Vitamin D Metabolism and Function During Pregnancy and the Neonatal Period*

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ABSTRACT

Recent evidence suggests that vitamin D plays an important role in calcium homeostasis during pregnancy and early extrauterine life. Vitamin D is metabolized by successive hydroxylations to 25-hydroxyvitamin D and then to 1,25-dihydroxyvitamin D, the most potent known metabolite of the vitamin. During pregnancy, the concentrations of this metabolite in maternal serum increase in parallel with the increased need to absorb dietary calcium. 1,25-Dihydroxyvitamin D is produced in the fetoplacental unit as well as in the maternal kidneys. Receptors for 1,25-dihydroxyvitamin D appear to be present in the placenta suggesting that the placenta may be a target for vitamin D action. Developmental changes in vitamin D metabolism and action have been documented in the neonate as well as in the mother and fetus. Clinical studies indicate that adequate vitamin D intake is important during pregnancy. Administration of vitamin D or its metabolites appears to be useful in the treatment of neonatal disorders.

Introduction

Pregnancy and the post-natal period offer significant challenges in calcium homeostasis for the mother, the fetus, and the newborn. During late gestation, the fetus draws upon the abundant maternal supply of calcium to meet fetal needs for bone growth. A healthy and well-nourished mother adapts to the mineral needs of the fetus by increasing her intestinal absorption of mineral rather than by sacrificing her own bone mineral. At birth, the newborn is abruptly cut off from its placental supply of minerals and must quickly develop its own efficient system of intestinal calcium absorption.

Early clinical observations of vitamin D deficient mothers indicated that their newborn infants had definite signs of rickets and tetany. This suggested that fetal mineralization and early post-natal intestinal adaptation are dependent upon maternal vitamin D. Disturbances in vitamin D metabolism and action have been implicated in a variety of mineral problems of human development including neonatal hypocalcemia, dental enamel hypoplasia, and the rickets of prematurity.

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Experimental animal studies indicate that vitamin D plays an important role in increasing intestinal calcium absorption during pregnancy and in the neonatal period. The purpose of this review is to provide a brief summary of current concepts of vitamin D metabolism and action during pregnancy and the neonatal period. For a more extensive treatment, the interested reader is referred to the review of this topic by Gray et al.

Vitamin D Metabolism and Action in the Non-Pregnant State

The major target tissues for vitamin D action are the bone and the intestine. In the intestine, vitamin D promotes transcellular transport of calcium and phosphate, and in the bone it promotes bone resorption. Both processes are involved in the maintenance of normal blood concentrations of calcium and phosphate ions. Observations over the past 15 years have clearly demonstrated that vitamin D itself is an inactive precursor which undergoes successive hydroxylations to biologically active molecules. The parent vitamin (figure 1) is first converted to 25-hydroxyvitamin D (25-OHD) in the liver by a hydroxylase activity that can be studied in hepatic microsomes. The 25-OHD is hydroxylated in kidney mitochondria to either 1,25-dihydroxy vitamin D (1,25(OH)\textsubscript{2}D), the most biologically potent metabolite, or to 24,25-dihydroxy vitamin D (24,25-(OH)\textsubscript{2}D), a relatively inactive metabolite. The production, regulation, and action of these major vitamin D metabolites constitute the vitamin D-endocrine system. Details of these pathways have been reviewed recently. Vitamin D may be obtained from dietary sources or by the ultraviolet phototransformation of 7-dehydrocholesterol in the skin. The amount of vitamin D that is produced in the skin varies seasonally and geographically with the intensity of ultraviolet radiation in sunlight and the extent of exposure of skin to the sun. Vitamin D is transported in the blood by a vitamin D binding protein (DBP) that also binds 25(OH)D. Vitamin D binding protein is a serum protein with a molecular weight of 52,000 and is identical with human group specific component. Production of the potent metabolite 1,25(OH)\textsubscript{2}D is increased, and production of the relatively inactive kidney metabolite 24,25(OH)\textsubscript{2}D is decreased during periods of increased calcium demand (e.g., bone growth, pregnancy, lactation, and adaptation to a low-mineral diet). In contrast, 24,25(OH)\textsubscript{2}D production is increased and 1,25(OH)\textsubscript{2}D synthesis is decreased when mineral supplies are adequate for skeletal demands. Other metabolites of vitamin D are known to occur but their physiological significance is unclear. Because the amounts of these other metabolites have not been studied during pregnancy, they will not be considered here.

