Archives of Disease in Childhood, 1978, **53**, 784–787

Calcium intake in the first five days of life in the low birthweight infant

Effects of calcium supplements

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SUMMARY Sixteen low birthweight infants were allocated to two groups. Both groups 1 and 2 received a formula with Ca/PO_4 ratio of 1·21. Group 2 infants received a supplement of 800 mg/kg per day of Ca and Mg lactate, and the daily Ca, Mg, and PO_4 levels were measured. Calcium intakes (mg/kg per day) were, comparing groups 2 and 1: 82 v. 33 on the 1st day; 133 v. 45 on 2nd; 170 v. 56 on 3rd; 224 v. 72 on 4th; 263 v. 88 on 5th. Magnesium intake (mg/kg per day) was 4·9 v. 3·8 on the 1st day; 8·3 v. 5·3 on 2nd; 9·8 v. 6·5 on 3rd; 15·5 v. 8·3 on 4th; 16·0 v. 10·0 on 5th. Phosphate intake was similar in both groups. Mineral content of vomits and regurgitations showed more Ca than P, with a ratio of 1:68. Comparing the two groups, in the supplemented infants, serum Ca rose from the 3rd day by an amount which was related to Ca intake: serum Mg was lower from the 4th day and was negatively correlated with Ca intake.

Early neonatal hypocalcaemia (ENH) is a clinical condition (Tsang and Oh, 1970) experienced by most preterm infants in the first 24–48 hours of life, which can give rise to serious complications—such as heart failure (Troughton and Singh, 1972) and other cardiac disorders (Colletti *et al.*, 1974; Doménech *et al.*, 1976), and to difficulties in management (Volpe, 1973; Weiss *et al.*, 1975), or, at a later stage, to mental disturbances (Forfar, 1974), or dental defects (Purvis *et al.*, 1973; Stimmler *et al.*, 1973).

Pathogenesis remains obscure. Among factors which may be involved are hypoparathyroidism (Anast *et al.*, 1972; David and Anast, 1974), disorders of, or lack of, vitamin D (Hillman and Haddad, 1974), and hypercalcitonism (Hillman *et al.*, 1977), but there is no evidence of their direct implication in the production of this disorder of homeostasis. Some perinatal events may predispose to ENH (Bergman, 1974; Tsang *et al.*, 1976). Alimentary factors are important: e.g. calcium/phosphate ratios and the quality and quantity of fat (Southgate *et al.*, 1969; Barltrop and Oppé, 1970, 1973).

Balance experiments allow the rate of mineral gain by the neonate to be measured, but for obvious reasons it is necessary to start after the 5th day of life (Widdowson, 1965; Day *et al.*, 1975). Because ENH occurs before this time, and in view of the placental Ca transfer rate, it seems important to quantify the total intake of Ca, P, and Mg in this early period of life.

The purpose of the investigation was to find out whether supplements of Ca and Mg to the diets of low birthweight infants would increase their serum Ca.

Patients and methods

Sixteen neonates of low birthweight were studied. They were between 34 and 38 weeks' gestation, determined by the mothers' last menstrual period and the scoring method of Dubowitz, and between 1420 and 2470 g. They were assigned to two groups. Mean birthweight, gestation, height, and Apgar scores were not significantly different in the two groups.

Group 1 (9 infants). These received a formula with lactose and normal total fat content, but partially substituted by vegetable fat. The mineral content is shown in the Table. Ca:P ratio measured by us, is near the lower limit given by the Committee on Nutrition of the American Academy of Pediatrics (1976).

Received 8 November 1977

Table *Mineral content of the basic formula*

Content (mg/100 ml)	*According to label*	*Results of analysis* (n = 45)*
Ca	49	$55 \cdot 32 \pm 0 \cdot 16$
Mg	4·76	$6 \cdot 32 \pm 0 \cdot 04$
PO_4	39·20	$45 \cdot 55 \pm 0 \cdot 08$
Ca/PO_4 ratio	1·25	$1 \cdot 21 \pm 0 \cdot 002$

*Mean ±SEM.

