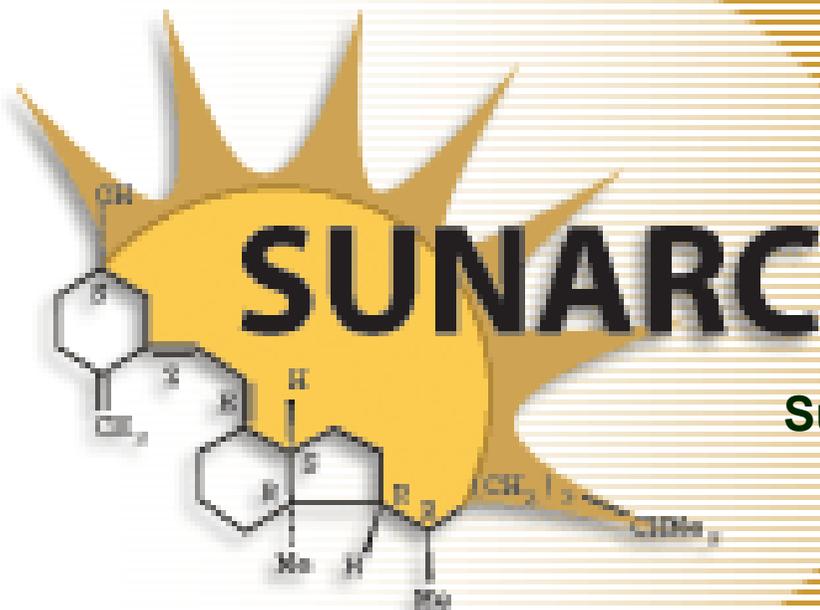


Importance of vitamin D for pregnant women and developing fetuses

A presentation in London
On May 17, 2011

by **William B. Grant, Ph.D.**



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www.vitaminDCouncil.org

Outline

- Overview of pregnancy problems in the UK
- Factors for low vitamin D during pregnancy
- Mechanisms of vitamin D
- Effects of low vitamin D for the mother
- Effects of low vitamin D for the fetus
- Recommendations
- The 100 health conditions study

Overview of pregnancy problems that might be related to vitamin D in the UK

- Anemia: 12% in first trimester, rising to 50% in third trimester
- Cesarean section rates: 13.6% to 31.9%
- Gestational diabetes: 6% (U.S. study)
- Bacterial vaginosis: 3.5% for those without symptoms
- Influenza-like illness during pregnancy: 2%
- Pre-eclampsia rates: 5.2/1000 pregnancies
- Sepsis: 1.13 deaths/100,000 pregnancies

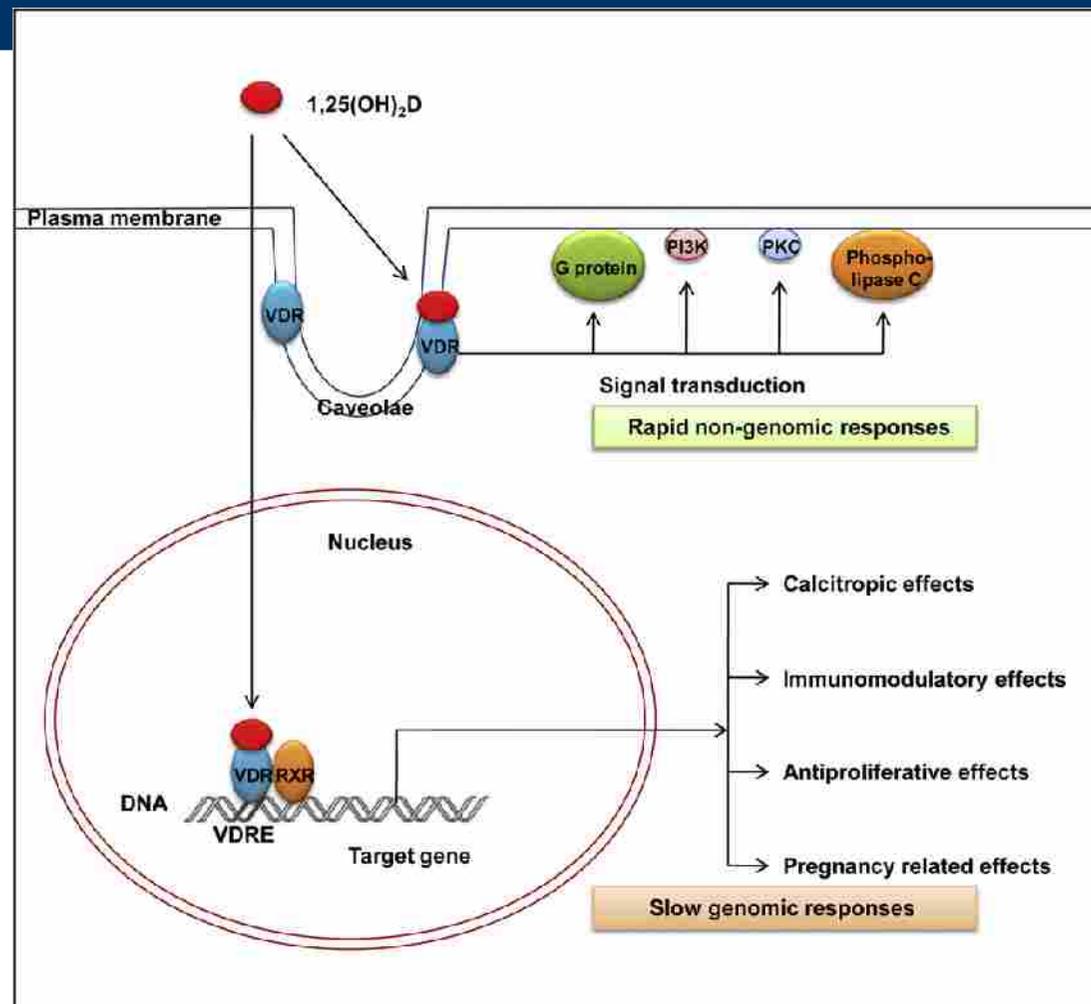
Risk factors for low vitamin D levels during pregnancy

