Repeated betamethasone treatment of pregnant sheep programs persistent reductions in circulating IGF-I and IGF-binding proteins in progeny

Kathryn L. Gatford, Julie A. Owens, Shaofu Li, Timothy J. M. Moss, John P. Newnham, John R. G. Challis, and Deborah M. Sloboda.

Research Centre for Early Origins of Adult Disease, Discipline of Obstetrics and Gynecology, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide; School of Women’s and Infant’s Health, The University of Western Australia, Perth; Women and Infants Research Foundation of Western Australia, Subiaco, Perth, Australia; and Canadian Institutes of Health Research Group in Fetal and Neonatal Health and Development, Departments of Physiology and Obstetrics and Gynecology, University of Toronto, Ontario, Canada

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Gatford KL, Owens JA, Li S, Moss TJ, Newnham JP, Challis JR, Sloboda DM. Repeated betamethasone treatment of pregnant sheep programs persistent reductions in circulating IGF-I and IGF-binding proteins in progeny. Am J Physiol Endocrinol Metab 295:E170–E178, 2008. First published May 20, 2008; doi:10.1152/ajpendo.00047.2008.—Exposure to synthetic glucocorticoids in utero markedly improves survival after preterm birth, but repeated exposures impair fetal and postnatal growth and are associated with evidence of insulin resistance in later life. The insulin-like growth factor (IGF) axis is an important regulator of growth and metabolism before and after birth. We have therefore investigated the effects of repeated maternal betamethasone injections on plasma IGF-I, IGF-II, and IGF-binding proteins (IGFBP) in fetal and postnatal progeny in the sheep. Pregnant sheep carrying male fetuses were injected with saline or betamethasone at 104, 111, and 118 days of gestation (dG). Plasma samples were collected postmortem from fetuses before (75, 84, 101 dG) or after one (109 dG), two (116 dG), or three (121–122, 132–133, 145–147 dG) doses of saline or betamethasone and from progeny at 42 and 84 days of age. Fetal weight was reduced after two or more maternal betamethasone injections, and this effect persisted to term. Repeated betamethasone exposures reduced plasma IGF-I and total IGFBP in fetuses at 133 dG and progeny at 84 days, and reduced plasma IGFBP-3 at 84 days. Fetal plasma IGF-II tended to increase transiently at 109 dG following the first betamethasone injection. Fetal, placental, and/or postnatal weights correlated positively with concomitant plasma IGF-I, IGF-II, and total IGFBP. We conclude that repeated exposure to synthetic glucocorticoids in utero programs the IGF axis before and after birth, which may contribute to the adverse effects of betamethasone exposure on growth and metabolism.

antenatal glucocorticoids; pregnancy; programming; insulin-like growth factor-binding protein

INJECTION OF WOMEN in preterm labor with synthetic corticosteroids accelerates fetal lung maturation and consequently markedly reduces mortality and morbidity in their premature infants (47). Follow-up of infants born to mothers enrolled in the first randomized control trial (RCT) of a single betamethasone course given to women in preterm labor showed improved neonatal and childhood outcomes (47). Although blood pressure and health-related quality of life scores were similar in 31-year-old adults whose mothers had betamethasone or saline before preterm delivery, those who were exposed to synthetic corticosteroids in utero had larger insulin responses to an oral glucose challenge, suggestive of insulin resistance (12, 47). In Australia, over 90% of obstetricians choose betamethasone as the synthetic corticosteroid for use in cases of threatened preterm labor, with smaller numbers using alternates, including dexamethasone (46). Although dexamethasone has cost advantages over betamethasone, recent data from the United States National Institute of Child Health and Human Development Neonatal Research Network support use of betamethasone in preference to dexamethasone, due to better long-term neurodevelopmental outcomes, as well as higher neonatal survival rates following preterm birth (31).

Clinically, use of repeated glucocorticoid administration to mothers at continued risk of preterm labor appears widespread, although it is not recommended (42, 46). An initial report from a large RCT concluded that repeated courses of synthetic corticosteroid were more effective than single doses in decreasing respiratory distress syndrome and severe lung disease in infants (11), and single doses did not reduce the risk of respiratory distress syndrome in infants born >7 days after exposure to corticosteroids (36). Nevertheless, repeated, but not single, exposure to synthetic corticosteroids reduced size at birth (9, 11) and increased neonatal blood pressure of infants (37).