Group 2 (7 infants). These received the same formula but supplemented with 800 mg/kg per day Ca lactate containing 13·5 mg Ca and 0·45 mg Mg element in each 100 mg of the salt, divided in 7 doses and mixed with each feed.

In both groups feeding was started between the first 6 and 12 hours of life and with a schedule rising from 50 kcal/kg (0·21 MJ/kg) on the 1st day to 120 kcal/kg (0·50 MJ/kg) on the 5th. Energy intake was calculated from manufacturer's data.

The concentrations of Ca, Mg, and P in the diet were measured by taking an aliquot of each feed. They were dried and ashed at 450°C and then dissolved in HCl. Ca and Mg were measured by atomic absorption spectrophotometer, and P by the method of Fiske and Subbarow. Vomits and regurgitations were collected on ashless filter paper (Whatman no. 541), processed in the same way, and subtracted from intake.

Blood samples were obtained daily before the first feed in the morning.

Informed parental consent was obtained. All figures appearing in the text are expressed as mean ±SEM. Comparison of means was made by Student's *t* test.

Results

Because results were not significantly different in appropriate-for-gestation age (AGA) and small-for-gestational age (SGA) infants, comparisons were made only between groups 1 and 2.

Mineral intake. In group 1 Ca intake was 33 ± 3 mg/kg per day on 1st day, rising to 88 ± 2 mg/kg per day on day 5. In group 2 Ca intake was 82 ± 17 mg/kg per day on 1st day, rising to 263 ± 19 mg/kg per day on day 5.

There was a parallel rise in P intake in both groups and no significant differences between them. On the 5th day P intake was 73 ± 2 in group 1 infants and 82 ± 5 in group 2.

After the 1st day there were differences in Mg intakes between the two groups. Throughout the 5 days, Mg intake per day ($3 \cdot 8 \pm 0 \cdot 3$ to $16 \cdot 0 \pm 1 \cdot 0$ mg/kg per day) was within the wide range of the Mg supplied by most milk formulae, although the Mg intake of group 2 was in the upper part of the range.

Plasma minerals concentration. The Figure shows that serum total Ca began to rise significantly from the 3rd day with a rising trend in group 2, reaching $9 \cdot 25 \pm 0 \cdot 19$ v. $7 \cdot 77 \pm 0 \cdot 35$ mg/100 ml on the 5th day. Levels of significance are shown. Two days after the supplementation ended, total serum Ca in group 2 was $8 \cdot 70 \pm 0 \cdot 26$ mg/100 ml. At the 7th day of life, for group 1, this figure was $8 \cdot 25 \pm 0 \cdot 35$ mg/100 ml.

Serum P (Figure) showed little change in either group, with an initial and final mean of 5·6 and 5·5 mg/100 ml in group 1; and 4·52 and 5·27 in group 2. Serum Mg showed higher values in group 1 from the 4th day. On the 1st day the lower level of group 1 was owing to the presence of two babies with hypomagnesaemia (0·9 and 1·1 mg/100 ml). Apart from these, all values were above the accepted lower limit for adults (1·4 mg/100 ml).

Correlations. Correlations were sought between all variables analysed, including weight and gestational age. None was significant, except calcaemia and Ca intake ($r = 0 \cdot 55$; $P<0 \cdot 01$), and magnesaemia and Mg intake ($r = 0 \cdot 54$; $P<0 \cdot 01$), the first day values having been excluded because of their known higher values. A negative correlation between serum Mg level and Ca intake ($r = -0 \cdot 81$; $P<0 \cdot 001$) was noted in group 2 .

Discussion

The incidence of ENH even in babies born of mothers not at risk for this complication raises the point that Ca is among a number of elements which should normally accumulate in the last trimester of pregnancy. If the placental pump ceases there are two mechanisms available for maintaining Ca homeostasis—via the external nutrients supply or from bone resorption. Three considerations are pertinent to neonatal Ca regulation: (1) placental supply, (2) bone Ca reservoir, and (3) alimentary supply. According to Shaw (1973, 1976) the placental transfer at term is about 150 mg/kg per day, and this is because an active transport mechanism (Armstrong *et al.*, 1970) maintains a higher cord blood Ca level, $10 \cdot 36 \pm 0 \cdot 11$ mg/100 ml, than that of venous maternal blood, $9 \cdot 58 \pm 0 \cdot 10$ ($n = 12$; $P<0 \cdot 001$) (Moya and Doménech, 1976). A large proportion of the plasma Ca is ionised (Delivoria-Papadopoulos *et al.*, 1967) and these high levels in the fetus stimulate calcitonin and inhibit parathormone secretion producing conditions favourable to the

