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ANALYSIS OF FETAL BONE METABOLISM EMPLOYING ASSAYS OF THE CARBOXYTERMINAL PROPEPTIDE OF TYPE 1 PROCOLLAGEN AND THE PYRIDINOLINE CROSS-LINKED CARBOXYTERMINAL TELOPEPTIDE OF TYPE 1 COLLAGEN

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In an effort to elucidate the physiology of fetal bone metabolism, we studied markers of bone formation and resorption. Cord blood levels of P1CP (the carboxy-terminal propeptide of type 1 procollagen) and 1CTP (the pyridinoline cross-linked carboxy-terminal telopeptide of type 1 collagen) were measured in 74 newborns (40 healthy newborns, 34 preterm newborns with no complications) at birth and 8 healthy infants during the first year of life. The cord blood levels of P1CP and 1CTP in the 74 newborns were 1423.5 ± 611.6 and 95.8 ± 34.2 ng/ml (mean ± SD), respectively. There were significant negative correlations between the concentrations of P1CP or 1CTP and gestational age, birth weight, birth length and head circumference ($p<0.0001$). Comparisons among the levels of P1CP and 1CTP and the rate of standard fetal weight gain, revealed the curves of P1CP and 1CTP levels to nearly parallel the curves of the standard fetal weight gain rate in male and female newborns. P1CP and 1CTP levels corresponded to birth weight as well as gestational age, with the influences of other factors being negligible. We also assayed P1CP and 1CTP in 8 healthy infants under one year of age, and found that a high P1CP value and low 1CTP value resulted in a 4-fold increase in the mean P1CP/1CTP ratio, as compared to the newborns. In contrast, the P1CP/1CTP ratio was nearly constant during the preterm and term periods. The results suggest that high turnover reflects high bone remodeling activity which corresponds to rapid morphological changes in the fetal period, that high turnover processes are strongly associated with physical growth as well as gestational age in immature fetal bone and that bone formation is the dominant process in healthy infants during the first year of life.

Introduction

Although high bone metabolic activity has been demonstrated in the fetal and neonatal periods[1)~3)], the details of bone metabolism in early life remain unclear. Research attention has focused on bone metabolism in the fetal period. Osteomalacia and osteoporosis have been recognized in neonates, infants and children and have been attributed to various pathogenic origins[1)2)4)~6)]. Bone metabolism in the fetus, neonates and children differs from that of adults. Bone growth occurs with various physiological changes from the fetal period through

childhood. Notably, the fetus is floating in the amnion and is thus exposed to less gravity. The neonate is usually recumbent, while the infant posture changes from lying to standing. Therefore, it is important to elucidate the metabolic process of bone formation and resorption to evaluate growth and development in the fetal period as well as during childhood.

Extensive research on the serum concentration of the carboxy-terminal propeptide of type 1 procollagen (P1CP), which reflects bone formation, and on pyridinoline cross-linked carboxy-terminal telopeptide of type 1 collagen (1 CTP), reflecting bone resorption[7)~10)], has demo nstrated the efficacy of these biochemical markers for assessing metabolic bone disease, osteoblastic bone metastases and hormone therapy[11)~16)]. In the field of pediatrics, the serum P1CP and 1CTP concentrations have been measured in healthy children and children with growth disorders due to hormone therapy[16)~19)]. To date, however, there has been no satisfactory description of the bone metabolic characteristics of the fetal period based on P1CP and 1CTP measurements. Our study was designed to clarify the processes of bone formation and resorption in the fetal period.

Subjects and Methods

1. Subjects

1) Newborns

Seventy-four newborns (40 healthy newborns, 34 preterm newborns who were born prematurely because of maternal cervical asthenia or trachelitis without any complications) who were born in the Maternal and Perinatal Center of Tokyo Women's Medical College Hospital from August 1995 to October 1996 were studied. Thirty-four were born preterm, 40 at term (AGA: appropriate for gestational age). There were 41 males and 33 females. Informed consent was obtained from the parents of all 74 newborns prior to beginning the study. All met the following criteria.

(1) The birth weight, length and head circumfrence were within ± 1.5 SD for the gestational age.

(2) There were no major congenital anomalies, infections or metabolic disorders, including hepatic and renal dysfunction, and the Apgar score at five minutes after birth was at least nine.

(3) Healthy mothers; no mdeication used during pregnancy.

2) Infants

Eight healthy infants, from 1 month to 1 year old, who were followed at the out-patient pediatrics clinic of Tokyo Women's Medical College Hospital were also studied. None had infection, hepatic dysfunction or renal dysfunction. The weights, heights and head circumferences of all infants were within ± 2 SD for their age. Informed consent was obtained from the parents.

The 74 newborns and 8 infants were divided into four groups according to gestational age for statistical comparison of P1CP and 1CTP (Table 1).