- Obesity
- Dark skin
- Covering up with clothes or sunscreen when in the sun
- No or low vitamin D supplements (Hollis recommends 6000 IU/d)
- Long-term hospitalization during pregnancy
- Recommendation to limit fish consumption due to mercury contamination

Vitamin D mechanisms

- Calcium absorption and metabolism
- Activation of vitamin D receptors, thereby regulating expression of hundreds of genes
- Reducing inflammation and viral infections through effects on cytokine production
- Reducing bacterial infections through induction of cathelicidin and defensins
- Effects on cellular differentiation, proliferation and apoptosis

Genomic and non-genomic responses of vitamin D receptor binding to 1,25(OH)₂D.



Shin et al.
Placenta (2010)

Vitamin D effects on pregnancy and the placenta

- “Production (of 1,25(OH)₂D) thus exceeds clearance and 1,25(OH)₂D levels increase, being two-fold higher in serum of women in the third trimester of pregnancy than in non-pregnant or post-partum women.”
- “Collectively, the data suggest that 1,25(OH)₂D aids implantation and maintains normal pregnancy, supports fetal growth through delivery of calcium, controls secretion of multiple placental hormones, and limits production of proinflammatory cytokines.”
- Shin et al., Placenta, 2010.

How low vitamin D levels impact pregnancy outcomes to mother

- Anemia
- Primary Cesarean section
- Gestational diabetes
- Bacterial vaginosis
- Influenza-like illness during pregnancy
- Pre-eclampsia
- Sepsis
- Risk of diabetes
- Tooth loss

Anemia - 1

- There is rapidly mounting evidence that a primary risk factor for anemia is vitamin D deficiency, in addition to iron deficiency.
- Anemia is defined as any hemoglobin value <11 g/dL in any trimester.
- In my opinion, reduced risk of anemia may be one of the more important reasons to encourage adequate vitamin D levels during pregnancy.

Anemia - study of pregnant women with HIV in Tanzania

- “Women with low vitamin D status had 46% higher risk of developing severe anemia during follow-up, compared to women with adequate vitamin D levels (RR: 1.46; 95% CI: 1.09, 1.96).”
- Vitamin D status had a protective association with HIV disease progression, all-cause mortality, and development of anemia during follow-up in HIV-infected women.”
- Metha et al., J Infect Dis. 2010

Anemia - Intervention study in Los Angeles

- A study in Los Angeles found that increasing serum 25(OH)D levels reduced the requirement for erythropoiesis stimulating agent for chronic kidney disease patients with anemia. In a 4-month study with vitamin D supplements for one group, placebo for the other:
 - “The low-to-normal vitamin D group showed a significant reduction in dose of 24% (1,415 units, $p = 0.025$). The normal-to-low group, however, showed a 22% increase in dose of 1,270 units (NS).” [Lac et al. Clin Nephrol. 2010]

Anemia – study in China

- “The overall prevalence of anemia was 58.6%, ranging from 48.1 to 70.5% in the five areas.
- The prevalence of anemia depended on the level of education: with 52.9, 62.4 and 66.5%, for college, secondary school and primary education, respectively, and the difference was statistically significant ($p = 0.005$).
- Results showed that higher birth weight was associated with Hb concentrations ranging from 90 to 140 g/l, whereas lower birth weight occurred below 80 g/l and above 140 g/l Hb.”
- Ma et al., Med Princ Pract, 2009