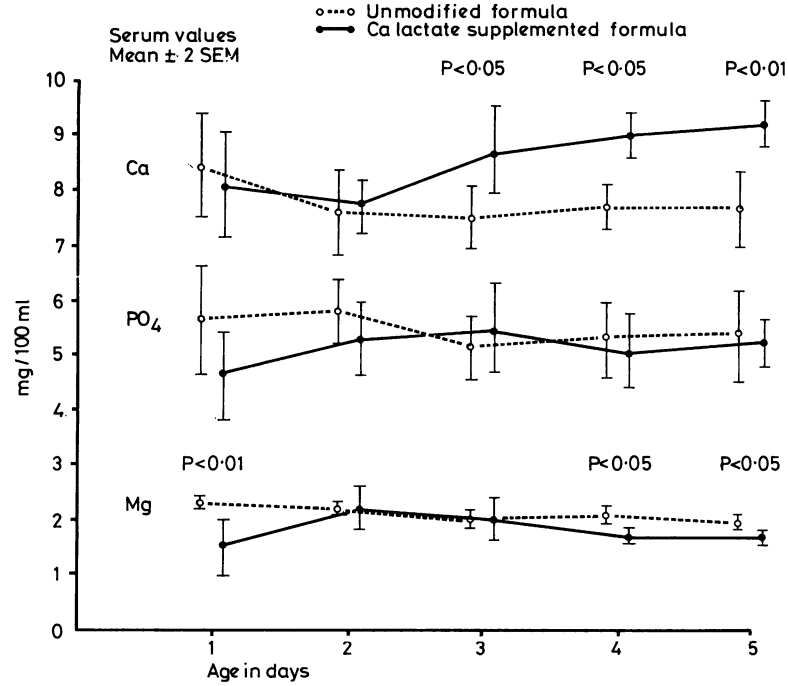

Figure *Plasma concentrations of calcium, magnesium, and phosphate.*

accelerating Ca accumulation during the last trimester of pregnancy (Pitkin, 1975).

After delivery the placental Ca flow is abruptly interrupted and the fetal situation is maintained by means of some degree of parathyroid inertia and some hypercalcitonism (Bergman *et al.*, 1974; David and Anast, 1974; Hillman *et al.*, 1977); Ca homeostasis should then depend on osseous mobilisation or on exogenous supply. Bone contribution is limited in the neonatal period, because Ca reserves are considerably smaller in the newborn, 0·71% of body weight (Stearns, 1939), than at older ages, 1·6% of body weight (Walser, 1961). These reserves may be reduced by a restriction of dietary Ca by the pregnant mother, at least in the rat (Moya and Vento, 1976), although there is no exact parallel with humans, since in rats blood Ca levels do not fall despite the low Ca content of the diet. Local food habits, with poor Ca supply or with natural chelants for this cation may aggravate this situation in the pregnant woman through maternal hypocalcaemia (Watney *et al.*, 1971). Moreover the skeleton of a baby born prematurely, in contrast to what occurs in the same period of intrauterine life, fails to mineralise significantly within the first 28 days of extrauterine life (McIntosh *et al.*, 1977).

Concerning alimentary supply we have seen how with a rather generous caloric schedule and a conventional formula, the actual Ca intake in the first 5 days was 32, 45, 55, 71, and 87 mg/kg, and with an appropriate Ca/PO_4 ratio. In a previous series of infants (Moya and Doménech, 1976), we observed a negative Ca and Mg balance in one baby because of a tendency to regurgitate. In the first day the loss was 4 mg/kg Ca and 1·4 mg/kg Mg. In the present study the mineral content of vomits and regurgitations was measured. In group 1 the total Ca regurgitated was higher than P, thus the daily Ca/P ratio in this regurgitated material was greater than in the feed formula, 1·68, 1·66, 1·61, 1·97, 1·34. In group 2 this ratio was higher, because the P regurgitated was kept at the same level as in group 1—2·90, 1·85, 2·51, 1·95, 3·05. Despite its addition, the Mg content in the regurgitated material of this group was not as high. The number of vomits and regurgitations did not differ significantly in either group.

