Archives of Disease in Childhood, 1975, **50**, 786.

Relation between changes in plasma calcium in first week of life and renal function

L. STIMMLER, G. J. A. I. SNODGRASS, Y. GUPTA, J. K. STOTHERS, and D. BROWN
From Guy's Hospital and The London Hospital, London, and Barking Hospital, Barking, Essex

Stimmler, L., Snodgrass, G. J. A. I., Gupta, Y., Stothers, J. K., and Brown, D. (1975). *Archives of Disease in Childhood*, **50,** 786. **Relation between changes in plasma calcium in first week of life and renal function.** (1) Of 71 infants fed on reconstituted dried or evaporated cow's milk, 31 showed a fall in plasma calcium between the 1st and 6th days of life, whereas in 35 breast-fed infants this occurred in only 5. (2) Those artificially-fed infants who had shown a rise in plasma calcium over this period had significantly lower plasma creatinine values and significantly higher excretion of creatinine than those infants who showed a fall in calcium levels. (3) Artificially-fed infants who had shown a rise in calcium had a significantly lower plasma osmolality and significantly higher osmolar excretion in the urine than those infants who showed a fall in plasma calcium. (4) It is suggested that a delay in the normal increase in glomerular filtration rate during the first week of life in some infants leads to phosphate retention. This, together with a higher dietary intake of phosphate, leads to a decrease of the plasma calcium to hypocalcaemic levels.

In a previous study (Snodgrass *et al.*, 1973) it was found that the plasma calcium concentration invariably decreased during the first 24 hours of life regardless of the method of feeding. The mean decrease of plasma calcium was 1·5 mg/dl over this period, with a level at 24 hours of $8 \cdot 9 \pm 0 \cdot 7$ mg/dl. By the end of the first week of life the mean plasma calcium in breast-fed infants had increased to $9 \cdot 7 \pm 0 \cdot 6$ mg/dl, whereas those fed with evaporated milks showed no mean change at all.

When blood samples were obtained both at 24 hours of age and between days 6 and 8, it was found that only 3 out of 33 breast-fed infants showed a fall of calcium, whereas 18 out of 46 babies receiving Carnation or half-cream Regal feeds showed decreases, some as great as 2·5 mg/dl. Calcium levels at one week of age were inversely correlated with plasma inorganic phosphorus concentrations. It seemed likely therefore that the lower calcium levels in the artificially-fed babies were related to the higher phosphate content of such feeds. McCory *et al.* (1952) showed that infants suffering from hypocalcaemic convulsions had a lower renal clearance of inulin than non-convulsing infants.

The present study was undertaken to see if differences in renal function accounted for the observation that among those receiving evaporated or dried milks there were some who showed an increase in plasma calcium concentration and some who showed a fall.

Received 10 February 1975.

Methods

A total of 106 infants, gestational age 37 to 41 weeks, were studied after obtaining the mothers' permission in each case. Of these, 35 were breast fed and 71 were artificially fed on Ostermilk, Carnation, Full-Cream Cow & Gate, or Full-Cream National Dried milk.

Venous blood was obtained from the antecubital fossa at 18–30 hours of age without stasis and this was repeated on day 6 of life. A 24-hour collection of urine was also made on day 6 from the males in the sample, of whom 13 were breast fed and 44 were artificially fed. Each collection was analysed for creatinine, calcium, and osmolality. In these male infants the day 6 blood sample was obtained as nearly as possible to the midpoint of the urine collection. The previous study (Snodgrass *et al.*, 1973) had shown no sex difference in plasma calcium levels over the first 8 days of life.

Calcium was estimated by autoanalyser using the method of Wieme and Van Raepenbusch (1962), i.e. at a calcium level of 11·3 mg (quality control) 1SD was $\pm 0 \cdot 14$ mg/dl. Creatinine was estimated by the Jaffé reaction using a Technicon Autoanalyser, and osmolality by freezing point depression using an Advanced Instrument Osmometer.

