Effect of Antenatal Steroids on Haemodynamics in the Normally Grown and Growth Restricted Fetus

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Abstract: The administration of antenatal glucocorticoids to women in preterm labour confers clear and significant benefits on perinatal outcomes, decreasing the incidence of respiratory distress syndrome and intraventricular hemorrhage in preterm babies, thereby reducing rates of mortality and morbidity. However, there is an evolving body of research addressing the non-pulmonary consequences of antenatal glucocorticoid administration, particularly in the growth restricted fetus. In particular, synthetic glucocorticoids, such as betamethasone and dexamethasone, are strong modulators of vascular structure and function such that antenatal glucocorticoids may have profound and lasting effects on fetal/neonatal cardiovascular. This review examines the clinical and experimental literature on the benefits and risks of antenatal glucocorticoids in the well-grown preterm infant and in infants affected by intrauterine growth restriction (IUGR), highlighting the significant lack of specific information on the effects of antenatal glucocorticoids in IUGR infants. This is important because IUGR is associated with preterm birth and so the IUGR fetus is likely to be exposed to antenatal glucocorticoids. Recent experimental studies have shown that the fetal hemodynamic actions of exogenous glucocorticoids are profoundly different in IUGR fetus compared with the well-grown fetus with possible adverse implications for the development of the immature brain. Such observations merit caution clinically and further investigation.

Keywords: Fetus, placenta, growth restriction, glucocorticoids, cardiovascular, brain.

INTRODUCTION

The seminal work of the late Sir Graham “Mont” Liggins in the 1960s revolutionized perinatal medicine and has been responsible for the survival of thousands of preterm infants who would otherwise have died. While examining the contribution of glucocorticoids to provoke parturition in sheep, Liggins serendipitously observed that when fetuses had been exposed to glucocorticoids, as preterm newborn lambs they unexpectedly survived. Just a short time later, Liggins and Howie [2] published the landmark paper reporting the first randomized controlled trial (RCT) in human pregnancy in which the synthetic glucocorticoid betamethasone was administered antenatally to the mother and improved survival and lung function in preterm neonates. In this innovative trial, the regimen for betamethasone administration was two 12mg injections to the mother, administered 24 hours apart. At the time, Liggins noted that the mechanisms by which the steroids ‘aerated’ the lungs and improved survival were not known, but, as in the lambs, appeared to be the result of accelerated surfactant activity [1, 2], a particularly novel and insightful observation given that surfactant research was still in its infancy [3].

During the 1980s and early 1990s, while the use of glucocorticoids in clinical practice increased, there remained large variability in practice between institutions and nations [4]. In the mid-1990s, with the aim of guiding and improving practice, the National Institutes of Health (NIH) and the Royal College of Obstetricians and Gynaecologists (RCOG) both published consensus statements recommending the administration of antenatal glucocorticoids to women at risk for preterm delivery prior to 34 weeks gestation [5, 6]. Rates of glucocorticoid use increased steadily from then on.

In high-resource countries, approximately 10% of babies are born preterm, at less than 37 weeks gestation. Of these, up to 30%, or 3% of all births, are born prior to 34 weeks and are therefore suitable for a course of antenatal glucocorticoids. Since consensus statements by leading authorities were introduced the proportion of women who deliver prior to 34 weeks and received a course of antenatal glucocorticoids has become very high across developed countries at over 70% [7, 8]. For babies born prior to 34 weeks, systematic review of available RCTs demonstrate that a single course of glucocorticoids prior to preterm birth increases survival by almost 50% and decreases respiratory distress syndrome (RDS) and other morbidities of prematurity, in particular intraventricular hemorrhage by similar extents [9].

