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Janna L. Morrison and Sandra Orgeig
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Antenatal Glucocorticoid Treatment of The Growth-restricted Fetus: Benefit or Cost?

Janna L. Morrison, PhD, and Sandra Orgeig, PhD

Women at risk of preterm labor are commonly treated with antenatal glucocorticoids to reduce neonatal complications, including respiratory distress syndrome. Despite the benefits of antenatal glucocorticoid for neonatal lung function, they are associated with negative cardiovascular outcomes. Among this population, there is a group of intrauterine growth-restricted fetuses in which substrate supply is reduced and these fetuses must undergo a range of cardiovascular adaptations to survive. Interestingly, the cardiovascular changes caused by antenatal glucocorticoid in normally grown fetuses are contrary to the cardiovascular adaptations that the intrauterine growth-restricted fetus must make to survive. Hence, the possibility exists that antenatal glucocorticoid in intrauterine growth-restricted infants may compromise cardiovascular development. This review first provides an overview of general antenatal glucocorticoid effects, before outlining the effects on cardiorespiratory development in normally grown fetuses, the cardiovascular adaptations that occur in the intrauterine growth-restricted fetus and finally integrating this with the very limited evidence for the effect of antenatal glucocorticoid in intrauterine growth-restricted infants.

KEY WORDS: Intrauterine growth restriction, surfactant, antenatal glucocorticoids, preterm delivery, blood pressure.

INTRODUCTION

In 2002, 7.9% of babies in Australia were born preterm (<37 weeks gestation).1 Women at risk of preterm labor between 24 and 34 weeks gestation are commonly treated with antenatal synthetic glucocorticoids (GCs), either dexamethasone or betamethasone.2 This treatment reduces the incidence of neonatal complications associated with preterm birth such as respiratory distress syndrome (RDS),3 necrotizing enterocolitis, and intraventricular hemorrhage (IVH).4 Antenatal GC also decreases neonatal mortality4,5 and improves neonatal outcomes.6 The evidence is that antenatal GC is most effective when administered between 7 days and 24 hours before delivery.7 As 50% of women in threatened preterm labor do not deliver within 7 to 14 days of initial antenatal GC,8 it has in the past been common practice to repeat the course of antenatal GC at weekly intervals until delivery occurred.9,10 However, the benefits of repeated courses of GC have not been established by evidence from randomized controlled trials.11

One main conclusion of a 1994 meeting of the National Institutes of Health Consensus group on the use of GC was that studies in animals be performed to determine the pathophysiological and metabolic mechanisms of the benefits and risks of antenatal GC, especially repeated antenatal GC.7 A revisit in 2000 by the NIH Consensus Development Conference12 on the use of repeat courses of antenatal GC, led to the recommendation for the continued practice only of a single course of GC, and that the use of multiple courses be restricted only to well-designed randomized clinical trials aimed at testing both the short-term and the long-term risks and benefits. This conclusion is reaffirmed in the latest Cochrane review on antenatal GC in women at risk of preterm labor which concludes that a single course of
antenatal GC is recommended to accelerate fetal lung maturation, but further research is required concerning the optimal dose to delivery interval, optimal corticosteroid to use, effects of multiple pregnancies, and to confirm the long-term effects into adulthood, especially of multiple doses.

Among the population of babies at risk of preterm delivery, there is also a group of babies that are growth restricted (Figure 1). Whether antenatal GC for this subset of infants is of benefit is not clear. Intrauterine growth restriction (IUGR) occurs when substrate supply is reduced and does not meet fetal demands. This can be the result of a decrease in nutrient supply, for example, an undernourished woman, or a decrease in oxygen, for example, a pregnant women living at high altitude. Many IUGR babies are born to women with adequate substrate supply but where there is a restriction in placental transport capacity resulting in a decrease in delivery of both oxygen and glucose to the fetus. It is not clear whether oxygen or glucose is the major driver for the fetal adaptations to reduced substrate supply. The fetus adapts to a decreased substrate supply by slowing its growth, as well as undergoing important cardiovascular adaptations. In particular, there is a redistribution of blood flow to the brain, adrenals, and heart at the expense of the peripheral organs to survive in a suboptimal environment. This results in relative brain sparing.