2. Methods

Measurement of P1CP and 1CTP

Cord blood was obtained at birth from the 74 newborns and peripheral venous blood from the 8 infants. After serum separation, the sampels were stored at −80°C. P1CP and 1CTP were measured by radioimmunoassay with an RIA reagent kit purchased from Orion Diagnostica, Espoo, Finalnd. Serum P1CP and 1CTP were measured according to the methods of Melkko et al[7)] and Risteli et al[9)], respectively. We incubated 100 μl standard solutions and serum samples with 200 μl of ^{125}I-P1CP or ^{125}I-1CTP and 200 μl of anti-P1CP or anti-1CTP for 2 h at 37°C, then added 500 μl of separation reagent containing the second antibody (rabbit) and polyethyleneglycol. After 30 min at room temperature, the bound fraction was separated by centrifugation at 2,000 G, 4°C, for 15 min, or in the case of 1CTP assay, for 30 min. Finally, we aspirated the supernatants and counted the radioactivites of the pellets.

Table 1 Clinical profiles of the 74 newborns and 8 healthy infants

	Gestational age(w)			
	29<～≦34 n=9	34<～≦38 n=25	38<～≦40 n=40	1m～1y n=8
Sex ratio(F/M)	2/7	9/16	23/17	3/5
BW(g)	1,831.2±365.4	2,541±511	3,036±317	6.4±1.7kg
BL(cm)	42.1±2.4	46.4±2.8	49.2±1.4	61.4±7.8
HC(cm)	30.0±2.4	32.4±1.4	33.5±1.1	41.7±3.8

BW : birth weight, BL : birth length, HC : head circumference, F/M : female/male, w : week, m : month, y : year, mean±SD.

3. The data analysis and related comparisons

1) Serum P1CP and 1CTP data analysis

Student's t test and regression analysis, employing Stat View, were used to determine the statistical significance of differences between mean values.

2) Relations of P1CP and 1CTP to gestational age

According to gestational age, the 74 newborns were divided into 3 groups (29<～≦34 weeks, 34<～≦38 weeks, 38<～≦42 weeks) (Table 1) and their mean ± SD of P1CP and 1CTP values were compared.

3) Analysis of P1CP and 1CTP in relation to growth

The correlations among P1CP, 1CTP, BW (birth weight), BL (birth length), HC (head circumference at birth) and gestational age were analyzed by regression analysis.

To determine the relationships between P1CP and 1CTP values with the rates of fetal growth in female and male newborns, we superimposed the P1CP and 1CTP curves on the rate of their fetal weight gain.

According to the fetal weight gain data for females and males obtained in the investigation counducted by the Japanese Ministry of Welfare in 1994[20], we calculated the rate of fetal weight gain using the following formula:

Rate of fetal weight gain=

$$\frac{\text{weight}(n+1)-\text{weight}(n)}{\text{weight }(n)}\times 100\%$$

n: gestational weeks

In order to identify the independent effects of gestational age and physical growth on P1CP and 1CTP values, we subdivided the selected newborns into two groups (<38 w, >38 w) based on the gestational age with similar bith weights (<38 w group; n=4, mean ± SD 2,776.3 ± 41.9 g, >38 w group; n=9, 2,780.0 ± 59.4 g) (Fig. 6). We also subdivided the selected newborns with similar gestational ages into another two groups based on birth weight (<2,900, >2,900 g). The gestational age was 37.3 ± 0.3 weeks in the <2,900 g group (n=12), 37.6 ± 0.4 weeks in the >2,900 (n=8). The P1CP and 1CTP levels were compared between the subdivided groups (Fig. 7).

4) Analysis of P1CP and 1CTP in relation to other factors

The relationship of P1CP and 1CTP with serum Ca, P, ALP and other factors were determined by regression analysis. The gender differences in P1CP and 1CTP values were analyzed using Student's t test.

Results

The obtained P1CP and 1CTP value and their relations to gestational age

The average cord serum levels of P1CP and 1CTP in all 74 newborns were 1,423.5 ± 611.6 and 95.8 ± 34.2 ng/ml (mean ± SD). There were significant negative correlations between P1CP and gestational age ($p<0.0001$, $r=-0.579$) and 1CTP and gestational age ($p<0.0001$, $r=-0.622$) (Fig. 1). Comparisons among the gestational age subgroups showed the same tendency (Fig. 2). In the 29～34 weeks gestation group, P1CP was the highest, at 1970.5 ± 1011.2 ng/ml and 1CTP was also

