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Bone Metabolism in Pregnant Women Exposed to Single Compared With Multiple Courses of Corticosteroids

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Abstract

OBJECTIVE—To compare markers of maternal bone metabolism between women who received a single compared with multiple courses of antenatal corticosteroids.

METHODS—This is an analysis of serum samples from a previously reported randomized, placebo-controlled, multicenter trial. Women at risk for preterm delivery after an initial course of corticosteroids were randomly assigned to weekly courses of betamethasone (active) or placebo. Serum levels of carboxy terminal propeptide of type I procollagen (PICP) and cross-linked carboxy terminal telopeptide of type I collagen (ICTP) were measured to assess the rate of bone formation and resorption, respectively, at three time points. The placebo group (n=93) was compared with the active group, receiving four or more courses of betamethasone (n=112).

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RESULTS—There were significant ($P<.001$) increases in PICP and ICTP between baseline and delivery in both groups. Cross-linked carboxy terminal telopeptide of type I collagen, but not PICP, was lower with corticosteroid exposure immediately before administration of the fourth study course ($P<.001$). No significant differences in PICP and ICTP were seen between groups at delivery.

CONCLUSION—Increasing levels of PICP and ICTP with advancing gestation are consistent with physiologic changes in maternal bone metabolism. Multiple courses of corticosteroids for fetal maturation are not associated with persistent or cumulative effects on maternal bone metabolism as measured by PICP and ICTP.

A single course of corticosteroids given to pregnant women at risk for preterm delivery reduces the risks of prematurity-related complications, including the risk of death, respiratory distress syndrome, and intraventricular hemorrhage by 50% or more.^{1–6} Currently there is near universal use of antenatal corticosteroids in the setting of anticipated preterm delivery.

With observations by Liggins and others^{4,5} that the optimal benefit of antenatal corticosteroids may not last beyond 7 days, the 1994 National Institutes of Health Consensus Development Conference statement called for additional research on the potential benefits and risks of repeated administration of antenatal corticosteroids. A second National Institutes of Health Consensus Development Conference in 2000 specifically examined the question of repeat courses of antenatal corticosteroids, concluding that insufficient risk and benefit data exist to support routine use of repeat courses of antenatal corticosteroid in clinical practice. The use of multiple courses of steroids has been continuously debated^{7–10} and has been the subject of multicenter trials in the United States, United Kingdom, and Australia.^{1–3, 11–14}

Although there have been proven benefits to using antenatal corticosteroids, there has also been concern over possible fetal and maternal adverse effects, particularly with repeated courses. Possible detrimental fetal effects include neurodevelopmental delay, growth delay, and adrenal suppression. Studies of maternal adverse effects have focused primarily on infection.⁶ Only a few studies have examined the effect of a single course of antenatal corticosteroids on maternal bone metabolism, and no adverse effects were reported.^{15, 16}

Our study addresses whether repeated courses of antenatal corticosteroids have an effect on maternal bone metabolism, using two markers of bone turnover, the carboxy terminal propeptide of type I procollagen (PICP) and the cross-linked carboxy terminal telopeptide of type I collagen (ICTP). Carboxy terminal propeptide of type I procollagen, an extension propeptide that facilitates collagen polymerization, is a serum marker of bone formation. Crosslinked carboxy terminal telopeptide of type I collagen is released by bone-specific proteases and is a marker of bone resorption. Both PICP and ICTP have been shown to be specific markers for their respective changes in bone in various biochemical studies.^{17–20} The specific aim of our study was to compare PICP, ICTP, and their ratio between women who received a single compared with multiple courses of antenatal corticosteroids.

MATERIALS AND METHODS

This is an analysis of serum samples from a previously reported,¹ randomized, double-masked, placebo-controlled, multicenter trial conducted between March 2000 and April 2003 at participating centers of the National Institute of Child Health and Human Development, Maternal-Fetal Medicine Units (NICHD MFMU) Network. Our study was designed to compare markers of maternal bone metabolism (PICP, ICTP) between women who received a single course compared with multiple courses ($n\geq 4$) of antenatally administered corticosteroid. This study was approved by the Committee for the Protection of Human Subjects Institutional Review Board at the University of Texas Health Science Center Houston.

