Bone mineral content and body size 65 to 100 weeks' postconception in preterm and full term infants

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SUMMARY A total of 36 preterm and 22 full term infants were weighed and measured at 65 to 100 weeks' postconception. It was found that the preterm infants were on average significantly lighter by 1008 g and shorter by 3.8 cm than those born at full term. Despite the smaller size of preterm infants, mean values of bone mineral content in the mid-forearm were not significantly different between the two groups. In contrast, near 40 weeks' postconception the mean bone mineral content observed in 35 of the preterm infants was significantly smaller than that observed in eight of the full term infants.

Our results suggest that there is a phase of rapid mineral accretion between 40 and 60 weeks' postconception. This 'catch up' in mineral accretion reduces the perinatal mineralisation deficit that might otherwise persist into childhood.

In most preterm infants, by 40 weeks' postconception there is a substantial deficit in bone mineral accretion relative to full term infants observed at birth.^{1 2} Application of single photon absorptiometry to the mid-forearm has shown that those most seriously affected are infants born with extremely low birth weight (that is, <1000 g)³; by 40 weeks their bone mineral content is lower by about 35% after accounting for reduced weight and crown-heel length.² Preterm infants with higher birth weights are similarly undermineralised by about 20%.¹

Attempts to accelerate postnatal mineral accretion in preterm infants have had variable success (unpublished observations).^{4 5} Radiographically detectable osteopenia has reportedly been ameliorated by vitamin D supplementation.⁶ Our own measurements, however, did not show more rapid mineral accretion in preterm infants when the daily vitamin D₂ intake was raised from the standard 400 IU to 1000 IU (unpublished observations). There is stronger evidence that the rate can be increased by mineral supplementation,^{4 7} but the response is dependent on the way the supplement is administered, its amount, and whether or not vitamin D extra to the standard daily supplement is added.⁴ Our results using mineral supplemented formula feeds showed a significant improvement in accretion rate up to 40 weeks' postconception⁸; however, by

40 weeks the preterm infants were still undermineralised relative to full term peers.

The thrust of supplementation studies towards restoration of mineral accretion rate to its in utero values arises partly from the desire to minimise known complications of neonatal osteopenia. It is not known, however, whether this is simply a short term problem or whether it has a long term impact on skeletal development. The purpose of the present study was to compare weight, crown-heel length, and bone mineral content in preterm and full term infants 65 to 100 weeks' postconception in order to determine whether or not effects of prematurity were detectable beyond the neonatal period. Differences in weight gain and linear growth were anticipated and particular emphasis was therefore placed on the bone mineral measurements.^{9 10}

Patients and methods

This study was authorised by the local ethics committee. In all, 58 infants born between May 1984 and February 1988 were examined. They were all white singletons whose parents gave informed consent for the investigations to be performed. Of the 58, 36 infants (18 of each sex) had been born prematurely and comprised the 'preterm group', group P. The remaining 22 (15 boys), who were

born after approximately 40 weeks' gestation, comprised the 'full term group', group F, and served as controls.

Infants in group P had been born in or referred to our neonatal intensive care unit during a 30 month period commencing July 1984. While in the unit they had been included in studies of the efficacy of various feeding regimes in promoting bone mineral accretion during the neonatal period.⁸ After discharge from the unit they all received conventional formula feeds.

Of the 22 full term infants in group F, nine had previously served as controls in another study when much younger, and participated in the present investigation because their parents were prepared to bring them from home for remeasurement. The other 13 infants were recruited from the local general paediatric ward and were measured while inpatients. They were selected initially on the basis of age and race from all cases presenting with acute non-serious illness who had no history or signs of bone, liver, or renal disease. Patients who had received medication that in any way might have influenced mineral metabolism were rejected, as were those who had not been born at full term (assessed from birth case notes) and those who were below the 10th centile for weight on standard charts.¹¹ With four exceptions, all the full term infants received formula feed from birth; the remainder were breast fed, with weaning commencing at about 3 months of age.

Gestational age (completed weeks), calculated from maternal menstrual history and confirmed by either external examination¹² or ophthalmoscopic examination of the lens,¹³ had been documented in each case. For group P, gestational age ranged from 26 to 31 weeks with mean (SD) 28.5 (1.8) weeks and for group F ranged from 37 to 42 weeks with mean 39.3 (1.5) weeks.