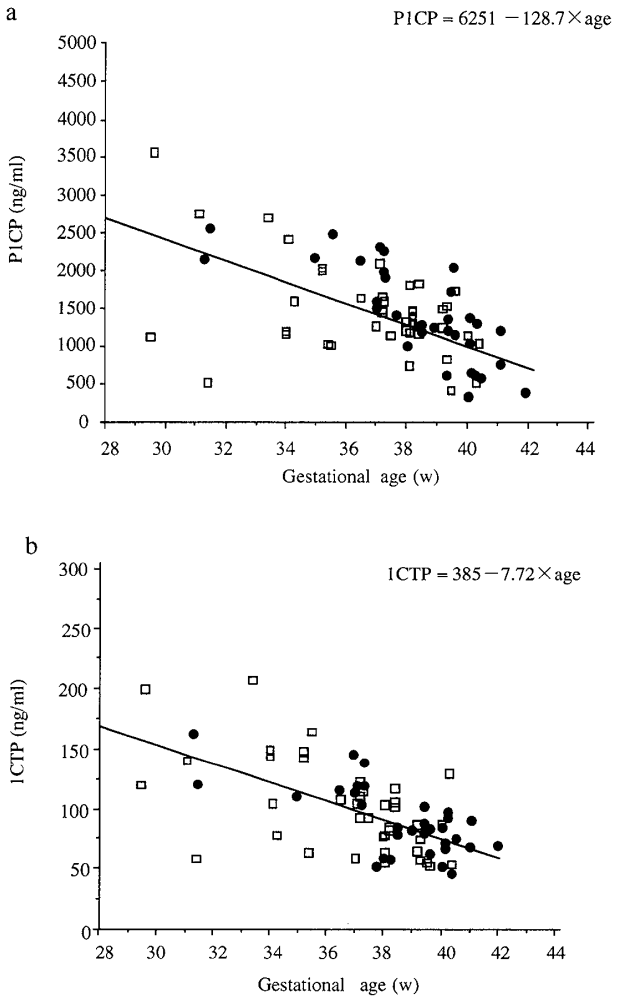

Fig. 1 Relationships between P1CP (a), 1CTP (b) and gestational age in 74 newborns (preterm and term)
a: r=−0.579, p<0.0001, b: r=−0.622, p<0.0001, ●: female, □: male.

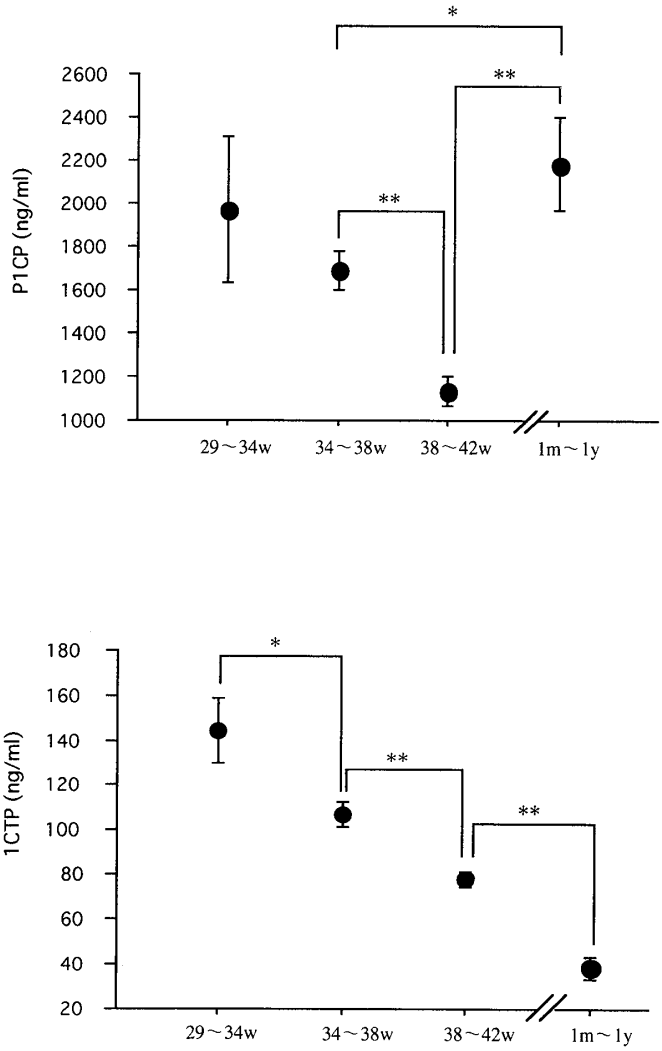

Fig. 2 Mean values of P1CP and 1CTP in each age group
Mean values of P1CP and 1CTP in preterm babies were higher than in term babies. The P1CP level was higher, the 1CTP level lower, in healthy infants at one month to one year of age than in newborns. mean ± SD, *: p<0.05, **: p<0.0001.

highest, at 144.4 ± 44.3 ng/ml. In the 34~38 weeks gestation group, the P1CP level had decreased to 1,688.9 ± 418.7 ng/ml and 1CTP to 106.9 ± 28.1 ng/ml. In the term babies, born at 38~42 week gestation, the P1CP level was only 1,134.5 ± 427.3, 1CTP only 77.9 ± 18.7 ng/ml. The P1CP level of the 34~38 week gestation group was significantly higher than that of the 38~42 week gestation group. The 1CTP level in the 29~34 week gestation group was significantly higher than that of the 34~38 week gestation group. This tendency was also observed in the 38~42 week gestation group.