In the original trial,¹ women with intact membranes at risk for spontaneous preterm delivery between 23 weeks 0 days and 31 weeks 6 days were eligible for study participation if they remained pregnant 1 week after receiving a single full course of corticosteroids (dexamethasone or betamethasone). Participants were randomly assigned to receive weekly courses of betamethasone or placebo, based on a previously described randomization design scheme.¹ Numbered kits were prepared using randomization sequences created by the independent data coordinating center. The randomization sequences, stratified by clinical center, type of qualifying course and whether the patient was an inpatient or outpatient, were generated using the urn design. At randomization the patient was assigned to the next sequentially numbered kit. Of all patients enrolled in the trial, 63.4% received four or more study courses. For the purpose of this study, we define the active group as those women receiving four or more weekly courses of betamethasone and the placebo group as those receiving four or more weekly injections of a like-appearing placebo at the same time interval after the single qualifying course of corticosteroids. There were no significant differences between the active and the control placebo groups with respect to maternal age, education, race, marital status, smoking status, and parity (Table 1). The median latency period from first study dose to delivery in those women receiving four or more courses was 62 days.

Maternal venous blood samples were collected at the time of randomization, immediately before administration of the 4th study course, and the morning after delivery. After collection, these blood samples were centrifuged, and serum was frozen at -20°C for later analysis. Samples were received at our laboratory as de-identified, numbered serum aliquots and were analyzed masked to the treatment group (active or placebo). All samples were run in duplicate for both the ICTP and PICP assays. If a greater than 10% discrepancy in calculated concentrations of the serum markers was noted between duplicate samples, the sample was rerun. A standard curve was established for each microtiter plate, and serum marker concentrations were calculated from the standard curve for each plate, to minimize interplate variation. Only samples with absorbance values within the established standard curve were assigned a marker concentration. Those samples outside the standard curve for each plate were rerun at three serial dilutions, to obtain a valid serum marker concentration.

Serum PICP levels were determined using the procollagen type I C-peptide EIA kit (Takara Bio. Inc., Shiga, Japan). This assay used a “sandwich” enzyme-linked immunosorbent assay technique. A microtiter plate coated with a mouse monoclonal anti-PICP antibody was simultaneously reacted with sample and peroxidase-labeled anti-PICP antibody. With incubation, PICP was bound to the anti-PICP (solid-phase) on one side, and tagged by peroxidase-labeled anti-PICP on the other. Reaction with peroxidase and substrate resulted in color development, with intensity proportional to PICP concentration. This concentration was quantified by specific absorbance using an EIA plate reader at OD450. Accurate sample concentrations were determined by comparison of specific absorbances to a standard curve run for each microtiter plate. Results were reported in micrograms per liter. The intraassay coefficient of variation was 4.5–7.4%, and that for interassay was 4.3–6%. The assay detection limit was reported at 10 micrograms/L.

Serum levels of ICTP were determined using the UniQ ICTP EIA assay kit (Orion Diagnostica, Espoo, Finland). This is a competitive-inhibition enzyme-linked immunosorbent assay whereby the ICTP in the serum samples competes with high-affinity ICTP epitopes previously adsorbed onto microtiter plates for binding to a peroxidase-labeled goat-anti-rabbit antibody. This is followed by chromogenic development, subsequent determination of absorbance spectrophotometrically (OD450), and quantitation of ICTP concentration by comparison to a calibration standard for each microtiter plate. Results are reported in micrograms per liter. For analyte concentrations in the range of 1.0–50 micrograms/L, ICTP, the intraassay coefficient

of variation was 3.5–9.4%, and that for interassay precision was 6.4–9.8%. The assay detection limit was reported at 0.3 micrograms/L.

Data were analyzed at the Biostatistics Center, George Washington University, Rockville Maryland. Comparisons between groups for continuous variables were made using the Wilcoxon rank sum test. Pair-wise comparisons were made using the Wilcoxon signed rank test. Box-and-whisker plots were used to provide graphic representations of the distributions of the serum markers and were generated using SAS statistical software (SAS Institute Inc., Cary, NC).

RESULTS

Serum samples from 93 women randomly assigned to receive placebo and 112 women receiving four or more study courses of betamethasone were assayed for PICP and ICTP concentrations at three time points: randomization (mean gestational age of 27 weeks in both groups), immediately before the fourth weekly corticosteroid/placebo injection (mean gestational age of 30 weeks in both groups), and delivery (mean gestational age of 36 weeks in both groups).

Median values and ranges for each serum marker at the three time points for both study and placebo groups are presented in Table 2. There were significant increases in PICP and ICTP between baseline and delivery in both groups ($P<.001$). With the exception of significantly lower ICTP levels in the active group at 4 weeks, no significant differences in PICP or ICTP were seen between the groups at any other time point. Graphic representation of serum concentrations of PICP and ICTP at the three time points studied is presented in Figures 1 and 2.

