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Bone metabolism in fetuses of pregnant women exposed to single and multiple courses of corticosteroids

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Abstract

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Objective—To estimate the effect of single and recurrent doses of antenatal corticosteroids on fetal bone metabolism.

Study Design—A secondary analysis of a cohort of pregnant women from a previously reported randomized, placebo-controlled, multi-center trial of women at risk for preterm delivery who received weekly courses of betamethasone (active) or placebo after an initial course of corticosteroids. Umbilical cord serum levels of carboxy terminal pro-peptide of type I pro-collagen (PICP) and cross-linked carboxyterminal telopeptide of type I pro-collagen (ICTP) were measured to assess the rate of fetal bone formation and resorption, respectively. Analysis was stratified according to number of repeat antenatal study courses of betamethasone or placebo (1–3 vs. ≥ 4 courses not including the initial course).

Results—Of the 251 umbilical cord serum samples, the median serum ICTP levels, but not PICP levels, were significantly lower with repeat betamethasone exposure compared to placebo (55 vs. 57.9 mcg/L, respectively, $p=0.01$). In the fetuses exposed to ≥ 4 repeat study courses, there was a significant decrease in median ICTP levels between repeat betamethasone exposure and placebo (53.4 vs. 58.6 mcg/L, respectively, $p=0.04$) but there was no difference between groups in the fetuses exposed to 1 – 3 repeat study courses (57.4 vs. 56.7 mcg/L, respectively, $p=0.29$).

Conclusion—Levels of umbilical cord serum markers of bone resorption but not formation are reduced in fetuses exposed to repeat courses of antenatal betamethasone. Up to 4 courses of antenatal betamethasone do not appear to affect fetal bone metabolism.

Introduction

The clinical efficacy of antenatal corticosteroids in reducing the risk of respiratory distress syndrome, intraventricular hemorrhage, and infant mortality is well established.¹ The 1994 and 2000 National Institutes of Health Consensus Development Conferences recommended routine administration of a single course of antenatal corticosteroids for those women at risk of preterm birth between 24–34 weeks gestational age. The use of repeat courses of antenatal corticosteroids, on the other hand, remains controversial and insufficient data exists to support its practice.^{2, 3}

Despite the undisputed neonatal benefits of antenatal corticosteroids, there is also concern over potential maternal and fetal adverse effects on bone metabolism, particularly with repeat doses. Two biochemical markers of bone turnover have been used to study maternal and fetal bone metabolism patterns. Type I collagen is the main constituent of bone accounting for approximately 90% of its organic matrix with very little contribution from non-skeletal tissue to the circulating propeptide.^{4,5} Carboxy terminal propeptide of type I procollagen (PICP) and cross-linked carboxy terminal telopeptide of type I collagen (ICTP) are specific and reliable serum markers of bone formation and resorption, respectively. Both serum markers are released in a 1:1 stoichiometric relationship with formation or resorption of type I collagen.^{4–8} The specificity of both markers to their respective bone changes has been confirmed by histomorphometry and calcium kinetic studies.^{4,6}

Maternal and fetal bone metabolism patterns are independent of each other making transplacental transport of PICP and ICTP unlikely.^{9–11} Single and repeat courses of antenatal corticosteroids have not been shown to have a persistent or cumulative effect on maternal bone metabolism as measured by PICP and ICTP.^{12–14} In one study, a transient decrease in maternal PICP levels was noted after 24 hours of administration of a single course of corticosteroids without any effect on ICTP levels.¹³ We identified two published studies evaluating the effects of antenatal corticosteroids on fetal bone metabolism (Pubmed 1992 to 2008; Medline 1992 to 2008 search terms: fetal bone metabolism, PICP, ICTP, antenatal corticosteroids; English publications). Both studies concluded that a single course of antenatal

corticosteroids reduced umbilical cord levels of PICP without an effect on ICTP levels.^{15, 16} Little is known about the effect of repeat courses of antenatal corticosteroids on fetal bone metabolism. Our study addresses the effects of single versus repeat courses of antenatal corticosteroids on fetal bone metabolism as measured by umbilical cord blood biochemical markers, PICP and ICTP. The null hypothesis is that there is no difference in fetal bone metabolism markers between those exposed to a single dose of corticosteroids versus those exposed to repeat courses.

