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ROLE OF VITAMIN D IN PREGNANCY – A Review

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ABSTRACT

Vitamin D has traditionally been viewed as a fundamental hormone in the regulation of phosphorus and calcium and bone metabolism. In recent years, the discovery of a new world of extra skeletal and particularly immune modulator effects renewed the interest of research on vitamin D. In the present experiment we are studying the role of vitamin D in pregnancy.

***Keywords*:** Vitamin D , Calcium levels

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INTRODUCTION

Vitamin D, synthesized in the skin, enters the circulation bound to vitamin D-binding protein. Dietary vitamin D2 or D3 enters the circulation through lymphatic system. Subsequently both vitamins D2 and are metabolized similarly In the liver, vitamin D is metabolized by vitamin D-25-hydroxylase to form 25-hydroxyvitamin D J25(OH)d3. The enzyme is located in the mitochondrial and microsomal fractions of the hepatic cells (Ponchon and De Luca, 1969; De Luca, 1984).

There are two forms of vitamin D. Vitamin D3 (cholecalciferol) is produced from the conversion of 7-dehydrocholesterol in skin and vitamin D2 (ergocalciferol) is produced in mushrooms and yeast. The biologically active form of vitamin D is 1,25(OH)2D. This requires hydroxylation of vitamin D in the liver to 25(OH)D (25-hydroxyvitamin D), which then undergoes renal hydroxylation to form 1,25(OH)2D. Although 25(OH)D has low biological activity, it is the major form of circulating vitamin D. Serum 25(OH)D concentrations are generally thought to reflect nutritional status. Production of 1,25(OH)2D in the kidney is tightly regulated by plasma parathyroid hormone (PTH) as well as serum calcium and phosphate levels. The interaction of 1,25(OH)2D with nuclear vitamin D receptors influences gene transcription. Nuclear receptors for 1,25(OH)2D are present in a range of tissues including bone, intestine, kidney, lung, muscle and skin. Similar to steroid hormones, 1,25(OH)2D acts via signal transduction pathways linked to vitamin D receptors on cell membranes. Major sites of action include intestine, bone, parathyroid, liver and pancreatic beta cells. Its biological actions include increases in intestinal calcium absorption, transcellular calcium flux and opening gated calcium channels allowing calcium uptake into cells such as osteoblasts and skeletal muscle. The biological effects of 1,25(OH)2D are diverse. It inhibits PTH secretion and adaptive immunity, while promoting insulin secretion and innate immunity. It also inhibits cell proliferation and stimulates their differentiation. The largest source of vitamin D in adults is synthesis from solar radiation; half an hour of sunlight delivers 50 000 iu of vitamin D with white-complexioned skin.3 Dietary intake of vitamin D makes a relatively small contribution to overall vitamin D status as there is little vitamin D that occurs naturally in the food supply. Melanin absorbs ultraviolet B (UVB) from sunlight and diminishes cholecalciferol production by at least 90%.5 Dietary vitamin D is absorbed from the intestine and circulates in plasma bound to a vitamin D binding protein. Pre-eclampsia and neonatal hypocalcaemia are the most prevalent complications of maternal hypocalcaemia and are clearly associated with substantial morbidity. A statistical association of glucose intolerance and hypovitaminosis D has been demonstrated. Maternal vitamin D is important to fetal bone development.6,7 Fetal lung development and neonatal

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immune conditions such as asthma may relate in part to maternal vitamin D levels. Although it is not clear whether maternal vitamin D supplementation will prevent these conditions, a strategy for supplementation and treatment of maternal vitamin D deficiency is proposed.

Circulating osteocalcin level (Zerwekh et al., 1985). In the past, human milk was thought to be an adequate source of antirachitic activity for neonates and growing infants. Even before the discovery of vitamin D, McCollum et al (7) and Park (8) stated that rickets was attributable to the lack of sunlight and a dietary factor X. They observed that factor X was found in "good breast milk" and cod liver oil and that, although rickets did develop among breast-fed children, it was rarely as severe as that among artificially fed infants. Those investigators did not know that the source of vitamin D in the mother's milk was the mother's exposure to the sun, which cutaneously generated large amounts of vitamin D. Early attempts to quantify the antirachitic potential in human milk were crude and yielded little information. Specker et al (13) determined that the antirachitic content of human milk was lower among African American than white mothers. If a lactating mother has limited sun exposure and/or limited vitamin D intake (such as occurs with the current 400 IU DRI), then the vitamin D content of her milk is poor, especially if she has darker pigmentation.