As shown in Table 3, data were also analyzed as PICP/ICTP ratio at each time course for both groups. There were significant decreases in PICP/ICTP ratio between baseline and delivery in both the active and placebo group ($P=.007$ and $P<.001$, respectively). With the exception of a significantly higher PICP/ICTP ratio in the active group at 4 weeks, no significant differences were noted between the groups at any other time point. Graphic representation of the PICP/ICTP ratio at the three time courses is presented in Figure 3.

DISCUSSION

In our study, serum levels of both maternal PICP and ICTP increased significantly between randomization and delivery in both those receiving repeated corticosteroid courses and those receiving placebo after a single corticosteroid course. These findings are consistent with the physiologic increase in maternal bone turnover during pregnancy. In normal pregnancy, markers of bone turnover increase with gestational age.^{21–28} Carboxy terminal propeptide of type I procollagen decreases in early pregnancy, with a nadir at 12 weeks, followed by a steady rise throughout pregnancy, peaking at 38 weeks. Cross-linked carboxy terminal telopeptide of type I collagen is maintained at a steady-state level (1.5–4 micrograms/L) until 14 weeks, after which it rises throughout pregnancy to peak levels near term. This physiologic adaptation is postulated to occur in preparation for the large sequestration of calcium by the fetus. Two thirds of total body calcium accumulated in the fetus is transported during the third trimester.²³ Because bone contains 99% of the body's calcium stores, increasing bone turnover with advancing gestational age may represent mobilization of maternal skeletal calcium to supply the fetus.²²

Ogueh¹⁵ reported similar findings in a cohort of 14 women receiving a single complete course of dexamethasone for fetal lung maturation before preterm delivery. Serum markers of bone metabolism increased between the time of antenatal corticosteroid dose and delivery, without

significant alteration in the pattern of bone resorption. In a second study by Ogueh,¹⁶ one mineral densitometry was performed on a cohort of women receiving a single complete antenatal course of dexamethasone, with comparison to a control group of pregnant women not exposed to antenatal corticosteroids. Bone mineral density assessed by dual photon X-ray absorptiometry at the proximal femur and lumbar spine in both groups was similar, further suggesting that antenatal corticosteroid administration is not associated with an uncoupling of bone formation and bone resorption leading to bone loss.

In our study, we did not demonstrate a change in serum markers of bone metabolism with the administration of four or more courses of corticosteroids as compared with a single course. The absence of a dose-dependent response suggests that corticosteroid administration for fetal maturation is not associated with persistent or cumulative effects on maternal bone metabolism in pregnancy.

We did observe a significantly lower concentration of ICTP at 4 weeks among those exposed to repeated doses of antenatal corticosteroids as compared with the placebo group ($P<.001$). Although it has been previously demonstrated that a transient suppression of bone metabolism occurs after a single course of dexamethasone administration,¹⁵ this occurred within 24 hours of administration, and recovery was demonstrated after 48 hours. The fact that ICTP levels were lower in the repeated corticosteroids group at the four weeks time point may suggest that the effects of antenatal corticosteroids last longer than previously suggested, or that there is a cumulative but short-lived effect when repeated courses are administered. The clinical significance of this observation is unclear, because there was no difference in ICTP concentration between groups at the time of delivery.

Under normal conditions, bone formation and resorption are coupled processes, and PICP and ICTP are closely related. Only with an imbalance in these coupled processes can bone turnover result in a net change in bone mass and structure.^{17, 20} Therefore, the PICP/ICTP ratio should give more reliable results than a single marker. At delivery, we found no change in the ratio of bone formation to resorption with multiple courses of antenatal corticosteroids compared with a single course of corticosteroids. This finding strengthens our assertion that the rate of maternal bone remodeling is not modified chronically by repeated corticosteroid courses. However, the significantly increased PICP/ICTP ratio before the fourth study course may suggest a subacute effect of antenatal corticosteroids.

Previous studies of the relationship between pregnancy and bone mass in humans have had conflicting results.²⁹ Our prospective investigation demonstrated a significant increase in serum levels of both PICP and ICTP between randomization and delivery in both the active and placebo groups. We also noted a significantly decreased ratio of bone formation to bone resorption at delivery compared with baseline in both groups, a situation suggesting an unfavorable change in overall bone remodeling during pregnancy. Although the pregnancy may be associated with an increase in maternal bone turnover and possibly an unfavorable change in overall bone remodeling, our data indicate that corticosteroids administration for fetal maturation does not seem to influence this trend.