The P1CP level of infants from one month to one year of age (2180.5 ± 615.9 ng/ml) (mean ± SD) was significantly higher than that of the 38~42 weeks gestation group (p< 0.0001). The 1CTP level in infants (38.5 ± 14.1 ng/ml) was significantly lower than that of the 38~42 week gestation group (p<0.0001).

The mean value of the P1CP/1CTP ratio was 15.4 ± 5.8 in the 74 newborns at birth, but was significantly higher (61.5 ± 20.8) in 1m to 1y infants (p<0.0001, Fig. 3). The ratio was 4-fold higher in 1m to 1y infants than in newborns at birth. In contrast, the P1CP/1CTP ratio was

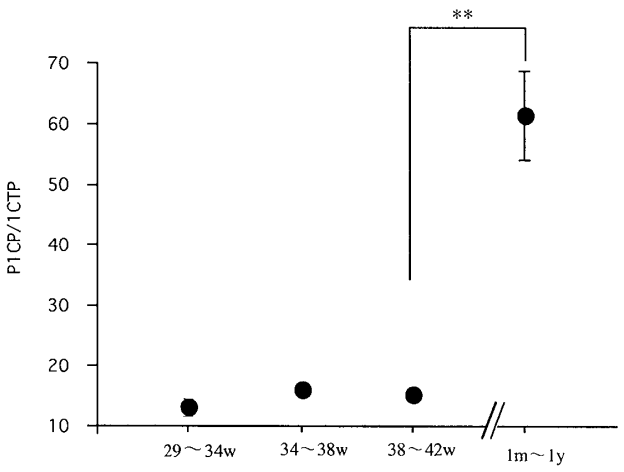

Fig. 3 P1CP/1CTP ratio changes in each age group
The P1CP/1CTP ratios were higher in 1m-1y infants than in newborns. Values are expressed as means ± SD, **: $p<0.0001$.

nearly constant during the preterm and term periods.

The obtained P1CP and 1CTP level versus physical growth

Table 2 shows the relationships among clinical factors. P1CP and 1CTP showed strong correlations with BW, BL and HC as well as with gestational age. The rate of standard fetal weight gain is a marker to growth velocity. The relations between the P1CP and 1CTP levels and the rate of fetal weight gain in female and male newborns are demonstrated in Fig. 4 and Fig. 5, respectively. The high rate of fetal weight gain reflects rapid weight gain which continues through 36 gestational weeks, then the rate of gain gradually diminishes between 36 and 43 weeks in female and between 37 and 44 weeks in male newborns. The curves of P1CP and 1CTP serum levels approximate the curves for the rate of standard fetal weight gain.

As shown in Fig. 6, we found P1CP and 1CTP levels in the <38 weeks group to be higher than those in the >38 weeks group. The P1CP level in the <2,900 g birth weight group was significantly higher than that in the >2,900 g birth weight group (Fig. 7). The 1CTP levels in the <2,900 g birth weight group were relatively higher as compared to those in the >2,900 g birth weight group but the difference did not reach statistical significance.

Table 2 The correlations among factors in 74 newborns

	r value	p value
P1CP, 1CTP	.586	<.0001
P1CP, gest age	−.579	<.0001
P1CP, BW	−.519	<.0001
P1CP, BL	−.470	<.0001
P1CP, HC	−.264	.0229
P1CP, Ca	−.196	.0937
P1CP, P	.034	.7745
P1CP, ALP	.399	.0004
1CTP, gest age	−.622	<.0001
1CTP, BW	−.531	<.0001
1CTP, BL	−.498	<.0001
1CTP, HC	−.448	<.0001
1CTP, Ca	.032	.7878
1CTP, P	.126	.2874
1CTP, ALP	.350	.0021
gest age, Ca	−.009	.9363
gest age, P	−.494	<.0001
gest age, ALP	−.117	.3222
Ca(mg/dl), P(mg/dl)	.414	.0002
Ca(mg/dl), ALP	.172	.1440
P(mg/dl), ALP	−.024	.8420

P1CP: the carboxyterminal propeptide of type 1 procollagen, 1CTP: the pyridinoline cross-linked carboxyterminal telopeptide of type 1 collagen, BW: birth weight, BL: birth length, HC: head circumference, Ca: calcium, P: phosphorus, ALP: alkaline phosphatase.

P1CP and 1CTP versus other factors for the entire newborn group

There was no significant gender difference in P1CP or 1CTP values in either of the gestational groups (Fig. 8). There were no significant correlations of serum Ca and P with either the P1CP or the 1CTP level. The P1CP and 1CTP levels showed positive correlations with ALP (Table 2).

