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Influence of a single course of antenatal betamethasone on the maternal-fetal insulin-IGF-GH axis in singleton pregnancies

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Design. A prospective, observational, pilot study consisting of four groups of pregnant women: I) received betamethasone and delivered <2 weeks post treatment; II) received betamethasone and delivered >2 weeks post treatment; III) untreated women who delivered <37 weeks (preterm controls); IV) untreated women who delivered >37 weeks (term controls). Maternal and mixed umbilical cord blood was collected at delivery and analyzed for insulin, glucose, IGF-I, IGF-II, IGFBP-1, IGFBP-3, GH, GHBP.

Results. Betamethasone increased maternal insulin, glucose and IGF-I levels without affecting IGFBPs. In the fetal compartment, betamethasone treatment was associated with a delayed suppressive effect on GH

and a sustained suppressive effect on IGF-II levels. There were no differences in infant size or neonatal morbidities between patients who delivered <2 weeks or >2 weeks post betamethasone treatment. In Group IV, birth weight correlated positively with cord IGF-I levels ($r^2=0.41$, $p=0.0098$) and negatively with cord IGFBP-1 levels ($r^2=0.51$, $p=0.0039$), and ponderal index correlated negatively with cord IGFBP-1 levels ($r^2=0.27$, $p<0.05$).

Conclusions. A single course of antenatal betamethasone influences the maternal-fetal insulin-IGF-GH axis, particularly fetal IGF-II levels, without measurable anthropometric changes at birth. Whether these effects have implications beyond the neonatal period remains to be determined.

**INFLUENCE OF A SINGLE COURSE OF ANTENATAL BETAMETHASONE ON THE
MATERNAL-FETAL INSULIN-IGF-GH AXIS IN SINGLETON PREGNANCIES**

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ABSTRACT

Objective. We examined the hypothesis that a single course of antenatal betamethasone influences the maternal-fetal insulin-IGF-GH axis.

Design. A prospective, observational, pilot study consisting of four groups of pregnant women: I) received betamethasone and delivered <2 weeks post treatment; II) received betamethasone and delivered >2 weeks post treatment; III) untreated women who delivered <37 weeks (preterm controls); IV) untreated women who delivered >37 weeks (term controls). Maternal and mixed umbilical cord blood was collected at delivery and analyzed for insulin, glucose, IGF-I, IGF-II, IGFBP-1, IGFBP-3, GH, GHBP.

Results. Betamethasone increased maternal insulin, glucose and IGF-I levels without affecting IGFBPs. In the fetal compartment, betamethasone treatment was associated with a delayed suppressive effect on GH and a sustained suppressive effect on IGF-II levels. There were no differences in infant size or neonatal morbidities between patients who delivered <2 weeks or >2 weeks post betamethasone treatment. In Group IV, birth weight correlated positively with cord IGF-I levels ($r^2=0.41$, $p=0.0098$) and negatively with cord IGFBP-1 levels ($r^2=0.51$, $p=0.0039$), and ponderal index correlated negatively with cord IGFBP-1 levels ($r^2=0.27$, $p<0.05$).

Conclusions. A single course of antenatal betamethasone influences the maternal-fetal insulin-IGF-GH axis, particularly fetal IGF-II levels, without measurable anthropometric changes at birth. Whether these effects have implications beyond the neonatal period remains to be determined.

Key Words: betamethasone; growth hormone; insulin; insulin-like growth factors; maternal; umbilical cord

INTRODUCTION

Antenatal betamethasone is administered to women at risk for threatened preterm delivery between 24 and 34 weeks to advance fetal lung maturation and reduce neonatal morbidity and mortality (1,2). The beneficial effects of betamethasone begin 24 hours following administration and may begin to abate by 7-10 days (3-5). This prompted the use of repeated courses of antenatal steroids in women who have not delivered within 7 days of initial treatment, and who were still at risk for preterm delivery. Human and animal studies have demonstrated adverse effects on fetal growth including decreased birth weight and decreased brain size and weight with multiple courses of antenatal steroids (6-13). These adverse effects may persist to adult life (14-15).

The control of fetal and postnatal growth depends on multiple hormones, including insulin, IGF-I, IGF-II, and GH. IGFs circulate in the serum bound to IGF binding proteins (IGFBPs) and produce mitogenic effects by acting on IGF-I and insulin receptors (16). Studies have shown that low birth weight is associated with decreased IGF-I, IGF-II and IGFBP-3 and elevated level of IGFBP-1 (17-19). Although GH has minimal influence on fetal somatic growth due to a paucity of GH receptors, the fetus produces large amounts in late gestation and the IGF-GH axis appears to be functional in utero (20).