Long-term systemic corticosteroid therapy has been demonstrated to have metabolic effects on bone, including bone loss.³⁰ Prior studies have established that the mechanism of bone loss secondary to steroid use is predominantly by way of decreased bone formation, from the direct and indirect suppression of the osteoblast. Additionally, increased bone resorption, and increased collagenase activity, leading to the degradation of mature bone contribute to bone loss associated with steroid therapy. This effect has not been demonstrated after antenatal corticosteroid administration, perhaps due to the short duration of therapy. In our study, with a longer duration of therapy and a higher number of subjects, repeated courses of fluorinated

corticosteroids (betamethasone) given in pregnancy did not show an adverse effect on bone metabolism.

Although it can be argued that the concentration of serum markers used to measure the rates of bone metabolism may also reflect changes in type I collagen formation and degradation from other sites, including skin, connective tissue, and uterine tissue, bone histomorphometry studies show that type I collagen propeptides from most nonskeletal tissues contribute very little to the circulating propeptide pool.^{17, 20, 28}

We are challenged to provide treatment that is of maximal benefit to mother and fetus, with a minimum of risk to both patients. Antenatal corticosteroid administration improves neonatal outcomes; however, questions remain regarding the usefulness of repeated courses with regard to associated maternal and fetal risks and benefits. Repeated courses of antenatal corticosteroid for fetal maturation are not associated with persistent or cumulative effects on maternal bone metabolism in pregnancy.

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Fig. 1. Serum carboxy terminal propeptide of type I procollagen (PICP) concentration in active and placebo groups (box-and-whisker plot of the log transformed data).

Fig. 2. Serum cross-linked carboxy terminal telopeptide of type I collagen (ICTP) concentration in active and placebo groups (box-and-whisker plot of the log transformed data).

Fig. 3. Ratio of serum carboxy terminal propeptide of type I procollagen (PICP) to cross-linked carboxy terminal telopeptide of type I collagen (ICTP) concentration in active and placebo groups (box-and-whisker plot of the log transformed data).

Table 1

Group-Specific Demographic Characteristics

Demographic Characteristic	Active Group (n_112)	Placebo Group (n_93)	P
Race/ethnicity statistic			.96 [*]
African American	43	35	
White	33	29	
Other	36	29	
Marital status statistic			.61 [*]
Married	67	50	
Divorced	9	7	
Never married	36	36	
Smoking status statistic			.78 [*]
No	92	75	
Yes	20	18	
Parity statistic			.82 [*]
Nulliparous	11	10	
Multiparous	101	83	
Years of schooling completed (mean)	12	11.8	.82 [†]
Maternal age (mean)	26.2	26.0	.82 [†]

Data are n unless otherwise specified.

^{*} From χ^2 test.

[†] From the Wilcoxon rank sum test.

Table 2

Serum Concentration of Carboxy Terminal Propeptide of Type I Procollagen (in Micrograms per Liter) and Cross-linked Carboxy Terminal Telopeptide of Type I Collagen (in Micrograms per Liter) of Women in Active and Placebo Groups

Time Point	PICP		ICTP		P
	Active Group (n=112)	Placebo Group (n=93)	Active Group (n=112)	Placebo Group (n=93)	
Randomization	115.8 (50.8–1200.1)	129.7 (39.0–454.7)	4.7 (2.2–15.5)	4.5 (1.4–8.5)	.37
4 wk	123.5 (53.0–630.8)	131.6 (3.7–862.5)	3.9 (1.2–11.1)	5.5 (1.9–15.5)	<.001
Delivery	173.3 (45.8–926.1)	157.5 (37.1–1501.9)	8.1 (2.8–30.4)	8.3 (2.2–22.3)	.82

PICP, carboxy terminal propeptide of type I procollagen; ICTP, cross-linked carboxy terminal telopeptide of type I collagen.

Data are median (range).

Table 3

Ratio of Serum Carboxy Terminal Propeptide of Type I Procollagen to Cross-linked Carboxy Terminal Telopeptide of Type I Collagen Concentration in Active and Placebo Groups

PICP/ICTP			
Time Point	Active Group (n=112)	Placebo Group (n=93)	P
Randomization	25.0 (4.5–295.4)	27.6 (9.0–172.5)	.40
4 wk	33.3 (9.3–254.8)	23.8 (1.4–209.3)	.002
Delivery	23.7 (2.5–267.1)	19.8 (6.1–160.0)	.44

PICP, carboxy terminal propeptide of type I procollagen; ICTP, cross-linked carboxy terminal telopeptide of type I collagen.

Data are median (range).