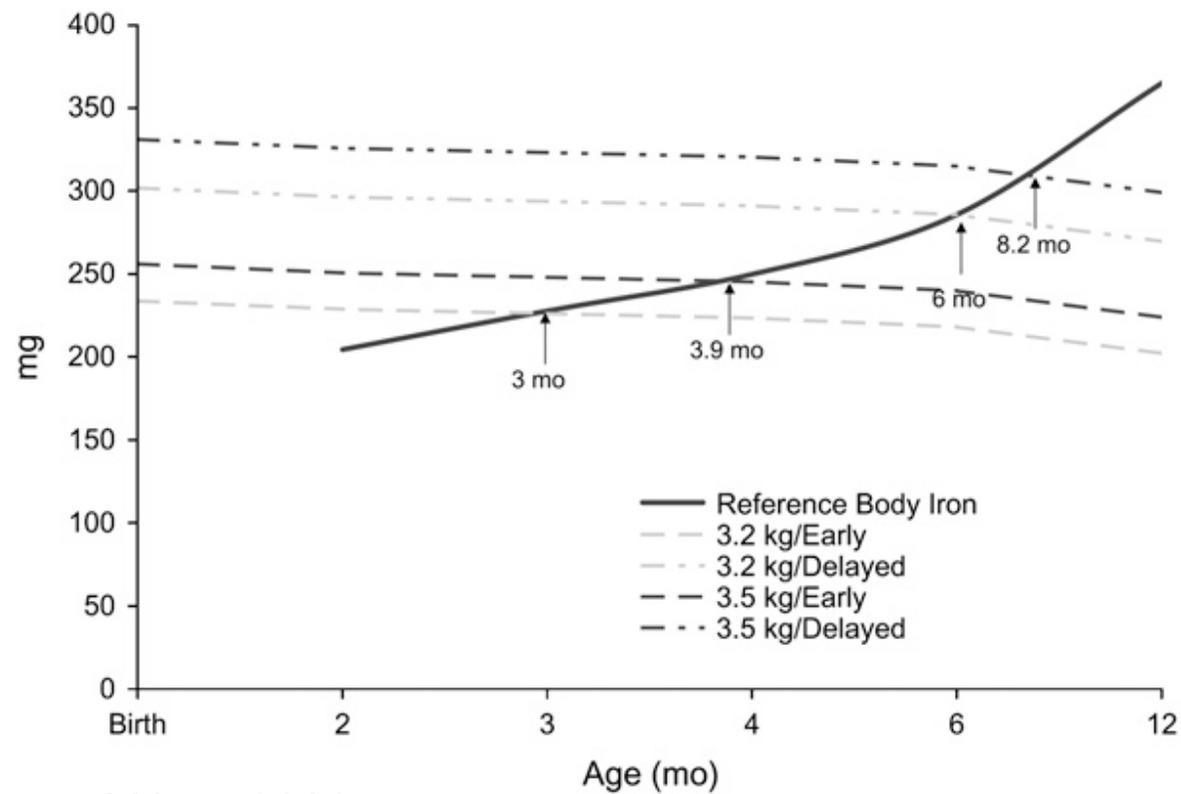
Anemia – study in Burkina Faso - 1

- “An intention-to-treat, double-blind, randomized controlled trial compared 30 mg Fe + folic acid and 13 other micronutrients (UNIMMAP; UNICEF/WHO/UNU multiple micronutrient supplement for pregnant and lactating women) with 60 mg Fe + folic acid (IFA) only in rural Burkina Faso. Home visitors directly observed tablet intake. Mixed-effects models were used for the data analysis.
- At inclusion, 43.2% of the 1268 participants were anemic.”
- Roberfroid, Am J Clin Nutr, 2011

Anemia – study in Burkina Faso - 2

- “On average, the hemoglobin concentration decreased over gestation by 0.019 g/dL (95% CI: 0.012, 0.025 g/dL) per week in the IFA and UNIMMAP groups. An increment in hemoglobin concentration per micronutrient tablet [β (\pm SE) = 0.006 \pm 0.001 g/dL; $P < 0.0001$] was observed only in women who were anemic at inclusion, whereas a decrease was observed in the other mothers (-0.003 \pm 0.001 g/dL; $P = 0.002$, P for interaction < 0.0001); the finding was similar in both the IFA and UNIMMAP groups. Women with baseline anemia achieved the same hemoglobin concentration (mean \pm SD: 11.1 \pm 0.64 g/dL) as their counterparts who received \pm 180 tablets of either UNIMMAP or IFA.”