TABLE I

Plasma levels of calcium and creatinine and osmolality on day 1 (means ± SD)

	Calcium (mg/dl)	Creatinine (mg/dl)	Osmolality (mOsm/kg)
Breast-fed infants (day 1)	8·6±9·0 (35)	1·00±0·30 (20)	266±14 (12)
Cow's milk-fed infants (day 1)	8·8±0·9 (71)	1·02±0·25 (38)	270±15 (15)
Breast-fed infants (day 6)	9·4±0·7 (35)	0·66±0·29 (14)	270±11 (14)
Cow's milk-fed infants (day 6)	8·8±0·9 (71)	0·80±0·30 (37)	278±20 (17)

Figures in parentheses = number of tests performed.

Results

The mean plasma calcium, creatinine, and osmolality levels on day 1 are given in Table I. Not surprisingly there is no significant difference at this early time between any of the parameters, whether the infants were breast fed or artificially fed. A distribution histogram of calcium levels (Fig. 1)

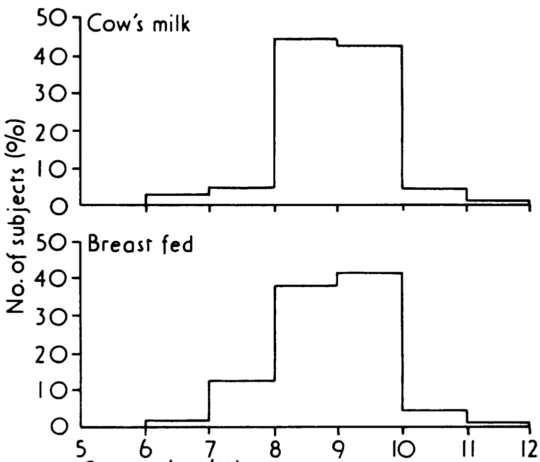

FIG. 1.—*Distribution of plasma calcium levels at 24 hours of age in breast-fed and artificially-fed infants.*

indicates a fairly symmetrical spread around the mean. The corresponding plasma levels for day 6 are also given in Table I. As in our previous study (Snodgrass *et al.*, 1973), there was no significant difference in the mean calcium level between day 1 and day 6 in the artificially-fed infants, but there was a significant increase in those who were breast fed ($P<0\cdot01$). A histogram of calcium values on day 6 (Fig. 2) shows that whereas there is a symmetrical distribution of calcium levels around the mean in the breast-fed group, there is a marked

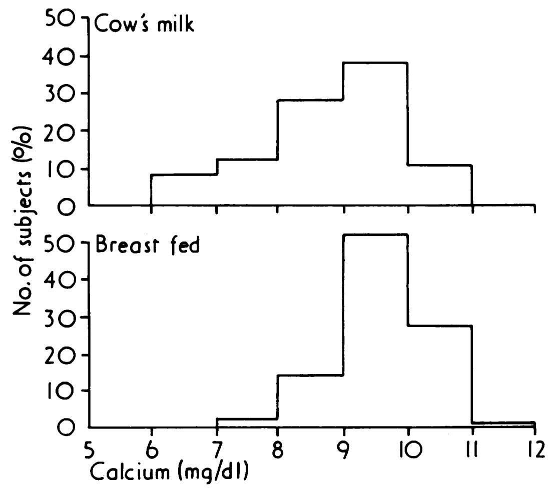

FIG. 2.—*Distribution of plasma calcium levels on day 6 of age in breast-fed and artificially-fed infants.*

skew to the left for the artificially-fed infants. Fig. 3 shows the changes in calcium levels between day 1 and day 6 and, as in the previous study, 90% of breast-fed infants showed an increase over these 5 days of which the largest was 2·1 mg/dl. Only 4 individuals showed a fall of which the greatest was 0·8 mg/dl. Artificially-fed infants who showed an increase of calcium showed increments of a similar magnitude as breast-fed infants, but 45% actually showed decreases of up to 2·1 mg/dl. The lowest calcium levels were found in those infants whose calcium levels had decreased by day 6. Urinary calcium excretion levels are given in Table III. Total urinary calcium excretion over 24 hours was 0·9±0·6 mg* in the breast-fed infants and 1·6±1·2 mg in the artificially-fed infants ($P<0\cdot05$).

*Throughout this paper data are presented as means ±SD.