In sheep, like humans, repeated maternal injections of betamethasone at doses similar to those used clinically in women impair fetal growth, whereas in most studies (6, 40, 41, 51), although not all (27), a single injection did not impair fetal growth. Sheep whose mothers were injected with four doses of betamethasone at 7-day intervals from 104 days gestational age [104 days gestation (dG), term ~150 dG] also had greater insulin responses to an glucose challenge as young adults and higher fasting plasma insulin-to-glucose ratio in adulthood than those whose mothers received saline (41, 50). This suggests insulin resistance also occurs in the sheep following repeated fetal exposure to synthetic corticosteroid.

A mechanistic link between in utero exposure to synthetic corticosteroids and these later adverse outcomes may be programming of the insulin-like growth factor (IGF) axis, which is important for growth and metabolism before and after birth. Gene deletion studies in mice have shown that IGF-I is the most critical IGF for fetal and postnatal growth, whereas IGF-II regulates placental and fetal, but not postnatal, growth.
fication of zfx and zfy gene fragments, as previously reported (16). All progeny in this study were intact males (i.e., not castrated).

All ewes received an intramuscular injection of 150 mg medroxyprogesterone acetate (Depo Provera; Upjohn) at 100 dG to reduce pregnancy losses due to subsequent glucocorticoid treatment (41, 52). Ewes were then randomly allocated to control or betamethasone groups. Animals in the betamethasone group received intramuscular injections of 0.5 mg/kg body wt betamethasone (Celestone Chronodose; Schering Plough) at 104, 111, and 118 dG. Animals in the control group received saline injections of a comparable volume (5–6 ml) at the same gestational ages. Betamethasone was chosen for its clinical relevance, since it is the main synthetic corticosteroid used in cases of threatened preterm labor within Australia (46). Plasma samples were collected at postmortem before (75, 84, 101 dG), during (109, 116 dG), or after (121, 132, 146 dG and at 42 and 84 postnatal days of age) either saline or betamethasone injections. For fetal collections, pregnant ewes were killed with captive bolt, fetuses were delivered by Caesarean section, umbilical arterial blood was collected, and fetuses were weighed and then killed by decapitation. For collection from postnatal progeny pregnant ewes that had received three injections of betamethasone or saline during pregnancy were permitted to deliver spontaneously, and lambs were kept with ewes until the time of death. At postmortem, blood samples were collected by jugular venipuncture; lambs were sedated with ketamine (15 mg/kg) and xylazine (0.1 mg/kg; Troy Laboratories, Smithfield, NSW, Australia) and then killed by decapitation.

Measurement of plasma IGF-I, IGF-II, and total IGFBP. Plasma IGF-I and -II were measured by RIA after separation of IGF and IGFBP by size-exclusion HPLC under acidic conditions (44). Maternal and fetal plasma samples were injected onto separate HPLC columns, dedicated to ovine postnatal or fetal samples, respectively. Four fractions of eluate (fraction 1, containing IGFBP; fraction 2, interpeak; fraction 3, containing IGF, and fraction 4, postpeak) were routinely collected for each acidified plasma specimen, using times determined for each column based on elution times of 125I-labeled IGF-I and IGF immunoreactivity. Recovery of 125I-IGF-I was 100.0 ± 0.9% for seven HPLC runs of fetal plasma and was 103.6% for a single HPLC run containing all postnatal samples for the study. Plasma IGF-I concentrations were measured by analysis of neutralized HPLC fraction 3, in a RIA specific for IGF-I (20), using a rabbit polyclonal antibody to human IGF-I (GroPep Australia). Total IGFBP concentrations were measured by analysis of neutralized HPLC fraction 1 in the same assay. Because IGFBP bind to and sequester 125I-IGF-I in this assay, they can be measured due to their effect of reducing the amount of 125I-IGF-I in the immunoprecipitated pellet, giving an apparent IGF concentration that reflects the total amount and binding affinity of IGFBP present in plasma. Samples were assayed in triplicate. Inter- and intra-assay covariances for an HPLC eluate fraction 3 pool prepared from ovine plasma containing 124.5 ng/ml IGF-I were 9.8 and 7.3% respectively (n = 5 assays). Covariance for extraction and assay of a fetal plasma quality control pool containing 235 ng/ml IGF-I, and included in each HPLC run of fetal samples, was 17.2% (n = 7 HPLC runs).