Iron stores decrease in first year

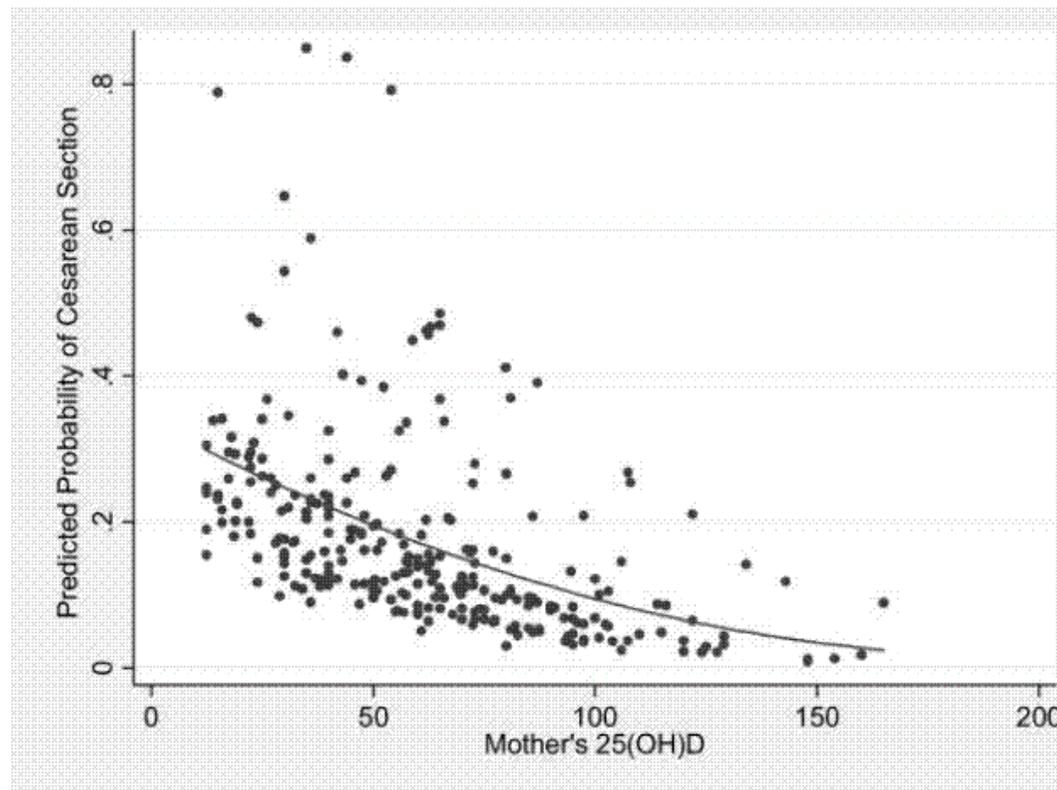


Chapparo, J Nutr. 2008

Primary Cesarean section

- 25(OH)D levels were measured at time of birth.
- There was an inverse association with having a cesarean section and serum 25(OH)D levels. We found that 28% of women with serum 25(OH)D less than 37.5 nmol/L had a cesarean section, compared with only 14% of women with 25(OH)D 37.5nmol/L or greater (P = 0.012).
- In multivariable logistic regression analysis controlling for race, age, education level, insurance status, and alcohol use, women with 25(OH)D less than 37.5 nmol/L were almost 4 times as likely to have a cesarean than women with 25(OH)D 37.5 nmol/L or greater (adjusted odds ratio 3.84; 95% confidence interval 1.71 to 8.62).
- Merewood et al., J Clin Endocrinol Metab. 2009