Forty years on since Liggins and Howie published their landmark clinical trial findings, it is perhaps timely that we reflect on our progress and advances regarding antenatal glucocorticoid therapy. Much has changed in the field of antenatal glucocorticoid therapy. Our knowledge of the mechanisms of action of glucocorticoids on the lungs has significantly improved, with the likely preterm lung matura-tion contributed by a range of biochemical and physiological changes over time. To this day, the methods of prescribing betamethasone remain the same as in the original Liggins and Howie trial, two 12mg injections, given 24 hours apart [5]. Further, as first noted by Liggins and Howie [1], and confirmed in subsequent trials [10], the beneficial effects of
glucocorticoids are transient, with no difference in the incidence of RDS between glucocorticoid-exposed and placebo groups when birth occurred seven or more days after treatment. This is important because about half of women and babies treated with glucocorticoids remain undelivered after one week [7, 10], and are therefore likely to be exposed to repeat doses of glucocorticoids. The risks, if any, associated with repeated steroid exposure remain poorly defined but are likely to be greater when compared to a single course of steroids. In this regard, experimental animal data consistently demonstrate that antenatal glucocorticoid treatments decrease body weight [11-13], with altered growth in developing lambs dose-dependent on glucocorticoid exposure [14]. In humans, repeat doses of antenatal glucocorticoids are associated with modestly reduced head size and birth-weight, both of which are normalized by time of discharge from hospital a few days later [15]. Intriguingly, the mechanisms by which exogenous glucocorticoids reduce fetal growth still remain largely unknown but are likely to include effects exerted via the placenta and possibly on the fetal vasculature. Indeed, it is now widely published that synthetic glucocorticoids, particularly betamethasone and dexamethasone, have a variety of other non-pulmonary side effects, including being potent regulators of vascular tone. These effects led us to question whether antenatal glucocorticoids benefit all preterm fetuses or whether there was a subgroup of preterm fetuses in whom glucocorticoids may be detrimental? In particular, there were emerging human and experimental animal data to suggest that the intrauterine growth restricted (IUGR) fetus responded to exogenous glucocorticoids quite differently to the well-grown fetus, specifically in its hemodynamic responses with potential consequences on the developing brain. Since glucocorticoids may not confer benefit to the preterm growth restricted fetus as is documented in the preterm well-grown fetus [16], it is pertinent to ask whether the short- and long-term effects of glucocorticoids on fetal cardiovascular function in the IUGR fetus may cause harm. Accordingly, in this review we will explore the mechanisms of action, and potential consequences, of synthetic glucocorticoids in both the well-grown and the IUGR fetus.

I. GLUCOCORTICOID ADMINISTRATION IN THE WELL-GROWN FETUS

Endogenous glucocorticoids play an essential role in the normal maturation of the fetal lungs prior to birth, with human and animal studies showing that increasing glucocorticoid availability over the course of late pregnancy corresponds with indices of increasing lung maturity [17-19]. Following Liggins’ serendipitous observations, exogenous, synthetic glucocorticoids, most commonly betamethasone or dexamethasone, have been used antenatally at preterm gestations to mimic and accelerate these maturational effects of endogenous cortisol in the lungs. Betamethasone and dexamethasone act via glucocorticoid receptor [25] and most likely via several mechanisms [31]. Furthermore, mechanisms of action may differ in the ewe or fetus does not alter heart rate [11, 25], whereas dexamethasone administration, to either the ewe or fetus, results in a biphasic fetal heart rate response, with an initial fall in fetal heart rate followed by a significant tachycardia [27, 28]. The primary decrease in fetal heart rate following dexamethasone is accompanied by a decrease in heart rate variability, which rebounds over time to a significant increase in heart rate variability [28]. These observations are notable, and may be of concern, because it is thought that alterations in heart rate variability are associated with impaired cardiac function, and reduced beat-to-beat fetal heart rate variability is indicative of fetal hypoxaemia and compromise, at least in the intrapartum setting [29, 30].

The mechanisms by which synthetic glucocorticoids mediate these cardiovascular effects have been investigated and are likely to reflect a variety of physiological actions – further evidence of the non-specific and extra-pulmonary actions of synthetic glucocorticoids. Indeed, direct and indirect actions at the level of the autonomic nervous system, the heart and/or the peripheral circulation have been postulated. The synthetic glucocorticoids betamethasone and dexamethasone act via glucocorticoid receptor binding, in contrast to cortisol that acts via both glucocorticoid and mineralocorticoid receptors. This suggests that glucocorticoid-induced hypertension is mediated predominantly via the glucocorticoid receptor [25] and most likely via several mechanisms [31]. Furthermore, mechanisms of action may differ in different vascular beds [31, 32] such that in some fetal vessels glucocorticoids induce vasodilatation [33], but more of that later. Wire myograph studies of fetal femoral arteries show that the increased vascular tone in the fetus following exogenous glucocorticoids arises from increased calcium mobilization [31], consistent with previous in vitro and in vivo observations in adult blood vessels [34, 35]. The contraction response of the vascular smooth muscle to increased calcium mobilization also likely underlies the observation in adult vasculature that glucocorticoids increase vessel responsiveness to noradrenaline [20]. However, increased vascular
responsiveness to noradrenaline following glucocorticoid exposure does not appear to occur in the fetus [31, 36], at least as a direct effect.

