2016; 101(2)

What Happens when Vitamin D and Dietary Calcium are not Maintained?

Hypocalcaemia

↓

Hyperparathyroidism

↓ ↓

↑Alkaline phosphatase Hypophosphataemia

↓

Osteomalacia and Rickets

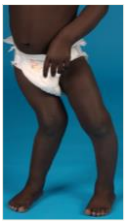
Clinical Features of Nutritional Rickets

- Metabolic Disturbance
  - Hypocalcemic seizures
  - Neonatal tetany
  - Laryngospasm
- Skeletal abnormalities
  - Bowed legs
  - Pathological fractures
  - Craniotabes
- Growth and Developmental abnormalities
  - Failure to thrive
  - Developmental Delay
  - Cardiomyopathy and death
  - Association with iron deficiency anaemia

Limb Deformity

Genu Valgum

Genu Varum



Wind Swept

Treatment of Nutritional Rickets

Vitamin D2 or D3

Age	Daily oral dose for 3 months	Single dose (D3>D2)	Maintenance daily dose
< 3 months	2000 IU	N/A	400 IU
3 to 12 months	2000 IU	50,000 IU	400 IU
12 months to 12 years	3000 - 6000 IU	150,000 IU	600 IU
> 12 years	6000 IU	300,000 IU	600 IU

Reassess response to treatment after 3 months as further treatment may be required.

IU to µg: divide by 40

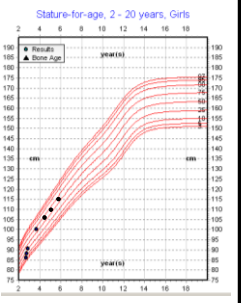
Calcium

Ensure a daily calcium intake of at least 500mg

Munns et al JCEM 2016; 101(2)

Follow-up Images

6 months 18 months 30 months



Prevention of Rickets

- **First 12 months of life**
  - 400 IU/day (10µg) prevents rickets in infants and is recommended for **all** infants in the 1st year of life
- **Beyond 12 months of age**
  - Everybody needs to meet their nutritional requirement for vitamin D (diet or supplementation), which is at least 600 IU/day (15µg), as recommended by the IOM.
  - **Supplement**
    - All children with a history of symptomatic vitamin D deficiency requiring treatment.
    - Children and adults at high risk of vitamin D deficiency, with factors that reduce synthesis or intake of vitamin D.
    - Pregnant women

Munns et al JCEM 2016; 101(2)

Prevention of Osteomalacia during Pregnancy and Congenital Rickets

- **Pregnant women should receive 600 IU/day of supplemental vitamin D.**
  - Ensures adequacy of maternal 25OHD
  - Prevents elevated cord blood ALP, increased fontanelle size, neonatal hypocalcaemia and congenital rickets, and
  - Improves dental enamel formation.
- Pregnant women do not need calcium intakes above recommended non-pregnant intakes to improve neonatal bone.

Munns et al JCEM 2016; 101(2)

Public health strategies for Rickets Prevention

- **Provide Vitamin D Supplementation for**
  - ALL infants from birth to at least 12 months of age
  - ALL pregnant women
  - ALL risk groups, for life

Incorporate Vitamin D Supplementation into Childhood primary health care programs AND Antinatal care programs

Munns et al JCEM 2016; 101(2)

Public health strategies for Rickets Prevention

Food Fortification

- Fortify staple foods with vitamin D and calcium, as appropriate.
- Food fortification can prevent rickets and improve vitamin D status if
  - appropriate foods are used
  - sufficient fortification is provided
  - fortification is supported by relevant legislation
  - the process is adequately monitored
  - Indigenous food sources of calcium should be promoted or subsidized in children

Munns et al JCEM 2016; 101(2)

Take Home Messages

- Vitamin D deficiency = 25OHD <30 nmol/L
- Deficient Calcium Intake <300 mg/day
- Rickets
  - Radiological diagnosis, occurring when low calcium intake is combined with low 25OHD (LCMS)
  - Affects cardiac & skeletal muscle, and bones
  - Features reversible & fully preventable, but long-term sequelae & deaths if untreated
- Supplement
  - ALL infants 1st year of life (400IU, 10µg)
  - ALL pregnant mothers (600IU, 15µg)
  - ALL risk groups, for life
- Food fortification programs should be considered for high-risk populations

Munns et al JCEM 2016; 101(2)

Thank you

The University of Sydney

Centre for Children's Bone & Musculoskeletal Health