Discussion

Type 1 collagen is the most abundant collagen species in many soft tissues and accounts for over 90% of the organic matrix of bone. It is synthesized from the precursor molecule type 1 procollagen, which has both an amino-terminal end and a carboxy-terminal end in the

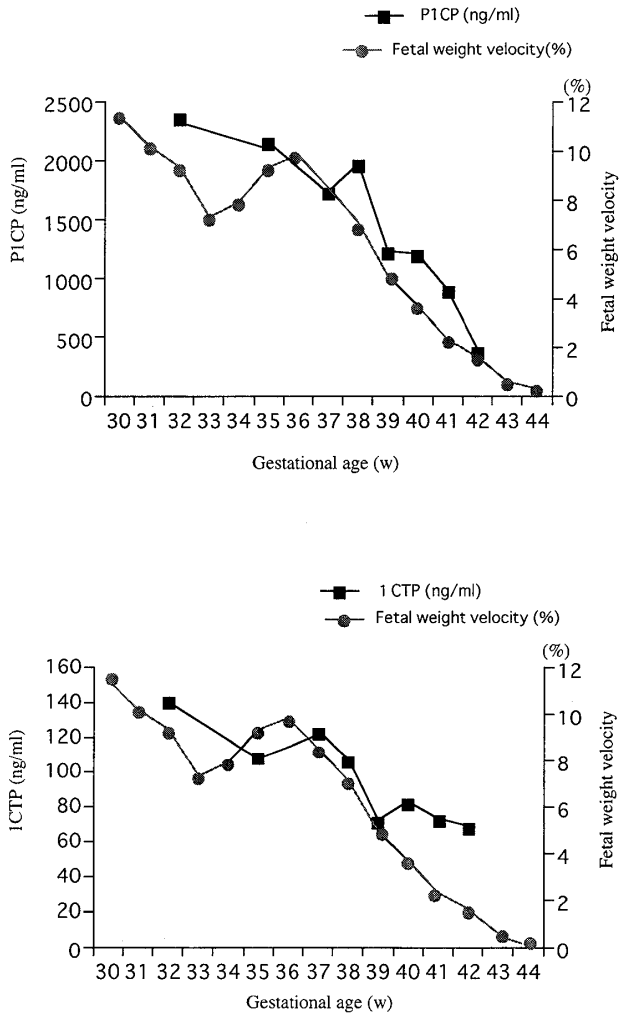

Fig. 4 The P1CP and 1CTP values at birth in 33 female newborns versus the rate of standard weight gain in the female fetus
Number of subjects in each gestational week: 32 w; n=2, 35w ; n=1, 37 w; n=4, 38 w; n=4, 39 w; n=5, 40 w; n=7, 41 w; n=9, 42 w; n=1. The standard weight gain rate data for the female fetus are based on an investigation by the Welfare Ministry of Japan, 1994.[20].

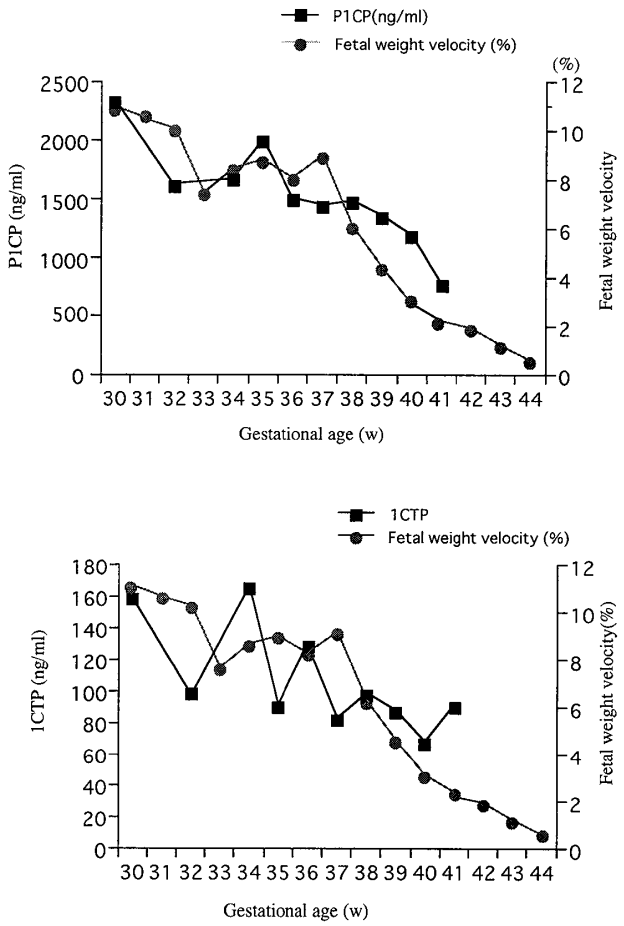

Fig. 5 The P1CP and 1CTP values at birth in 41 male newborns versus the rate of standard fetal weight gain
Number of subjects in each gestational week: 30 w; n=2, 32 w; n=2, 34 w; n=3. 35 w; n=2, 36 w; n=4, 37 w; n=2, 38 w; n=8, 39 w; n=9, 40 w; n=7, 41 w; n=2. The standard weight gain rate data for the male fetus are from an investigation by the Welfare Ministry of Japan, 1994[20].

