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Metabolic Studies in Congenital Vitamin D Deficiency Rickets

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Abstract. Congenital rickets in 3 newborns of mothers with advanced nutritional osteomalacia, healed with maternal breast milk feeding when mothers alone were given calcium supplements and 7.5 mg of intravenous D_2 and the mother baby pair protected from sunlight. Maternal plasma biochemistry indicated more severe vitamin D deficiency compared to their newborns (intrauterine foetal priority). The first dose of 7.5 mg of vitamin D_3 and calcium supplements to mother healed osteomalacia but did not appear to heal the rickets of their breast fed infants (extrauterine maternal priority for vitamin D). A second dose given at 3 months interval healed the rickets in their infants and the biochemistry of the mother and baby returned towards normal. Congenital rickets developed when maternal bone mineral and vitamin D stores had been completely exhausted. Raised IPTH levels in the newborn suggested that foetal parathyroids were responsive to hypocalcaemic stimulus. **(Indian J Pediatr 1995; 62 : 55-61)**

Key words : *Rickets; Congenital rickets; Vitamin D deficiency*

Congenital rickets due to maternal malnutrition is well recognised entity, raising the interesting possibility that foetal, bone mineral metabolism is dependent on transplacental transfer of vitamin D and its metabolites.[1-4]

The aim of this study was to determine the role of maternal breast milk feeding to the baby in the regulation of mineral and vitamin D metabolism and healing of congenital rickets. The babies were kept totally breast-fed and the mothers alone were treated with vitamin D_3 and calcium.

Material and Methods

During the past sixteen years we have had the opportunity to examine 165 infants born to mothers with severe osteomalacia. Six of these showed the effects of maternal vitamin D deficiency. Three had neonatal hypocalcemia with tetany and three had congenital rickets without tetany. The three infants with tetany had to be treated with intravenous and oral calcium and have not been included in the present study. The study therefore comprises only 3 children with congenital vitamin D deficiency rickets.

Each mother of the newborns with congenital rickets received 2 g elemental calcium per day and two doses of vitamin D_3 7.5 mg intravenously at interval of three months. This was done to provide the maximum time for the action of first dose of vitamin D_3. The mother-baby pairs were protected from direct sunlight by constantly keeping them in room with dark

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curtains. This was done to make sure that the only source of vitamin D for the baby was maternal breast milk. The babies were exclusively breast-fed and did not receive any medication. A written informed consent from both the parents was obtained in each case of participation in the study. The prior approval of the institutional ethical review board was also obtained for the study.

Plasma IPTH levels were determined by radioimmunoassay method of Reiss and Canterbury,[5] plasma levels of 25-HCC were determined by competitive protein-binding radioassay technique of Haddad and Chyu.[6] In case 3, the assay for 25-HCC and parathyroid hormone (N-tact) were performed by radioimmunoassay kits (INCSTAR Corporation, USA). Total calcium concentration in plasma, breast milk and urine were determined by Atomic Absorption Spectrophotometer (Model Unicam sp90A, series 2), plasma alkaline phosphatase by the method of King and Armstrong[7] and plasma inorganic phosphorus by the technique of Fiske and Subbarow.[8]

Results

The brief clinical, biochemical and radiological investigations of the three cases are described as follows :

Case 1

Mother : J.M., a Muslim, para 4, aged 28 years was admitted to the Metabolic and Endocrine Ward on April 14, 1974, four days after caesarean section, for treatment of her advanced osteomalacia with deformities. She did not seek prenatal care until the time of delivery. Her previous deliveries were normal and children were breast-fed until the age of 12 months or more. Her daily dietary intake (mean of 3 days recall) was calories 673, protein 19.5 g, calcium 98 mg and vitamin D 15 I.U. Following the delivery of her third child, she developed back pain, and muscular weakness which became progressively worse in the present pregnancy.

On examination she was bed-ridden, had flexion deformities at hips and knees, generalised forward flexion at the spine, tender bones and loss of strength in her grips. She had parasthesias with positive Chvostek's and trousseous signs. Both of her breasts were lactating. Skeletal X-rays

