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Metabolism and action of vitamin D in the fetus

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The metabolism of vitamin D has been studied in human and rat fetuses together with the influence of vitamin D and its derivatives on fetal growth, embryonic cartilage and fetal length. Although the results are not complete, it could be concluded that vitamin D metabolism in the fetus is not dependent on the mother nor the fetoplacental unit but principally on the fetus itself as demonstrated in the rat and humans.

The sources of vitamin D include endogenous synthesis of cholecalciferol (D3) through photochemical reactions in the epidermis and from ingested foods (D2 and D3). The vitamin must then be transformed by the organism into its active form. The first step is a rapid hydroxylation of C-25 in the liver with an easily saturated negative feedback system. The 25(OH)D derivative then circulates bound to a high affinity alpha globulin or DBP. The 25(OH)D form has little inherent biological activity, but rather serves as a reservoir for ulterior modifications. A C-I hydroxylation can then take place via the action of 1 alpha hydroxylase in the proximal tubule of the kidney except during the gestational period. The resulting 1.25(OH)2D then circulates in both free and bound to DBP forms. The free form has a very powerful biological activity through specific cytoplasmic and nuclear receptors in target organs, thus the bones and the intestine. This derivative is under several steroid and non-steroid hormonal controls. In particular, it is activated by PTH and repressed by orthophosphates and its own feedback system. The 25(OH)D form can also be hydroxylated in the C-24 or C-26 positions or transformed into a lactone. Trihydroxylate metabolites, namely 1,25,26(OH) 3D and 1,24,25(OH) 3D, are known as well as glucosiduronates. Thus far, only to 24,25,(OH) 2D has been attributed an important role in bone and cartilage metabolism, after having long been considered to be of little interest.

Clearly, calcium and phosphate intakes need to be modified in the mother during pregnancy and lactation. In the last four months of gestation alone, 20–30 g of calcium are necessary for fetal mineralization. Vitamin D and its metabolites play an important role in this adaptive measure, first in the pregnant mother and then in fetal calcium metabolism. New data concerning the topic are summarized below from the works of

American [5, 6], and Belgian [1, 2] authors. In the pregnant mother, the concentration of 25(OH)D and 24, 25(OH)2D is stable while that of 1,25(OH)2D rises; this rise depends on an increase in D binding protein, and the free fraction only rises in late gestation. There exists a fetal–maternal correlation for the concentrations of the 3 metabolites, 25(OH), 1,25 and 24,25(OH)2D, that of the fetus being half of the mother's. On the other hand, the free form of the three metabolites is higher in the fetus due to low concentrations of D binding protein. The existence of a fetal–maternal gradient in spite of 25 and 1,25(OH)2D transplacental transfer suggests an active transport system, a fetal production, or both. The fetal kidney as well as the fetal and maternal placentas can produce 1,25(OH)2D and so do probably some other fetal organs. Little is known as to the timing of the appearance of 1,25(OH)2D intestinal or bony receptors. The placenta is known to contain some and to synthesize D binding protein as well.

It appears that the reservoir form or 25(OH)D has a low concentration in the fetus. The 1,25(OH)2D active form can be transferred by the mother or synthesized by the fetal kidney or placenta which is also responsible for the calcium via the vitamin D dependent CaBP. Much remains, however, to be elucidated as many studies appear contradictory and many technical and ethical problems still remain.

Several yet unpublished studies from our laboratory have been carried out on the topic [3, 4, 7], certain aspects of which I should like to summarize here.

A study analysed the influence of vitamin D and its derivatives on fetal growth, embryonic cartilage, and fetal length. The findings did not differ between fetuses of mothers deprived of vitamin D and pregnant non-restricted mothers. Four restricted pregnant rats had very low 25(OH)D and undetectable 1,25(OH)2D levels on the 17th day of gestation in comparison with six restricted mothers on the 21st gestational day. On the 16th gestational day both deprived and non-deprived fetuses had a zone of cellular hypertrophy in the diaphyseal centre of the tibial cartilageneous skeleton, and the matrix remained uncalcified. The same was true on the 17th gestational day, but with a more pronounced hypertrophy as seen in specimens stained with toluidine blue. Calcium phosphate deposits were also identical in both groups as revealed by Von Kossa staining. In spite of severe maternal vitamin D restriction, the plasma concentration of the vitamin D metabolites was adequate in the fetus. Although no conclusions could be drawn as to the role of vitamin D in fetal growth and mineralization, the fact that these metabolites were detectable in the fetus despite severe maternal deprivation suggests that they may have a physiological role during gestation.

The second study begun in 1980 was terminated only this year due to technical difficulties. To study vita-

min D metabolism during fetal life required analyses of 50 fetal specimens for each dosage of 25(OH)D, 24,25(OH)2D and 1,25(OH)2D metabolites. Certain tissues (liver, intestine, bone) were shown to be capable of hydroxylating the 25(OH)D form to the 1,25(OH)2D form, a function which these tissues lose in postnatal life. The peak activity of this hydroxylase occurred on day 19. Parathyroidectomy in the pregnant mother on the 21th gestational day led to a decrease in both maternal and fetal synthesis of 1,25(OH)2D in vitro. On the other hand, maternal renal synthesis of 24,25(OH)2D was stimulated, that of the feto-placental unit was inhibited. The pregnant rat's dihydroxylated derivatives had stabilized between the 16th and 19th days much more than in the non-pregnant rat. In the parathyroidectomized pregnant rat, circulating levels of 1,25(OH)2D were comparatively lower, they however still rose by the end of gestation. Studies of tissue synthesis of 1,25(OH)2D suggested that the late gestational increment was not simply due to its synthesis. The fetal-maternal gradient of vitamin D metabolites was maintained whether or not the mother had undergone parathyroidectomy. There existed no correlation between the fetal levels of vitamin D metabolites and the synthetic capacity of the fetoplacental unit nor with maternal variations.

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