In the present paper we are discussing the role of Vitamin D in pregnancy.

MATERIALS AND METHODS

Low maternal vitamin D intake in pregnancy is associated with wheeze and asthma in the offspring.49 Low cord blood 25(OH)D concentrations have been associated with respiratory syncytial virus bronchiolitis50 and respiratory infections.51 There are plausible physiological mechanisms for an association between prenatal vitamin D status and immune development. The metabolite 1,25(OH)2D has been shown in animal and in vitro models to have an immune-modulatory role and low levels of neonatal vitamin D have been linked to childhood asthma.49,52 Maternal vitamin D supplementation is associated with cord blood gene expression of tolerogenic immunoglobulin such as immunoglobulin-like transcripts 3 and 4 (ILT3 and ILT4).53 Cord blood 25(OH)D is correlated with mononuclear cell release of IFN-γ and hence Th1 cell development.54 More research is needed on the potential association between maternal vitamin D in fetal lung development and childhood allergy; there are ongoing studies investigating long-term neonatal putative benefits of adequate maternal vitamin D.Prolactin has been suggested as one of such hormones (Mainoya, 1978).In vitro prepration (Kostial et al . , 1969a; Kostial et al.,1979b; Toverud et al.,1976) have confirmed the increased intestinal calcium absorption in lactating rats. In the studies of Fournier and Susbielle (1952) when the diet contained 100 mg calcium per day, calcium absorption in lactating rats was 50% of the dietary intake as compared to 10% in controls. When the dietary calcium

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was reduced to 27mg/day, the intestinal absorption of calcium was almost 100%. Increased intestinal calcium absorption may be attributed to the increased level of plasma l,25(OH)2D in view of the well known action of the hormone on-calcium binding protein synthesis. However, the intestinal calcium absorption remains high even in vitamin D deprived lactating rat (Toverud et al.,1978). Halloran and De Luca (1980b) studied the intestinal calcium absorption by everted gut sac technique. Duodenum sac of the lactating rat which had been deprived of vitamin D for long time (and had undetectable circulating levels of 25(OH)D and l,25(OH)2D) showed significantly higher calcium absorption than the duodenum sac of a non-lactating rat. It may be added that the duodenum sac of a vitamin D replete lactating rat showed still higher calcium absorption. From these experiments it has been concluded that while vitamin D is important for the increased active transfer of calcium in the intestine during lactation, there is also a vitamin D independent component of active transfer associated with pregnancy and lactation.

DISCUSSION

While scanning the literature on intestinal calcium absorption in lactating women it may be pertinent to note the species difference in calcium metabolism. In the rat the calcium requirement of the fetus is almost negligible as compared to the calcium requirement during lactation, while the daily fetal calcium requirement in the last two months of human pregnancy usually exceeds the amount of calcium secreted in the milk (Spray, 1950). This fact may explain why firm evidence for enhanced calcium' absorption from the intestine in lactating women is not available. Some studies have revealed enhanced calcium absorption in the later months of pregnancy but no further increase during lactation (Heaney and Skillman, 1971).

Daily vitamin D supplementation with oral cholecalciferol or ergocalciferol is safe in pregnancy. The 2012 recommendation from UK Chief Medical Officers and NICE guidance state that all pregnant and breastfeeding women should be informed about the importance of vitamin D and should take 10 micrograms of vitamin D supplements daily.56,57 Particular care should be taken over high-risk women. The recommendations are based on the classical actions of vitamin D, although many of the nonclassical actions of vitamin D may be beneficial. As mentioned above, the review and meta-analysis by Aghajafari et al. found associations between vitamin D insufficiency and risk of gestational diabetes, pre-eclampsia, bacterial vaginosis and SGA infants.16 Of course this does not necessarily demonstrate that correction during pregnancy will reduce these risks. Three categories of vitamin D supplementation are recommended. 1. In general, vitamin D 10 micrograms (400 units) a day is recommended for all pregnant women in accord with the national guidance.56 This should be available through the Healthy Start programme.58 2. High-risk women are advised to take at least 1000 units a day (women with increased skin pigmentation,