Various ionic and endocrine factors can control renal hydroxylation of 25(OH)D. Both hypocalcemia and hypophosphatemia enhance 1,25(OH)\textsubscript{2}D synthesis. Extensive studies both in vivo and in vitro indicate that parathyroid
hormone (PTH) directly stimulates the kidney's production of 1,25(OH)_2D and PTH is considered a major regulator of 25(OH)D metabolism under hypocalcemic conditions. Gonadal and pituitary hormones and adrenal steroids have also been implicated in controlling kidney 1α-hydroxylation of 25(OH)D. It is not clear yet whether these endocrine factors directly or indirectly regulate the kidney 1α-hydroxylase activity.¹³,³¹

**Vitamin D Metabolism during Pregnancy**

Recent evidence indicates that the feto-placental unit produces 1,25(OH)_2D. In contrast to nephrectomized nonpregnant rats, nephrectomized pregnant rats did produce 1,25(OH)_2D.²³,⁶⁹ In vitro studies have shown that rat placenta, human decidua tissue and fetal kidney can form 1,25(OH)_2D.⁶⁵,⁶³,⁷⁰ These experiments suggested that 1,25(OH)_2D synthesized in the fetus and placenta could reach the maternal circulation. It is less clear whether maternal 1,25(OH)_2D can reach the fetal blood. Maternal 25(OH)D and vitamin D can be transported across the placenta to the fetus,²⁵ but evidence exists for a placental barrier to maternal 1,25(OH)_2D in rats.⁴⁷ A compartmentalization of maternal and feto-placental 1,25(OH)_2D also is suggested by the existence of a two to three-fold concentration gradient of 1,25(OH)_2D between the human maternal blood and umbilical vein blood.⁶⁰ Thus the fetal tissues may be exposed primarily to 1,25(OH)_2D from the feto-placental unit rather than to 1,25(OH)_2D from the mother. These concepts are illustrated in figure 2.

Independent feto-placental production of 24,25(OH)_2D has been suggested from both in vivo studies of ^3^H-25(OH)D metabolism in vitamin D-deprived pregnant rats and in vitro production of 24,25(OH)_2D in placental extracts.²³,⁴¹,⁷⁰ The production of radioactive 1,25(OH)_2D and 24,25(OH)_2D from ^3^H-25(OH)D has been studied in pregnant rats; ^3^H-1,25(OH)_2D was found to be higher on the maternal side compared to the fetal side whereas ^3^H-24,25(OH)_2D is found in higher amounts in the fetus compared to the mother.⁴¹ These ratios may reflect different placental transport rates for the two metabolites, or may be a sign of independent endocrine controls of vitamin D metabolism in the mother and fetus. The extent to which these factors are important is unknown at present, but these results further indicate the complexities of vitamin D metabolism during pregnancy.

**Functions of Vitamin D during Pregnancy and the Neonatal Period**

During gestation the mother adapts to the calcium needs of the fetus by in-
creasing her intestinal absorption of calcium. Considerable evidence suggests that 1,25(OH)\(_2\)D is important in producing this maternal intestinal adaptation as indicated by the increased production of this metabolite, the higher intestinal content of a vitamin D dependent protein, and the blunting of these responses in vitamin D-deficient pregnant rats.

The molecular mechanism for vitamin D-dependent intestinal calcium transport is not understood in detail. However, it is well known that 1,25(OH)\(_2\)D can control the synthesis of specific vitamin D-dependent proteins. The best characterized of these proteins is the intestinal vitamin D-dependent calcium binding protein (CaBP). The function of this CaBP is unknown, but the concentration of this protein closely parallels intestinal calcium transport rates under many conditions.

Using an antiserum to the intestinal vitamin D-dependent CaBP, the present authors and others have described a protein similar or identical to intestinal CaBP in rat and mouse placenta. During late gestation in rats and mice, both maternal intestinal CaBP and placental CaBP increased in association with mineralization of the fetal skeleton and the increased maternal absorption of calcium.

It has been assumed that before birth the fetal intestine does not transport large amounts of calcium. However, after loss of the placenta, the neonate must regulate calcium absorption to meet its bone growth requirements. Observations in human infants and rat pups have documented that developmental changes in vitamin D metabolism and action occur. For example, the ability to regulate 25(OH)D homeostasis in infants and rats is dependent upon gestational age. Similarly, gestational development controls the appearance of intestinal 1,25(OH)\(_2\)D receptors and the increases in intestinal CaBP and intestinal active calcium transport in experimental animals. These observations suggest an important role of vitamin D in the neonatal period as well as during pregnancy.