However, the important issue is that antenatal GC cause cardiovascular changes in normally grown fetuses including decreased fetal cerebral blood flow, decreased brain growth, and increased blood pressure (see Figure 1) that are contrary to the cardiovascular adaptations that the IUGR fetus must make to survive. Hence, there is a possibility that antenatal GC in IUGR infants may compromise cardiovascular development.

The epidemiological evidence suggests that preterm birth of babies small for their gestational age occurs in pregnancies treated with antenatal GC as often as it does in those not exposed to GC. There are conflicting data on whether antenatal GC is or is not associated with a reduction in the complications associated with preterm delivery in these growth restricted fetuses. A prospective study of 380 pregnancies, in which 155 women were treated with antenatal GC, found that the reduction in IVH was greater in growth restricted fetuses. Moreover, a larger study of 19759 very low-birth-weight neonates found that antenatal GC lowered the risk of RDS, IVH, and death in both normal and growth-restricted fetuses, with betamethasone being more effective than dexamethasone. In addition, antenatal GC of early preterm growth-restricted fetuses was associated with increased survival without disability or handicap at 2 years of age, compared with untreated infants, suggesting a significant benefit for treatment of early preterm growth-restricted fetuses, although these children were physically smaller at school age. However, a study of 1148 neonates found that there was no difference in the incidence of RDS, IVH, or necrotizing enterocolitis in growth-restricted fetuses whether they were treated with antenatal GC or not.

Despite these conflicting retrospective epidemiological studies on whether antenatal GCs are or are not associated with benefits in IUGR fetuses, there are virtually no experimental data in animal models of IUGR which examine the effects of GC on cardiorespiratory function. Specifically, the question arises as to whether IUGR babies derive a lung development benefit that outweighs the potential cardiovascular costs of antenatal GC (Figure 1). In this review, we first provide a brief overview of the broad physiological effects of antenatal GC on normally grown preterm infants, before concentrating on the evidence for the benefit of antenatal GC for cardiovascular and respiratory (lung and pulmonary surfactant) development in normally grown infants. In addition, we summarize the cardiovascular, lung structural, and pulmonary surfactant adaptations that occur in response to decreased substrate supply leading to IUGR. We then integrate this information with the very limited evidence for the effect of antenatal GC in IUGR infants before concluding with a series of questions that remains to be addressed to

Figure 1. Preterm fetuses have less mature lungs than full-term fetuses due to endogenous GC concentrations. IUGR fetuses have higher GC concentrations and thus the benefits of antenatal GC to lung development may in fact compromise cardiovascular function in IUGR fetuses at risk of preterm delivery. IUGR indicates intrauterine growth restriction; GC = glucocorticoid.
answer the question: Do antenatal GC in IUGR infants represent a benefit or a cost?

**THE BENEFITS AND RISKS OF SINGLE AND MULTIPLE COURSES OF ANTENATAL GCs ON OVERALL PHYSIOLOGICAL DEVELOPMENT IN NORMALLY GROWN FETUSES**