osteoblast[21)22)]. The partial splitting of the carboxy-terminal end of the molecule, before collagen fiber assembly, forms the carboxy-terminal propeptide of type 1 procollagen (P1 CP). P1CP can be found in blood and is regarded as a marker of bone formation during growth[7)18)]. On the other hand, the carboxy-terminal pyridinoline cross-linked telopeptide domain of type 1 collagen (1CTP) is liberated into blood as an immunologically intact fragment, which resists further degradation. It is thus regarded as marker of bone resorption[10)]. Therefore, the P1CP/1CTP ratio reflects the balance between bone formation and resorption activities[4)]. Recent studies measuring the levels of P1CP and 1CTP by RIA have clinical significance, as a means of assessing whether there is abnormal growth in infants and children, including those with growth disorders[4)17)~19)23)]. Employing in vitro studies of type 1 procollagen propeptides, Trivedi et al (1991) measured the serum concentrations of P1CP in 442 healthy children and found that there was marked variability in the first 4 years of life. The

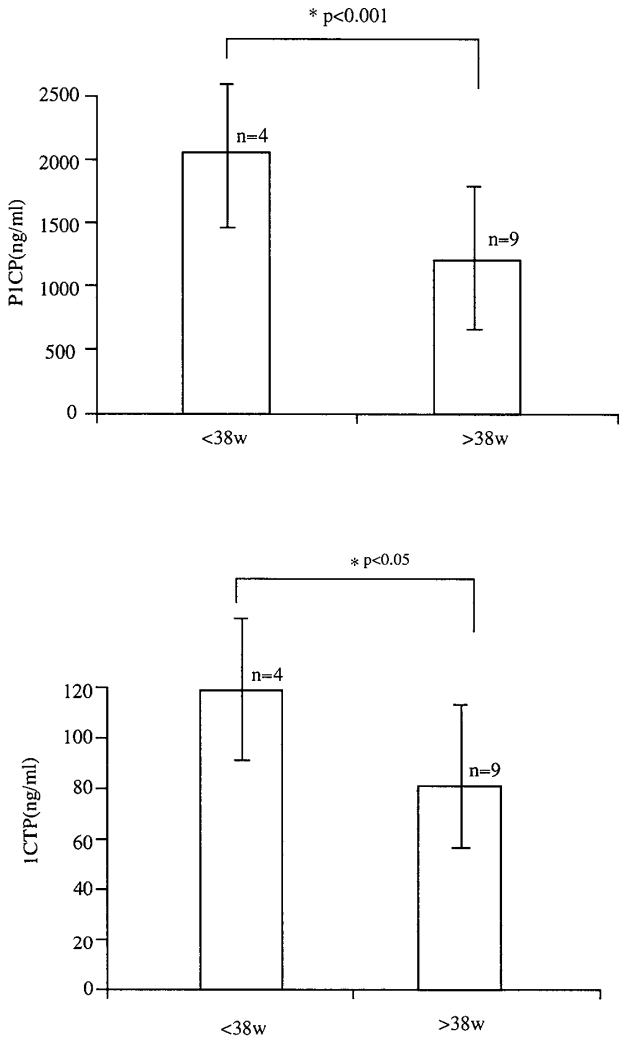

Fig. 6 P1CP and 1CTP changes in two groups with similar birth weights
Serum levels of P1CP and 1CTP were higher in <38 w than in >38 w newborns. The birth weight of the <38 w group was 2,776.3 ± 41.9 g (mean ± SD), that of the >38 w group 2,780 ± 59.4 g, mean ± SD.