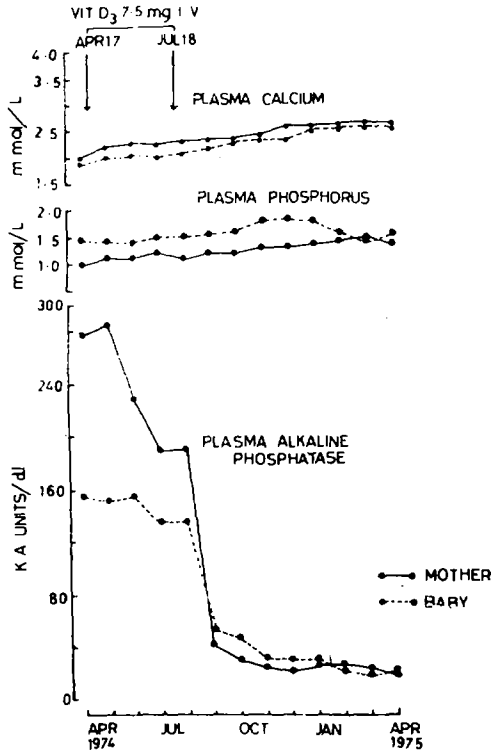

Fig. 1. Plasma biochemistry in mother-baby pair (Case 1)

showed triradiate pelvis, multiple looser's zones in ischiopubic rami and the long bones. Undecalcified sections of her iliac bone showed trabeculae with minimal calcium and wide coverage of unmineralised osteoid.[9] Her haemoglobin was 9.6 g/dl, plasma protein 6.0 g/dl. She had low plasma calcium and inorganic phosphorus and a high alkaline phosphatase. Her plasma levels of 25-HCC were <2 ng/ml and IPTH levels were raised. Breast milk output, its calcium content and the urinary excretion of calcium were low. She had generalised aminoaciduria characteristic of vitamin D deficiency (Figures 1-3). There was no laboratory evidence of intestinal malabsorption or renal disease. She was treated as described above.

Baby: Female infant, born at 40 weeks of gestation by a caesarean section, weighing 2.2 kg, head circumference 36 cm, crown to heel length 45 cm. The newborn had frontal and parietal bossing, widely open anterior fontanelle, swelling at the wrists and ankles. The baby had no tetany. Her plasma and urinary biochemistry and X-rays confirmed the diagnosis of rickets.

Case 2

Mother : J.N., 32 years, Muslim, para 6, was transferred to metabolic ward on January 1, 1978, three days after caesarean section for treatment of her osteomalacia. The previous deliveries were normal and each child was breast-fed until the age of 15-18 months. She was 38 weeks pregnant on her first visit to hospital. During her present pregnancy, she had developed low back pain, waddling gait, muscular weakness and became bed-ridden. She had bony tenderness, muscular hypotonia, numbness and tingling in hand and feet and flexion deformities of hips and the spine. Her skel-

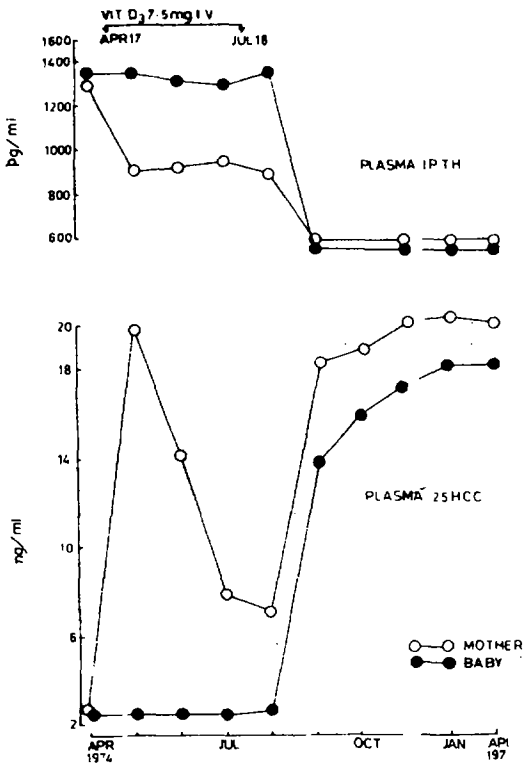

Fig. 2. Plasma IPTH and 25-Hydroxycholecalciferol in mother-baby pair (Case 1)

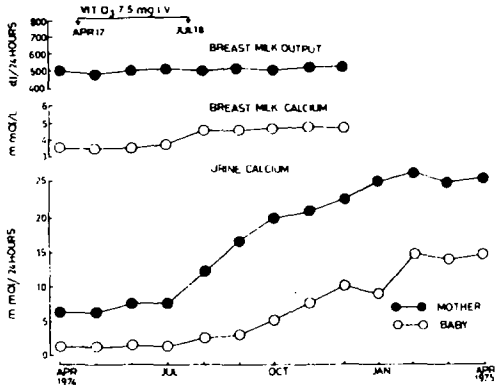

Fig. 3. Breast milk output and urinary calcium in mother-baby pair (Case 1)

etal radiographs showed triradiate pelvis with multiple pseudofractures in the ischiopubic ramiou and generalised rarefaction of the spine with codfishing of the vertebrae. Her plasma and urinary biochemical findings confirmed the diagnosis of nutritional osteomalacia (Table 1). There was no laboratory evidence of intestinal malabsorption or renal disease. In view of her pelvic deformities an elective caesarean section was performed.

