Vitamin D
Part III
Perinatal applications.

By Heidi Fritz, ND

INTRODUCTION

This is the third in a series of articles reviewing the clinical applications of vitamin D. Previous installments have reviewed nomenclature and physiology, applications in infectious disease and autoimmunity, depression, and cardiovascular disease. This article focuses on perinatal use of vitamin D during pregnancy, breastfeeding, and infancy, and reviews current recommendations.

PREVALENCE OF DEFICIENCY

Vitamin D deficiency/ insufficiency among Canadian pregnant women is rampant. Up to 89% of pregnant women in Newfoundland and Labrador are vitamin D insufficient and 6.6% are deficient during the winter, while 64% are insufficient and 1.7% are deficient during the summer (Sloka 2009). In the northern US (Pittsburg), a latitude close to the southern parts of Canada, 5% and 42.1% of white women and 9.7% and 56.4% of white infants, respectively, have been found to be vitamin D deficient [defined in this study as 25(OH)D<37.5nmol/L] and insufficient [25(OH)D 37.5-80nmol/L] at delivery (Bodnar 2007). These numbers were even higher in black women and infants, and similar results were found at <22 week gestation (Bodnar 2007).

These figures are alarming given the potential protective effects of vitamin D and risks of hypovitaminosis consistently reported in the literature.

OUTCOMES

Between three and five percent of pregnancies are complicated by pre-eclampsia, a serious condition presenting as hypertension accompanied with proteinuria; preeclampsia is thought to be due in part to certain immunological perturbations (Laresgoiti-Servitje 2010, Roberts 2001). Controlled trials with vitamin D have demonstrated a protective effect against preeclampsia. Administration of an estimated 900IU as part of a complex vitamin and fish oil combination was associated with a 31.5% reduced risk of preeclampsia (95% CI 11-47%, P=0.0047) (Olsen 1990). Marya et al. (1987) found that 1,200 IU/d of vitamin D with 375mg calcium non-significantly reduced incidence of preeclampsia (6 vs 9% in controls, respectively). Observational evidence has yielded mixed results.

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Table 1. Impact of Vitamin D on Infant Health: Observational Studies

Reference	Design	Outcomes
Atopy		
Erkkola 2009	Population based birth cohort: N=1,669 children with HLA-DQB1-conferred susceptibility to type I diabetes were studied for associations between incidence of allergic rhinitis and atopic eczema at age 5 and maternal intake of vitD during pregnancy.	Maternal intake of vitD from food was negatively related to risk of asthma, HR 0.80 (95%CI 0.64-0.99) and allergic rhinitis, HR 0.85 (95%CI 0.75-0.97). VitD supplements alone at a mean intake of 1.4mcg or 56 IU/d were not associated with either outcome.
Devereux 2007	UK birth cohort: N=2,012 mother-child pairs included for analysis of vitD intake during pregnancy and development of asthma by age 5.	The highest quartile of vitD intake was associated with ↓risk of "ever wheeze" (OR 0.48, 95%CI 0.25-0.91), with similar findings for wheeze in the previous year, and persistent wheeze. Lower maternal vitD intake was also associated with ↓bronchodilator response (P=0.04).
Camargo 2007	Project Viva prebirth cohort in Massachusetts, N=1,194 mother-child pairs. Maternal intake of vitD was studied for associations with recurrent wheeze at age 3.	The highest quartile (724 IU) had ↓risk of having a child with recurrent wheeze compared with the lowest quartile (356 IU), OR 0.39, 95%CI 0.25-0.62). Every 100 IU increase was associated with 18-19% ↓risk, regardless of source, diet or supplemental.
Multiple sclerosis		
Bayes 2010	Retrospective study of 1,309 Scottish MS patients compared with national (N=6,198,352) and regional (N=664,447) controls.	Excess MS births occur in the spring months, with 22% more than expected based on comparison with non-MS populations (P<0.0001). Fewer MS births occurred in autumn, with 16% fewer births compared with regional controls (P=0.01).
Salzer 2010	Case control study of 9,361 cases and 12,116,853 controls from the Swedish population.	Significantly more (11%) cases with MS than expected were born in June (p<0.05). More (5%) cases of MS than expected were born in February-July vs August-January.
Willer 2005	Retrospective cohort of 17,874 Canadian patients and 11,502 British patients with multiple sclerosis, and population controls. Data pooled with datasets from Denmark and Sweden.	In the pooled analysis, significantly fewer (8.5%) people with MS were born in November and significantly more (9.1%) were born in May. The effect of month of birth was most evident in Scotland, where MS prevalence is highest.
Type I Diabetes		
Hypponen 2001	Finnish Birth Cohort, N=10,366 children born in 1966 were studied for an association between vitD supplementation during the first year of life and risk of type I diabetes by 1997.	Risk of type I diabetes ↓88% among those who received regular supplementation vs no supplementation, adjusted RR 0.12 (95%CI 0.03-0.51). Those who regularly took 2,000 IU daily had 78% ↓risk, RR 0.22 (0.05-0.89). Those suspected of having rickets had drastically ↑risk, RR 3.0 (1.0-9.0).
Brekke 2007	All Babies in Southeast Sweden (ABIS) Cohort, N=11,081 included in analysis at 1 year, 8805 at 2.5 years. Investigated for association between supplementation of vitD in pregnancy and infancy (recommended dose = 400 IU/d) and risk of diabetes measured by autoantibodies against glutamic acid decarboxylase (GADA) and islet antigetn-2 (IA-2) in offspring at 1 and 2.5 years.	Supplementation with this dose was not associated with autoantibodies at 1 or 2.5 years. Use of vitD in pregnancy was associated with ↓diabetes related autoimmunity at 1 year but not 2.5 years: AOR 0.707, 95%CI 0.520-0.962).