The effects of multiple courses of antenatal steroids on fetal growth, birth weight, brain weight, and growth factors in both human and animal subjects are well-documented (6-13,21-24). However, there is a relative paucity of information regarding the effects of a single course of

antenatal betamethasone on the maternal insulin-IGF-GH axis, and no information on the fetal insulin-IGF-GH axis. Furthermore, a significant number of preterm deliveries occur after the beneficial effects of betamethasone have abated, yet no studies have compared differences in growth factors between patients who deliver while the drug is still in effect, and after the drug effect has declined. Therefore, we conducted a prospective, observational, pilot study to examine the hypothesis that a single course of antenatal betamethasone influences the maternal-fetal insulin-IGF-GH axis. Our hypothesis was tested with two specific objectives: 1) to determine the differences in response to a single course of antenatal betamethasone between the maternal and fetal compartments; and 2) to compare time-dependent effects of betamethasone between patients who delivered <2 weeks and >2 weeks post treatment.

MATERIALS AND METHODS

Patients. The study was approved by the Institutional Review Board of Long Beach Memorial Medical Center. Informed consent was obtained from all the women enrolled in the study. Authorization for use and disclosure of protected health information according to the Health Information Portability and Accountability Act (HIPAA) guidelines was also obtained. We conducted a prospective observational pilot study on 43 singleton pregnancies over a one-year period. Patients with pre-eclampsia, chronic hypertension, diabetes and chorioamnionitis were excluded. The study consisted of four groups: 1) Group I (n=13) were women who received betamethasone therapy for threatened premature delivery, before 34 weeks of gestation and who delivered <2 weeks after the first dose; 2) Group II (n=8) were women who received betamethasone therapy and who delivered >2 weeks after the first dose; 3) Group III (n=7) were untreated women who delivered before 37 weeks gestation; and 4) Group IV (n=15) were untreated women who delivered at term (>38 weeks gestation). Preterm labor was defined as the presence of regular uterine contractions associated with cervical dilation at a gestational age of less than 37 weeks. Betamethasone treatment consisted of two doses (12 mg per dose) given by intramuscular injection 24 hours apart. Maternal data included age, mode of delivery, race, preterm premature rupture of membranes (PPROM), smoking status and drug abuse. Infant outcome data included gestational age at delivery (weeks), gender, birth weight (grams), head circumference (centimeters), body length (crown to heel in centimeters), ponderal index [weight in grams x 100/(length in centimeters)³]. Apgar scores at 1 minute and 5 minutes, and length of hospital stay (days), need for surfactant and need for oxygen therapy. Prior to discharge, neonatal outcomes such as RDS, symptomatic patent ductus arteriosus (PDA), sepsis, necrotizing

enterocolitis (NEC), apnea, IVH, bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP) were recorded.

Sample collection. Maternal blood and mixed umbilical cord blood were collected at delivery in EDTA tubes (plasma) and tubes with no preservative (serum) on ice and taken to the laboratory for processing. The samples were centrifuged at 3,000 rpm for 20 minutes at 4°C and the resulting plasma and serum were aliquoted and frozen at -20°C until analysis.

Insulin. Plasma insulin levels were determined using commercially available active insulin enzyme-linked immunosorbent kits (Diagnostic Systems Laboratories, Webster, TX). The assay is an enzymatically amplified “one-step” sandwich type immunoassay. Standards, controls and unknown plasma samples were incubated with anti-insulin antibody in microtitration wells pre-coated with another anti-insulin antibody. After incubation and washing, a developer was added and the absorbance was determined at 450 nm. The absorbance is directly proportional to the concentration of insulin in the sample. Concentrations in the samples were calculated from a standard curve which ranged from 0 through 300 $\mu\text{IU/mL}$. The sensitivity of the assay was 0.26 $\mu\text{IU/mL}$, and the intra- and inter-assay coefficient of variations were <10%.

Glucose. Glucose levels in maternal blood and umbilical cord were measured at the bedside immediately following delivery, using the reflectance meter Reflolux S (Accucheck III). High as well as low blood glucose levels can be determined with excellent precision.

IGF-I and IGF-II. Active IGF-I and IGF-II levels were determined in serum using commercially available non-extraction enzyme-linked immunosorbent kits (Diagnostic Systems Labs). The kits use an enzymatically amplified “two-step” sandwich-type immunoassay. In the assay, standards, controls and pre-diluted samples were incubated in microtitration wells which were coated with anti-IGF-I or IGF-II antibody. All samples underwent a pre-treatment step on the same day of the assay to separate IGFs from their binding proteins. After incubation and washing, the wells were treated with an anti IGF-I or IGF-II detection antibody labeled with horse-radish peroxidase. After washing, the plate was developed and the absorbance measured at 450 nm. The absorbance measured is directly proportional to the IGF-I or IGF-II levels. Concentrations in the samples were calculated from a standard curve which ranged from 0 through 600 ng/mL for IGF-I and 0 through 2200 ng/mL for IGF-II. The sensitivity of the assay was 0.015 ng/mL for IGF-I and 2.2 ng/mL for IGF-II. The intra- and inter-assay coefficients of variations were <12% for IGF-I and IGF-II.