Exogenous glucocorticoids also decrease vascular smooth muscle cell adenylate cyclase activity and cAMP and thereby increase vascular tone [31, 37]. Like noradrenaline responsiveness, the decrease in cAMP may be mediated via increased calcium mobilization as calcium inhibits adenylate cyclase activity [38]. Increased fetal vascular response to angiotensin II (AGII) is also induced by glucocorticoids [32, 36, 39], via both increased AGII [39] and increased expression of angiotensin receptors AT1 and AT2 [32]. Last, glucocorticoids increase fetal vascular responsiveness to endothelin (ET-1) [39]. All of these mechanisms are likely to play roles, to differing extents in different vessels, in the acute hypertensive response of the fetus to glucocorticoid administration. In addition to these acute effects, high levels of antenatal glucocorticoid exposure impairs nephrogenesis in the developing kidneys [41] and suppresses the responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis [42]. These mechanisms have been proposed as a mechanistic link with long-term programming dysfunction such that fetal exposure to excessive glucocorticoids – whether endogenous or exogenous – may lead to increased risks of cardiovascular disease in adulthood. For example, newborn lambs that had been exposed to antenatal betamethasone have raised blood pressure and cardiac output compared to lambs not treated with steroids [43]. However, reassuringly, no changes in resting blood pressure in sheep followed through to adulthood have been observed [44]. Similarly, in humans, while blood pressure is significantly higher in newborn babies whose mother was treated with antenatal dexamethasone [45], and one study showed that blood pressure in late childhood remained higher in those children [46], the majority of studies have failed to demonstrate that in utero exposure to acute dose exogenous glucocorticoids, administered in preparation for preterm birth as opposed to chronic exposure such as in maternal asthma, is associated with any increased cardiovascular risks [47, 48]. Indeed, a 20-year follow-up of preterm infants exposed to a single course of betamethasone between 26 and 32 weeks gestation, systolic blood pressure was significantly lower than in the placebo-treated group while diastolic blood pressure was not different [47]. Further, the cohort of children reported in Liggins and Howie’s original randomized trial [2] have now been followed through to 31 years of age with no evidence of hypertension, HPA suppression, or other adverse cardiovascular effects [48]. While the long term effects of antenatal glucocorticoid exposure remain to be fully elucidated it would appear that, at the present time, there are either no or minimal deleterious cardiovascular effects such that the risk:benefit ratio is firmly weighted in favour of benefit for those fetuses at risk of preterm birth before 34 weeks’ gestation. It is fair to say though that we will not know the full effects of antenatal glucocorticoids until the treated and untreated cohorts from the earliest randomized studies enter middle age, when cardiovascular disease is likely to become identifiable.