This study was designed to examine the effectiveness of supplementing Ca intake to prevent early neonatal hypocalcaemia. In group 2 only one baby suffered from hypocalcaemia and on the first day. By contrast, in group 1, 5 out of the 9 infants had a serum Ca<7 mg/100 ml at least in one sample, needing oral or parenteral Ca administration. Serum Mg reflected the extra Ca intake, with lower levels at the end of the study, and we found 3 cases of symptomless hypomagnesaemia (<1·4 mg/100 ml) all of which subsided spontaneously. Competition of divalent cations in the absorbing process carried out by the enterocyte may explain this—a hypothesis in keeping with the negative correlation found between serum Mg level and Ca intake.

We have shown that on a conventional formula the infants in this study had received 87 mg/kg per day of Ca by day 5. As a fetus of 36 weeks' gestation may receive placentally 150 mg/kg per day, the conventional formula would appear to provide too little Ca. When infants received supplements of Ca lactate, a Ca intake of 150 mg/kg per day was achieved between the 2nd and 3rd day of life, and these infants exhibited significantly higher levels of serum Ca on days 4 and 5. As there was no change in the plasma P, these data suggest that a useful amount of the additional Ca was absorbed.

References

Anast, C. S., Mohs, J. M., Kaplan, S. L., and Burns, T. W. (1972). Evidence for parathyroid failure in magnesium deficiency. *Science*, **177**, 606–608.

Armstrong, W. D., Singer, L., and Makowski, E. L. (1970). Placental transfer of fluoride and calcium. *American Journal of Obstetrics and Gynecology*, **107**, 432–434.

Barltrop, D., and Oppé, T. E. (1970). Dietary factors in neonatal calcium homoeostasis. *Lancet*, **2**, 1333–1335.

Barltrop, D., and Oppé, T. E. (1973). Calcium and absorption by low birthweight infants from a calcium-supplemented milk formula. *Archives of Disease in Childhood*, **48**, 580–582.

Bergman, L. (1974). Studies on early neonatal hypocalcemia. *Acta paediatrica Scandinavica*, Supplement 248, 1–25.

Bergman, L., Kjellmer, I., and Selstam, U. (1974). Calcitonin and parathyroid hormone-relation to early neonatal hypocalcemia in infants of diabetic mothers. *Biology of the Neonate*, **24**, 151–160.

Colletti, R. B., Pan, M. W., Smith, E. W. P., and Genel, M. (1974). Detection of hypocalcemia in susceptible neonates. *New England Journal of Medicine*, **290**, 931–935.

Committee on Nutrition of the American Academy of Pediatrics (1976). Commentary on breast-feeding and infant formulas, including proposed standards for formulas. *Pediatrics*, **57**, 278–285.

David, L., and Anast, C. (1974). Calcium metabolism in newborn infants. *Journal of Clinical Investigation*, **54**, 287–296.

Day, G. M., Chane, G. W., Radde, I. C., Reilly, B. J., Park, E., and Sheepers, J. (1975). Growth and mineral metabolism in very low birthweight infants. II. Effects of calcium supplementation on growth and divalent cations. *Pediatric Research*, **9**, 568–575.

Delivoria-Papadopoulos, M., Battaglia, F. C., Bruns, D. P., and Meschia, G. (1967). Total protein-bound and ultrafilterable calcium in maternal and fetal plasmas. *American Journal of Physiology*, **213**, 363–366.

Doménech, E., Moya, M., Bosch, V., Paredes, C., and Marco, V. (1976). Valor diagnóstico del alargamiento del intervalo Q-T en la hipocalcemia neonatal. *Medicina española*, **75**, 367–373.

