Vitamin D in pregnancy and lactation

October 2014

Dr Pamela von Hurst
Co-Director, Vitamin D Research Centre
Massey University
Overview of presentation

• Vitamin D 101
  • Metabolism
  • Sources
  • Measuring status
• Pregnancy and lactation
• Roles in health and disease – current evidence
  • Regulation of the immune system
  • Respiratory infections
25-hydroxyvitamin D
or
25(OH)D
Vitamin D Receptor

• The vitamin D receptor (VDR) is a nuclear receptor
• Identified in a wide range of tissues throughout the body
• Responsible for expression and suppression of over 200 genes
• Is activated by binding with 1,25-dihydroxyvitamin D
Endogenous production

- UVB only (not UVA)
- UVB does not pass through glass
- Influences are many and varied
  - Geographical latitude
  - Time of day
  - Season
  - Skin colour
  - Area of skin exposed
  - Air pollution
  - Age
Dietary Sources

• Considering intake
  • 400 – 600 IU/day (10 – 15 µg/day)   Aust/NZ 2006 NRVs
  • 10 – 15 minutes in the summer sun – 10,000 IU
  • 2000 IU/day needed to correct deficiency

• Fortified foods – milk, yoghurt, spreads
• Fatty fish e.g. salmon, sardines

• Supplements, cod liver oil
  • Max OTC supplement 1000 IU/day
  • Monthly Rx 50,000 IU Cal-D-Forte
Vitamin D Status

- 25(OH)D concentration measured in serum
- 20 ng/ml = 50 nmol/L (ng/ml x 2.495 = nmol/L)
- Currently in NZ 50 nmol/L considered adequate
- North America 75 nmol/L considered adequate

What is the right answer?
Maasai median $25(OH)D = 104 \text{ nmol/L}$

Luxwolda and Muskiet, 2012 Br J Nutr
Vitamin D in pregnancy

• Maternal dietary calcium absorption not so dependent on vitamin D status
• $1,25(\text{OH})_2\text{D}_3$ levels more than tripled by end of first trimester – the pregnancy paradox
  • Not driven by calcium homeostasis
  • Not controlled by PTH
  • Highly correlated with circulating 25(OH)D
• Role during pregnancy? likely involved in tolerance to prevent rejection of the fetus
Why do we care if a pregnant woman is vitamin D deficient?

- A vitamin D deficient mother gives birth to a deficient infant
- A vitamin D deficient mother has low levels of vitamin D in breast milk
- As a preprohormone, effects of metabolites go beyond bone and calcium metabolism
- Epidemiological studies link deficiency with whole host of inflammatory and long-latency diseases
  - Breast, prostate, and colon cancers
  - Multiple Sclerosis
  - Cardiovascular Disease
  - Diabetes
  - Resistant tuberculosis and other infections
Metabolism of Vitamin D Under Conditions of Adequate Vitamin D Supply

When vitamin D supplies are adequate, flow of 25(OH)D through endocrine pathway on right, and other potential pathways, including its utilization by peripheral tissues for paracrine regulation on left, is not compromised.
Substrate matters. With vitamin D deficiency: System is starved for substrate: trace amounts of vitamin D found because immediately metabolized to 25(OH)D and then to 1,25(OH)₂D.
Maternal and infant status closely related