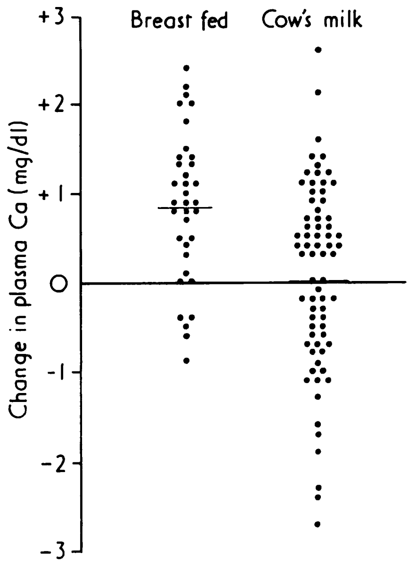

FIG. 3.—*Changes in plasma calcium between day 1 and day 6 of life (in mg/dl) in breast-fed and artificially-fed infants.*

On day 1 the mean plasma creatinine levels were $1 \cdot 0 \pm 0 \cdot 3$ mg/dl in both breast-fed and artificially-fed groups (Table I). By day 6 (Table II) the plasma creatinine levels had fallen to $0 \cdot 7 \pm 0 \cdot 3$ mg in the breast-fed and $0 \cdot 8 \pm 0 \cdot 3$ mg/dl in the artificially-fed group. In the artificially-fed infants there was a negative correlation between changes in plasma calcium and the plasma creatinine ($r = 0 \cdot 443$, $P < 0 \cdot 01$).

A crude estimate of creatinine clearance was obtained from the plasma creatinine obtained in the middle of the urine collection period on day 6, and the total 24-hour urinary creatinine excretion. The mean creatinine clearance was $2 \cdot 12 \pm 0 \cdot 82$ ml/min. Because of the difficulties of assessing surface area in the newborn the results were expressed in terms of body weight and were $0 \cdot 53 \pm 0 \cdot 2$ ml/kg per min in the cow's milk group and $0 \cdot 57 \pm 0 \cdot 2$ ml/kg per min in the breast-fed babies. In the artificially-fed infants there was a positive correlation between the change in plasma calcium and creatinine clearance ($r = 0 \cdot 404$, $P < 0 \cdot 05$).

Mean plasma osmolalities on day 1 were 270 ± 15 mOsm/kg and 266 ± 14 mOsm/kg in the cow's milk and breast milk groups, respectively. On day 6 the mean plasma osmolality in the cow's milk group was 278 ± 20 mOsm/kg and 270 ± 11 mOsm/kg in the breast-fed babies. There was a significant negative correlation between changes in plasma calcium level and plasma osmolality in the artificially-fed infants ($r = 0 \cdot 864$, $P < 0 \cdot 001$). The 24-hour osmolar excretion in artificially-fed infants was 30 ± 15 mOsm/24 hours which was significantly greater than the excretion of $14 \cdot 4 \pm 10$ mOsm/24 hours obtained in the breast-fed infants ($P < 0 \cdot 01$).

It has already been shown that a substantial number of artificially-fed infants showed a fall in plasma calcium level between days 1 and 6, causing a skewed distribution of calcium levels on day 6, whereas this was an unusual occurrence in the breast-fed infants.

Further analysis of data was undertaken to compare those artificially-fed infants who had a raised level or an identical calcium level between day 1 and day 6 with those who had a fall. The results are summarized in Tables III and IV. The mean weight of those who showed a rise in calcium level was $3 \cdot 32 \pm 0 \cdot 68$ kg and was not significantly different from those that showed a fall ($3 \cdot 27 \pm 0 \cdot 54$, $P > 0 \cdot 1$). The milk intake was almost identical in the two groups (32 ± 7 ml/kg per day and 34 ± 6 ml/kg per day, respectively). Urine output was 137 ± 36 ml in those infants showing a rise in calcium level and 109 ± 49 ml in those who showed a fall. This difference was not significant ($P > 0 \cdot 05$).