IGFBP-1 and IGFBP-3. Active IGFBP-1 and IGFBP-3 levels were determined in serum using commercially available non-extraction enzyme-linked immunosorbent kits (Diagnostic Systems Labs). This kits use an enzymatically amplified “two-step” sandwich-type immunoassay. In the assay, standards, controls and samples were incubated in microtitration wells which were coated with anti-IGFBP-1 or IGFBP-3 antibody. After incubation and washing, the wells were treated with an anti IGFBP-1 or IGFBP-3 detection antibody labeled with horse-radish peroxidase. After washing, the plate was developed and the absorbance measured at 450 nm. The absorbance measured is directly proportional to IGFBP-1 or IGFBP-3 levels. Concentrations in the samples were calculated from a standard curve which ranged from 0 through 160 ng/mL for IGF-I and 0

through 100 ng/mL for IGF-II. The sensitivity of the assay was 0.25 ng/mL for IGFBP-1 and 0.04 ng/mL for IGF-II. The intra- and inter-assay coefficients of variations were <12% for IGF-I and IGF-II.

GH and GHBP. GH and GHBP levels in serum were determined using active ultrasensitive GH and active GHBP enzyme-linked immunosorbent assay kits (Diagnostic Systems Laboratories). The GH and GHBP kits use an enzymatically amplified “one-step” and “two-step” sandwich-type immunoassay, respectively. In the assay, standards, controls and samples were incubated with a biotinylated anti GH or GHBP antibody in microtitration wells which were coated with another anti human GH or GHBP capture antibody. After incubation and washing, the wells were treated with horse-radish peroxidase. After washing, the plate was developed and the absorbance measured at 450 nm. The absorbance measured is directly proportional to IGFBP-1 or IGFBP-3 levels. Concentrations in the samples were calculated from a standard curve which ranged from 0 through 500 pg/mL for GH and 0 through 500 pmol/L for GHBP. The sensitivities of the GH and GHBP assays were 0.66 pg/mL and 1.69 pmol/L, respectively. The intra- and inter-assay coefficient of variations were <10%.

Statistical Analysis. The Chi-square test was used to assess categorical variables and Fisher’s exact test was used for cells that contained ≤ 5 observations. Analysis of variance (ANOVA) was used to determine differences among the groups for normally-distributed data, and the Kruskal-Wallis test was used for non-normally-distributed data. Post hoc analysis was performed using the Student-Newman-Keuls test for significance. Simple correlations were performed to assess relationships between body weight and growth factors. Significance was set at $p < 0.05$ and data are reported as

mean \pm SEM, where applicable. All analyses were two-tailed and performed with GraphPad Prism (GraphPad Software Inc., San Diego CA).

RESULTS

Patient Demographics. A total of 53 women with singleton pregnancies were enrolled in the study. Ten patients were excluded because samples were not collected (n=4), they delivered at another hospital (n=2), or they delivered greater than 37 weeks in the treated groups (n=4). A total of 21 patients were antenatally treated with betamethasone (13 patients delivered <2 weeks and 8 patients delivered >2 weeks post treatment). The rate of cesarean delivery was comparable among the groups, as were race and infant gender. As expected, the incidence of PPRM was higher in Groups I (7/13, 54%, $p<0.05$), II (6/8, 75%, $p<0.05$), and III (6/7, 86%, $p<0.05$) compared to Group IV (0%). Mean birth weight (grams) in Groups I, II, and III were 1897.5 ± 164.1 , 2020.0 ± 168.5 and 2364.7 ± 149.3 respectively, compared to Group IV (3655.2 ± 162.2 , $p<0.001$). Mean gestational ages (weeks) for Groups I, II and III were 31.5 ± 0.7 , 31.1 ± 0.7 , and 33.9 ± 0.6 respectively, compared to Group IV (39.9 ± 0.3 , $p<0.001$). Maternal age (years) in Groups I (25.2 ± 1.3 , $p<0.01$) and II (23.7 ± 1.5 , $p<0.01$) was significantly lower than Group IV (39.9 ± 0.3), but not Group III (28.1 ± 2.6 years). Among the preterm groups I, II and III there were no differences in head circumference, length (crown to heel), or ponderal index. Neonatal clinical outcomes were comparable between Groups I, II, and III.

Effect on Insulin and Glucose. Maternal plasma insulin levels ($\mu\text{IU/mL}$) were significantly higher in Group I (23.3 ± 3.5 , $p<0.05$) than Groups II (11.8 ± 1.9), III (10.3 ± 2.4), and IV (13.8 ± 2.7), however, there were no differences in umbilical cord plasma insulin levels among the groups (Figures 1A and 1B). Similarly, maternal glucose levels (mg/dL) were higher in Group I (105.5 ± 7.2 , $p<0.05$), compared to Groups IV (84.6 ± 1.7). Mixed umbilical cord glucose levels

were also higher in Group I (89.2 ± 5.9 , $p < 0.05$) and Group III (88.7 ± 7.6 , $p < 0.05$) compared to Groups II (67.0 ± 3.3) and IV (71.1 ± 3.1) as demonstrated in Figures 2A and 2B.