Clinically, women are treated with either dexamethasone or betamethasone. Both are fluorinated corticosteroids that have identical biological activity, that cross the placenta and are not inactivated by the GC inactivating enzyme, 11β-HSD2 (type 2 isoform of 11β-hydroxysteroid dehydrogenase). Although the treatment regimes are slightly different, the total dose given is 24 mg over a 24 to 48 hours period. Both treatment regimens result in an estimated 75% occupancy of available corticosteroid receptors, which is thought to provide a near-maximal induction of antenatal corticosteroid receptor-mediated response in fetal target tissues. Although both drugs were equally recommended by the NIH Consensus study in 1994, a recent analysis of trial data suggests that the relative risk ratios for several negative outcomes (including RDS, IVH, fetal or neonatal infection, neonatal death and stillbirth) are lower after betamethasone treatment compared with dexamethasone treatment. Moreover, the authors caution that a lower dose of both drugs may provide equivalent benefits but reduce the risks. They suggest that these questions need to be addressed by further randomized controlled trials. The following discussion addresses first the effects in response to a single course of antenatal corticosteroids followed by a discussion of the effects of multiple doses. In each, we first discuss the positive effects followed by the detrimental effects.

Overwhelmingly the use of a single course of GC is associated with positive outcomes for the infant. Since the observation by Liggins that fetal exposure to a single course of GC specifically induces pulmonary surfactant synthesis, clinical observations have shown that antenatal GC reduces the incidence of RDS by ~50% and also reduces the risk of IVH and neonatal death. Experimental studies have also shown improvement in fetal lung mechanics after very short treatment-to-delivery times, with concomitant alterations in lung structure.

However, some studies have demonstrated adverse long-term health effects such as the development of glucose intolerance and hypertension in later life, as well as a reduction in physical growth in school age children after a single course of antenatal GC. The negative effects on blood pressure were not borne out in 2 long-term follow-up studies of 2 cohorts of individuals treated antenatally with a single course of GC. One study demonstrated no changes in blood pressure at 6 years of age and the other demonstrated no changes in blood pressure at 30 years of age. Moreover, further long-term studies from the same group demonstrated no differences between individuals treated with a single course of GC antenatally compared with those that received no treatment in a wide range of psychological parameters including cognitive functioning, working memory and attention, psychiatric morbidity, handedness, and health-related quality of life in adulthood. In addition, there were no differences in the prevalence of wheeze or asthma at 30 years of age and in various lung function parameters. Hence, overall, there is little evidence of negative long-term outcomes of a single dose of antenatal GC.

However, after more prolonged and multiple dosage treatments, some experimental animal studies demonstrate positive effects, such as changes in the surfactant system. Given the NIH recommendations that more research is required to evaluate the relative risk-to-benefit ratios of multiple doses of GCs and that all treatment with multiple doses be restricted to patients enrolled in randomized controlled trials, a few such trial studies have recently been published. These have discovered that exposure to repeat doses of antenatal GC reduce neonatal morbidity, as determined by incidence of RDS and severe lung disease, relative to a single dose. In addition, babies exposed to repeat GC needed less oxygen therapy and shorter duration of mechanical ventilation. A follow-up study of the same cohort of babies at 2 years of age revealed no difference in the rate of survival free of major disability, in body size, blood pressure, use of health services, respiratory morbidity, or child behavior scores. However, children exposed to repeat doses were more likely to warrant assessment for attention problems. Hence, it appears that the short-term benefits support the use of repeat doses of GC in women who remain at risk of very preterm birth 7 or more days after an initial course.

However, there is significant evidence, predominantly from retrospective cohort studies, that multiple dose GC treatment is associated with numerous negative outcomes. These include an overall GC-induced growth restriction, a reduced body weight and head circumference at birth, and a smaller brain surface area with fewer cortical convolutions. These latter changes together with evidence of increased brain water content suggest that antenatal treatment with multiple courses of GC may...
delay brain maturation, but in this small cohort there appeared to be no effect on brain size. In addition, experimental animal studies have shown that antenatal GC administration reduces cerebral blood flow due to an increase in cerebral vascular resistance leading to a decrease in oxygen delivery. Moreover, there are deleterious effects on cerebral myelination and significant alterations in the function of the hypothalamic-pituitary-adrenal axis. These changes may affect later neurodevelopment. Multiple courses of antenatal GC treatment have also been associated with adverse fetal outcomes such as pituitary-adrenal suppression, as evidenced by reduced fetal plasma cortisol levels and neonatal infection (reviewed in Ref 36). As antenatal GC are administered maternally, there have also been reports of maternal adrenal suppression, maternal gestational diabetes, and increased risk of maternal infections. A very recent randomized controlled trial comparing single versus weekly doses of antenatal GC found no difference in functional residual capacity or lung compliance in preterm infants. As this study found no additional benefit of multiple doses of GC, the authors suggested that this trial did not support the use of multiple doses of GC.