Primary Cesarean section vs. 25(OH)D

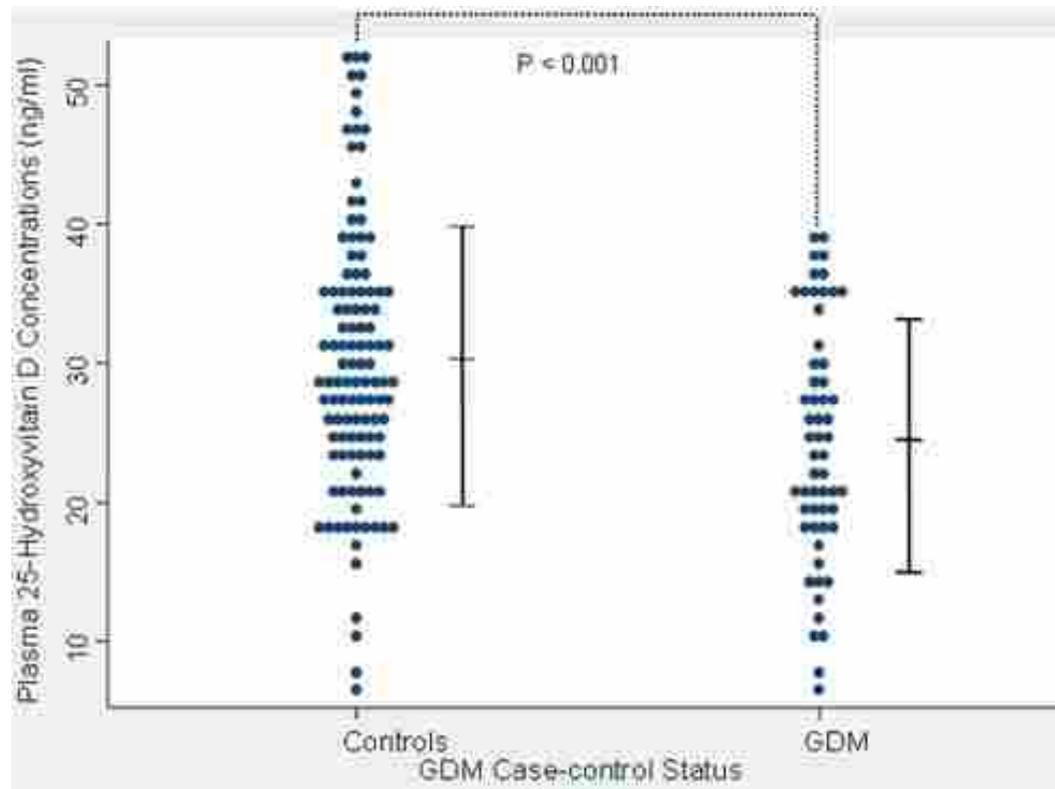


Merewood et al., J Clin Endocrinol Metab. 2009

Gestational diabetes and low 25(OH)D

- “Among women who developed GDM, maternal plasma 25(OH)D concentrations at an average of 16 weeks of gestation were significantly lower than controls (60.5 vs. 75.3 nmol/L, $P < 0.001$).
- Approximately 33% of GDM cases, compared with 14% of controls ($P < 0.001$), had maternal plasma 25(OH)D concentrations consistent with a pre-specified diagnosis of vitamin D deficiency (< 50 nmol/L).
- Each 12.5 nmol/L decrease in 25(OH)D concentrations was related to a 1.29-fold increase in GDM risk (OR (95% CI): 1.29 (1.05-1.60)).”
- Zhang et al., PLoS One, 2008

Gestational diabetes and low 25(OH)D



Zhang et al., PLoS One, 2008

Bacterial vaginosis - 1

- BV appears to be an important cause of infertility [Mania-Pramanik, 2009].
- BV is often associated with preterm delivery and miscarriage, increasing risks by of 2.4 for preterm birth, and 6.6 for miscarriage [Donders, BJOG. 2009].

Bacterial vaginosis - 2

- The first study reporting a correlation between serum 25-hydroxyvitamin D [25(OH)D] levels and prevalence of BV was by Bodnar et al. [2007]:
 - “Prevalence of BV was compared to 25(OH)D levels in the first trimester of pregnancy. While an inverse relation was found between BV and 25(OH)D for black women, no correlation was found for white women.”

Bacterial vaginosis - 3

- In a cross-sectional study in the United States:
- “Vitamin D deficiency was associated with BV only in pregnant women (adjusted odds ratio, 2.87; 95% confidence interval, 1.13-7.28).”
- Hensel, Am J Obstet Gynecol. 2010

Influenza-like illness during pregnancy

- Influenza is largely seasonal due to the annual cycle of solar UVB and vitamin D production [Cannell et al., 2006, 2008]
- Two randomized controlled trials found greatly reduced risk of influenza with 1200-2000 IU/d vitamin D3 [Aloia and Li-Ng, 2007; Urashima et al., Am J Clin Nutr. 2010]
- Pregnant women are at particular risk for influenza, likely due to lower 25(OH)D levels.

Hyperthermia (fever) during pregnancy: risk of birth defects

- “An episode of hyperthermia is not uncommon during pregnancy. The consequences depend on the extent of temperature elevation, its duration, and the stage of development when it occurs. Mild exposures during the preimplantation period and more severe exposures during embryonic and fetal development often result in prenatal death and abortion.”

Fever during pregnancy - 2

- “Hyperthermia also causes a wide range of structural and functional defects. The central nervous system (CNS) is most at risk probably because it cannot compensate for the loss of prospective neurons by additional divisions by the surviving neuroblasts and it remains at risk at stages throughout pre- and postnatal life.”

Fever during pregnancy - 3

- “In experimental animals the most common defects are of the neural tube, microphthalmia, cataract, and micrencephaly, with associated functional and behavioral problems.
- Defects of craniofacial development including clefts, the axial and appendicular skeleton, the body wall, teeth, and heart are also commonly found. Nearly all these defects have been found in human epidemiological studies following maternal fever or hyperthermia during pregnancy.”