Effect on GH and GHBP. Maternal and mixed umbilical cord serum GH levels (pg/mL) are presented in Figures 3A and 3B and appear to follow a similar pattern. A non-significant decline in maternal serum GH levels were noted in Group II (Figure 3A), however, umbilical cord serum GH levels were significantly suppressed in II (1.8 ± 0.34 , $p < 0.001$) compared to Groups I (14.3 ± 1.5), III (11.6 ± 1.8) and IV (11.8 ± 1.2) (Figure 3B). No differences in maternal GHBP levels were noted among the groups. GHBP was not detected in umbilical cord serum (data not shown).

Effect on IGF-I and IGF-II. Maternal and mixed umbilical cord serum IGF-I levels (ng/mL) are presented in Figures 4A and 4B. Maternal serum IGF-I levels were significantly increased in Groups I (24.2 ± 3.2 , $p < 0.05$) and II (27.8 ± 3.0 , $p < 0.05$) compared to Group II (14.6 ± 3.3) and Group IV (15.2 ± 2.8). In contrast, umbilical cord serum IGF-I levels remained comparable among the groups (Figure 4B). While no changes in maternal serum IGF-II levels (ng/mL) were noted among the groups, umbilical cord serum IGF-II levels were significantly lower in Groups I (480.5 ± 36.9 , $p < 0.01$) and II (285.7 ± 45.9 , $p < 0.001$) than Groups III (672.8 ± 49.2) and Group IV (605.3 ± 43.5) (Figures 5A and 5B).

Effect on IGFBPs. No differences in maternal or umbilical cord serum IGFBP-1 was noted among the groups (data not shown). Similarly, there were no differences in maternal serum IGFBP-3 (Figure 6A). Conversely, umbilical cord serum IGFBP-3 levels (ng/mL) were

significantly lower in Groups I (209.5 ± 7.0 , $p < 0.001$), II (198.6 ± 6.7 , $p < 0.001$) and III (209.1 ± 7.4 , $p < 0.001$) compared to Group IV (255.5 ± 5.2).

Relationships between Birth Weight, Ponderal Index, IGF-I, and IGFBP-1. In Group IV only, birth weight correlated positively with umbilical cord serum IGF-I levels ($r^2 = 0.41$, $p = 0.01$) (Figure 7A) and negatively with umbilical cord IGFBP-1 levels ($r^2 = 0.47$, $p = 0.005$) (Figure 7B). Ponderal index also correlated negatively with umbilical cord serum IGFBP-1 levels in Group IV ($r^2 = 0.27$, $p < 0.05$) (Figure 7C).

DISCUSSION

The present observational pilot study examined the effects of a single course of antenatal betamethasone on the insulin-IGF-GH axis in the maternal and fetal compartments. For comparison, we examined maternal and fetal levels in a non-treated preterm control group and a non-treated term control group. It is standard obstetric practice at our institution to administer antenatal betamethasone to all women at risk for preterm delivery between 24 and 34 weeks gestation. Therefore, it was difficult to recruit non-treated preterm controls and this resulted in a small number of patients in Group III. We found that in the maternal compartment a single course of antenatal betamethasone increased insulin, glucose and IGF-I levels without affecting IGF binding protein levels. In the fetal compartment, there was a delayed suppressive effect on GH levels and a sustained suppressive effect on IGF-II levels as noted in Group II. While IGF-I levels also declined in the fetal compartment in Group II, this did not achieve statistical significance with ANOVA. These findings prove our hypothesis that exposure to a single course of antenatal steroids affects the maternal and fetal insulin-IGF-GH axis. However, these effects appear to differ between the maternal and fetal compartments. Whether these hormonal effects are sustained during postnatal growth and development remains to be determined.

The effect of antenatal steroids on insulin and glucose in humans have been documented (25,26). Insulin promotes nutrition transport, glycogen deposition, and fat storage, as well as GH-stimulated IGF-I by the liver (16). Elevated insulin and glucose levels in the maternal compartment may be responsible for the high maternal IGF-I levels. While such a response did not achieve statistical significance in the fetal compartment, similar findings of insulin resistance

have been reported by Dalziel et al. (25) in a 30-year follow-up study of patients who received a single course of antenatal betamethasone. Elevated glucose levels in cord blood from the preterm controls may be due to stress of premature birth. Our findings of decreased fetal growth hormone levels corroborate those of Ballard et al. (34). Since GH plays a minor role in fetal growth, the clinical significance of this finding is unclear and the effects on postnatal growth and development remain to be determined. GHBP was not detected in the umbilical cord. This may reflect the GH receptor status, confirming a paucity of GH receptors in the fetus (36).