### The Impact of Antenatal GCs on Cardiorespiratory Development in Normally Grown Fetuses

#### Cardiovascular Development

The impact of antenatal GC on the fetal cardiovascular system depends on the type and dose of GC as well as on whether the route of administration is maternal or fetal. In sheep, there is an increase in umbilical blood flow in response to maternal betamethasone treatment. In pregnant ewes infused for 48 hours with betamethasone, fetal cerebral blood flow and oxygen delivery are reduced due to increased cerebrovascular resistance. It has been suggested that this may account for the decreased brain growth observed at term in human fetuses following either single or repeated GC treatments. Glucocorticoid acts to increase vascular resistance through a variety of mechanisms, including enhanced sensitivity to vasoconstrictors and decreased sensitivity to vasodilators. Infusion of a high dose of betamethasone or a low dose of dexamethasone in fetal sheep for 48 hours during late gestation results in peripheral vasoconstriction and an increase in fetal blood pressure of about 8 to 10 mm Hg. Exposure of the fetus to the same low dose of dexamethasone, however, does not alter the fetal pressor and femoral responses to vasopressinergic, adrenergic, and angiotensinergic agonists. Administration of a single high dose of dexamethasone in pregnant ewes initially decreases fetal heart rate, short-term heart rate variation, fetal breathing movements, and PaO2, and these changes are then followed by increases in the fetal heart rate and in the short-term heart rate variation. Intrafetal infusion of cortisol, the endogenous GC, results in an increase in both fetal blood pressure and the fetal vascular reactivity to increasing doses of angiotensin II but not noradrenaline. Cortisol infusion to the fetus at 129 days for 5 days increases blood pressure to that observed in 140 days gestation fetuses as well as plasma angiotensin II, renin, and angiotensinogen concentrations. The immediate rise in blood pressure is renin-angiotensin system independent but thereafter is renin-angiotensin dependent. Thus, exposure of the sheep fetus in late gestation to either excess endogenous or exogenous GC results in changes in the vascular reactivity of the different circulatory regions to vasoconstrictor agents. This leads to an increase in fetal blood pressure with a decrease in fetal heart rate. There is also a decrease in the incidence of fetal breathing movements that are required for lung development.

### Lung Development

Specifically, antenatal GC alters lung structure as it results in a thinning of alveolar walls, a higher proportion of alveolar ducts, and a lower alveolar wall fraction in preterm sheep. These structural indices result in a higher average alveolar volume and improved lung function within 2 days after treatment. Improved lung function is measured by improved lung compliance, greater pulmonary surfactant stability (ie, sustained ability to lower surface tension), and the ability of the surfactant to improve lung compliance in surfactant-deficient animals. These effects occurred after a single treatment 48 hours before delivery. However, increased surfactant lipid content and saturation as well as increased expression of surfactant proteins (SPs) in alveolar (ie, lavageable) surfactant is only manifest after repeated doses over a prolonged period of time of 7 to 21 days. Furthermore, Ballard et al argued that the enhanced responsiveness with repetitive dosing could indicate either that the process of GC-induced lung maturation is reversible and/or gestational age dependent. It is likely that part of the difference in responsiveness is related to whether antenatal GC occurs before or after alveolarization with treatment being most effective before...
alveolarization has begun, as tested in monkeys, whereas late and repetitive treatment actually causes an inhibition of subsequent lung development. In sheep, repetitive doses at 7 days intervals improve fetal lung function cumulatively when delivered preterm; however, when delivery is delayed until term, there appear to be no differences between treated and untreated newborns. From explant cultures of human lungs, from clinical studies and animal studies, it appears that the antenatal GC effect only lasts as long as GCs are present. For example, stimulation of SP mRNAs in lung tissue occurs cumulatively with repetitive doses; however, this increase is completely reversible 7 days after treatment. Hence, once GCs are removed from the system, the effect is not lasting (reviewed in Ref 64). In conclusion, the experimental data from lung studies suggest clear respiratory benefits for a preterm infant of multiple doses at 7 days intervals starting before alveolarization, but there remain concerns about fetal growth as a whole, brain development, and cardiovascular function.

