EFFECT OF HYPO AND HYPER VITAMIN D LEVEL DURING PREGNANCY ON REPRODUCTIVE FUNCTION

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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 and effect of vitamin D such as Hypo/Hyper in pregnancy.

Keywords: Vitamin D , Calcium levels , Hypovitaminosis and Hypervitaminosis

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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 D3 are metabolized similarly in the liver, vitamin D is metabolized by vitamin D-25-hydroxylase to form 25-hydroxyvitamin D $\Delta^{25}(\text{OH})d3$. The enzyme is located in the mitochondrial and microsomal fractions of the hepatic cells (Ponchon and De Luca, 1969; De Luca, 1984).

Liu and Chu (1943) described in detail the effects of vitamin D deficiency in pregnancy. The clinical, biochemical, radiological and histopathological features of osteomalacia seen in pregnant and lactating women (Fourman and Royer, 1968) are too well known to warrant repetition. In babies born to such mothers neonatal hypocalcemia (Cockburn et al., 1980) or even congenital rickets have been reported (Maxwell et al., 1939; Liu et al., 1940; Snapper, 1956). The possible role of vitamin D in reproductive function has attracted attention only recently. Sunde et al. (1978) observed abnormal embryonic development of chicks when hens were put on vitamin D deficient diet. Henry and Norman (1978) studied the effect of administration of vitamin $1,25,(\text{OH}^\Delta^\Delta)$ and $24,25(\text{OH})2\text{D3}$ in hens. Eggs from hens receiving $1,25(\text{OH})2\text{D3}$ or $24,25(\text{OH})2\text{D3}$ alone were virtually incapable of hatching. Normal egg hatch-ability was seen only in hens receiving either the parent vitamin D or both of its dihydroxylated metabolites. Halloran Halloran and De Luca (1980a) maintained weanling female rats on vitamin D-deficient diet. Such animals showed poor growth and hypocalcemia as compared to vitamin D replete rats. It was found that the likelihood of vitamin D deficient rats becoming pregnant was roughly one half as great as in the vitamin D replete females. Moreover even when the rats became pregnant, only 40% of the vitamin D deficient females reached full term and gave birth to normal litter as compared to 80% incidence in vitamin D replete female rats. Moreover mean litter size was 7.8 in vitamin D deficient females as compared to 11.2 in vitamin D replete rats. Mean birth weight of each pup was however similar in the two groups.

Histological examination of the fetal tissues did not reveal any abnormality in the liver, kidney, brain, or spleen. Examination of the fetal bones, however, revealed a slight yet significant increase in the amount of osteoid in trabecular bone surfaces (Miller et al., 1982). Vitamin D deficiency during pregnancy seems to cause adverse effects in the offspring that become more evident during the postnatal life. Brommage and Neuman (1981) have observed growth retardation in the pups at the age of 12-14 days when the mother was not given vitamin D during pregnancy. Hypocalcemia, hypophosphatemia and impaired bone calcification was observed by the age of 23 days (Halloran et al., 1979; Halloran and De Luca, 1980c). Boass et al. (1981a) undertook a systemic study of the effect of short term vitamin D deprivation of the mother from 6th day of pregnancy on the suckling and weaned pups. By 15th
day, serum 25(OH)D was undetectable and body weight was reduced by 26%. Serum calcium and phosphate levels were also reduced. In 19 days old pups the ratio of bone weight to body weight was not reduced but the ash weight as a percentage of bone weight.

Excess of vitamin D in the diet of pregnant rats leads to a persistent defect in bone formation in the pups. Administration of 20,000 or 40,000 IU of vitamin D per day to pregnant rat from 10th day to 21st day of gestation induced severe growth retardation of suckling pups. Osteogenesis of long bones was impaired as evidenced by retarded epiphyseal ossification and persistence of endochondral bone trabeculae within the diaphysis (Ornoy et al., 1968). There was increased number of bony trabeculae but these often had wide borders of osteoid. Thus many of these changes resemble those seen in rickets but there is absence of the characteristic epiphyseal changes (Follis, 1955; Yendt et al., 1955).

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 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
bronchiolitis and respiratory infections. 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. 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). Cord blood 25(OH)D is correlated with mononuclear cell release of IFN-γ and hence Th1 cell development. 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 preparation (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 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 1,25(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 1,25(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, 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. Many 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 nursing infants’ vitamin D status improved significantly (Ala 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)D2 concentrations. This increase was more pronounced among mothers who received 3600 IU/d vitamin D2. A similar profile was observed for circulating vitamin D2. It is of interest that, in both groups, circulating 25(OH)D3 concentrations decreased although the mothers were receiving 400 IU/d vitamin D3. 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.

REFERENCES