<table>
<thead>
<tr>
<th>Locale</th>
<th>Study participants</th>
<th>25(OH)D (nmol/L) Mean (SD)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delhi</td>
<td>N=29 Urban mothers, 23 (5) years, summer</td>
<td>21.8 (10.7)</td>
<td>Goswami (2000)</td>
</tr>
<tr>
<td></td>
<td>N=29 Newborns of mothers above</td>
<td>16.6 (5.0)</td>
<td></td>
</tr>
<tr>
<td>UAE</td>
<td>N=90 New mothers</td>
<td>25.6 (10.0)</td>
<td>Saadi (2009)</td>
</tr>
<tr>
<td></td>
<td>N=92 Newborns of mothers above (2 x twins)</td>
<td>13.7 (9.9)</td>
<td></td>
</tr>
<tr>
<td>Delhi</td>
<td>N=342 Lactating mothers, 24.6 (2.8) years</td>
<td>19.5 (8.3)</td>
<td>Marwaha (2011)</td>
</tr>
<tr>
<td></td>
<td>N=342 Exclusively breastfed infants,  6-8 weeks</td>
<td>22.2 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Delhi</td>
<td>N=180 Lactating mothers</td>
<td>27.1 (14.4)</td>
<td>Seth (2009)</td>
</tr>
<tr>
<td></td>
<td>N=180 Exclusively breastfed infants,  2-24 weeks</td>
<td>28.8 (20.7)</td>
<td></td>
</tr>
</tbody>
</table>
Neonates and infants

- Neonatal hypocalcaemia – convulsions
- Neonatal rickets – fractures presenting at or shortly after birth

- Berlin 1987 – four cases of neonatal rickets in infants born to mothers with vitamin D deficiency (25(OH)D < 25 nmol/L) and (later diagnosed) osteomalacia. One infant with radial fracture, all four had craniotabes.

Auto-immune conditions

- Type 1 diabetes mellitus
- Multiple Sclerosis
- Inflammatory bowel disease

- Role of vitamin D
  - Regulation of immune system (dendritic cell maturation)
  - Protection of pancreatic islet cells
  - Expression of neural growth factor, tight junction proteins
  - Secretion of insulin
Type 1 diabetes

- Autoimmune destruction of pancreatic β-cells
  - Process begins in infancy – auto-antibodies detectable in first year
  - β-cell destruction can begin in infancy
  - By diagnosis 80% have been destroyed
  - Both genetic and environmental factors

- Prevalence increasing

- Incidence much greater in high latitude countries:
  - 400 x more likely in Finland than Venezuela

- Most common in people of European descent

- Seasonal variation in diagnoses
Type 1 DM and supplementation

Figure 2  Odds ratios (95% CI) of effect of vitamin D supplementation in infancy on development of type 1 diabetes.

Arch Dis Child 2008;93:512–517. doi:10.1136/adc.2007.128579
Multiple Sclerosis

• A chronic degenerative, often episodic disease of the central nervous system marked by patchy destruction of the myelin that surrounds and insulates nerve fibres

• Vitamin D status and risk of disease inversely correlated in longitudinal studies

• 30% lower risk in highest 25(OH)D quintile compared with lowest

• 5 year follow up in young adults; >100nmol/L reduced risk by 60% compared with <100nmol/L

Multiple Sclerosis

- Season of birth in Norway
  - 11% greater risk if born in April, 5% lower risk if born in November


*Figure 2. Pooled analysis of observed/expected births in people with multiple sclerosis in Norway (n = 6649) with 95% confidence intervals.*
Multiple Sclerosis

• Season of birth in Australia
  • Increased risk of MS for those born in November – December compared with May – June
  • Ambient solar radiation during first trimester highly significant
  • ~ 50% increased risk of developing MS with lowest levels of solar radiation

• Scotland – highest rate of MS in the world: 200/100,000
• Combination of genes plus environment?
Respiratory infection
Tuberculosis

- Cod liver oil and TB - Earliest case reports in 1846
- Light therapy (heliotherapy) used to treat lupus vulgaris in 1895

Niels Ryberg Finsen (1860-1904)
Vitamin D identified

• Vitamin D identified as the active ingredient in cod liver oil, isolated and used to treat lupus in 1945, and pulmonary TB in 1946
• Subsequent widespread distribution of penicillin by 1945 resulted in shift in focus of treatment for infectious diseases

• Interest was lost in the potential role for vitamin D in respiratory infections, especially bacterial infections
Rickets