The finding of higher serum IGF-I in the maternal compartment in response to steroid administration corroborates those of Miell et al. (27) who demonstrated that dexamethasone administered to male volunteers significantly increased the serum concentrations of IGF-I. In contrast, a study by Ogueh et al. (28) examining the effects of antenatal dexamethasone in 12 pregnant women showed no change in maternal plasma IGF-1 or IGF bioactivity up to 48 hours post treatment. In our study, although maternal IGF-I levels were elevated in both treated groups, betamethasone did not affect maternal IGFBP-1 or IGFBP-3 levels to suggest that IGF-I bioactivity was impaired. Maternal serum levels of IGF-I appear to rise progressively throughout pregnancy, and are suggested to have an impact on birth weight (19). We found that maternal IGF-I was not associated with birth weight. Similar findings were reported by Chellakooty et al. (29), who found that elevated maternal IGF-I was associated with placental growth and not fetal growth rate or birth weight. Considering the known effects of betamethasone on organ maturation, it is tempting to speculate that betamethasone-induced maternal IGF-I may have a positive influence on placental growth. However, we did not measure placental weight and

therefore it should be noted that our data can only make inferences about the role of maternal IGF-I in placental growth.

IGF-II circulates in serum at 2-5 times that of IGF-I. Like IGF-I it is a mitogenic polypeptide that is important for fetal growth. It is highly expressed in the fetal adrenal glands and it stimulates fetal adrenal growth (30-33). The significant finding of suppressed umbilical cord IGF-II may suggest perturbations in the development of the fetal adrenal cortex, an effect that is known to be associated with antenatal steroids. IGFBP-1 limits the availability of free IGF-I in the fetus. It is regulated by intracellular glucose and insulin (16), and inhibits the growth promoting effects of IGF-1 and GH (18). Therefore, we were not surprised to find that positive correlations between birth weight and umbilical cord IGF-I, and negative correlations between birth weight, ponderal index, and umbilical cord IGFBP-I in the term untreated group.

Our study has several limitations including small sample size. However, similar to a previous study using a sample size of 12 pregnant women (28) we demonstrated that a single course of antenatal betamethasone does not adversely influence IGFBPs in the maternal compartment. We did not determine differences between umbilical cord artery and vein, as this would more accurately reflect fetal effects. We also acknowledge that fetal hormonal levels are influenced by many factors, including body fat, sex, mode of delivery, and stress. Nevertheless, these fetal outcomes were not different between the preterm treated and untreated groups. In conclusion, a single course of antenatal betamethasone is associated with different responses in the maternal and fetal compartments. However, there were no differences in infant size or neonatal morbidities between deliveries that occurred <2 weeks and >2 weeks post treatment, as

previously demonstrated (36). While a single course of antenatal betamethasone may not lead to measurable anthropometric changes, there are significant effects on fetal growth factors, particularly IGF-II which may have implications well beyond the neonatal period.

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FIGURE LEGENDS

Figure 1. Effects of a single course of antenatal betamethasone on insulin levels in maternal (A) and mixed umbilical cord (B) plasma. A significant increase in maternal insulin levels were noted in the betamethasone-treated group that delivered <2 weeks post treatment. Group I (n=13) are betamethasone-treated patients who delivered <2 weeks post treatment; Group II (n=8) are betamethasone-treated patients who delivered >2 weeks post treatment; Group III (n=7) are untreated patients who delivered <37 weeks; and Group III (n=15) are untreated patients who delivered >37 weeks gestation. Data are presented as mean±SEM and analyzed using one-way ANOVA.

Figure 2. Effects of a single course of antenatal betamethasone on glucose levels in maternal (A) and mixed umbilical cord (B) blood. A significant increase in maternal glucose levels were noted in the betamethasone-treated group that delivered <2 weeks post treatment. Blood glucose levels were significantly higher in Groups I and III compared to Groups II and IV. Study groups are as described in Figure 1. Data are presented as mean±SEM and analyzed using one-way ANOVA.

- Figure 3.** Effect of a single course of antenatal betamethasone on IGF-I levels in maternal (A) and mixed umbilical cord (B) serum. Betamethasone induced a sustained increase in maternal IGF-I levels. Study groups are as described in Figure 1. Data are presented as mean \pm SEM and analyzed using one-way ANOVA.
- Figure 4.** Effect of a single course of antenatal betamethasone on IGF-II levels in maternal (A) and mixed umbilical cord (B) serum. A sustained suppression in umbilical cord IGF-I levels were noted with betamethasone treatment. Study groups are as described in Figure 1. Data are presented as mean \pm SEM and analyzed using one-way ANOVA.
- Figure 5.** Effect of a single course of antenatal betamethasone on IGFBP-3 levels in maternal (A) and mixed umbilical cord (B) serum. Umbilical cord IGFBP-3 levels were significantly lower in all preterm groups. Study groups are as described in Figure 1. Data are presented as mean \pm SEM and analyzed using one-way ANOVA.
- Figure 6.** Effects of a single course of antenatal betamethasone on maternal (A) and mixed umbilical cord (B) serum GH levels. Umbilical cord GH levels were suppressed in the betamethasone-treated group that delivered >2 weeks post treatment. Study groups are as described in Figure 1. Data are presented as mean \pm SEM and analyzed using one-way ANOVA.