Materials and Methods

Experimental Overview

This study was a secondary analysis of a cohort of pregnant women from a previously reported, randomized, double-masked, placebo-controlled, multicenter trial of single versus weekly courses of antenatal corticosteroids 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.³ Our study of fetal bone metabolism markers was approved by the Committee for the Protection of Human Subjects Institutional Review Board at the University of Texas Health Science Center at Houston.

Participants

This secondary analysis included only a cohort of women with singleton gestations from the previously reported NICHD MFMU Network trial on antenatal corticosteroids.³ These women were at risk for preterm delivery with intact membranes between 23 weeks 0 days and 31 weeks 6 days who were randomized to receive weekly courses of betamethasone or placebo, based on a previously described randomization design scheme, one week after receiving a single full course of corticosteroids (betamethasone or dexamethasone).³ In our secondary analysis we excluded patients with preterm premature rupture of membranes (PPROM) prior to randomization, confirmed fetal lung maturity, chorioamnionitis, major fetal anomaly, nonreassuring fetal status, systemic corticosteroid in pregnancy and insulin-dependent diabetes.

Biochemical Measurements

A subset of umbilical cord serum samples was received from the NICHD MFMU Network as de-identified, numbered serum aliquots. These umbilical cord serum samples had been stored at -20°C . Both PICP and ICTP are stable during storage at -20°C and after several freeze-thaw cycles which we avoided as much as possible. We were blinded with respect to treatment group (corticosteroid vs placebo) for each sample. All samples were run in duplicate for both the PICP and ICTP assays. If a greater than 15% discrepancy in calculated concentrations of the serum marker was noted between duplicate samples, the sample was rerun. If after three separate runs this discrepancy did not improve, the sample was excluded from the study. A standard curve was established for each microtiter plate, and serum marker concentrations were calculated from the standard curve for each plate, in order to minimize interplate variation.

Assay

Serum levels of type I procollagen C-peptide (PICP) levels were determined by using the procollagen type I C-peptide enzyme immunoassay (EIA) kit (Takara Bio Inc., Shiga Japan; www.takara-bio-co.jp). This assay utilized a “sandwich” enzyme-linked immunosorbent assay (ELISA) technique. A microtiter plate coated with a mouse monoclonal anti-PICP antibody was simultaneously reacted with sample and peroxidase-labelled anti-PICP antibody. With incubation, PICP was bound to the anti-PICP (solid-phase) on one side, and tagged by peroxidase-labelled 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 (mcg/L). The intraassay coefficient of variation was 4.5–7.4% and that for interassay was 4.3–6%. The assay detection limit was reported as 10 mcg/L.

Serum levels of type I carboxy terminal telopeptide (ICTP) were determined using the UniQ ICTP EIA assay kit (Orion Diagnostica, Espoo, Finland; www.oriondiagnostica.fi). This is a competitive-inhibition ELISA whereby the ICTP in the serum samples competes with high affinity ICTP epitopes previously adsorbed onto microtiter plates for binding to a peroxidase-labelled 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 (mcg/L). The intraassay coefficient of variation was 3.5–9.4% for analytes in the range of 1.0–50 mcg/L and that for interassay precision was 6.4–9.8%. The assay detection limit was reported at 0.3 mcg/L.

Statistical Analysis

The primary outcomes of interest for this secondary analysis were the fetal bone metabolism markers. Because this was a secondary analysis of all available umbilical cord serum samples, the study was not “powered” to a particular level. However, we determined from the literature that a 10% change in ICTP or PICP between two groups corresponded to about one-third of a standard deviation. To detect an effect size of one-third standard deviation we had 74% power with a sample size of 250. Data were analyzed at the Biostatistics Center, George Washington University, Rockville MD. Categorical variables were compared using the chi-square or Fisher’s Exact tests, where appropriate. Continuous variables were compared using the Wilcoxon Rank-Sum test. Multivariable linear regression analyses included study group assignment, infant gender, ethnicity, and either gestational age at delivery, birth weight, or small for gestational age (SGA) status which was based on a birth weight less than the 10th percentile of published standards.¹⁷ It was previously reported that birth weight was reduced in infants exposed to 1–3 courses of steroids with significant reduction in those receiving ≥ 4 courses.³ Based on these results, we stratified our data according to number of repeat antenatal study courses of betamethasone or placebo (1 to 3 vs. ≥ 4 courses without including the initial course). A nominal two-sided P value less than 0.05 was considered to indicate statistical significance; no adjustment was made for multiple comparisons. Box-and-whisker plots were used to provide graphic representation of the distribution of the serum markers and were generated using SAS statistical software (SAS Institute Inc, Cary, NC).