"Higher levels of maternal vitamin D have been associated with improved fertility, lower risk of gestational diabetes, lower risk of Cesarean section, and improved birth outcomes such as birth weight and early growth."

Higher levels of maternal vitamin D have been associated with improved fertility (Ozkan 2009), lower risk of gestational diabetes (Zhang 2008), lower risk of Cesarean section (Merewood 2009), and improved birth outcomes such as birth weight and early growth (Maxwell 1981, Morley 2006). Of note, one study found that follicular fluid 25(OH)D concentrations were an independent predictor of the success of IVF in infertile women (Ozkan 2009). After adjusting for age and BMI, each ng/ml increase in follicular fluid 25(OH)D increased the likelihood of clinical pregnancy by 7%, and follicular fluid 25(OH) D was well correlated with serum levels (Ozkan 2009). It was hypothesized that vitamin D may improve ovarian steroidogenesis or benefit endometrial receptivity.

Supplementation of vitamin D and/or higher vitamin D levels in infancy may also reduce risk of adult disease. See Table 1. Prospective studies have shown that supplementation with up to 2,000 IU vitamin D daily during the first year of life reduces risk of type 1 diabetes by 78% (Hypponen 2001), schizophrenia by 77% (McGrath 2004), and preeclampsia in adulthood by 51% compared to unsupplemented infants (Hypponen 2007).

Observational evidence suggests that newborns with lower 25(OH)D are more likely to be affected by acute lower respiratory tract infections in hospital (Karatekin 2009). Infants born to women with higher intake of vitamin D have lower risk of developing asthma, wheeze, and allergic rhinitis compared to those with lower intakes (Camargo 2007, Devereux 2007, Erkkola 2009).

With respect to multiple sclerosis (MS), a consistent association has been found between MS and increased frequency of spring births (when body stores of vitamin D are lowest) and lower frequency of fall births (when body stores are highest) (Bayes 2010, Salzer 2010, Willer 2005), suggesting a gene-environment interaction between vitamin D status in utero/at birth and expression of MS.

PERINATAL VITAMIN D PHYSIOLOGY

In utero, the major contributor to fetal vitamin D status is maternal circulating 25(OH)D; although the precursor cholecalciferol (vitD3) is able to cross the placenta, it is present in relatively low concentrations in both maternal and fetal circulation. The active form of vitamin D, 1,25(OH)2D, does not cross the placenta; however, 1α-hydroxylase present in the placenta is able to synthesize it from 25(OH)D. (Greer 2008)

After birth, infant status depends almost entirely on delivery from breastmilk, formula, or oral supplementation, especially given recommendations for limited sun exposure. Formula is fortified with approximately 400 IU/L vitamin D. The vitamin D activity of human milk – sometimes termed "antirachitic acitivity" – is measured as a combination of vitamin D metabolites, including vitamin D2 (ergocalciferol), vitamin D3 (cholecalciferol), 25(OH) D2, and 25(OH)D3 (Taylor 2008). Levels of 1,25(OH)2D are insignificant.