Figure 7. Relationship between birth weight and umbilical cord IGF-I (A), birth weight and IGFBP-1 (B), and ponderal index and IGFBP-1 (C) levels in Group III (term controls). Birth weight was positively associated with IGF-I and negatively with IGFBP-1, while ponderal index was negatively associated with IGFBP-1. Study groups are as described in Figure 1. Data are presented as mean \pm SEM and analyzed using one-way ANOVA.

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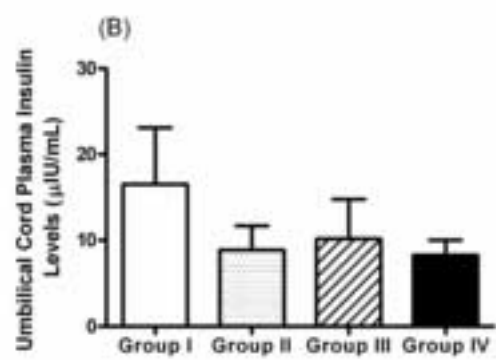
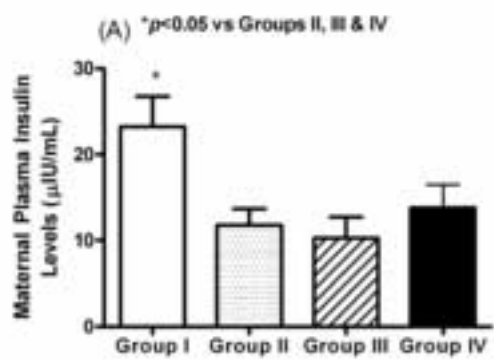


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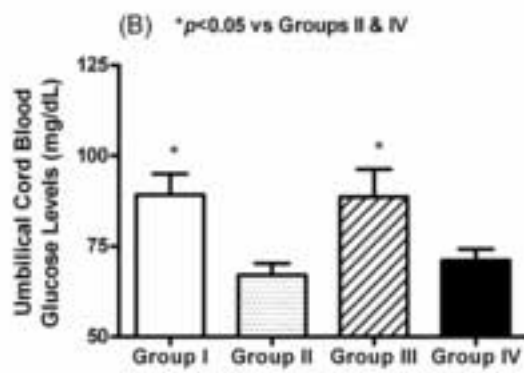
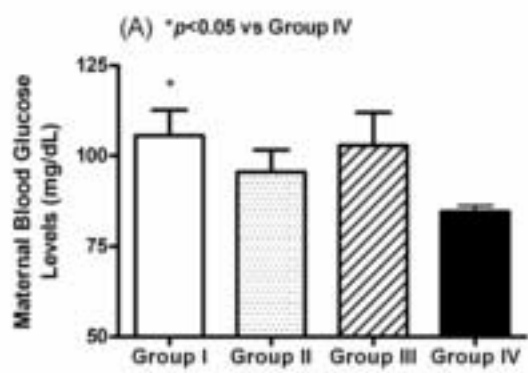


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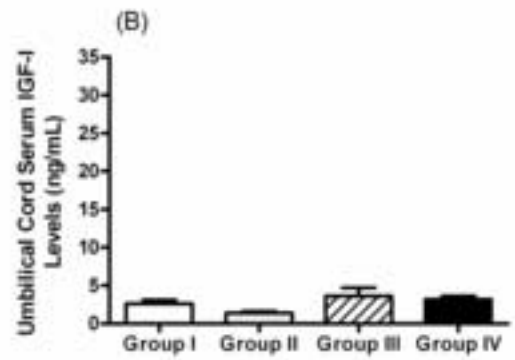
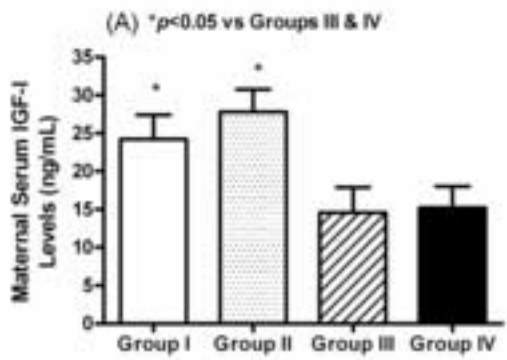