On up to three occasions but usually two, near to 40 weeks' postconception and in the period 65 to 100 weeks' postconception, the bone mineral content (mg/cm) was measured at the middle of the forearm of each infant by photon absorptiometry as described in previous publications.¹⁻³ The radiation exposure involved in this procedure is very small, and only a narrow area of the forearm is irradiated during a scan; skin entrance dose is 0.03 mG per investigation. Weight (g) and crown-heel length (cm) were usually measured whenever a scan was performed.

In the postconceptional age range 37 to 45 weeks, complete data (that is weight (W), crown-heel length (CHL), and bone mineral content (BMC)) were obtained in 34 of the 36 preterm infants comprising group P; one had no measurements taken in that period, and in one infant crown-heel

length was not measured. Results obtained at that time ('term data') are denoted by W1, CHL1, and BMC1, with PA1 denoting postconceptional age. Eight randomly selected members of group P (five boys) were also scanned while attending outpatient clinics when aged between 46 and 53 weeks' postconception; the resulting 'intermediate data', denoted by W2, CHL2, BMC2, were complete except in one case in whom weight and crown-heel length were not measured on the day of that scan. All 36 infants in group P were later scanned in the period 68 to 101 weeks' postconception, again when they attended for outpatient review. In three infants, neither weight nor crown-heel length was measured on the day of the final scan. Results obtained at that later time ('endpoint data') are denoted by W3, CHL3, and BMC3.

Soon after birth, in the postconceptional age range 39 to 43 weeks, complete data (that is, W1, CHL1, and BMC1) were obtained in eight (four boys) of the 22 full term infants comprising group F. All 22 infants were later scanned in the period 65 to 102 weeks' postconception. The data obtained in that interval (W3, CHL3, and BMC3) were complete. None of the full term infants had measurements taken at intermediate times.

Descriptive statistics for the term, intermediate, and endpoint data are given in tables 1, 2, and 3 respectively.

STATISTICAL ANALYSIS

Calculations performed on the data included simple linear regression, F tests of the significance of the difference in slopes of regression lines,¹⁴ and analysis of variance and covariance using type of birth

Table 1 Descriptive statistics for observations of weight (W), crown-heel length (CHL), and bone mineral content (BMC) obtained around 40 weeks' postconception in both the preterm (P) and full term groups (F) (term data). PA denotes postconceptional age

	PA1 (weeks)	W1 (g)	CHL1 (cm)	BMC1 (mg/cm)
Group P:				
Mean	40.4	2620	46.15	118.8
SD	1.6	739	4.14	41.3
Maximum	44.6	4005	52.90	224.0
Minimum	37.4	1270	38.70	65.0
No of subjects	35	35	34	35
Group F:				
Mean	41.0	3344	50.38	190.9
SD	1.2	401	1.33	20.4
Maximum	42.7	3885	52.50	216.0
Minimum	39.1	2795	48.60	165.3
No of subjects	8	8	8	8

Table 2 Descriptive statistics for observations of weight (W), crown-heel length (CHL), and bone mineral content (BMC) obtained between 46 and 53 weeks' postconception in the preterm group (P) (intermediate data). No intermediate data on group F were available

	PA2 (weeks)	W2 (g)	CHL2 (cm)	BMC2 (mg/cm)
Group P:				
Mean	49.6	4029	53.71	207.9
SD	2.8	701	3.71	44.5
Maximum	52.7	4850	59.00	286.3
Minimum	46.1	2950	48.80	155.7
No of subjects	8	7	7	8

Table 3 Descriptive statistics for observations of weight (W), crown-heel length (CHL), and bone mineral content (BMC) obtained in the postconceptional age range 65–100 weeks approximately in both the preterm (P) and full term groups (F) (endpoint data)

	PA3 (weeks)	W3 (g)	CHL3 (cm)	BMC3 (mg/cm)
Group P:				
Mean	86.2	8148	71.23	301.8
SD	7.9	1229	4.00	80.0
Maximum	101.0	10 750	78.50	490.3
Minimum	68.4	5150	60.90	184.9
No of subjects	36	33	33	36
Group F:				
Mean	77.2	8732	72.26	279.0
SD	11.3	1203	4.66	73.0
Maximum	101.5	11 300	85.00	390.9
Minimum	65.3	6900	64.50	174.1
No of subjects	22	22	22	22

(preterm, full term) as a factor. Multiple regression analysis including a dummy independent variable based on type of birth was used to fit parallel regression lines to the data where appropriate.¹⁴ These techniques were applied using postconceptional age rather than time since birth as an independent variable. The resulting models can if necessary be used to predict the outcome of comparisons between preterm and full term infants of similar ages expressed as time since birth. Standard errors are denoted throughout by SE. Where error limits bound a mean point value, SE refers to the standard error of the mean. Where error limits about a regression line are given, SE refers to the standard error of the estimated mean.