Cholecalciferol is the major contributer to the vitamin D activity of breastmilk: the concentration of 25(OH)D in milk is approximately 1% that of circulating maternal levels, while the concentration of cholecalciferol is 20-30% of maternal levels (Taylor 2008). Given the prevalence of maternal inadequacy, breastmilk has been found to contain approximately 22 IU/L according to one estimate (Greer 2008). For this reason, breastmilk is no longer considered an adequate source of vitamin D for infants, and several medical bodies have issued recommendations for supplementation of all breastfed infants.

CURRENT RECOMMENDATIONS

INFANCY

Following the report of 104 confirmed cases of rickets in Canada between 2002-4, the Canadian Pediatric Society (CPS) now recommends that "Total vitamin D intake from all sources during the first year should be 200 IU/day in the premature infant (recommendation grade A) and 400 IU/day in the full-term infant, with an increase to 800 IU/day from all sources between October and April north of the 55th parallel (approximate latitude of Edmonton) and between the 40th and 55th parallel in individuals with risk factors for vitamin D deficiency other than latitude alone (recommendation grade B)" (2007). The CPS also points out that since vitamin D requirements depend in part on weight, and infant weight triples within the first year of life, infant requirements may increase even within the first year. For instance, requirements may reach 1,200 IU by 18 months if the child is 12kg (2.µg/kg/d). Evidence seems to support general use of 400 IU daily to achieve adequate levels (>80nmol/L) in many infants, though certain populations and older infants may require more. See Table 2.

MATERNAL: PREGNANCY & BREASTFEEDING

The CPS recommends supplementation of 2,000 IU of vitamin D3 for pregnant and lactating mothers, with suggestion that up to 4,000 IU may be required. Wagner, Taylor, and Hollis have conducted several studies investigating optimal dosing of vitamin D in pregnancy and lactation, and have published a thorough review on the topic (Taylor 2008). Findings of their review indicate that up to 6,400 IU per day is required to achieve optimal vitamin D status in these women.

RCTs have consistently found 2,000 and 4,000 IU doses more effective in raising maternal and infant vitamin D levels compared to lower doses; however in some studies even these doses have not been sufficient to reverse inadequacy. In a study of women given vitamin D as 2,000 IU per day or 60,000 IU per month, only 30% of subjects achieved serum 25(OH)D ≥50nmol/L after three months (Saadi 2007).

A randomized, controlled trial of breastfeeding mothers supplemented with 6,400 IU of vitamin D3 for six months found that the vitamin D levels found in their breast milk