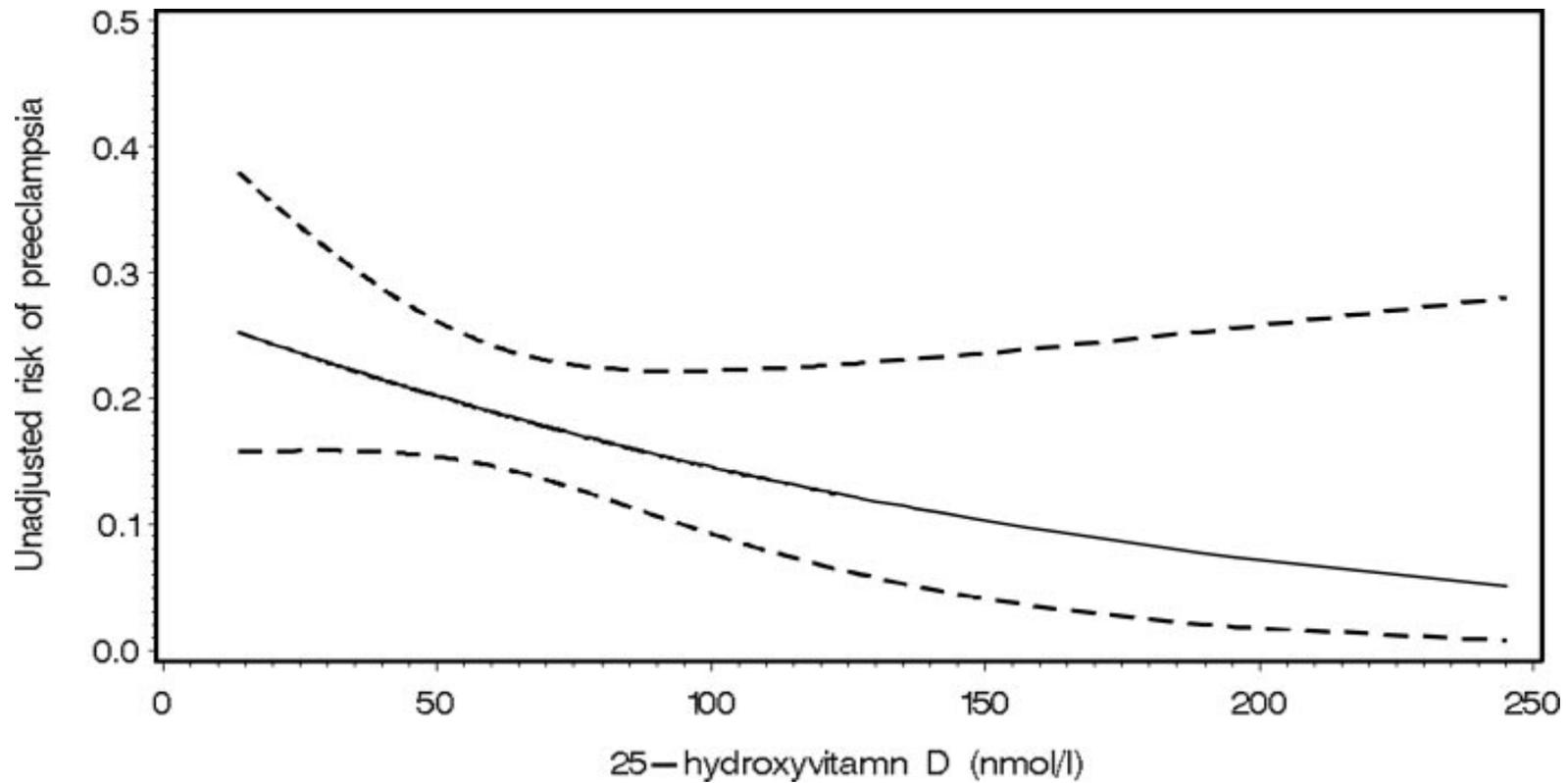
Fever during pregnancy - 4

- “Suggested future human studies include problems of CNS function after exposure to influenza and fever, including mental retardation, schizophrenia, autism, and cerebral palsy.”
-
- Edwards MJ. Birth Defects Res A Clin Mol Teratol. 2006.

Pre-eclampsia

- “Vitamin D has been suggested to affect the balance between T helper (Th1) and (Th2) type cytokines by favouring Th2 domination. We investigated the association between infant vitamin D supplementation and later pre-eclampsia, a disorder suggested to be dominated by Th1 response. We used data on 2969 women born in the Northern Finland Birth Cohort 1966 of whom 68 (2.3%) had pre-eclampsia in their first pregnancy. Risk of pre-eclampsia was halved (OR 0.49, 95% confidence interval (CI) 0.26-0.92) in participants who had received vitamin D supplementation regularly during the first year of life and this association was not affected by adjustment” for numerous factors. “These data suggest that vitamin D intake in infancy may affect long-term programming of the immune response pattern.”
- Hyppönen et al., Eur J Clin Nutr. 2007

Pre-eclampsia vs. 25(OH)D



Bodnar, J Clin Endocrinol Metab. 2007

Sepsis and vitamin D

- “The human cathelicidin LL-37, for example, has modest direct antimicrobial activity under physiological conditions, but has been demonstrated to have potent antiendotoxin activity in animal models, as well as the ability to resolve certain bacterial infections.
- Human epidemiological studies support the role of UVB and vitamin D in reducing risk of sepsis.”
- Mookherjee N, Rehaume LM, Hancock RE. Cathelicidins and functional analogues as antiseptics molecules. *Expert Opin Ther Targets*. 2007 Aug;11(8):993-1004.