Results

Figs 1, 2, and 3 show the individual term data for weight, crown-heel length, and bone mineral con-

Fig 1 The association between body weight and postconceptional age in preterm and full term infants (endpoint data). The regression line shown fits the data on the full term infants.

Fig 2 The association between crown-heel length and postconceptional age in preterm and full term infants (endpoint data). The regression line shown fits the data on the full term infants.

tent in relation to postconceptional age. Although in previous studies of younger infants it had been necessary to apply logarithmic transformations to all three measurements,^{2 8 15} there was no evidence in the current endpoint data that such a transformation was necessary at these higher postconceptional ages. Linear regression analysis was therefore applied to the raw data, starting with the observations on the full term infants. The equations, correlation coefficients, and associated significance levels of the resulting regression lines shown in figs 1 to 3 were:

$W3 = 3873 + 62.96 \cdot PA3 \text{ g}$ $r = 0.59, p < 0.005$
 $CHL3 = 46.00 + 0.3402 \cdot PA3 \text{ cm}$ $r = 0.83, p < 0.001$
 $BMC3 = -16.80 + 3.832 \cdot PA3 \text{ mg/cm}$ $r = 0.60, p < 0.005$

Preliminary inspection of the distributions of the observations on preterm infants relative to the regression lines shown in figs 1 and 2 indicated that weight and crown-heel length may be reduced in preterm infants relative to full term infants of comparable postconceptional age. In contrast, inspection of the results shown in fig 3 led us to conclude that there was no clear difference between values of bone mineral content in preterm and full term infants.

Regression analysis of the weight data for preterm infants shown in fig 1 resulted in a regression line having a slope not significantly different from the line illustrated. Analysis of variance and covariance showed type of birth (whether preterm or full term) to be a significant factor ($p < 0.005$) and multiple regression analysis was therefore performed using type of birth as a dummy variable. The two parallel lines which resulted are shown in the model illustrated in fig 4. The group centroid is indicated on each regression line; the ends of each line indicate the limits of the data. The common slope was 50.2 g/week (standard error of the slope, $SES = 16.4$ g/week), the lower of the two intercepts was 3851 g (SE = 341 g); the time separation of the two lines was therefore approximately 20 weeks. The multiple correlation coefficient was 0.44.

Similar analysis of the data for crown-heel length for preterm infants shown in fig 2 also resulted in a

Fig 3 The association between bone mineral content of the mid-forearm and postconceptional age in preterm and full term infants (endpoint data). The regression line shown fits the data on the full term infants.

Fig 4 Model of changes in weight with increasing postconceptional age in preterm and full term infants. SE denotes standard error of the mean for point values and standard error of the estimated mean for regression lines.

line with a slope not significantly different from the line illustrated, and analysis of variance and covariance again showed type of birth to be a significant factor ($p < 0.001$). The two parallel lines resulting from multiple regression analysis of the endpoint data are shown in the model illustrated in fig 5. Their common slope was 0.313 cm/week ($SES = 0.045$ cm/week), the lower intercept was 44.50 cm and the difference of the intercepts was 3.76 cm ($SE = 0.935$ cm); the time separation of the two lines was

Fig 5 Model of changes in crown-heel length with increasing postconceptional age in preterm and full term infants. SE denotes standard error of the mean for point values and standard error of the estimated mean for regression lines.

approximately 12 weeks. The multiple correlation coefficient was 0.49.

Analysis of variance and covariance did not show type of birth to be a significant factor in the 'term data' for bone mineral content (fig 3) and a single regression line was therefore fitted to the combined observations on preterm and full term infants. That common line is shown in the model illustrated in fig 6. Its slope was 2.43 mg/cm/week ($SES=0.96$ mg/cm/week) and it passed through the value 286.8 mg/cm at 80 weeks' postconceptional age ($r=0.32$; $p<0.02$). The error bars drawn in fig 6 about the common line indicate the 2SE limits of the estimated mean (that is, the ordinate of the regression line at any postconceptional age).

Figs 4, 5, and 6 contain exponential curves from 10 to 40 weeks of age based on our previously published data on growth in utero¹⁵; 2SE limits of the estimated mean logarithmic values were computed at equally spaced intervals and antilogarithms taken to derive the error limits shown. In each figure the following are also included:

- (1) A point on the in utero curve plotted at the mean gestational age of group P. This is the estimated mean value of the independent variable at birth for the preterm infants.
- (2) The mean values with 2SE limits of the term data for groups P and F (from table 1). In the case of group F, infants with term data comprised only a small subset ($n=8$) of those with endpoint data ($n=22$).
- (3) The mean value with 2SE limits of the

intermediate data for group P (from table 2); again infants with those data comprised only a small subset ($n=7$ or 8) of those with endpoint data ($n=33$ or 36).