Plasma IGF-I concentrations were measured by analysis of HPLC fraction 3 in a RIA specific for IGF-II (8), using a rabbit polyclonal antibody against human IGF-II (GroPep). Samples were assayed in triplicate. Inter- and intra-assay coefficients of variation for an HPLC eluate fraction 3 pool prepared from ovine plasma containing 167 ng/ml IGF-II were 3.4 and 9.0%, respectively (n = 3 assays). Covariance for extraction and assay of a fetal plasma QC containing 396 ng/ml IGF-II, and included in each HPLC run of fetal samples, was 16.4% (n = 7 HPLC runs).

Ligand blotting of IGFBPs. Ligand blots for individual IGFBP were performed using all individual plasma samples available for saline- and betamethasone-treated fetuses at 121–122 and 132–133 dG, and saline- and betamethasone-treated postnatal progeny at 42 and 84 days of age. A similar ligand blot was performed using plasma...
IGF axes after repeated betamethasone in utero

Fetal and postnatal weight. Fetal weight at 109 dG was not reduced after one injection of betamethasone to the mother \((P = 0.9)\), compared with fetuses of saline-injected ewes (Fig. 1A). At 116 dG, however, fetuses whose mothers had received two betamethasone injections were lighter \((P = 0.022)\) than those whose mothers had received two injections of saline (Fig. 1A). Similarly, three maternal injections with betamethasone reduced fetal weight at 122–123 dG \((P = 0.006)\), and this persisted to 132–133 dG \((P = 0.028)\), and tended to at 145–147 dG \((P = 0.059)\) (Fig. 1A). Between 122–123 dG and 145–147 dG, after three maternal doses of betamethasone or saline, fetal weight increased with increasing gestational age \((P < 0.001)\) but was reduced by maternal betamethasone treatment \((P < 0.001)\). A maternal course of three betamethasone injections did not change progeny weight at 42 days \((P = 0.33)\) or 84 days \((P = 0.17)\) of postnatal age (Fig. 1B).

**Fetal and postnatal plasma IGF-I and -II.** Plasma IGF-I concentrations increased with gestational age in control fetuses between 75 and 146 dG \((P < 0.001, \text{Fig. 2A})\). Fetal plasma IGF-I was not reduced after one or two maternal betamethasone injections \((109 \text{ dG}: P = 0.95; d116: P = 0.27, \text{Fig. 2A})\). Exposure to three maternal betamethasone injections did not alter fetal plasma IGF-I at 122–123 dG \((P = 0.204)\) or near term at 145–147 dG \((P = 0.226)\) but reduced fetal plasma IGF-I at 132–133 dG \((P = 0.008, \text{Fig. 2A})\). Between 122–123 dG and 145–147 dG, two-way ANOVA indicated that fetal plasma IGF-I did not change with gestational age but was reduced by maternal betamethasone treatment \((P = 0.004, \text{Fig. 2A})\). Maternal betamethasone treatment did not affect plasma IGF-I in 42-day-old progeny \((P = 0.93)\) but reduced plasma IGF-I in 84-day-old progeny \((P = 0.012, \text{Fig. 2B})\).

Plasma IGF-II concentrations changed with gestational age in control fetuses \((P < 0.001)\), increasing up to 121–122 dG and then decreasing to term (Fig. 2C). Fetal plasma IGF-II tended to increase at 109 dG after one maternal betamethasone injection \((P = 0.069)\), but exposure to two or three maternal betamethasone injections did not alter fetal plasma IGF-II later in gestation \((P > 0.5)\) for each. Between 122–123 dG and 145–147 dG, two-way ANOVA indicated that fetal plasma IGF-II decreased with increasing gestational age \((P = 0.006)\) and was not changed by maternal betamethasone treatment \((P > 0.5)\) (Fig. 2C). Maternal betamethasone treatment did not alter plasma IGF-II in 42-day-old progeny \((P = 0.998, \text{Fig. 2D})\) or 84-day-old progeny \((P = 0.210, \text{Fig. 2D})\).