THE IMPACT OF ANTENATAL GCs ON CARDIOVASCULAR DEVELOPMENT IN THE GROWTH-RESTRICTED FETUS: COST OR BENEFIT?

Brain Sparing and Blood Flow Redistribution

A series of elegant studies on the pathophysiological effects of fetal GC exposure in the normally grown fetal sheep has shown that single or repeated antenatal GC causes a reduction in placental weight and a symmetrical restriction of fetal body growth due to their effects on cardiovascular function. However, there is less information regarding the impact of antenatal GC on the fetus that has undergone a series of physiological adaptations to a reduced placental substrate supply by reducing its growth.

The sheep has been used extensively as an experimental model for IUGR with a range of methods used to induce poor placental substrate supply to the fetus, including the surgical ablation of the majority of endometrial caruncles prior to conception, experimental induction of maternal hyperthermia, ligation of an umbilical artery or embolization of the placenta in late gestation, and maternal overnutrition in the pregnant adolescent ewe. We have extensive experience with the carunclectomy (Cx) model of IUGR to define the fetal cardiovascular and neuroendocrine adaptations to restriction of placental substrate supply. In this model, most of the caruncles (placental implantation sites) are removed from the uterus of nonpregnant ewes (carunclectomy), which results in restricted placental size and hence poor fetal growth by late gestation as shown in Figure 2 (Ref 16 and data from Morrison and McMillen laboratories). In this model, we define fetuses as IUGR if their body weight is 2 standard deviations from the control mean and if mean gestational PO2 is <17 mm Hg. These Cx IUGR fetuses have a similar arterial blood gas and metabolite profile (hypoxemia, hypercapnia, and hypoglycemia) when compared to the growth-restricted human fetus. In the Cx IUGR sheep fetus, as in the growth-restricted human fetus, substrate delivery to the periphery is likely reduced and body growth is restricted while brain growth relative to body growth is spared. This brain sparing effect is observed as early as 110 to 130 days gestation (Figure 3).

The brain sparing effect observed in IUGR fetuses is likely due to a redistribution of blood flow that maintains substrate supply to the brain and heart at the expense of the peripheral organs and tissues due to the actions of circulating vasoactive hormones including the catecholamines, noradrenaline and adrenaline, and cortisol, which are elevated in the IUGR fetus. Cortisol is elevated in the IUGR fetus from 127 days gestation compared to the normally grown fetus. This redistribution of blood flow is critical for survival of the IUGR fetus, yet it is unclear whether antenatal GC exposure alters the fetus’ ability to
maintain this adaptation to reduced substrate supply. In fact, in a recent study in a single umbilical artery ligation sheep model of IUGR, betamethasone caused an equivalent fall in carotid artery blood flow in IUGR fetuses but a large rebound increase in carotid blood flow that was not observed in control fetuses. These results suggest that the IUGR fetus may be at a greater risk of brain injury after treatment with synthetic GC than the normally grown fetus due to the cerebral vasodilatory response.