Results

There were 285 umbilical cord serum samples that were assayed for PICP and ICTP concentrations. Thirty four samples were excluded due to a greater than 15% discrepancy in duplicated samples after three separate runs. Thus, the umbilical cord serum samples from 114 women randomized to receive repeat placebo study courses and 137 women randomized to receive repeat betamethasone study courses from the Network trial were included (n=251). Forty-one women in the placebo group and 46 women in the betamethasone group received 1–3 repeat courses, while 73 women in the placebo group and 91 women in the treated group, respectively received ≥ 4 repeat study courses. There were no significant differences between placebo and active group with respect to maternal and infant characteristics (Table 1).

Mean time from randomization to delivery was not significantly different between groups (Table 1). Mean gestational age at delivery for the 1–3 study course group was 33.8 ± 4.5 weeks

for the placebo group and 32.7 ± 4.5 weeks for the active group ($p = 0.27$). In the ≥ 4 study course group the mean gestational age at delivery was 36.1 ± 2.8 weeks for the placebo group and 36.3 ± 2.9 weeks for the active group ($p = 0.61$). Mean birth weight in the placebo group was 2528.4 ± 784.5 g and 2376.1 ± 799.3 g in the active group ($p = 0.15$). There were 31 SGA infants overall.

Table 2 summarizes the median values of PICP and ICTP levels in each group. When comparing all samples, there was no difference in median serum PICP levels but ICTP concentrations were significantly lower in the betamethasone group compared with placebo (55.0 vs. 57.9 $\mu\text{g/L}$, respectively $p = 0.01$). There was no significant difference in PICP levels (422.0 vs. 478.0 $\mu\text{g/L}$) or ICTP levels (57.4 vs. 56.7 $\mu\text{g/L}$, respectively, $p = 0.29$) among those receiving 1–3 courses when comparing betamethasone with placebo. Fetuses exposed to ≥ 4 repeat study courses did not have significantly increased PICP levels compared with placebo ($p = 0.17$) but did have decreased median serum ICTP levels compared to placebo (53.4 vs. 58.6 $\mu\text{g/L}$, respectively, $p = 0.04$). Graphical representation of the median fetal serum PICP and ICTP concentrations according to the number of study courses are presented in Figure 1 and Figure 2, respectively. Multivariable analysis, controlling for infant gender, ethnicity (African-American vs other), and either gestational age at delivery, birth weight, or SGA infants showed that the repeated steroid group was significantly associated with lower ICTP levels. Although ICTP levels were decreased in the univariable analysis in the overall group (single vs repeat corticosteroid group) and within those who received ≥ 4 courses, there was no difference in effect between those who received 1–3 courses and those who received ≥ 4 courses in the multivariable analysis.

Discussion

The results of our study demonstrate that repeat courses of betamethasone are associated with reduced umbilical cord serum levels of ICTP, the marker for fetal bone resorption. Our data are consistent with prior studies in adults⁸ and children¹⁸ which also showed that corticosteroid treatment resulted in reduced serum concentration of ICTP. Based on the available studies, there is no conclusive data on the effects of corticosteroids on fetal bone metabolism.^{15, 16}

We found that ICTP levels were decreased in the univariable analysis in the overall group (single vs repeat corticosteroid group) and within those who received ≥ 4 corticosteroid courses but not those in the 1–3 course group. However, we did not see a dose-effect by the number of corticosteroid courses in the multivariable analysis. This may have been due to a lack of power or the effect of other confounding variables. Based on previous studies, suppression of bone formation is evident within 2–4 days of treatment followed by recovery to pretreatment levels within 1–2 weeks in adults.^{19, 20} When we controlled for time from last corticosteroid course (data not shown), our results were unchanged.