**Fetal and postnatal plasma IGFBPs.** Plasma total IGFBP concentrations increased with gestational age in control fetuses \((P = 0.021, \text{Fig. 2E})\). Fetal plasma total IGFBP was not reduced after one or two maternal betamethasone injections \((109 \text{ dG}: P = 0.59; d116: P = 0.51, \text{Fig. 2E})\). Exposure to three maternal betamethasone injections did not alter fetal plasma total IGFBP at 122–123 dG \((P = 0.637)\) or near term at 145–147 dG \((P = 0.355)\) but reduced fetal plasma total IGFBP at 132–133 dG \((P = 0.015, \text{Fig. 2E})\). Between 122–123 dG and 145–147 dG, two-way ANOVA indicated that fetal plasma IGFBP decreased with increasing gestational age \((P = 0.006)\) and was not changed by maternal betamethasone treatment \((P > 0.5)\) (Fig. 2C). Maternal betamethasone treatment did not alter plasma IGFBP in 42-day-old progeny \((P = 0.998, \text{Fig. 2D})\) or 84-day-old progeny \((P = 0.210, \text{Fig. 2D})\).
dG and 145–147 dG, two-way ANOVA indicated that fetal plasma total IGFBP decreased with increasing gestational age (P = 0.049) and was reduced by maternal betamethasone treatment (P = 0.026, Fig. 2E). Maternal betamethasone treatment did not alter plasma total IGFBP in 42-day-old progeny (P = 0.87) but tended to reduce plasma total IGFBP in 84-day-old progeny (P = 0.088, Fig. 2F).

Western ligand blots of fetal and postnatal plasma using 125I-IGF-II as ligand exhibited five bands (Fig. 3): from top, a doublet of two bands at 42–50 kDa (IGFBP-3), a single band at 33 kDa (IGFBP-2), and fainter bands at ~28 (IGFBP-1) and ~24 (IGFBP-4) kDa. On the basis of apparent differences in IGFBP-3 and IGFBP-2 abundances apparent in plasma pools at each age (Fig. 3), we then analyzed IGFBP abundance in individual plasma samples from fetuses at 121–122 dG and 132–133 dG and in postnatal progeny at 42 and 84 days age. Limited sample volumes precluded further analysis in fetuses at 146 dG. As expected, the relative abundance of IGFBP-2 in plasma was higher in the fetus than postnatally (Fig. 4). The abundance of plasma IGFBP-3 at 84 d postnatal age was reduced (P = 0.016) in progeny whose mothers had received three doses of betamethasone during pregnancy, compared with progeny of saline-treated ewes (Fig. 4). Maternal betamethasone treatment did not alter plasma abundance of individual IGFBPs in fetuses, or at 42 d postnatal age (Fig. 4).