Baby : The male infant born at 38 weeks of gestation, weight 2.5 kg, head circumference 34 cm, crown-heel length 44 cm. He had wide wrist, soft skull bones, widely separated sutures and large fontanelle. There were no clinical signs of tetany. The plasma biochemistry and skeletal radiographs confirmed the clinical diagnosis of rickets (Table 1).

Case 3

Mother : N.J., para 6, aged 34 was transferred from another hospital on August 5, 1990, 5 days after emergency caesarean section done for obstructed labour. Her previous 5 deliveries were conducted normally at home. Her each child was breastfed up to the age of 2 years. She developed generalised aches and pains after 3rd delivery and was mostly confined to bed after birth of her 5th child 2 years back. Her mean daily dietary intake (3 days recall) was calories 1300, proteins 35 g, calcium 200 mg and vitamin D less than 10 I.U.

She was bed-ridden with flexion deformities at hips and knees, extremely tender bones and had excruciating pain even at the touch of blanket. She had numbness and spasms of her both hands and feet. Her characteristic radiological and biochemical findings (Table 1) confirmed the diagnosis of severe vitamin D deficiency osteomalacia. There was no laboratory evidence of renal tubular defects or intestinal malabsorption. She was treated as described earlier.

Baby : Male child born at 36 weeks of gestation, weighed 2.3 kg, head circumference 35 cm. He had soft skull bones, widely separated sutures and open anterior fontanelle, prominent costochondral junction, wide wrist. He had no clinical signs of hypocalcaemia. Skeletal radiographs showed splaying, cupping and irregular metaphyses at wrist, ankles and knees. The baby was breast fed and protected from sunlight. The subsequent follow up of the child is shown in Table 1.

Discussion

We have studied in three sets of mother-baby pairs, a rare metabolic situation where the mothers with severe vitamin D deficiency osteomalacia gave birth to newborns with congenital rickets who had elevated plasma levels of IPTH, low 25-HCC and calcium. Plasma calcium and 25-HCC values were similar in mothers and their respective newborns and suggested maternal stores as the critical factor in determining infant level at birth and dependence of mineral homeostasis in the newborn on the transplacental transport of vitamin D and calcium.

The maternal plasma biochemistry showed more severe vitamin D deficiency than their babies. The mothers appeared to offer transplacental priority for transfer of 25-HCC and calcium to their foetuses, at the expenses of their own stores (intrauterine foetal priority. Extremely low plasma 25-HCC levels in these three sets of mother-baby pairs suggested that the transplacental cross-over of 25-HCC be-

TABLE 1. Biochemical Investigations in Mother-Baby Pairs

		Case 2				Case 3			
		Mother		Baby		Mother		Baby	
		Initial	After Treatment	Initial	After Treatment	Initial	After Treatment	Initial	After Treatment
Plasma									
Calcium	(mmol/1)	1.5 (6.0)	2.4 (9.6)	2.1 (8.4)	2.4 (9.6)	1.4 (5.6)	2.4 (9.6)	2.1 (8.4)	2.3 (9.2)
Phosphorus	(mmol/1)	1.0 (3.1)	1.5 (4.7)	1.2 (3.7)	1.4 (4.3)	1.2 (3.7)	1.4 (4.3)	1.1 (3.4)	1.4 (4.3)
Alk. Ptase	(KAU/d1)	290.0	75.0	70.0	50.0	280.0	68.0	100.0	50.0
25-HCC	(ng/ml)	2.5	19.0	2.5	15.8	2.5	18.8	Undetectable	15.8
IPTH	(pg/ml)	1500	600	1400	600	600	80	528.0	65.0
Urine									
Calcium	(mmol/1)	2.3 (9.2)	14.0 (56.0)	Undetectable	5.0 (20.0)	3.8 (15.2)	19.5 (78.0)	Undetectable	6.0 (24.0)
Breast Milk									
Output	(ml)	600.0	748.0			610.0	900.0		
Calcium	(mmol/1)	4.3 (17.2)	7.0 (28.0)			4.0 (16.0)	8.5 (34.0)		

Figures in parentheses indicate values in mg/100 ml

The after treatment values are 3 months after second intravenous injection of vitamin D (7.5 mg) to the mother. 1,25 $(OH)_2D$ levels done in case 3 only, were undetectable in mother baby pair before treatment. After treatment, the 1,25 $(OH)_2D$ level in mother was 14.6 pg/ml and 22.3 pg/ml in the baby

came negligible, when the maternal bone mineral and 25-HCC stores had been completely exhausted.