Cerebrovascular and Brain Effects

Consideration of the cardiovascular effects of exogenous antenatal glucocorticoids is not only relevant to direct cardio-vascular changes and subsequent cardiovascular disease risks. The development and function of other fetal organs may be affected, either directly or indirectly, by the cardiovascular changes. In particular, the fetal brain may be susceptible to cardiovascular changes induced by preterm exposure to synthetic glucocorticoids. Specifically, in addition to increasing systemic (peripheral) vascular resistance, via the various mechanisms detailed above, exogenous glucocorticoids increase cerebral vascular resistance by the same mechanisms, leading to both decreased overall cerebral blood flow [11, 23, 49] and impaired region-specific cerebral oxygen delivery [49]. In experimental animals, the consequences of these changes in brain haemodynamics are significant. The glucocorticoid-induced decreases in cerebral blood flow are associated with alterations in non-linear electrocortic activity indicating dysfunction of complex neuronal activity and abnormal cerebral substrate metabolism [50, 51]. At the cellular level, synthetic glucocorticoids increase cell death and oxidative stress [11], disrupt normal patterns of myelination within the fetal sheep brain [52], and reduce neuronal cell number in primates [53]. Administration of single or repeat doses of antenatal glucocorticoids is also associated with reduced brain weight of sheep at term [44, 54], an effect which persists into adulthood [44]. Although animal studies suggest adverse effects of exogenous glucocorticoids on the developing brain, it is reassuring to find that human adult follow-up studies to date have not shown reduced cognitive or behavioural capacity in those groups exposed to a single course of antenatal synthetic glucocorticoids [47, 55]. Whether this is true for subjects exposed to repeated antenatal glucocorticoids remains uncertain. Repeated dose administration, particularly with dexamethasone, was associated in a non-randomized trial with increased rates of white matter injury and neurodevelopmental impairment at 2 years of age [56]. In contrast, in a similarly non-randomized study, multiple courses of betamethasone conferred protection against subsequent cerebral palsy in comparison to a single course, although multiple courses did increase hyperactive / attention deficit behaviour, albeit with no effect on intelligence quotient, in children at 3 or 6 years of age [57]. The findings from these studies, and studies like them, are difficult to interpret because they do not take into account the indication for the repeated steroid administration. It is possible that it is the on-going risk of preterm birth, perhaps secondary to recurrent placental abruptions for example, rather than the glucocorticoid administration per se that confers the increased risk of adverse neurodevelopmental outcome. In this regard, the longer term outcomes from the randomized trials of single versus multiple glucocorticoid courses should provide more meaningful and consistent insight. Overall, these studies have been reassuring [58, 59]. While the US follow-up study observed a possible increased risk in cerebral palsy in children exposed to multiple courses of betamethasone compared to those exposed to a single course, this effect was non-significant and when combined with the negative findings of the Australian study suggest that multiple courses do not increase the future prevalence of cerebral palsy. Importantly, in both of the initial RCTs underlying these studies betamethasone, not dexamethasone, was the glucocorticoid that was used. Further, in the Australian study children exposed to multiple courses had a higher rate of hyperactivity behaviour than those ex-
posed to a single course [59], confirming the non-controlled studies [56, 57].

While in this discussion we have implied that increased cerebral vascular resistance and decreased cerebral blood flow following glucocorticoid administration is an adverse effect, it is interesting to note that these cerebrovascular changes may in fact be protective. It has been suggested that the transient decreases in cerebral blood flow may underlie reduced rates of intraventricular hemorrhage observed in newborns following preterm exposure to synthetic glucocorticoids [24]. Whether these systemic and central haemodynamic changes are beneficial or otherwise, that glucocorticoids exert these effects is important to recognize and for the clinician to be aware of. Further, it is only more recently that it has become apparent that the haemodynamic effects of glucocorticoids in different fetal states also differs. In particular, the haemodynamic effects of glucocorticoids in the growth restricted fetus are profoundly different to those in the well-grown fetus.

II. GLUCOCORTICOID ADMINISTRATION IN THE GROWTH-RESTRICTED FETUS

There is a paucity of data and perhaps, until recently, even a lack of debate on whether antenatal glucocorticoid administration provides significant benefit to the IUGR fetus. The original 1994 NIH consensus statement advocating the prescribing of antenatal glucocorticoids for preterm lung maturation acknowledges that there were insufficient data to specifically address the effectiveness of antenatal steroids in high-risk pregnancies such as IUGR [5]. Since this time, only a handful of studies have specifically addressed this issue, and there remains no clear consensus on the risks and benefits of antenatal glucocorticoids on lung maturation and non-pulmonary effects in the IUGR fetus [60-62]. This is important because fetal growth restriction is associated with an increased risk of preterm birth and so IUGR fetuses are very likely to be exposed to antenatal glucocorticoids [62, 63]. Further, IUGR fetuses face heightened rates of perinatal mortality and morbidity and so any intervention, with potential for both benefit and harm, merits careful and specific examination in this cohort of fetuses. In this regard, a recent review of the literature comparing the outcomes of IUGR infants who did and did not receive antenatal glucocorticoids suggested that antenatal glucocorticoid administration does not improve neonatal outcomes [16]. Specifically, in contrast to normally grown fetuses, there was no difference in the incidence of RDS or neonatal death between IUGR infants treated with glucocorticoids and those that were not [16]. Why should this be the case? Most commonly, IUGR is caused by placental insufficiency [64] and is therefore associated with chronic fetal hypoxia and raised levels of stress hormones, including endogenous glucocorticoids [65]. It is likely that the increased endogenous glucocorticoids accelerate fetal lung maturity spontaneously, without the need for exogenous glucocorticoids. While this has certainly been observed in experimentally induced IUGR [66-68], most recently a study specifically addressing the additive effects of IUGR and betamethasone suggests that exogenous glucocorticoids do confer additional lung maturation in the IUGR fetus [69].