Relationships between growth and the IGF axis. Fetal and placental weights did not correlate with plasma IGF-I, IGF-II, or total IGFBP concentrations at 109 dG after administration of one dose of saline or betamethasone to the mother (P = 0.26 for all). At 116 dG, after administration of two doses of saline or betamethasone to the mother, fetal weight tended to correlate positively with fetal plasma total IGFBP, and placental weight correlated positively with fetal plasma IGF-I (Fig. 5). At 121–122 dG, after administration of three doses of saline or betamethasone to the mother, fetal weight correlated positively with fetal plasma IGF-I and total IGFBP (Fig. 5). At 132–133 dG, fetal weight correlated positively with fetal plasma IGF-I and total IGFBP (Fig. 5). At 145–147 dG, fetal weight correlated positively with fetal plasma IGF-II. Placental weights at 132–133 and 145–147 dG did not correlate with fetal plasma IGF or IGFBP concentrations (Fig. 5). Postnatally, progeny body weight at 42 days of age correlated positively with plasma IGF-I, IGF-II, and total IGFBP, whereas body weight at 84 days of age correlated positively with plasma IGF-II (Fig. 6).
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cannot be excluded. The present study was designed to com-
injections with betamethasone, although longer-term responses
Plasma IGF-I and total IGFBP were not decreased in plasma
total IGFBP concentrations in fetuses after the third injection.
from the pregnant ewe with betamethasone once per week for 3 wk
consistent changes in the IGF axis before and after birth. Injecting
synthetic glucocorticoids before birth programs or causes per-
showed, for the first time in any species, that exposure to
programs the IGF axis in the fetus and progeny.
DISCUSSION
Repeated administration of betamethasone to the mother
axis in the fetus and progeny. We have shown, for the first time in any species, that exposure to
synthetic glucocorticoids before birth programs or causes per-
stant changes in the IGF axis before and after birth. Injecting
pregnant ewe with betamethasone once per week for 3 wk
from ~0.7 of term to 0.8 of term decreased plasma IGF-I and
total IGFBP concentrations in fetuses after the third injection.
Plasma IGF-I and total IGFBP were not decreased in plasma
collected from fetuses shortly after the first or second maternal
injections with betamethasone, although longer-term responses
cannot be excluded. The present study was designed to com-
pare long-term effects of three repeated betamethasone expo-
exposures, rather than fewer exposures, since we have previously
shown that this treatment regimen suppresses fetal and progeny
growth in sheep, whereas single doses do not (6, 39–41, 51).
Betamethasone did not alter circulating concentrations of IGF
or IGFBP at 42 days postnatal age, when any effects of
glucocorticoid exposure were hidden by the large interanimal
variation in circulating IGF-I and IGFBP. Importantly, however,
suppression of IGF-I and total IGFBP abundance after
three maternal doses of betamethasone was apparent at 84 days
of postnatal age in the present study. The suppression of fetal
plasma IGF-I and IGFBP after exposure to repeated glucocor-
ticoids contrasts with the changes reported by Kajantie et al.
(29) in cord blood collected from preterm human infants, who
reported increasing IGF-I and IGFBP-3 with increasing number
of antenatal betamethasone treatments. Whether this re-
flects additional stresses associated with preterm birth or spe-
cies differences is not clear. In addition, pregnant ewes in the
present study were treated with progesterone to prevent pre-
term labor, although this cotreatment is not routine in women
reated with betamethasone, and it is possible that progesterone
might modify effects of subsequent repeated betamethasone
exposure. The effects of repeated exposure to synthetic glu-
cocorticoids on fetal plasma IGF-I contrast with known effects
of chronically elevated endogenous glucocorticoid (cortisol),
which increases hepatic IGF-I mRNA expression but does not
alter plasma IGF-I (34). Given the lack of IGF-I suppression in
response to cortisol, we suggest that effects of repeated beta-
methasone on fetal plasma IGF-I abundance may be indirect
and may be a consequence of betamethasone-induced reduc-
tions in placental growth and function (6), and possibly nu-
trient transport, and that this may contribute to persistence of
reduced plasma IGF-I abundance to term. Reduced fetal
plasma IGF-I concentrations are thus a common feature of
several models of fetal growth restriction in the sheep, includ-
ing surgical restriction of placental growth (43), acute maternal
alcohol consumption (22), severe maternal undernutrition (5),
and in the present study, repeated in utero exposure to the
synthetic glucocorticoid betamethasone.
The most important finding of this study is that suppression
of circulating IGF-I and total IGFBP abundance following in
utero exposure to repeated courses of betamethasone persisted
postnatally at 84 days of age, ~110 days after the final beta-
methasone injection. Suppression of plasma total IGFBP
concentrations in the postnatal lambs paralleled that of IGFBP-3 specific-
ally. Circulating IGFBPs prolong the half-life of IGFs in
circulation but appear to decrease their bioavailability to re-
ceptors (19). In the present study, the magnitude of betametha-
sone-induced decreases in plasma IGF-I and total IGFBP or
IGFBP-3 in 84-day-old progeny were similar, however, implying
that the ratio of IGF to IGFBP in circulation, and thus its
bioavailability, would not be changed. Decreased circulating
IGFBP might, however, contribute to decreased circulating
IGF-I by decreasing its half-life in circulation. To our knowl-
edge, this is the first study to report that prenatal glucocorticoid
exposure programs the IGF axis beyond the neonatal period. It
is possible that glucocorticoid exposure has caused epigenetic
changes in the IGF-I and IGFBP genes or their upstream
promoters in a manner that persistently downregulated their
expression. Effects of glucocorticoids on DNA methylation or
on covalent modifications of histones on IGF and IGFBP gene
loci have not been reported, but histones of the hepatic IGF-I
locus are epigenetically modified in a rat model of IUGR, a
model that is characterized by elevated endogenous glucocorticoids (4, 21). Indeed, glucocorticoid exposure of rat hepatocytes in vivo induces differential demethylation of glucocorticoid responsive units within the promoter region of the tyrosine aminotransferase gene (54). Furthermore, demethylation of the Tat promoter persisted for at least 3 mo following glucocorticoid removal and increased subsequent glucocorticoid induction of the gene (54), demonstrating that glucocorticoids can induce persistent changes in gene expression through epigenetic mechanisms.