Forfar, J. O. (1974). Biochemical fits in the newborn. *Proceedings of the Royal Society of Medicine*, **67**, 375–377.

Hillman, L. S., and Haddad, J. G. (1974). Human perinatal vitamin D metabolism. I. Hydroxyvitamin D in maternal and cord blood. *Journal of Pediatrics*, **84**, 742–749.

Hillman, L. S., Rojanasathit, S., Slatopolsky, E., and Haddad, J. G. (1977). Serial measurements of serum calcium, magnesium, parathyroid hormone, calcitonin, and 25-hydroxy-vitamin D in premature and term infants during the first week of life. *Pediatric Research*, **11**, 739–744.

McIntosh, N., Shaw, J. C. L., and Taghizadeh, A. (1977). Accumulation of nitrogen and collagen in the femur of the human foetus, and the effects of premature birth (abstract). *Pediatric Research*, **11**, 1023.

Moya, M., and Doménech, E. (1976). Hipocalcemias neonatales. XIV Congreso Español de Pediatria, 27–30 October 1976, Barcelona (pp. 29–36 conference proceedings).

Moya, M., and Vento, M. (1976). Effects of low calcium diet over pregnant rats' and offsprings' calcium contents (abstract). *Pediatric Research*, **10**, 890.

Pitkin, R. M. (1975). Calcium metabolism in pregnancy: a review. *American Journal of Obstetrics and Gynecology*, **121**, 724–737.

Purvis, R. J., MacKay, G. S., Cockburn, F., Barrie, W. J. M., Wilkinson, E. M., Belton, N. R., and Forfar, J. O. (1973). Enamel hypoplasia of teeth associated with neonatal tetany: manifestation of maternal vitamin D deficiency. *Lancet*, **2**, 811–814.

Shaw, J. C. L. (1973). Parenteral nutrition in the management of sick low birthweight infants. *Pediatric Clinics of North America*, **20**, 333–358.

Shaw, J. C. L. (1976). Evidence for defective skeletal mineralization in low birthweight infants: the absorption of calcium and fat. *Pediatrics*, **57**, 16–25.

Southgate, D. A. T., Widdowson, E. M., Smits, B. J., Cooke, W. T., Walker, C. H. N., and Mathers, N. P. (1969). Absorption and excretion of calcium and fat by young infants. *Lancet*, **1**, 487–489.

Stearns, G. (1939). The mineral metabolism of normal infants. *Physiological Reviews*, **19**, 415–438.

Stimmler, L., Snodgrass, G. J. A. I., and Jaffe, E. (1973). Dental defects associated with neonatal symptomatic hypocalcaemia. *Archives of Disease in Childhood*, **48**, 217–220.

Troughton, T. K., and Singh, S. P. (1972). Heart failure and neonatal hypocalcaemia. *British Medical Journal*, **4**, 76–79.

Tsang, R. C., and Oh, W. (1970). Neonatal hypocalcemia in low birthweight infants. *Pediatrics*, **45**, 773–781.

Tsang, R. C., Strub, R., Brown, D. R., Steichen, J., Hartman, C., and Chen, I. W. (1976). Hypomagnesemia in infants of diabetic mothers: perinatal studies. *Journal of Pediatrics*, **89**, 115–119.

Volpe, J. (1973). Neonatal seizures. *New England Journal of Medicine*, **289**, 413–416.

Walser, M. (1961). Ion association. VI. Associations between calcium, magnesium, inorganic phosphate, citrate, and protein in normal human plasma. *Journal of Clinical Investigation*, **40**, 723–730.

Watney, P. J. H., Chance, G. W., Scott, P., and Thompson, J. H. (1971). Maternal factors in neonatal hypocalcemia, a study in three ethnic groups. *British Medical Journal*, **2**, 432–436.

Weiss, Y., Ackerman, C., and Shmilovitz, L. (1975). Localised necrosis of the scalp in neonates due to calcium gluconate infusions: a cautionary note. *Pediatrics*, **56**, 1084–1086.

Widdowson, E. M. (1965). Absorption and excretion of fat, nitrogen, and minerals from 'filled' milks by babies one week old. *Lancet*, **2**, 1099–1105.

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