Plasma creatinine levels on day 6 were $0 \cdot 67 \pm 0 \cdot 22$ mg/dl in those infants showing a rise in plasma calcium but was $0 \cdot 96 \pm 0 \cdot 32$ mg in those showing a fall ($P < 0 \cdot 0025$). Urinary creatinine

TABLE II

24-hour urinary excretion of calcium and creatinine and osmolality on day 6 (means ±SD)

	Calcium (mg/d)	Creatinine (mg/d)	Osmolality (mOsm/24 h)
Breast-fed infants	$0 \cdot 78 \pm 0 \cdot 46$ (13)	$14 \cdot 7 \pm 12 \cdot 1$ (13)	$14 \cdot 4 \pm 10 \cdot 0$ (13)
Artificially-fed infants	$1 \cdot 80 \pm 1 \cdot 39$ (44)	$19 \cdot 6 \pm 10 \cdot 2$ (44)	$30 \cdot 5 \pm 16 \cdot 7$ (32)
Significance (t test)	$P < 0 \cdot 01$	$P < 0 \cdot 1$	$P < 0 \cdot 01$

Figures in parentheses = number of tests performed.

TABLE III

Plasma levels of calcium and creatinine and osmolality on day 6 of life in artificially-fed infants (means ±SD)

	Calcium (mg/dl)	Creatinine (mg/dl)	Osmolality (mOsm/kg)
Infants who showed a rise in Ca	9·20±0·70 (41)	0·67±0·22 (20)	262±8·0 (10)
Infants who showed a fall in Ca	8·40±9·10 (30)	0·92±0·32 (17)	291±17·0 (7)
Significance of difference (t test)	—	P <0·0025	P <0·005

Figures in parentheses = number of tests performed.

TABLE IV

24-hour urinary excretion of calcium and creatinine and osmolality on day 6 in artificially-fed infants (means ±SD)

	Calcium (mg/24 h)	Creatinine (mg/24 h)	Osmolality (mOsm/24 h)
Infants who showed rise in plasma Ca	1·95±1·75 (24)	24·6±9·0 (24)	42·5±18·4 (18)
Infants who showed fall in plasma Ca	1·89±1·52 (20)	15·3±8·0 (20)	25·5±9·5 (14)
Significance of difference (t test)	P >0·01	P <0·0025	P <0·025

Figures in parentheses = number of tests performed.

excretion of 24·6±9 mg/24 hours was significantly greater in those showing a rise in calcium than in those with a fall, who only excreted 15·3±8 mg/24 hours ($P<0·0025$). There was also a significant difference in creatinine clearance between the two groups, the values obtained being 0·68±0·20 mg/kg per min in those showing a rise in calcium and 0·35±0·24 ml/kg per min in those who had a fall ($P<0·0025$) (Fig. 4).

Plasma osmolality was 262±8 mOsm/kg in those infants that showed a rise in calcium and 291±17 mOsm/kg in those that had shown a fall ($P<0·005$). Conversely, osmolar excretion was significantly greater in those infants with an increase in plasma calcium than those with a decrease (38·8±19·4 mOsm/24 h and 24·2±9·9 mOsm/24 h, respectively, $P<0·05$).

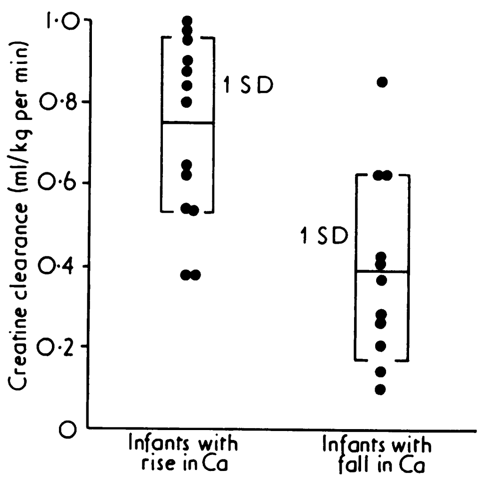

FIG. 4.—*Creatinine clearance per kg body weight on day 6 of life in bottle-fed infants. On the left are those babies whose calcium levels rose; on the right those whose levels fell.*

Discussion

Previous studies (Oppé and Redstone, 1968) have shown that mean plasma calcium levels in breast-fed infants at one week of age are greater than those found in infants fed with dried or evaporated milks. In the series described by Snodgrass *et al.* (1973) as many as 9% of infants on Carnation and Regal milk had calcium levels <7·0 mg/dl by one week of age. As was also noted by these authors, a substantial number of artificially-fed infants showed a fall in calcium levels, whereas almost all breast-fed and the remainder of the artificially-fed group showed a rise in plasma calcium over the first week of age. These factors are confirmed in our present study.