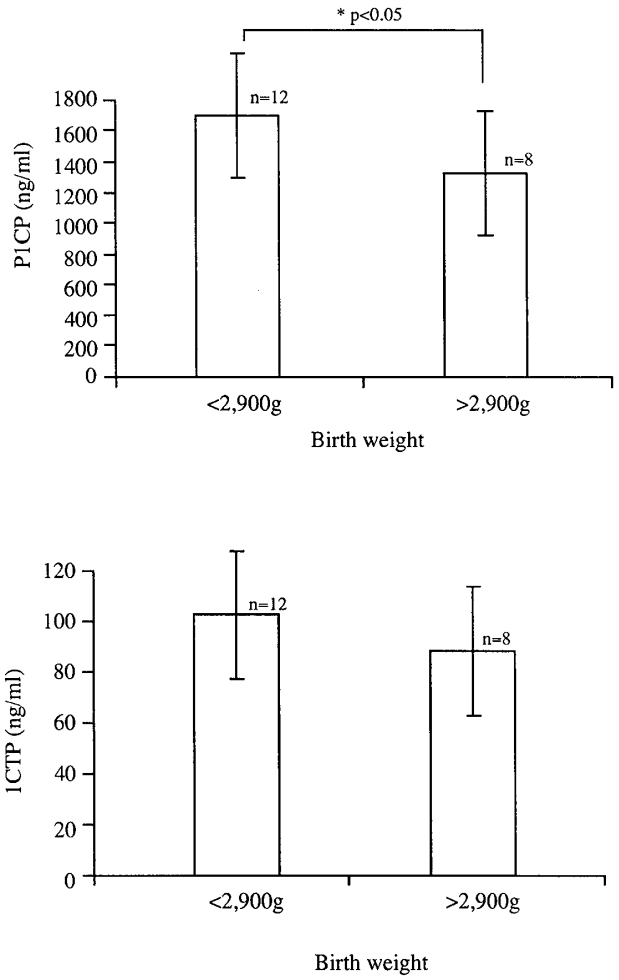

Fig. 7 P1CP and 1CTP changes in two groups with similar gestational ages
The P1CP and 1CTP levels of the low birth weight group (BW<2,900 g) were higher than those of the high birth weight group (BW>2,900 g). The gestational age of the low birth weight group averaged 37.3 ± 0.3 w (mean ± SD), that of the high birth weight group 37.6 ± 0.4 w (mean ± SD).

highest P1CP values were seen in infants younger than 3 months of age. The P1CP levels then decreased significantly with age. P1CP showed significant negative correlations ($p < 0.001$) with age, height and weight[17]. Saggese et al[19] (1992) observed that P1CP peaked during the first 2 years of life and then again during puberty in 300 healthy children and adolescents.

In this study, for the first time, we obtained the serum concentrations of P1CP and 1CTP in 74 healthy preterm and term newborns. We found that the mean values of P1CP and 1CTP in preterm newborns were higher than those in term newborns (Fig. 1, 2) and confirmed negative correlations of P1CP and 1CTP with gestational age, BW (birth weight) and BL (birth length) in newborns at birth (Table 2). Taubman et al[24] found that human type 1 procollagen from cord blood measured by RIA in newborns was approximately 12-fold higher than the adult serum level. Our results suggest that preterm newborns have higher bone turnover than term newborns. High turnover reflects high bone remodeling activity which corre-

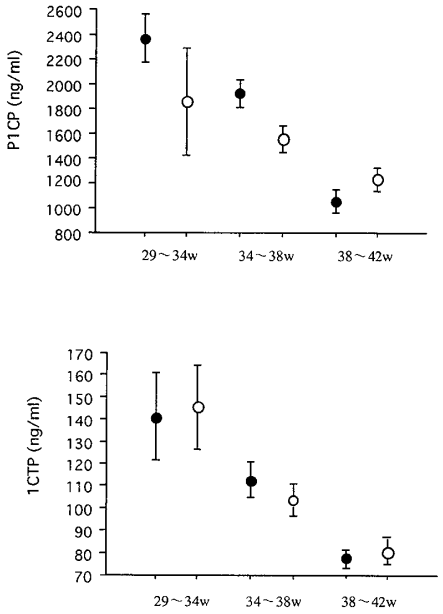

Fig. 8 Relationships of P1CP and 1CTP to gender in each gestational age group
There were no significant gender differences in P1CP or 1CTP values among gestational age groups. mean ± SD, ●: female, ○: male.

sponds to rapid morphological change in the fetal period.

Correlations between P1CP and height velocity in early childhood and the pubertal period have been reported[4)17)19)23)]. We devised curves of the standard fetal weight gain rate according to fetal weight gain data, in female and male newborns, obtained by the Welfare Ministry of Japan in 1994[20)]. We found that the P1CP and 1CTP levels approximated the curves of the standard fetal weight gain rate in female and male newborns (Fig. 4, 5). These results suggest that physical growth, along with gestational age, contributes to P1CP and 1CTP levels. This means that fetal bone remodeling and development depend on fetal physical growth. The fact that P1CP and 1CTP activities depend not only gestational age but also on birth weight (Fig. 6, 7) further underscores the importance of physical growth and gestational age to the fetal bone remodeling.