Diabetes mellitus - 1

- Vitamin D and calcium reduce the risk of diabetes.
- A Harvard study indicates that vitamin D and calcium work together to reduce the risk of T2DM. Those with a combined daily intake of > 1200 mg calcium and > 800 international units (IU) vitamin D had a 33% lower risk of T2DM compared to those with an intake of < 600 mg calcium and 400 IU vitamin D, respectively [Pittas et al., 2006].
- Similar results were found in Japan [Kirii et al., 2009] and Australia [Gagnon et al., 2011], although only vitamin D was important in Australia.

Diabetes mellitus - 2

- A meta-analysis of incidence of diabetes mellitus types 2 with respect to highest vs. lowest serum 25(OH)D quantile found an odds ratio of 0.57 (96% CI, 0.48-0.68).
- Parker et al., Maturitas, 2010

Diabetes mellitus – study in Birmingham

- “Women with Type 2 diabetes have a less satisfactory pregnancy outcome compared with the general population. Infants have a two-fold greater risk of stillbirth, a 2.5-fold greater risk of a perinatal mortality, a 3.5-fold greater risk of death within the first month and a six-fold greater risk of death up to 1 year compared with regional/national figures. They have an 11 times greater risk of a congenital malformation. We need to develop better educational and screening strategies if we are to improve.”
- Dunne, Diabet Med, 2003

Tooth Loss - 1

- Pregnancy without adequate vitamin D is associated with tooth loss by the mother.
- Vitamin D increases calcium absorption from oral intake, sparing the teeth.
- In addition, vitamin D induces production of cathelicidin and defensins, which fight caries-inducing bacteria.

Teeth – 2 (University of Sheffield, 1928)

- “It is interesting to note that even in sections of teeth in which caries appears to be completely arrested the dental tubules may contain micro-organisms. These, however, are apparently inactive.”
- Mellanby M, Pattison CL. The action of vitamin D in preventing the spread and promoting the arrest of caries in children. Brit Med J. 1928;2,:1079-82.

Overview of fetal problems that might be related to vitamin D in the UK - 1

- Premature delivery: 7%
- Small for gestational age
- Low birth weight: 6-7% (Scotland)
- Rickets: problem for Asians in the UK
- Cardiovascular malformations 5.7 cases per 1000 live births
- Infant heart failure
- Neonatal hypocalcemia and seizures

Overview of fetal problems in the UK that might be related to vitamin D - 2

- Respiratory infections
- Sepsis: 1%
- Craniotabes
- Anemia: 3% (12 mos), 9% (24 mos)?
- Type 1 diabetes mellitus
- Schizophrenia
- Autism: 6 per 1000 births

Premature delivery – Japan

- “Mean 25-OHD levels in spring, summer, fall, and winter were 14.3 ± 5.1 , 15.7 ± 6.4 , 13.7 ± 5.1 , and 13.9 ± 4.2 ng/ml, respectively.” (35.8, 39.3, 34.3, and 34.8 nmol/L)
- “Mothers with threatened premature delivery had significantly lower 25-OHD levels (11.2 ± 3.2 ng/ml) than those in mothers with normal delivery (15.6 ± 5.1 ng/ml).” (28.0 vs. 39.0 nmol/L)
- Shibata, J Bone Miner Metab, 2011

Small-for-gestational age

- “After confounder adjustment, there was a U-shaped relation between serum 25(OH)D and risk of SGA (small-for-gestational age) among white mothers, with the lowest risk from 60 to 80 nmol/L. Compared with serum 25(OH)D 37.5-75 nmol/L, SGA odds ratios (95% CI) for levels <37.5 and >75 nmol/L were 7.5 (1.8, 31.9) and 2.1 (1.2, 3.8), respectively. There was no relation between 25(OH)D and SGA risk among black mothers.”
- Comment: the finding for >75 nmol/L is surprising.
- Bodnar et al., J Nutr, 2010

Cardiovascular malformations – UK study

- “We found that 474 infants (16%) with cardiovascular malformations were born at <37 weeks of gestation, giving an OR for prematurity among infants with a cardiovascular malformation of 2.4 (95% CI: 2.2-2.7). More infants were born preterm with diagnoses of pulmonary atresia with ventricular septal defect (23%), complete atrioventricular septal defect (22%), and coarctation of the aorta, tetralogy of Fallot, and pulmonary valve stenosis (each 20%).”
- Tanner, Pediatrics, 2005

Infant heart failure – UK study

- “A retrospective review from 2000 to 2006 in southeast England. Sixteen infants (6 Indian subcontinent, 10 black ethnicity) were identified: All had been breast fed. Ten presented at the end of the British winter (February-May).
- Six had a cardiac arrest; three infants died. Eight were ventilated, two required mechanical circulatory support and 12 required intravenous inotropic support. Two were referred for cardiac transplantation.
- Median (range) of 25(OH)D 18.5 (0-46) nmol/l (normal range >35) and parathyroid hormone 34.3 (8.9-102) pmol/l (normal range <6.1).”
- Maiya et al., Heart, 2005