Those artificially-fed infants in the present study who showed a fall in calcium level had higher plasma creatinine levels with lower urinary creatinine excretion and lower creatinine clearance than those showing an increase. Sertel and Scopes (1973) have shown that creatinine clearance in the first day of life is only 16 ml/1·74 m^2. By one week of age creatinine clearance, though still only about one-third of the level in later childhood or adult life had doubled in value to 36 ml/1·74 m^2 per min. Hey (1973) has shown similar values in small premature infants, with similar increases in glomerular filtration in the first week of life. Such a rapid increase in glomerular filtration could not possibly be due to growth. It could either be due to an increase in functioning nephrons in immediate postnatal life, or to changes in the permeability of Bowman's capsule, or to an increase in effective filtration pressure. These changes may be related to the change to an extrauterine environment.

It is likely that there is considerable individual variability in the time taken for this adaption. This probably accounts for the difference in renal function between those that showed a rise and those that showed a fall. McCory and co-workers (1952) showed that in the newborn infant receiving cow's milk feeds the phosphate excretion was related to creatinine clearance. Therefore, it is likely that those infants who have delayed improvement in their glomerular filtration are unable to deal effectively with the excessive phosphate load in the cow's milk preparations. This results in a rise in extracellular phosphate and a lowering of extracellular calcium levels. Though significantly more calcium was found in the urine of artificially-fed infants than in those who were breast-fed, the absolute amounts were very small. It seems unlikely therefore that renal loss of calcium could explain the low levels of plasma calcium in hypocalcaemic infants.

Attention has been drawn to the high osmotic load imposed on infants by feeding with cow's milk (Taitz and Byers, 1972). This is reflected in the present study by a much greater osmolar excretion in cow's milk-fed infants than in those who were breast-fed. In artificially-fed infants, who had shown a rise in plasma calcium during the first 6 days, renal function enabled effective excretion of this osmotic load. This was characterized by the plasma osmolality remaining the same as on day 1 and also the same as in breast-fed infants. However, the poorer renal function of infants whose plasma calcium levels fell was shown by their plasma osmolality of 295 mOsm/kg on day 6 of life, which was significantly greater than the 262 mOsm/kg in those who showed a rise at this time.

The question remains as to whether those infants who had relatively impaired glomerular filtration on day 6 of life remain backward in terms of renal function. This seems unlikely because hypocalcaemic convulsions due to cow's milk feeds are rare after 12–14 days of age. It is, however, important to remember that glomerular filtration in all infants in the first 6 months is between 30–50% of that in older children and adults, and there are also severe limitations in the excretion of osmotic loads at this age.

We thank Sisters Catherine Carden and Barbara Nichols for help, Gay Cheeseman and Valerie Price for secretarial assistance, and Mr. Lawrence Armitage for illustrations.

References

Hey, E. (1973). *The Mammalian Fetus in vivo*, p. 314. Ed. by C. R. Austin. Chapman and Hall, London.

McCory, W. W., Forman, C. W., McNamara, H., and Barnett, H. L. (1952). Renal excretion of inorganic phosphate in newborn infants. *Journal of Clinical Investigation*, **31**, 357.

Oppé, T. E., and Redstone, D. (1968). Calcium and phosphorus levels in healthy newborn infants given various types of milk. *Lancet*, **1**, 1045.

Sertel, H., and Scopes, J. (1973). Rates of creatinine clearance in babies less than one week of age. *Archives of Disease in Childhood*, **48**, 717.

Snodgrass, G. J. A. I., Stimmler, L., Went, J., Abrams, M. E., and Will, E. J. (1973). Interrelations of plasma calcium, inorganic phosphate, magnesium and protein over the first week of life. *Archives of Disease in Childhood*, **48**, 279.

Taitz, L. S., and Byers, H. D. (1972). High calorie/osmolar feeding and hypertonic dehydration. *Archives of Disease in Childhood*, **47**, 257.

Wieme, R. J., and Van Raepenbusch, F. R. (1962). Automatic determination of calcium in blood and urine using corinth calcium. *Clinica Chimica Acta*, **7**, 883.

Correspondence to Dr. L. Stimmler, Guy's Hospital, St. Thomas Street, London SE1 9RT.