(4) A smooth free hand curve joining the mean values described above for preterm infants with the regression line or lines representing the endpoint data for preterm infants.

For weight and crown-heel length, standard curves are available which describe the expected mean values from age 28 weeks onwards¹¹; the standard weight curve for full term boys is shown in fig 4. The same figure also contains the regression line with its 2SE limits for the endpoint data on the full term group (dotted). In fig 5 the standard crown-heel length curve for boys is shown from 28 weeks.

Thus figs 4, 5, and 6 summarise how the mean values of weight, crown-heel length, and bone mineral content probably changed as postconceptional age increased in these groups of preterm and full term infants. In general terms, those figures should not be taken to describe the paths likely to be followed by any individual. For example, the paths followed by the individuals in the current study might have contained small plateau regions, not apparent in this set of data, that would only have been shown by frequently repeated sequential measurements throughout the whole age span.

Within the limitations of the available data, however, fig 4 clearly shows the sigmoidal shape of the growth curve for weight in both groups. Our in utero curve and the standard curve match up at 40 weeks; for the full term infants, the mean weight near to the time of birth, 3344 (284) g (2SE limits; 95% confidence interval is a factor of 1.18 greater), was consistent with the standard mean value of 3650 g approximately. The endpoint data on the full term infants were also consistent with the standard data for boys, the error limits of the regression line for full term infants (dotted) encompassing the standard curve. At all postconceptional ages group P had a lower mean weight than group F. For both the term data and intermediate data on group P, the mean value of weight was significantly lower than the standard value ($p<0.001$), and the two parallel lines representing the endpoint data had significantly different intercepts ($p<0.005$) as indicated above. The absolute mean weight difference between the groups increased with time, from about 700 g at 40 weeks to about 1100 g at 80 weeks. Relative to mean values in full term infants, these differences amounted to deficits of 21% and 13%. Viewing the two curves in fig 4 in a different way, the time lag between the two groups increased as postconceptional age increased: at about 40 weeks the preterm infants lagged behind the full term infants by about

Fig 6 Model of changes in bone mineral content of the mid-forearm with increasing postconceptional age in preterm and full term infants. SE denotes standard error of the mean for point values and standard error of the estimated mean for regression lines.

five weeks; around 80 weeks' postconception the preterm infants were about 20 weeks behind.

Fig 5 similarly shows the sigmoidal shape of the growth curve for crown-heel length in both groups. Our previously published regression equation describing length increase in utero systematically overestimated crown-heel length in the postconceptional age range 30 to 40 weeks; the standard curve in fig 5 lies below the exponential approximation to the in utero data. (The systematic error is evidence that the exponential approximation was invalid at the upper extreme of the age range examined.) With regard to the full term infants, the term data for crown-heel length (mean 50.38 (0.94) cm; 2SE limits) tended to be low but were reasonably consistent with the standard value (51.5 cm approximately). At higher postconceptional ages, the standard curve approached almost tangentially the upper of the two parallel regression lines describing the endpoint data. At all postconceptional ages, group P had lower mean values of crown-heel length than group F. For both the term data and intermediate data on group P, mean crown-heel length was significantly lower than the standard value ($p < 0.001$ and 0.02 respectively), and the two parallel lines representing the endpoint data had significantly different intercepts ($p < 0.001$) as mentioned above. The absolute difference between the groups in mean crown-heel length remained essentially constant from 40 weeks onwards at about 5 cm. Relative to values in full term infants, this amounted to a length deficit of about 10% at 40 weeks and 7% at 80 weeks. Again the time lag between the two groups increased as postconceptional age increased; at about 40 weeks the preterm infants lagged behind the full term infants by about five weeks; around 80 weeks' postconception the preterm infants were more than 10 weeks behind.