Respiratory infections - Turkey

- “During a one-year period, 305 hospitalized children (ages between 0 to 3 years) were evaluated for clinical and biochemical markers of vitamin D deficient rickets and related factors. Twenty-one of them (6.8%) were diagnosed as nutritional vitamin D deficiency and rickets. Most of the children diagnosed were under one year old (16/21, 76.2%). Fourteen vitamin D deficient rachitic children were admitted to the hospital with infectious conditions, and most of them were respiratory tract infection.”
- Tezer et al., Turk J Pediatr, 2009

Craniotabes - Japan

- “RESULTS: Craniotabes was present in 246 (22.0%) neonates, and the incidence had obvious seasonal variations, highest in April-May and lowest in November. At 1 month, 6.9% of them had elevated intact PTH over 60 pg/ml, and 37.3% had 25-OHD less than 25 nmol/L. When separately analyzed according to the method of feeding, 56.9% of breast-fed infants showed 25-OHD less than 25 nmol/L, whereas none of formula/mixed-fed infants did.
- SUMMARY: These results suggest that craniotabes in normal neonates is associated with vitamin D deficiency in utero, and the deficiency persists at 1 month in many of them.”
- Yorifuji, J Clin Endocrinol Metab, 2008

Autism – vitamin D hypothesis

- “Consumption of vitamin D containing fish during pregnancy reduces autistic symptoms in offspring. Autism is more common in areas of impaired UVB penetration such as poleward latitudes, urban areas, areas with high air pollution, and areas of high precipitation. Autism is more common in dark-skinned persons and severe maternal vitamin D deficiency is exceptionally common the dark-skinned.”
- Cannell, Med Hypotheses. 2008

Autism – study in the UK

- “A total of 86 children with ASD were identified in the ALSPAC cohort giving a prevalence of ASD of 61.9 per 10,000. There was some evidence for an excess of children with ASD being conceived during the summer months with a rate per 1,000 conceptions of 9.5 in summer compared to 5.1, 4.6, 5.7 in spring, autumn and winter, respectively. A doubling of the odds was suggested for summer compared to autumn (Odds ratio 2.08 [1.18, 3.70]). In agreement with previous research, there was a corresponding peak in spring births.”
- Hebert, Autism Research, 2010

Summary

- Vitamin D deficiency is common among pregnant women in the UK and elsewhere.
- There are many important health benefits from vitamin D for both mother and fetus.
- Based on a quick review of the literature for vitamin D during pregnancy as well as more detailed review for other diseases, it appears that serum 25(OH)D levels above 75-100 nmol/L are required for good pregnancy outcomes and fetal health and optimal health in general.

Suggestions for further research

- Additional advances can be made regarding vitamin D and pregnancy outcomes by
 - Measuring serum 25(OH)D levels of pregnant women 2-3 times during pregnancy and tracking outcomes as a function of 25(OH)D and other factors
 - Advising pregnant women to increase 25(OH)D levels with supplements and/or UVB irradiance and again noting effects

Additional thoughts

- The most dramatic results in the UK would probably come for those with darker skin and who tend to cover up when in the sun.
- The second most dramatic results might come by targeting those living in the more northern, less-sunny reaches of the UK, such as in Scotland.

Institute of Medicine Report on Vitamin D and Calcium, Nov. 30, 2010 – pregnant, nursing women

Age (years)	RDA Calcium (mg/d)	RDA Vitamin D (IU/d)	Serum 25(OH)D (nmol/L)	UL Vitamin D (IU/d)
14-18	1300	600	50	4000
19-50	1000	600	50	4000

Ross et al., J Clin Endocrin Metab. 2011

And a Scientific Review

- **“Recommendations were restricted to clinical practice and concern adult patients with or at risk for fractures, falls, cardiovascular or autoimmune diseases, and cancer. The panel reached substantial agreement about the need for vitamin D supplementation in specific groups of patients in these clinical areas and the need for assessing their 25(OH)D serum levels for optimal clinical care. A target range of at least 30 to 40 ng/mL (75-100 nmol/L) was recommended. As response to treatment varies by environmental factors and starting levels of 25(OH)D, testing may be warranted after at least 3 months of supplementation.”**
- **Souberbielle et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. Autoimmun Rev. 2010 Sep;9(11):709-15.**

100 Vitamin D-sensitive health conditions project

- I've been writing up the evidence that sunlight and vitamin D affect the risk of 100 types of health conditions.
- Scientific documents and patient friendly summaries for 75 health conditions will be online May 18, 2011 at www.VitaminDCouncil.org.
- Dr. John Cannell is the director of this organization.

Additional Resources

- <http://www.grassrootshealth.net/>
- <http://www.healthresearchforum.org.uk/>
- <http://www.pubmed.gov>
- <http://www.sunarc.org/>
- <http://www.vitamindcouncil.org/>

- For a copy of this presentation,
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