Table 2. Dosing: Effect on Maternal and Infant 25(OH)D Status

Reference	Design	Dose	Outcomes
		Supplementation to Mothers	
Saadi 2009	RCT: 90 breastfeeding mothers in the Middle East received one of two dosages of vitD2.	1. 2,000 IU daily 2. 60,000 IU/ mo vitD2 All infants received 400 IU/d of vitD2 x3 months.	Serum 25(OH)D concentrations at 3 months ↑significantly from baseline in infants of mothers in group 1 (13.9 vs. 49.6nmol/L, P<0.0001) and group 2 (13.7 vs. 44.6nmol/L, P<0.0001). Milk antirachitic activity ↑from undetectable (<20 IU/L) to a median of 50.9 IU/L. These results reflect a threefold ↑in infants' serum 25(OH)D and a 64% ↓in the prevalence of vitamin D deficiency.
Saadi 2007	RCT in 178 healthy lactating and nulliparous Arabian women given vitD2.	One of two schedules: 1. 2,000 IU vit D2/ d 2. 60,000 IU vitD2/ mo x 3 mo.	25(OH)D at 3 mo was significantly ↑than baseline in both lactating and nulliparous women (P<0.001 for both). However, only 21 of 71 (30%) women achieved 25(OH)D ≥50nmol/L at endpoint.
Wagner 2006	RCT: 19 fully lactating American women 1-month postpartum were given high dose vitD or 400 IU.	All mothers received a prenatal vitamin containing 400 IU vitD3, plus: 1. placebo 2. 6,000 IU vitD3 x 6mo. Infants of mothers in the control group only received 300 IU/ day.	At 6 months, serum 25(OH)D was 58.5 ng/mL in the high dose group, compared to 38.4ng/mL in the low dose group. Mean milk antirachitic activity in the high dose group increased to 873 IU/L (P<0.0003), versus 76.3 IU/L in the low dose group. Infants whose mothers were given high dose vitD were similar to infants who were directly given 300 IU/d x 6mo: 43ng/ml in the direct supplementation group versus 46ng/ml in the high dose maternal supplementation group. The rate of increase was similar in both groups.
Hollis 2004, Basile 2006	RCT in 25 fully breastfeeding mothers given vitD optimal vitamin D status, serum 25(OH)D ≥ 80nmol/L.	1. 2,000 2. 4,000 IU/day vitD3 + vitD2 x months 1-3 postpartum	25(OH)D ↑from 1 to 4 months in both groups: +11.5 +/- 2.3ng/ml for the 2,000 group, and +14.4 +/- 3.0ng/ml for the 4,000 group. The 4,000 IU/day regimen was more effective than 2,000 IU, however (P=0.03). In the pilot study (Hollis 2004), antirachitic activity of milk from mothers receiving 2,000 IU/d vitamin D increased by 34.2 IU/L, on average, whereas the activity in the 4,000 IU/d group increased by 94.2 IU/L. No adverse effects.
		Supplementation to Infants	
Wagner 2006	See above.		
Wagner 2010	Subanalysis of ongoing RCT involving 54 infants in the control group.	All infants in this analysis were given 400 IU/d vitD3 x 6mo, starting at 1 month.	Mean 25(OH)D levels in infants given 400 IU/d ↑ significantly from 16.0 +/-9.3ng/ml to 43.6 +/-14.1 at 4 months (P<0.0001) and remained relatively unchanged at month 7: 42.5 +/-12.1ng/ml.
Zeghoud 1994	RCT: 60 healthy infants were given one of 3 dosages of vitD3 from birth to 6-9 mo.	One of 3 dosages: 1. 2.5mg (100,000 IU) x 3 doses at birth, 3, and 6 mo 2. 5mg (200,000 IU) x 1 dose at birth 3. 15mg (600,000 IU) x 1 dose at birth	Two wk after a first dose of 15, 5, or 2.5 mg, 25(OH)D concentrations reached 307 +/- 160, 150 +/- 55, and 92 +/- 42nmol/L, respectively. Hypervitaminosis D (>300nmol/L at 2 weeks, >120 at 6 mo) was found in 50% of the children given 15mg, but not in the other infants. Serum calcium transiently ↑2 wk after 15mg but not after the lower doses.
Zeghoud 1997	RCT: Infants were assigned to receive one of two dosages of vitD2 from birth to 3 mo.	1. 500 IU 2. 1,000 IU vitD2/d in addition to fortified formula (~400 IU vitD3/L)	Infants without vitamin D deficiency showed similar changes in their serum calcidiol on either dose. In contrast, infants with subclinical vitamin D deficiency (25(OH)D ≤30nmol/L and iPTH ≤60ng/L) had normalized serum PTH within 1 mo only when they were given 1000 IU/d in addition to their formula.

were increased to 873 IU/L, maternal serum 25(OH)D was increased to 58.8ng/ml, and the serum 25(OH)D levels of infants was equal to that of the infants who had received direct oral supplementation of 300 IU per day (Wagner 2006). This level of maternal supplementation showed no toxic effects and provided adequate vitamin D to nursing infants without needing to supplement the infant (Wagner 2006). Use of 6,400 IU is clearly more appropriate for maternal supplementation than the lower studied doses.

CONCLUSION

Vitamin D deficiency/insufficiency is widespread among Canadian pregnant women and their infants. Maternal and infant supplementation of vitamin D is necessary to maintain adequate levels, and this has been shown to protect against preeclampsia, type I diabetes, and schizophrenia. The minimum recommended dose for infants is 400-800 IU daily, while breastfeeding women appear to require upwards of 6,000 IU daily. These doses have not been associated with any serious adverse effects.

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