Fig 6 illustrates the divergence and reconvergence of the mean bone mineral content values in the preterm and full term groups. For group F, the mean value of the term data lay very close to the line produced by backward extrapolation of the regression line through the endpoint data, that is, it appears from these results that the rate of increase of bone mineral content in the full term infants was constant from birth onwards. The postnatal rate of mineral accretion was less than the rate appertaining in utero, even at the very lowest gestational ages investigated in previous studies. The mean value of bone mineral content for the term data (group F) was somewhat lower than the mean value predicted by the exponential in utero curve; this finding was anticipated on the basis of the rather low mean value of crown-heel length observed in this subset of the full term infants (fig 5). The mean value of the

intermediate data for bone mineral content on the preterm infants lay close to the line joining the data on full term infants, implying that the deficit evident in the preterm infants at 40 weeks had been largely made up at 50 weeks' postconception. The mean values of the term data were significantly different between the two groups ($p < 0.001$), as expected from previous studies^{1,2}; near 40 weeks the mean value for group P was about 60% of the mean value for group F.

Discussion

Our weight and crown-heel length measurements are consistent with the common clinical observation that in the postconceptional age range 65 to 100 weeks, preterm infants are lighter and shorter than their full term peers.⁹ In the groups we studied the weight deficit was about 1000 g and the crown-heel length deficit was about 4 cm.

Those results, coupled with previous observations in preterm infants of substantial deficits in bone mineralisation at about 40 weeks' postconception,^{1,2} led us to expect that there might be a systematic, longer term mineralisation deficit in such cases. The null hypothesis tested in the analysis presented above was that no mineralisation deficit existed after 65 weeks' postconception, and contrary to expectations that hypothesis could not be rejected on the basis of the observations. Our present conclusion is therefore that we have no evidence of a longer term mineralisation deficit in preterm infants, despite their reduced body size, where mineralisation deficit here refers specifically to the mineral content of a 1.0 cm length of the mid-forearm, summated over the two bones.³

Although we and others have used that measurement to quantify osteopenia of prematurity in the neonate,^{1,2,4,7} it would not be valid to conclude from the results of this study that osteopenia of prematurity has been shown to be a self remitting condition with no long term consequences for skeletal status in the broadest sense. Mineralisation of the forearm bones at their metaphyses, which were not monitored in our study, might be affected by prematurity; there may also be persistent effects of prematurity on mineral accretion at other skeletal sites that are not mirrored in changes at the mid-forearm site.¹⁶

Furthermore, as prematurity is clearly associated with changed bone morphology (that is, reduced length of the long bones), the rate of matrix synthesis must itself be reduced, perhaps with secondary effects on mineralisation. For example, the lack of a mineralisation deficit in the mid-forearm may be partly a consequence of the fact that

linear growth is retarded in preterm infants, the available mineral supply being deposited in the diaphysis rather than in the metaphyses, because the latter grow less rapidly than they should in those cases. The bones of preterm infants are not only shorter; the distribution of mineral within the forearm bones appears to differ from that in full term infants. In such a situation, the limits of our present methodological approach have been reached, and future studies may need to include, for example, measurements of the length of the mineralised region in the radial diaphysis.

There are currently few published results with which our endpoint data can be compared. Although several groups have used peripheral absorptiometry to examine bone mineralisation in the first year of life,^{9 16-24} currently no other published study has involved both preterm and full term infants in the postconceptional age range 65 to 100 weeks. Previously published data from Chan and coworkers on somewhat younger full term infants²³ and preterm infants,¹⁷ who were rather heavier than our cases, however, are consistent with our findings. Comparison of their data from the two studies shows that by the postconceptional age of 56 weeks the mean value of bone mineral content observed in their preterm group (103 mg/cm) was similar to the mean value observed in their full term group (110 mg/cm).

If preterm and full term infants do in fact have very closely similar mean values of bone mineral content by about 60 weeks' postconception, yet differ substantially at 40 weeks, it is an obvious deduction that, in the interval 40 to 60 weeks, preterm infants must have a higher rate of mineral accretion than full term infants. Published data from several sources strengthen this conclusion and also highlight the large interindividual variability in the rate of mineral accretion. Between 40 and 56 weeks' postconception, preterm infants have been shown to increase their bone mineral content value by between 30% and 60% of the mean value observed in full term infants close to the time of birth.^{9 17 18} Over the same period term infants have been shown to increase their bone mineral content values by smaller amounts, in the range 11 to 45%.^{20 23}

Our observation of accelerated mineral accretion in the forearms of preterm infants between 40 and 60 weeks' postconception is therefore consistent with the findings of other workers. The acceleration appears to be of sufficient magnitude to reduce substantially the large mineral deficit which develops in preterm infants in the immediately postnatal period and which might otherwise persist into childhood. Detection of residual effects too small to be revealed by the current study would

require a different experimental approach, perhaps involving radiography and frequent sequential observations of individuals throughout the whole span of postconceptional age under investigation.

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