• Rachitic children noted as being more susceptible to respiratory infections (Hess, 1929; Hess, 1936; Elliot 1938)

• VDD rickets also impact on response to treatment for ARI.
  • Yemen 2008 – 24/79 children (2-24 months) with pneumonia failed to respond to treatment
  • Children had a higher rate of treatment failure if they also had rickets (21 out of 24)
  • All 24 were vitamin D deficient – 25(OH)D <30nmol/l

  (Banajeh, 2009)
Rickets

- 137 children admitted with severe pneumonia
- 101 (74%) of cases were also diagnosed with nutritional rickets
- More common in breast-fed (83.4%) than formula (40%)

Haider et al. JPMA 60:729; 2010
Bronchiolitis in infants

- Respiratory syncytial virus (RSV) leading cause of bronchiolitis and pneumonia in young children
- Prospective birth cohort study, Netherlands
- 156 neonates for first year of life, cord blood 25(OH)D

Outcomes:
- parent-reported LRTI symptoms ≥ 2 days
- Identification of RSV RNA in a nasal-throat swab

Results:
- 12% of infants developed RSV LRTI in first 12 months
- Cord blood 25(OH)D <50 nmol/l = 6.2 (95%CI, 1.6-24.9) times greater risk compared to >75nmol/l

Belderbos. Pediatrics 27(6), 2011
Clinical studies - interventions

• Mongolian school children and ARTI
  • 247 children, RCT with vitamin D fortified milk (300IU) or plain milk
  • Baseline 25(OH)D < 20 nmol/l
  • Increased in intervention group to median of 47 nmol/l
  • Vitamin D halved the risk of ARTI (RR 0.52)

Camargo et al. 2012 Pediatrics
Influenza

• British epidemiologist, Edgar Hope-Simpson proposed a number of epidemiological “conundrums” about influenza:
  • Why is influenza both seasonal and ubiquitous and where is the virus between epidemics?
  • Why are the epidemics so explosive?
  • What explains the frequent coincidental timing of epidemics in countries of similar latitudes?
  • Why did epidemics in previous ages spread so rapidly, despite the lack of modern transport?

Hope-Simpson. Epidemiol Infect. 99:5-54;1987
Hope-Simpson’s theory

• “... an unidentified seasonal stimulus, inextricably bound to solar radiation, substantially controls the seasonality of influenza”

Peak Month of Flu Activity 1982-83 through 2011-12, USA

http://www.cdc.gov/flu/about/season/flu-season.htm
Weekly ILI consultation rates in 1992-2010


© ESR 2010
25(OH)D of 22,000 Auckland adults measured at LabPlus, ADHB, between Jan 2002 and Sept 2003

Figure 1. Sine curve of best fit for 25-hydroxyvitamin D (25OHD) versus day of the year by age with measured mean monthly 25OHD for comparison

Note: The error bars represent the standard error of the mean.
What are the proposed mechanisms?

- VDR present in both macrophages and monocytes
- β-defensin and cathelicidin are important anti-microbial peptides in the innate immune system
- Vitamin D up-regulates the production of cathelicidin in the macrophages
- Also up-regulates β-defensin in the endothelial cells
- Vitamin D modulates the production of cytokines, suppressing inflammation
- Vitamin D preserves the integrity of the tight junctions and maintains the mucosal barrier – critical role in innate immunity
- Variations in serum 25(OH)D shown to correlate with monocyte cathelicidin
- Consequently, individuals with low 25(OH)D will be at greater risk of infection

Lui, 2006; Adams, 2009
What does this mean for NZ children?

• In summary:
  • Vitamin D deficient mothers give birth to VDD infants and have insufficient vitamin D in their breast milk
  • VDD (Foetal and post natal) contributes to risk of development of auto-immune conditions in genetically predisposed children
  • Infants and children with 25(OH)D concentrations above 75nmol/l probably have a greatly reduced risk of ARI, and will respond better to treatment