The first dose of vitamin D was used by mothers to replenish their own stores and had no effect on plasma biochemistry of their breast-fed newborns. After the second dose of vitamin D the plasma biochemical findings in the mother-baby pair returned towards normal and infants showed radiological healing of rickets. Mothers had priority for vitamin D and secreted it in breast milk only after they had replenished their own stores (extra uterine maternal priority). However, mothers continued to drain their calcium reserves via breast milk even in severe state of negative calcium balance suggesting low breast milk threshold for calcium.

Plasma IPTH levels in the rachitic new-

borns continued to remain elevated until the concentrations of 25-HCC and calcium in their plasma had started rising following the administration of second dose of vitamin D_3 to their mothers. The IPTH levels in cord blood are undetectable[10,11] at birth and its transplacental transfer does not occur. The raised levels in the newborns suggested the secretions from their own parathyroid glands. In absence of 25-HCC, these infants maintained their extracellular calcium concentration through PTH dependent mobilization of calcium from bone, retention by the kidney and perhaps enhanced intestinal absorption of calcium from breast milk. These observations suggest that the foetal parathyroids are physiologically active at birth and play an important role in maintenance of calcium homeostasis in the newborn. The unique combination of low 25-HCC, low calcium and high IPTH discovered in the babies is in contrast to the clinical situation where maternal hyperparathyroidism produces foetal and neonatal hypoparathyroidism and hypocalcaemia.

The 24-hour milk output ranged from 200 to 700 ml with calcium content of 3.5 to 4.2 mmol/litre (14.0 to 16.8 mg/100 ml). The intakes of calcium through the breast milk in the newborn ranged from 70 to 140 mg per 24 hours. Normal lactating Indian women (age, parity and social stata matched) produce 800-1000 ml of milk per day with the calcium content ranging from 7.5 to 13.5 mmol/litre (30.0 to 54.0 mg/100 ml) (our unpublished data). The radiographic findings of rickets, plasma and urinary biochemistry remained stationary in the infants until their mothers had received the second dose of vitamin D_3. These observations suggest that significant amounts of vitamin D and its metabolites were secreted in the maternal milk only after the mothers had replenished their own stores of vitamin D and were in positive calcium balance.

The fact that only 3 out of 165 newborns born to osteomalacia mothers had vitamin D deficiency rickets suggests that babies are usually more protected than their mothers against calcium and vitamin D deficiency in utero. This protection fails when maternal stores are completely exhausted. The healing of congenital rickets in these infants, suggests that vitamin D and its metabolites secreted in the milk possess potential antirachitic activity and explains the rarity of neonatal hypocalcemia and rickets in the breast fed babies.

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DISCONTINUING ANTIEPILEPTIC DRUGS IN CHILDREN WITH EPILEPSY

The optimal regimen for discontinuing antiepileptic medications in children with epilepsy is unknown. We randomly assigned 149 children to either a six-week or a nine-month period of drug tapering, after which therapy was discontinued. Each group was composed of patients who had been seizure-free for either two or four years before drug tapering was begun. Most patients were receiving one antiepileptic drug; none were taking more than two. The children were evaluated periodically during and after the taper period. Sixteen patients were lost to follow-up before the beginning for the taper period. Proportional-hazards regression analysis was used to assess the risk of seizure recurrence among the remaining 133 patients.

Seizures recurred in 53 patients (40 percent). The mean duration of follow-up was 39 months (range 11 to 105) for the patients who did not have a recurrence of seizures. Neither the length of the taper period (six weeks vs. nine months, P = 0.38) nor the length of time the patients were free of seizures before the taper period was begun (two years vs. four years, P = 0.20 significantly influenced the risk of seizure recurrence. The presence of mental retardation (relative risk, 3.1 : 95 percent confidence interval, 1.5 to 6.2) or spikes in the electroencephalogram at the time of tapering (relative risk, 1.9; 95 percent confidence interval, 1.0 to 3.4) increased the risk of seizure recurrence.

The risk of seizure recurrence during drug tapering and after the discontinuation of antiepileptic drug therapy in children with epilepsy is not different whether the medications are tapered over a six-week or nine-month period.

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