In the following sections clinical studies are summarized that define levels
of vitamin D metabolites in both the mother and the neonate.

**Plasma 25-Hydroxyvitamin D Concentrations in Mothers and Neonates**

The concentration of 25(OH)D has been measured in maternal and cord serum in a variety of geographical areas, including the United States, Europe, Japan, the Middle East, and England. The serum concentrations of 25(OH)D depend in part upon differing amounts of sunlight in different parts of the world and national differences in the supplementation of milk with vitamin D. In these various studies neonatal values ranged from 49 to 108 percent of the maternal level of 25(OH)D. The concentration of 25(OH)D in the maternal circulation appears to be a major factor governing the neonatal levels. Positive correlations between maternal and cord 25(OH)D levels are found in both term and premature births. These data are consistent with a passive transport or facilitated diffusion of maternal 25(OH)D into the fetal compartment. Most of these studies have indicated no change in infant or maternal 25(OH)D levels with gestation. Within a single geographic area the major factors governing maternal 25(OH)D appear to be ultraviolet exposure and prenatal care that assures an adequate dietary intake of vitamin D.

In an extensive study of women in a single geographic area (St. Louis), Hillman and Haddad observed that ultraviolet exposure was the major factor in determining maternal 25(OH)D in a group of women receiving prenatal care with similar vitamin D intakes (750 units per day). There was a three-fold seasonal difference in the serum levels of maternal 25(OH)D. No differences were observed between black and white women in either summer or winter 25(OH)D levels. These seasonal differences are similar to 25(OH)D changes observed in normal non-pregnant adults.

Osteomalacia is associated with a greater risk of rickets and early neonatal hypocalcemia in newborns of pregnant Asian women in the UK. These clinical problems are related to suboptimal vitamin D intake and calcium deficiency resulting from a vegan-vegetarian diet and inadequate ultraviolet exposure. Dent and Gupta were the first to report the plasma 25(OH)D levels during pregnancy in Caucasians and Asians in London. Both maternal and cord blood levels of 25(OH)D were substantially reduced in the Asian mother and baby compared to the Caucasian mother and infant pair. Subsequent studies have confirmed these observations and have found vitamin D supplementation for Asian pregnant women living in England to be beneficial for the infant’s health in reducing symptomatic neonatal hypocalcemia and improving intrauterine growth.

Pregnant women with a low vitamin D intake (100 to 200 units per day) from an urban population in New York had reduced maternal and cord 25(OH)D levels with an increased susceptibility of their premature infants to early neonatal hypocalcemia (<7 mg calcium per dl). In this study all of the infants were winter-born. The combination of reduced ultraviolet exposure and low maternal vitamin D intake most probably contributed to the low 25(OH)D values. Administration of 25(OH)D₃ after birth effectively prevented early neonatal hypocalcemia in a similar group of premature infants from this same urban area. In contrast to the previous data, no role for 25(OH)D deficiency in early neonatal hypocalcemia of premature was observed in various other studies. As reviewed by Wills et al. the degree and causes of early neonatal hypocalcemia can vary...
with vitamin D deficiency being one of many possible factors. Premature infants with normal cord 25(OH)D levels showed decreases in serum 25(OH)D and were not able to maintain normal 25(OH)D levels until 36 to 38 weeks gestation. Oral (400 units per day) or intravenous vitamin D (230 units per day) did not change the low 25(OH)D serum levels suggesting that a decreased rate of 25-hydroxylation may be a factor in impaired 25(OH)D homeostasis in prematures. In another study of premature infants (32 to 37 weeks of age), oral administration of higher amounts of vitamin D₃ (2,100 units daily) for five days increased serum 25(OH)D and 1,25(OH)₂D indicating that the hydroxylating enzymes were present. Similar results were observed in prematures as early as 24 hours after birth. Normal term infants were able to maintain their normal 25(OH)D levels and are able to increase their 25(OH)D concentration to normal levels if their cord levels were initially low.

**Plasma 24,25-Dihydroxy Vitamin D Concentration in Mothers and Neonates**

Reiter et al. reported that 24,25-(OH)₂D levels decrease in the maternal serum during late gestation. Likewise, two other studies found that pregnant women had lower serum values of 24,25(OH)₂D than nonpregnant adults. On the other hand, Seino et al. observed no difference in 24,25-(OH)₂D levels between normal adults and pregnant subjects. In two studies no correlation was observed between maternal serum 24,25(OH)₂D and cord 24,25(OH)₂D, whereas Weisman et al. found a positive correlation between maternal and cord 24,25(OH)₂D. All these studies observed that the cord values for 24,25(OH)₂D were approximately 65 percent to 86 percent the maternal values. The level of 24,25(OH)₂D in healthy newborns is about one-tenth the 25(OH)D levels. The serum concentrations of 24,25(OH)₂D did not differ between term and preterm neonates.

