RELATIONS OF PLASMA 25-HYDROXYVITAMIN D LEVELS IN MOTHERS, CORD BLOOD AND NEWBORN INFANTS, AND POSTNATAL CHANGES IN PLASMA 25-HYDROXY-VITAMIN D LEVELS

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Summary The plasma levels of 25-hydroxyvitamin D (25-OH-D) were determined in 27 healthy mothers and their infants as well as in the cord blood at the time of delivery, and in another 95 children of different ages. The plasma 25-OH-D levels in the infants, cord blood and mothers at the time of delivery were 11.4 ± 8.6 ng/ml (mean ± SD, n = 27), 12.8 ± 8.2 ng/ml (mean ± SD, n = 25) and 16.3 ± 8.1 ng/ml (mean ± SD, n = 27), respectively. These values are significantly lower (p < 0.01) than the value of 21.6 ± 10.1 ng/ml (mean ± SD, n = 17) in normal children (1–15 years of age). Significant correlations were found between the plasma 25-OH-D levels of the infants and the mothers, and between those of the mothers and cord bloods, with correlation coefficients of r = 0.62 (p < 0.01, n = 27) and r = 0.78 (p < 0.01, n = 25), respectively. The plasma 25-OH-D concentration was normally maintained at a low level for 1–2 months after birth and then rose. No significant correlation was found between the plasma 25-OH-D and plasma Ca levels. The above findings suggest that 25-OH-D is transferred from the mother to the infant through the placenta, but that the blood 25-OH-D level is low for a few months after birth, possibly owing to a low rate of 25-hydroxylation of vitamin D during this period.

Keywords plasma 25-OH-D, plasma calcium, perinatal period, cord blood, postnatal infants, transplacental transfer, 25-hydroxylation of vitamin D
In the neonatal period, the serum calcium (Ca) level generally drops within a few days after birth (1) and then gradually rises to the normal infant level at about 1–2 weeks (2). On the other hand, rarefaction and fraying at the metaphysis of the long bones, which are similar to rachitic changes, are frequently seen in X-ray films of early infants, especially premature infants, even when the serum Ca level has returned to normal.

Speculations on the pathogenesis of neonatal hypocalcemia have focused primarily on functional disturbance of the parathyroid glands or peripheral unresponsiveness to parathyroid hormone. However, with recent advances in studies on vitamin D metabolism, the roles of possible abnormalities in vitamin D metabolism in this condition in the neonatal period and early infancy have been discussed. In this study, we determined the normal levels of plasma 25-hydroxyvitamin D (25-OH-D) in infants and children of different ages to obtain further information on vitamin D metabolism in early infancy.

MATERIAL AND METHODS

1. Subjects. Twenty-seven pairs of healthy mothers and their infants were studied at the time of delivery, from February to March, 1975. Mixed arterial-venous cord blood and peripheral blood from the mothers were collected at the time of delivery. Plasma samples were obtained from the newborn infants at 1–2 days of life.

Another 95 infants and children of various ages were similarly studied during the spring, autumn and winter of the following two years. All infants were full-term and appropriately mature for their gestational age (AGA) (3) at birth, and none had any serious medical disorders during the neonatal period or at the time of study.

2. Methods. Plasma from heparinized venous blood samples from each subject, was stored at −20°C until use. The plasma level of 25-OH-D was determined by a competitive protein binding assay as reported previously (4). In brief, 0.5 ml of plasma was extracted with chloroform/methanol (50/50, by volume) and chromatographed on a Sephadex LH-20 column in chloroform/n-hexane (50/50, by volume) to separate 25-OH-D from vitamin D and 24(R),25-dihydroxyvitamin D. A specific binding protein from vitamin D-deficient rat serum was used for the assay. The 25-OH-D level measured by this method represents the total plasma level of 25-OH-D$_2$ plus 25-OH-D$_3$. Crystalline 25-OH-D$_3$ was used as a reference standard and $^3$H(26,27)-25-OH-D$_3$ was used as a tracer. Quantities of 0.5–5.0 ng of 25-OH-D could be measured and the coefficient of interassay variation was 11.8% ($n=6$).

Plasma calcium (Ca) and magnesium (Mg) concentrations were measured by atomic absorption spectrophotometry, and plasma inorganic phosphorus (P) by the modified Fiske-Subbarow method.

Information was obtained from each mother on her and her baby's daily vitamin D intake and estimated period of exposure to sunshine. These parameters
were difficult to assess precisely, but none of the mothers had received any vitamin supplements in the previous trimester. The estimated intake of vitamin D in the infants was less than 100 I.U. during the first week after delivery and 400–800 I.U. from 2 weeks after birth. No significant differences were found among the periods of exposure to sunshine of the groups of children of different ages.

