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

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

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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

3 months
6 months

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

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

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Lactation

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

Vitamin D in Pregnancy and Lactation

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

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Recommended Daily Allowance (RDA)</th>
<th>Upper Level Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 – 18 year old</td>
<td>600 IU daily</td>
<td>4000 IU daily</td>
</tr>
<tr>
<td>&gt;18 year old</td>
<td>600 IU daily</td>
<td>4000 IU daily</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Location</th>
<th>Westmead</th>
<th>Campbelltown</th>
<th>Malaga</th>
<th>ACT</th>
<th>Shepparton</th>
<th>Brisbane</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50 nmol/L</td>
<td>59%</td>
<td>55%</td>
<td>26%</td>
<td>65%</td>
<td>74%</td>
<td>91%</td>
</tr>
<tr>
<td>25 – 49 nmol/L</td>
<td>32%</td>
<td>34%</td>
<td>42%</td>
<td>31%</td>
<td>21%</td>
<td>6%</td>
</tr>
<tr>
<td>&lt;25 nmol/L</td>
<td>9%</td>
<td>12%</td>
<td>32%</td>
<td>4%</td>
<td>5%</td>
<td>3%</td>
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</tbody>
</table>

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

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Incidence

- Nutritional Rickets: 2.9, 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

Countries with Reports on Nutritional Rickets

<table>
<thead>
<tr>
<th>North America</th>
<th>South America</th>
<th>Europe</th>
<th>Asia</th>
<th>Africa/Middle East</th>
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<tr>
<td>Canada</td>
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<td>Denmark</td>
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<td>Vietnam</td>
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Vitamin D, Calcium and Nutritional Rickets

The 3 primary causes of rickets and osteomalacia

- Lack of Mineral Supply (Calcium, Phosphorus)
  - Calcium deficiency rickets
  - Hypophosphataemic rickets
- Lack of the Mineral Supplier (Vitamin D)
  - Vitamin D deficiency
  - Vitamin D resistance
- Lack of Mineral Deposition (TNSALP)'
  - Hypophosphatasia

What is the definition of vitamin D deficiency?

<table>
<thead>
<tr>
<th>Classified by serum 25OHD level</th>
<th>Serum 25OHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficiency</td>
<td>&gt; 50 nmol/L</td>
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<tr>
<td>Insufficiency</td>
<td>30-50 nmol/L</td>
</tr>
<tr>
<td>Deficiency</td>
<td>&lt; 30 nmol/L</td>
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</table>

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

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

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**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++)
  - Classified by dietary calcium intake: (1++)

<table>
<thead>
<tr>
<th>Calcium Intake</th>
<th>Sufficiency</th>
<th>Insufficiency</th>
<th>Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;500mg</td>
<td>300 – 500mg</td>
<td>&lt;300mg</td>
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Assessment: Dietary questionnaire specific to the diet of country/region

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

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**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

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

- Hypocalcaemia
- Hyperparathyroidism
- ↑Alkaline phosphatase
- Hypophosphataemia
- Osteomalacia and Rickets

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**Limb Deformity**

- Genu Valgum
- Genu Varum
- Wind Swept

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**Treatment of Nutritional Rickets**

**Vitamin D2 or D3**

<table>
<thead>
<tr>
<th>Age</th>
<th>Daily oral dose for 3 months</th>
<th>Single dose (12 weeks)</th>
<th>Maintenance daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 months</td>
<td>2000 IU</td>
<td>N/A</td>
<td>400 IU</td>
</tr>
<tr>
<td>3 to 12 months</td>
<td>2000 IU</td>
<td>50,000 IU</td>
<td>400 IU</td>
</tr>
<tr>
<td>12 months to 12 years</td>
<td>3000 - 6000 IU</td>
<td>150,000 IU</td>
<td>600 IU</td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>6000 IU</td>
<td>300,000 IU</td>
<td>600 IU</td>
</tr>
</tbody>
</table>

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))

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Follow-up Images

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

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.

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

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

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

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