**Plasma 1,25-Dihydroxy Vitamin D Levels in Mothers and Neonates**

The kidney metabolite, 1,25(OH)₂D, is considered the most potent of the vitamin D metabolites, and its production is increased during physiological demands for calcium. During early pregnancy, maternal 1,25(OH)₂D increases substantially and the high 1,25(OH)₂D maternal levels are sustained throughout gestation. Cord levels of 1,25(OH)₂D have been shown to be substantially lower than maternal 1,25(OH)₂D values by two to three-fold. Steichen et al have reported that 1,25(OH)₂D levels in the placental vein did not correlate with maternal levels. Observed cord 1,25-(OH)₂D levels were much lower than normal adult concentrations, but within 24 hours after birth neonatal 1,25(OH)₂D had increased to the adult levels. However, a report by Gertner et al indicated a correlation of fetal 1,25(OH)₂D with maternal 1,25(OH)₂D and much higher fetal 1,25(OH)₂D levels than the other reports. Seino et al found that the concentration of 1,25(OH)₂D in the cord blood of healthy infants was about 75 percent of the maternal concentrations and was two to three-fold higher than in adults or older children. Delayed mineralization of bone may be observed in premature infants, especially those with very low birth weights. This osteopenia of prematurity can be due to a dietary calcium and phosphorus deficiency rather than a vitamin D deficiency especially since 1,25(OH)₂D levels have been observed at a supranormal level in some infants. Administration of 1,25(OH)₂D also has been
shown to heal the rickets of prematurity.\textsuperscript{8} Very low serum 25(OH)D concentrations have been measured in extremely premature infants (<1,200 g) with clinical signs of severe rickets; short-term treatment with 4,000 units per day of vitamin D resulted in restoration of the serum calcium and healing of the rickets.\textsuperscript{38} Premature infants may have increased dietary requirements for calcium, phosphorus, and vitamin D owing to their immature organ development, their minimal stores of nutrients, and their need for “catch-up” bone growth.

Administration of 1,25(OH)\textsubscript{2}D has been advocated for treatment\textsuperscript{7,39} of neonatal hypocalcemia, but its use in prophylaxis of neonatal hypocalcemia is controversial.\textsuperscript{55} Kooh et al reported that 1,25(OH)\textsubscript{2}D produced a prompt rise of serum calcium in each of six patients, aged 13 to 56 days, who had experienced a protracted course of neonatal hypocalcemia. This response occurred with intravenous doses as low as 0.05 \textmu g per Kg body weight per day. Chan et al suggested that 1,25(OH)\textsubscript{2}D might be useful for prophylaxis of neonatal hypocalcemia. These authors reported that an oral dose of 1.0 \textmu g per day, starting at 12 hours after birth, increased the serum calcium measured at 48 hours after birth in premature newborns. In addition, oral calcium tolerance tests, performed 48 hours after birth, demonstrated significant increases in serum calcium at two and three hours after oral administration of calcium to these patients, suggesting that the intestine was responsive to 1,25(OH)\textsubscript{2}D in premature infants. By contrast, a dose of 0.05 \textmu g per Kg baby weight/day was ineffective, as was vitamin D\textsubscript{2} (400 IU) in increasing serum calcium at 48 hours after birth or in supporting a rise in serum calcium during the calcium tolerance test. Recently, Salle et al\textsuperscript{55} have argued against the prophylactic use of 1,25(OH)\textsubscript{2}D. These investigators found no effect of a daily oral dose of 0.5 \textmu g of 1,25(OH)\textsubscript{2}D on the course of early neonatal hypocalcemia in six premature infants; they argued that the results of Chan et al represented pharmacologic effects of 1,25(OH)\textsubscript{2}D and that “defective vitamin D metabolism is not a primary factor in the pathogenesis of early neonatal hypocalcemia.”

Summary and Conclusion

During pregnancy, vitamin D is metabolized to active metabolites both by the mother and by the feto-placental unit. Alterations of vitamin D metabolism appear to play an important role in the adaptations to the physiological stresses of pregnancy and the post-natal period. Vitamin D and its metabolites have promise in the therapy of some disorders of the neonatal period.

References