**Blood Pressure**

We have reported that although there was no difference in the mean arterial blood pressure between normally grown and IUGR fetal sheep, there was a direct relationship between blood pressure and the mean gestational PO2 in control animals, which was not present in the IUGR group. Importantly, in a recent series of studies in which we infused phentolamine, an α-adrenergic antagonist in IUGR and control fetuses, we demonstrated that the maintenance of mean arterial pressure in the IUGR fetal sheep depended to a significantly greater extent on α-adrenergic activation than in control fetuses, that the hypotensive response to α-adrenergic blockade was present before the onset of the prepartum cortisol increase, and that there was a direct relationship between the magnitude of the fetal hypotensive response and the fetal arterial PO2.

Infusion of an angiotensin-converting enzyme inhibitor after the onset of the prepartum increase in fetal cortisol concentrations from around 135 days gestation resulted in a greater hypotensive response in chronically hypoxic, growth-restricted fetal sheep when compared with normoxic fetuses. An earlier activation of GC receptors by betamethasone may augment this increase in angiotensin receptors and result in elevated fetal blood pressure that persists into adult life. Human newborns exposed to multiple courses of GCs have elevated blood pressure in the first week of life. Thus, the ability of the IUGR fetus to survive within a suboptimal environment and to respond appropriately to further impositions is dependent upon the capacity of the fetal cardiovascular system to respond appropriately. The key elements in this response include altered regulation of fetal blood pressure and a redistribution of cardiac output to maintain the growth and function of the fetal brain, adrenals, and heart. Any compromise of the fetal cardiovascular system to adapt will clearly have detrimental effects on fetal outcome and challenge fetal survival.

**THE IMPACT OF ANTENATAL GC TREATMENT ON PULMONARY DEVELOPMENT IN THE GROWTH-RESTRICTED FETUS: COST OR BENEFIT?**

**Lung Growth and Structure**

The normally grown fetus spares lung growth at fetal weights below 2.5 kg; however, the IUGR fetus does not spare lung growth from 110 to 137 days gestation.
(Figure 4; data from Morrison and McMillen laboratories). Close to term, IUGR fetuses demonstrate an increase in the volume of nonparenchyma, resulting overall in an increase in the number of airspaces per unit area, and a decrease in gas exchange surface density.

These changes in lung structure may represent arrested terminal air sac/alveolar development leading to a simplified acinar structure. This may lead to disturbed postnatal lung development with fewer, larger alveolar spaces with a more sparse septal network, reminiscent of the emphysematous lung.

Data from other animal models support these findings. Lung volume, alveolar airspace volume, and alveolar epithelial surface area were all reduced in guinea pigs born to mothers that were undernourished during the third trimester.

Similar impairments in lung structure were also described in growth-restricted postnatal rats where the mothers had been subjected to undernutrition (50% rations) during the final week (one third) of gestation.

Together, these data suggest that IUGR may lead to compromised neonatal lung function. It is not known if antenatal GC rescue lung development in the IUGR fetus.

**Pulmonary Surfactant**

Early studies indicated the possibility that growth-restricted infants demonstrate accelerated lung and surfactant maturation, due to an increase in the phosphatidylcholine to sphingomyelin ratio (PC/SM) in amniotic fluid of IUGR fetuses. There was speculation that this accelerated development may afford some protection to IUGR infants and that they may be at lower risk of RDS. The elevated plasma cortisol in IUGR fetuses was viewed as a possible mechanism for the stimulation of lung maturation.

However, other studies since then have shown that there is no evidence that infants that have been stressed by events such as IUGR, preeclampsia, or placental insufficiency are structurally immature. The primary difference between the study of Gagnon et al and that of Cock et al lies in the timing of growth restriction relative to gestation, that is, ~109 to 130 days or 120 to 140 days of gestation, respectively. It is possible that the levels of SP mRNA in the older fetuses had already reached their maximal expression and could not be stimulated further by cortisol.

Age exerted a specific effect on SP mRNA synthesis, suggests that there was a switch from lung cell proliferation to fetal lung cell maturation.