RESULTS

1. Plasma 25-OH-D levels in maternal, neonatal and cord blood

The plasma 25-OH-D levels of the 27 full-term newborn infants within two days after birth, and of the cords and mothers are shown in Fig. 1. The mean concentrations of plasma 25-OH-D of the mothers, the infants and the cords were $16.3 \pm 8.1$ (SD) ng/ml $(n=27)$, $11.4 \pm 8.6$ (SD) ng/ml $(n=27)$ and $12.8 \pm 8.2$ (SD) ng/ml $(n=25)$, respectively. The mean concentration in the plasma of the infants was significantly lower ($p<0.01$) than that of either the mothers or the cords. Moreover, all these levels were significantly lower ($p<0.01$) than the value of $21.6 \pm 10.1$ (SD) ng/ml $(n=17)$ in 1- to 15-year-old children reported previously (4).

![Fig. 1. Plasma 25-OH-D levels in perinatal and early infants. *$p<0.01$, **$p<0.001$, significant difference from the levels at 1–15 years of age. Values are means ± SD.](image-url)
As shown in Fig. 2, the plasma 25-OH-D levels in the maternal plasma were usually higher than those in their newborn infants, but in 5 of the 27 pairs of samples (19%) the plasma concentration was higher in the newborn infants than in their mothers. As shown in Fig. 3, there was a significant correlation between the plasma 25-OH-D concentrations in the newborn infants and their mothers ($r=0.62$, $p<0.01$, $n=27$). There was also a significant correlation between the concentrations in the maternal and cord plasma ($r=0.78$, $p<0.01$, $n=25$), as shown in Fig. 4. These results indicate that 25-OH-D is transported from the mother to the child through the placenta. This transfer seems to be facilitated in some cases.

2. Correlations of 25-OH-D levels with Ca, Mg and P concentrations in the blood of newborn infants

A slight but significant correlation ($r=0.58$, $p<0.01$, $n=25$) was found between
the 25-OH-D and Ca levels in the blood of the neonates. However, no significant correlation was found between the 25-OH-D level and the Mg or P levels, or between the plasma 25-OH-D and Ca levels in postnatal infants.

3. **Plasma 25-OH-D levels in children of different ages**

The plasma 25-OH-D levels in children of different ages are shown in Fig. 1. The level decreased just after birth, remained low for about 1–2 months and then gradually rose to the level observed in 1- to 15-year-old children.

**DISCUSSION**

It is well known that the serum Ca level tends to be low in the early neonatal period. The clinically significant problems of neonatal hypocalcemia, hypocalcemic tetany and postnatal rachitic bone changes in premature infants, are believed to be associated with derangements of perinatal Ca and/or vitamin D intake or metabolism.

We have determined the plasma 25-OH-D levels in the perinatal period and in infants and children of different ages. Our findings indicate that the plasma 25-OH-
D levels in mothers and their infants at the time of delivery were significantly lower than the normal level in older children, and that the low level was maintained for 1–2 months after birth and rose at 2–3 months of age.

There have been several reports on the blood 25-OH-D levels in the perinatal period (5–9). ROSEN et al. (5) found that the plasma 25-OH-D levels in premature infants with hypocalcemia at 48 hours after birth, and in their mothers were significantly low and proposed that the nutritional state of the mother may have been related to the low level in her premature baby. HILLMAN et al. (6, 7) determined the perinatal and postnatal concentrations of 25-OH-D in the sera of premature and twin infants, finding that the concentrations in the sera of cord blood from the newborn infants correlate with those in the maternal sera and that in serial samples from premature infants with low values of 25-OH-D in the cord blood, the decrease and increase in concentration of 25-OH-D after birth took longer than normal.

In this work we found a significant correlation between the plasma 25-OH-D values of mothers and their infants soon after birth ($r = 0.62, p < 0.01, n = 27$). This finding shows that 25-OH-D is transferred from the mother to the child through the placenta. Moreover, in some cases the level in the cord was higher than in the mother, suggesting active transfer of 25-OH-D. Our findings also suggest that the
Plasma 25-OH-D level in the blood of mothers is lower than the normal level in older children and that when the level in the mother is low, that in the newborn infant is correspondingly low, even when the infant is term-mature.

Studies on the 25-OH-D level in the postnatal period in rats (10) have suggested that suckling rats either have an insufficient vitamin D intake or do not synthesize 25-OH-D.

We estimated that the intake of vitamin D in infants was over 400 I. U. per day from two weeks after birth, but the plasma 25-OH-D level remained low for 1–2 months after birth. Thus, the rate of 25-hydroxylation of vitamin D may be low even in mature infants.

The slight correlation found between the blood Ca level and the blood 25-OH-D level may be due to the influence of calcium-regulating factors other than 25-OH-D.

The rachitic changes, sometimes observed in the metaphysis in X-ray films of the long bones of infants of 2–3 months of age (11) do not coincide well with time when the plasma 25-OH-D level is low. However, they may be influenced to some extent by the low level of plasma 25-OH-D in the early infant period.

In view of the fact that rickets in immature infants cannot always be prevented by administration of 400 I. U. of vitamin D, considered to be the physiological requirement (12, 13), the optimal dose of vitamin D in this period should be studied further.

REFERENCES

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