Plasma IGF-II tended to be increased transiently after the first betamethasone injection but was not altered following...
repeated maternal treatment with betamethasone, and postnatal plasma IGF-II abundance was not altered by prenatal betamethasone exposure. IGF-II expression in liver and muscle of late-gestation fetal sheep is downregulated by chronic exposure to cortisol (35), but our results imply that the synthetic glucocorticoid betamethasone does not downregulate expression of this gene.

Repeated glucocorticoid exposure: Consequences for prenatal and postnatal growth. Fetal growth was reduced after administration of repeated doses of betamethasone to the mother, and this persisted to term, as previously reported for this cohort (6). Effects on postnatal growth were not significant in the present cohort, most likely due to the limited animal numbers. In previous studies, however, weight of postnatal sheep progeny was reduced at 2–3 mo of age and normalized by 6 mo of age and in adults (39, 41). In humans, exposure to repeated glucocorticoids in utero reduces size at birth or increases risk of SGA (small for gestational age), particularly with increasing numbers of repeated courses (9, 11). In a recent RCT, repeat glucocorticoids did not affect growth up to two years of age, although at the doses used, birth weight was also not affected (10). Further follow-up studies of infants from existing randomized trials of repeat glucocorticoids, especially where higher doses have been used, may be warranted.

Consequences of glucocorticoid programming of the IGF axis. We have now shown that repeated in utero exposure to synthetic glucocorticoids at ∼0.7 to 0.8 of gestation in normally grown fetuses suppresses fetal, placental, and early postnatal growth (6, 26, 39, 41) and is associated with markers of insulin resistance and with altered capacity for hepatic glucose metabolism up to adulthood (41, 50). It also increases fetal plasma ACTH levels up to term (51), induces pituitary-adrenal hyperresponsiveness in young adult sheep at 1 yr of age, followed by adrenal hyporesponsiveness at 3 yr of age (49), and, as reported here, programs the IGF axis before and after birth in the sheep. In the present study, fetal and placental weights correlated positively with plasma IGF-I and total IGFBP, at some, but not all, ages; however, in all cases the direction of the relationship was positive, and programming of decreased IGF abundance may contribute to suppression of fetal growth following repeated exposure to maternal betamethasone. Positive correlations between IGF and IGFBP abundance and weights were far more consistent in postnatal progeny, providing stronger evidence that betamethasone exposure impairs postnatal growth through its actions on this axis. Insulin action may be particularly susceptible to programming by glucocorticoids; we have shown that a brief exposure to dexamethasone in early gestation programs increased insulin sensitivity of lipid metabolism in adult female offspring (23), and improved glucose tolerance in conjunction with increased first-phase glucose-stimulated insulin secretion in adult male offspring (13). It is possible that in utero programming of insulin action may occur at least in part via programming of the IGF axis, since low plasma IGF-I predicts later development of impaired glucose tolerance, type 2 diabetes, and cardiovascular disease in adults (17). The role of the IGF axis in mediating programming of postnatal metabolism by endogenous glucocorticoids merits further investigation.

Glucocorticoid programming of the IGF axis may also contribute to growth restriction during and after IUGR. The IUGR fetus is exposed to elevated glucocorticoids of maternal and fetal origin and has reduced protection from maternal glucocorticoids due to decreased placental expression of the glucocorticoid-inactivating enzyme 11β-hydroxysteroid dehydrogenase-2 (28, 48). Consistent with the current findings that repeated glucocorticoid exposure reduces circulating IGF abundance before and after birth, the IUGR fetus is characterized by reduced circulating IGFs before and after birth (14, 18, 30, 32, 33). The degree of comorbidity between premature delivery and fetal growth restriction means that many babies who are delivered prematurely and exposed to glucocorticoids are also growth restricted (11). The effects of increased exposure to endogenous glucocorticoids on the IGF axis in IUGR, and hence on the long-term growth and metabolic consequences, may be exacerbated by exposure to betamethasone.

Conclusions

We conclude that repeated maternal betamethasone treatment reduces the abundance of circulating IGF-I and IGFBP in fetal plasma, which persists into early postnatal life. This reduction in plasma IGF-I may contribute to the previously reported reductions in fetal and early postnatal growth and impairment of metabolic function following repeated exposure to elevated synthetic glucocorticoids in the sheep, and possibly in other species.

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Current addresses of D. M. Sloboda: The Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand; and T. J. M. Moss: Dept. of Physiology, Monash University, Clayton Vic 3800, Australia.

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