In direct contrast, chronic placental insufficiency during late gestation (120-140 days) did not change the SP-A, -B, or -C mRNA, or SP-A protein levels in the lung tissue of fetal sheep. There was also no correlation between SP mRNA or SP-A protein levels and cortisol levels. Furthermore, although DNA content decreased, relative to lung weight, the DNA concentration was higher in the growth-retarded sheep. As DNA concentration decreases across gestation, the increase found here suggests that the lungs of the growth-restricted fetuses were structurally immature. The primary difference between the study of Gagnon et al and that of Cock et al lies in the timing of growth restriction relative to gestation, that is, ~109 to 130 days and 120 to 140 days of gestation, respectively. It is possible that the levels of SP mRNA in the older fetuses had already reached their maximal expression and could not be stimulated further by cortisol.
seen in therapeutic interventions such as antenatal GC in various preterm models. However, the interaction between the effects of growth restriction and the antenatal GC treatment on lung and surfactant development has not been addressed.

**PERSPECTIVES**

In 2002, 7.9% of babies in Australia were born preterm (<37 weeks gestation). At present, clinically, all cases of threatened preterm delivery are treated with antenatal GC. The use of antenatal GC in women delivering after 34 weeks gestation tripled from 1998 to 2004 in Melbourne. Importantly, 6.4% of babies born in 2002 were of low birth weight (<2.5 kg). There is compelling evidence that these fetuses undergo dramatic cardiovascular adaptations in response to a decreased substrate supply to survive in a suboptimal environment. These include for example a redistribution of blood flow to the brain and heart at the expense of the peripheral organs. However, antenatal GC cause cardiovascular changes in normally grown fetuses (eg, decreased fetal cerebral blood flow, decreased brain growth, and increased blood pressure) that are contrary and apparently incompatible with the cardiovascular adaptations that the IUGR fetus must make to survive.

However, there is no experimental evidence that IUGR infants either at term or at postnatal life benefit from antenatal GC. To fully inform the clinical decisions regarding the use of antenatal GC in preterm infants, we require a complete and accurate cost-benefit analysis of antenatal GC on all groups of preterm infants, including growth-restricted and normally grown infants. We currently have no information on the differences in response between normally grown and IUGR fetuses to antenatal GC. Specifically, it is important to understand if, and how, the adaptations in blood pressure regulation and altered fetal, including brain, growth in IUGR fetuses may be affected by antenatal GC. In addition, the IUGR fetus demonstrates differences in lung structural and functional development relative to the normally grown fetus. It is important to understand the timing of lung and surfactant maturation during late gestation in IUGR fetuses, and it must be determined whether the IUGR fetus benefits from antenatal GC in the same way that a normally grown preterm fetus does.

In conclusion, data reviewed here will allow the clinician to continue to consider the beneficial role of GCs on lung maturation and thus survival of premature neonates but also create an awareness of the potentially negative effects of GCs on cardiovascular development, particularly in the IUGR fetus. The IUGR fetus undergoes cardiovascular adaptations, such as enhanced reliance on the sympathetic nervous system to maintain blood pressure and a redistribution of cardiac output to maintain brain, heart, and adrenal growth, to survive with reduced substrate supply. These adaptations may be compromised by GCs. In addition, due to higher plasma cortisol concentrations in the IUGR fetus, the benefits on lung development may be less significant in the IUGR fetus compared to the normally grown fetus. There is conflicting information that does not enable us to make clear predictions of the overall clinical benefits of antenatal GC treatment of the IUGR fetus. On one hand, there is the potential for lung maturational benefits, but on the other hand there is an increasing body of evidence to suggest that the cardiovascular adaptations that occur in IUGR infants are not compatible with the cardiovascular responses normally seen in response to antenatal GC. Therefore, it is imperative that experimental studies are performed that are designed to test the integrated cardiorespiratory responses to antenatal GC in normal and growth-restricted preterm infants as well as into postnatal life.

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