Normally, maternal serum PICP and ICTP levels steadily increase with advancing gestational age reaching peak levels at term.²¹ On the other hand, data on the normal physiologic pattern of bone metabolism in the fetus is limited. Some studies have suggested that fetal bone metabolism serum markers decrease with advancing gestational age.^{10, 22} Ogueh and colleagues¹⁰ found in normal pregnancies without antenatal corticosteroid exposure that umbilical cord blood levels of PICP and ICTP were higher than maternal levels and concluded that fetal and maternal bone metabolism are independent of each other. Carroll and colleagues¹² also examined maternal bone metabolism markers in women from the NICHD MFMU Network trial. The maternal serum PICP and ICTP levels at delivery in their study were lower than the umbilical cord serum levels in our study in both the single and repeat corticosteroid groups suggesting that maternal and fetal bone metabolism markers are independent of each other which is consistent with Ogueh's findings. Furthermore, taking these observations into

consideration, it is certainly possible that the decrease in ICTP levels we observed in the repeat corticosteroid group may not only have been influenced by in utero exposure to corticosteroids but also by the physiologic effect of advancing gestational age on the fetal bone metabolism profile. However, when controlling for gestational age at delivery and multiple variables, our results of decreased ICTP levels were confirmed. An association between fetal bone metabolism markers and birth weight has also been studied. Small for gestational age infants have been shown to have decreased markers of bone formation at all gestational ages and decreased markers of bone resorption at <36 weeks.²² Our study only included 31 SGA infants which is insufficient for evaluating the effect of antenatal corticosteroids on bone metabolism patterns in these infants.

The present study is the largest to date in estimating the effects of multiple courses of antenatal corticosteroids on fetal bone metabolism. Umbilical cord serum levels of ICTP are reduced in fetuses exposed to repeat courses of antenatal betamethasone. Further studies are needed to assess normal physiologic fetal bone metabolism patterns as well as the effect of antenatal corticosteroid exposure on fetal bone.

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Figure 1.

Cord serum concentrations of the type I procollagen C-peptide (PICP) in the active and placebo groups. Each box plot represents the median (black band) and the 25th and 75th percentiles, the error bars represent ranges of the values.

Figure 2.

Cord serum concentrations of the type I carboxy terminal telopeptide of type I collagen (ICTP) in the active and placebo groups. Each box plot represents the median (black band) and the 25th and 75th percentiles, the error bars represent ranges of the values. *P-value=0.04 for the difference between active and placebo groups. **P-value =0.01 for the difference between the active and placebo groups.

Table 1

Maternal and Infant Characteristics

	Placebo (N=114)	Active (N=137)	P
Parity			0.26
Nulliparous	16	13	9.5%
Multiparous	98	124	90.5%
Ethnicity			0.50
African American	56	59	43.1%
Caucasian	30	45	32.9%
Other	28	33	24.1%
Status			0.16
Married	62	78	56.9%
Divorced	6	15	11.0%
Never Married	46	44	32.1%
Tobacco use			0.95
Nonsmoker	87	105	76.6%
Smoker	27	32	23.4%
Education (years)*	12.1 ± 2.3	11.9 ± 2.4	0.48
Maternal Age (years)*	25.7 ± 5.9	26.0 ± 6.2	0.71
GA at randomization (weeks)*	28.2 ± 2.4	27.9 ± 2.3	0.46
GA at delivery*	35.3 ± 3.7	35.1 ± 3.9	0.87
1–3 courses	33.8 ± 4.5	32.7 ± 4.5	0.27
≥4 courses	36.1 ± 2.8	36.3 ± 2.9	0.61
Time from randomization to delivery (days)*	50.0 ± 26.9	50.3 ± 29.4	0.94
Number of courses*	3.7 ± 1.5	3.6 ± 1.2	0.95
Gender of offspring			

	Placebo (N=114)	Active (N=137)	P
Female	57	68	0.95
Male	57	69	50.4%
Birth weight *	2528.4 + 784.5	2376.1 + 799.3	0.15

* mean ± SD

Table 2

The PICP and ICTP levels in each group

	N	PICP (mcg/L) Median	Range	P value	ICTP (mcg/L) Median	Range	P value
All samples							
Placebo	114	479.1	150–1340	0.57	57.9	10–99	0.01*
Active	137	480.2	91–1608		55.0	4–81	
1–3 study courses	41	478.0	235–1023	0.37	56.7	14–99	0.29
Placebo	46	422.0	186–862		57.4	15–67	
Active							
≥ 4 study courses	73	480.1	150–1340	0.17	58.6	10–91	0.04*
Placebo	91	531.0	91–1608		53.4	4–81	
Active							