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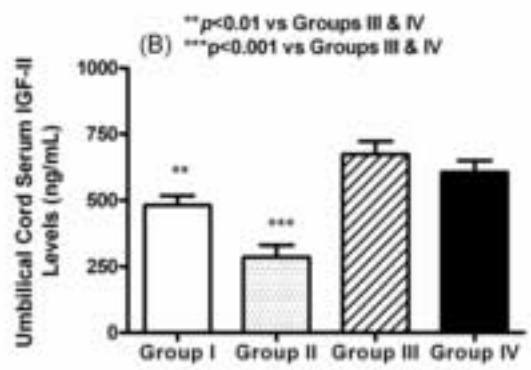
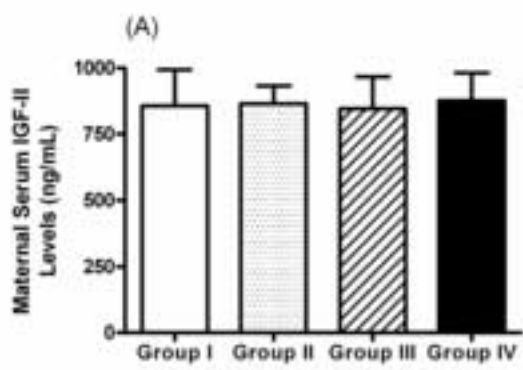


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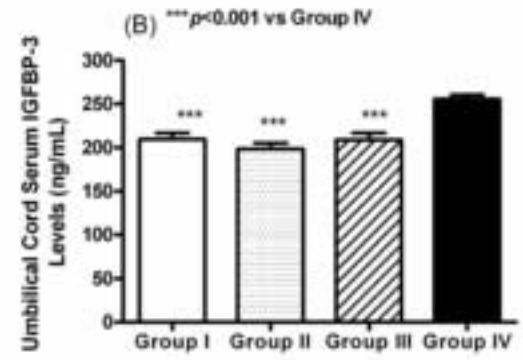
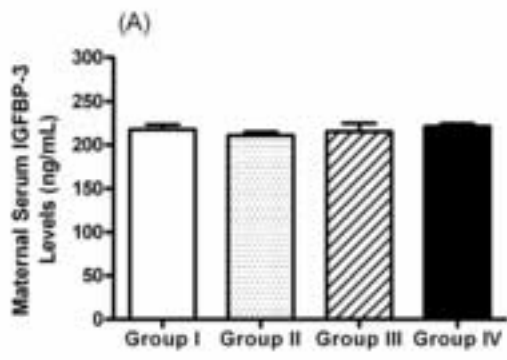


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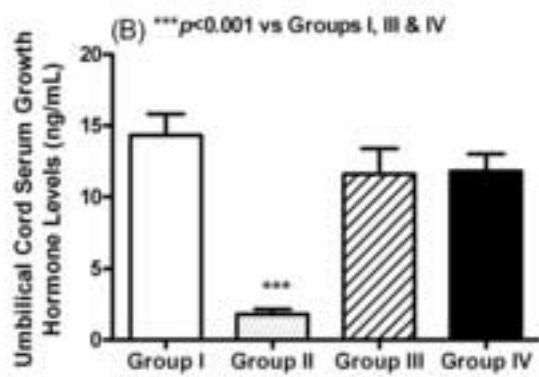
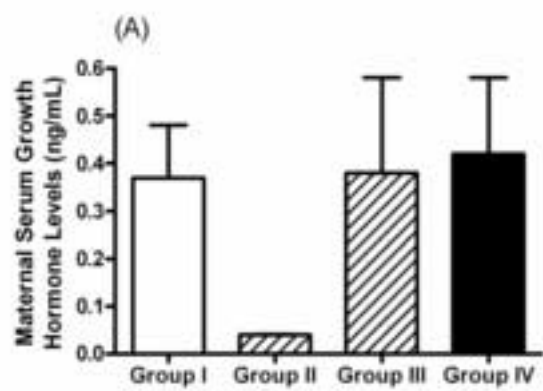
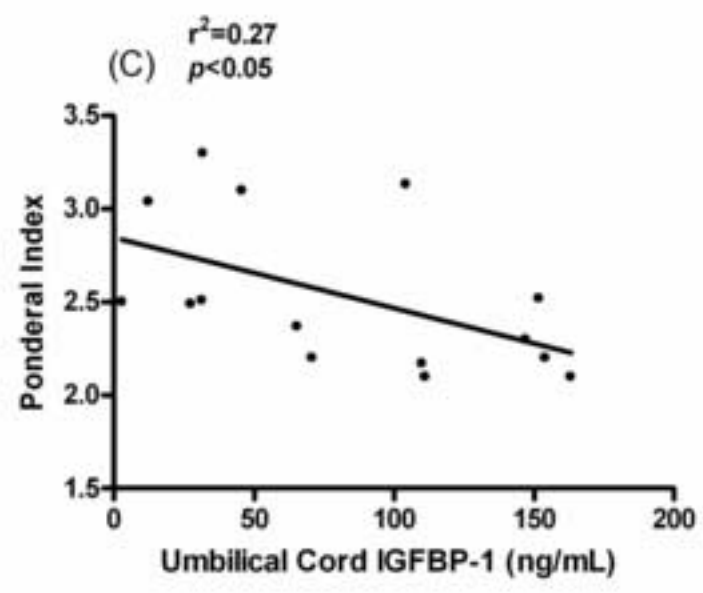
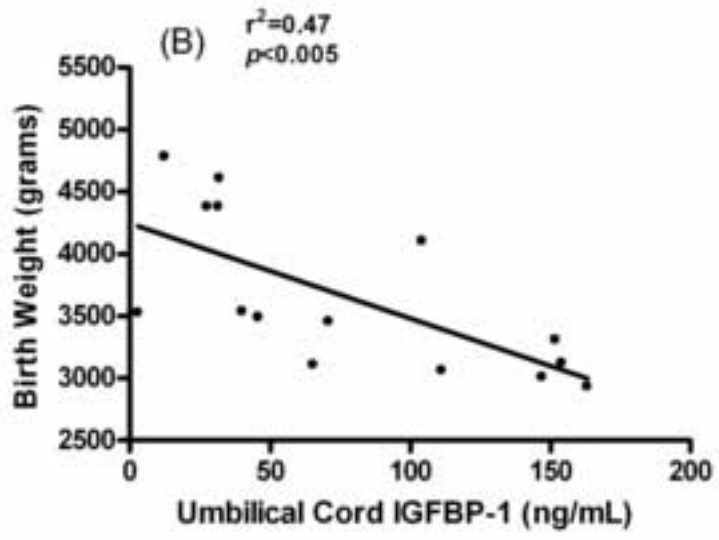
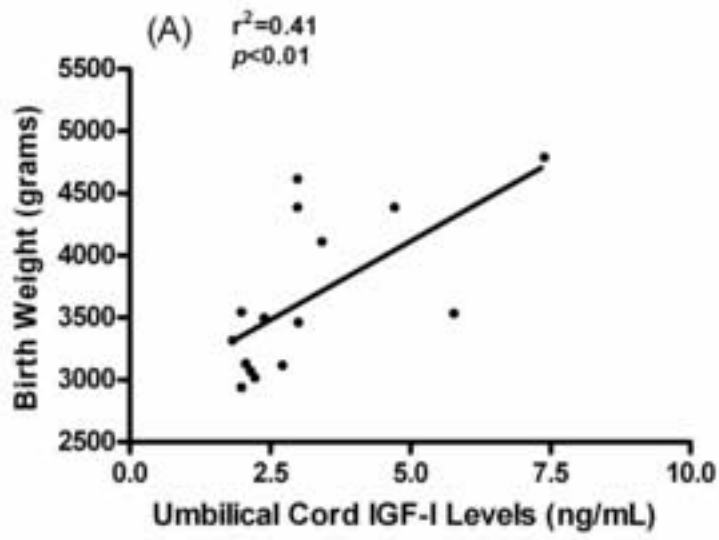