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reduced exposure to sunlight, or those who are socially excluded or obese).1,59 The RCOG has highlighted the importance of addressing suitable advice to these women.60 Women at high risk of pre-eclampsia are advised to take at least 800 units61 a day combined with calcium.62 Vitamin D may be inappropriate in sarcoidosis (where there may be vitamin D sensitivity) or ineffective in renal disease. Deficient renal 1-a hydroxylation necessitates the use of active vitamin D metabolites, such as 1a-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol. Specialist medical advice should be sought in such cases. The limitation to therapy compliance mostly relates to the calcium which has a side effect of tasting of chalk, rather than the vitamin D element of oral therapy. It is often more appropriate to give vitamin D alone for patient acceptability. However, this is limited by the availability of suitable agents; vitamin D cannot be prescribed at low doses without calcium. 800-unit formulations of cholecalciferol without calcium are available (e.g. Fultium-D3®, Internis, London; Desunin®, Meda, Bishop's Stortford, UK). There may be particular benefits of vitamin D/calcium supplementation in women at risk of pre-eclampsia.62,63 3. Treatment. For the majority of women who are deficient in vitamin D, treatment for 4–6 weeks, either with cholecalciferol 20 000 iu a week or ergocalciferol 10 000 iu twice a week, followed by standard supplementation, is appropriate.64,65 For women who require short-term repletion, 20 000 iu weekly appears to be an effective and safe treatment of vitamin D deficiency. A daily dose is likely to be appropriate to maintain subsequent repletion (1000 iu daily). In adults, very high doses of vitamin D (300 000–500 000 iu intramuscular [IM] bolus) may be associated with an increased risk of fractures and such high doses are not recommended in pregnancy. A 2011 study demonstrated that supplemental doses of 4000 iu cholecalciferol a day were safe in pregnant women and most effective compared to the lower doses.66Many studies have,, although revealed the improvement in intestinal calcium absorption in a lactating woman after vitamin D supplementation (Toverud and Toverud, 1931; Liu et al.,1937) . We have been able to identify only 3 prospective studies that examined vitamin D supplementation during lactation. Greer and Marshall (Greer and Marshall ., 1989) found that exclusively breastfed white infants nursed during the winter in a northern climate maintained a "minimally normal" vitamin D status for a period of 6 mo. It should be noted, however, that the circulating 25(OH)D concentrations among the breastfeeding infants declined as the study progressed, as noted in our own study. This decline occurred despite a maternal vitamin D intake of ~700 IU/d. A Finnish study showed that maternal supplementation with 1000 IU/d vitamin D resulted in a "minimal" increase in circulating 25(OH)D concentrations among nursing infants (Ala-Houhala ., 1985). The same investigators performed a similar study with 2000 IU/d maternal supplementation and found that the

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nursing infants' vitamin D status improved significantly (Alq Houhala et al.,1986). The increase in maternal circulating 25(OH)D concentrations during the 4-mo study period averaged 23 ng/mL. Supplementation with high-dose vitamin D for mothers resulted in increases in circulating 25(OH)D concentrations that were completely attributable to increased $25(OH)D_2$ concentrations .This increase was more pronounced among mothers who received 3600 IU/d vitamin D_2. A similar profile was observed for circulating vitamin D_2 It is of interest that, in both groups, circulating $25(OH)D_3$ concentrations decreased although the mothers were receiving 400 IU/d vitamin D_3. This observation reinforces the uselessness of a 400 IU DRI for adults. It is important to note that, while the mothers received 4000 IU/d vitamin D for a period of 3 mo, maternal 25(OH)D concentrations were elevated to and remained in a normal healthy range. Again, no adverse side effect was observed.

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