The factors accounting for higher levels of P1CP and 1CTP in perterm than in term newborns remain unknown, though PTH (parathyroid hormone) is a possible contributor. Although the significance of preterm PTH levels is controversial[1)2)25)], the serum PTH level is reportedly significantly higher in SGA (small for gestational age) than in AGA (appropriate for gestational age) newborns[25)]. In addition to increasing the osteoclast number, PTH also stimulates bone formation and acts directly on osteoblasts to promote bone formation activity[26)] thereby possibly contributing to increases in P1CP and 1CTP levels. It has been shown in adults, that excessive secretion of PTH due to RHP (renal hyperparathyroidism) can induce high bone turnover resulting in increased bone formation and bone resorption[27)]. Saggese et al[19)] found that P1CP increased in primary hyperparathyroidism and decreased in untreated deficits of PTH secretion or action. The study of Minton et al[25)] revealed the serum PTH concentration to be higher in preterm than term newborns at birth. They speculated that a reduced placental blood supply leads to deficient calcium intake with a resultant increase in PTH secretion[1)2)25)].

It should also be noted that maternal hormonal changes in pregnancy or changes in placental function can lead to high fetal bone turnover. Blumsohn et al[28)] demonstrated a significant negative correlation between E_2 (estrogen 2) levels and all markers of bone turnover at all pubertal stages.

Growth hormone (GH) is another possible contributor. Although no studies comparing P1CP and GH have been done in fetuses, a relatively good correlation has been recognized in early childhood and adolescence[4)17)18)23)].

ALP in newborns showed a statistically significant positive correlation with both P1CP and 1CTP in our study. ALP include a bone isozyme which comes from osteoblasts. Given the relatively weak correlation between ALP and gestational age, we speculate the P1CP and 1CTP are more accurate indicators of bone metabolism.

The clinical investigations of Trivedi et al[17)] (1991), Saggese et al[19)] (1992) and Kubo et al[4)] (1994) showed serum levels of P1CP to be

markedly elevated during infancy. We found that the serum concentration of PICP in 8 infants less than one year of age was significantly higher than that of newborns (34～38 w, 38～42 w) at birth while the serum level of ICTP was significantly lower in 1m to ly infants than in newborns (Fig. 3). Extensive ICTP research has been done in adults[9)10)29)], but there has been only one study focusing on children[4)]. It is necessary to accumulate more infant data for future comparisons.

The PICP/ICTP ratio reflects the balance between bone formation and resorption activities[4)27)], and may indicate which occupies the dominant position during a given period. It is interesting that the PICP/ICTP ratio is constant during the fetal period despite rapid changes in bone turnover. We observed the PICP/ICTP ratio in infants, less than 1 year of age, to be 4-fold higher than that of newborns at birth (Fig. 4). Bone formation is in a state of high activity in infants while bone resorption activity is relatively low, showing that bone formation is clearly the dominant process in the first year of life.

Conclusion

Based on our findings, we speculate that fetal bone metabolic activity is characterized by high turnover which is strongly associated with physical growth as well as gestational age, and that bone formation is the dominant process in the first year of life. Further accumulation of data from VLBW (very-low-birth-weight) infants is necessary to fully understand fetal bone metabolism.

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1型プロコラーゲンC末端プロペプチドおよび1型コラーゲン・cross-linked carboxyterminal telopeptideを用いた胎児期骨代謝の特徴の検討

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我々は，胎児の生理的な骨代謝を検討するため，骨形成および骨吸収に関する指標を検討した．検査の意義と方法を説明し，母から承諾の得られた74例の新生児（何も合併症のない早期産児34例，満期産児40例）における臍帯血および1歳未満の健康乳児8例の末梢血の血中P1CP（1型プロコラーゲンC末端プロペプチド）と1CTP（1型コラーゲン・cross-linked carboxyterminal telopeptide）を測定した．新生児74例における臍帯血中P1CP，1CTP値は，それぞれ，1423.5±611.6，95.8±34.2 ng/ml (mean±SD) であった．P1CPあるいは1CTP値と，妊娠週数，出生時体重，身長，頭囲の間にはそれぞれ有意な負の相関を認めた．($p<0.0001$)．妊娠週数に伴うP1CP，1CTP値の変化と，標準胎児体重増加率との関係を比べると，血中P1CPおよび1CTP値の曲線と標準胎児体重増加率の曲線はほぼ平行であった．血中P1CP，1CTP値は，出生時平均体重を等しくした妊娠週数の異なる2群間比較では，妊娠週数が少ない群ほど高値であった．また，出生時平均妊娠週数を等しくした体重の異なる2群比較では，体重が少ない群ほど高値であった．1歳未満の健康乳児8例におけるP1CP，1CTPの分析結果では，新生児の値に比し，P1CPが高値で，1CTPが低値であり，P1CP/1CTP比の平均値は新生児のそれに比べて4倍も高値であった．それに対し，出生児のP1CP/1CTP比の平均値は早期産児，満期産児に関係なく一定であった．我々の今回の検討結果から，胎生児期における骨代謝は著しく活発であり，その身体の発育と妊娠週数が骨代謝に強く関連している．また未熟児の骨代謝は未熟性が強いほど高回転性であり，1歳までの乳児では骨形成が優位に起こっている．