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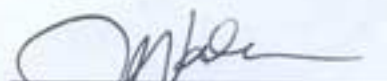
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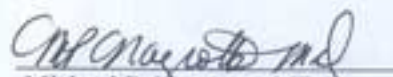

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Dear Dr. Le Roith:

We are submitting a manuscript entitled "Influence of a Single Course of Antenatal Betamethasone on the Maternal-Fetal Insulin-IGF-GH Axis in Singleton Pregnancies". A single course of antenatal betamethasone is being used as standard obstetric practice to advance fetal lung maturation in pregnancies at risk for preterm delivery. Although there is overwhelming evidence that multiple courses of antenatal steroids affect the maternal-fetal insulin-IGF-GH axis, there is a need for studies to examine the effects of a single course of betamethasone. The beneficial effects of betamethasone appear to last 7-10 days after treatment, however, a significant number of treated women deliver after the drug's beneficial effects have abated. We examined whether the effects of betamethasone on the maternal-fetal insulin-IGF-GH axis differ between these two groups. We believe that the results of our study have clinical implications and provide new and important information.


The authors warrant that the manuscript is being submitted only to *Growth Hormone & IGF Research* and will not be submitted elsewhere while under consideration. The manuscript is original and has not been published elsewhere other than as an abstract and should it be published in *Growth Hormone & IGF Research*, will not be published elsewhere, either in similar form or verbatim without the permission of the editors. A previous publication *Prostaglandins Other Lipid Med* 2005;78(1-4):139-59 used the same patients, however, the specimens obtained were analyzed differently, with different endpoints and outcomes. A copy of that article is available upon request. The authors are responsible for the reported research and have no financial or personal relationships with other people or organizations that could inappropriately influence this work. There are no conflicts of interest. The undersigned authors have participated substantially in the conception and design, analysis and interpretation of the data, and drafting and revision of the manuscript.

This study was conducted at Miller Children's Hospital, Long Beach, CA, in collaboration with the University of California, Irvine, Irvine, CA. A preliminary report of these findings was presented at the 2004 Pediatric Academic Societies Meeting in San Francisco, CA. The following names are submitted as potential reviewers:


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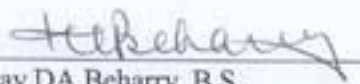
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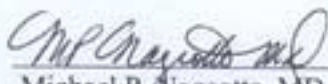
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