Cardiovascular Adaptations in IUGR

In the absence of exogenous glucocorticoids, the IUGR fetus demonstrates cardiovascular adaptation to placental dysfunction and a chronic, sustained low oxygen environment. This involves a preferential redistribution of cardiac output to the brain, heart and adrenals in an effort to maximize blood flow and sustain normal function and growth of these key organs [70]. While the basis of these cardiovascular adaptations are not fully understood, elevated fetal plasma levels of catecholamines appear important. During prolonged moderate fetal hypoxia, as occurs in IUGR secondary to placental dysfunction, there is increased sympathetic activity, accompanied by increased release of noradrenaline and adrenaline [71]. This rise in catecholamines in turn mediates centralization of fetal cardiac output leading to increased brain, heart and adrenal blood flow [72]. Furthermore, over the course of pregnancy, chronic fetal hypoxia alters arterial properties including endothelial vasodilator dysfunction and sympathetic hyperinnervation [73, 74], mechanisms that are thought to underlie in utero hypertension [75] and longer-term cardiovascular programming changes into childhood and later life [76, 77]. Blood flow redistribution is also mediated, at least in part, by the renin-angiotensin system. Fetal plasma concentrations of the potent vasoconstrictor angiotensin II are elevated in response to hypoxia [78], and likely to be a mechanism at play in the IUGR fetus, as evidenced by the ability of captopril, an angiotensin-converting enzyme inhibitor, to decrease blood pressure in the IUGR but not in the healthy well-grown fetus [79]. In clinical practice, these haemodynamic changes in the IUGR fetus, resulting in preferential cardiac output to the developing brain can be observed as a reduction in pulsatility index in the middle cerebral artery [80, 81]. This so-called “centralization” is thought to be protective to fetal brain growth resulting in distinctive asymmetric fetal growth restriction, characterized as sparing of the head circumference and musculoskeletal dimensions, with reduced abdominal circumference and little fat deposition [82]. Whether centralization protects neurodevelopment and function, as opposed simply to brain growth, remains uncertain and, as discussed below, increased cerebral blood flow may be causative of rather than protective of preterm brain injury.

In addition to these changes in blood flow distribution, if the IUGR is of placental origin, as is usually the case [64, 82, 83], the fetal heart is exposed to chronically increased after-load, over and above that created by the systemic hypertension, resulting in ventricular hypertrophy, particularly in the right ventricle [75], myocardial cell damage, and impaired function [84]. It is this hypertrophy and dysfunction that likely underlies the abnormal cardiac function in childhood [77].

Haemodynamic Effects of Glucocorticoids

Administration of antenatal glucocorticoids significantly disturbs the cardiovascular adaptations of the IUGR fetus. The differential effect of glucocorticoids in the IUGR fetus was first recognized clinically [85-89]. In pregnancies with severe IUGR secondary to placental dysfunction, the administration of antenatal glucocorticoids in preparation for pre-term birth was associated with altered fetoplacental blood flow, as detected using Doppler ultrasound [85, 87]. Specifi-
cally, in pregnancies with absent or reversed end-diastolic flow (AREDF) in the umbilical artery, the administration of either dexamethasone or betamethasone is associated with a transient return of flow in about two thirds of fetuses, lasting on average 2-3 days [85-87]. It was subsequently shown that these effects were, at least in part, likely to be due to vasodilatation in the placental [90, 91] and possibly fetal vasculature [86, 92, 93]. However, what these observational clinical studies were not able to address was whether these haemodynamic effects of exogenous glucocorticoids were beneficial or harmful [83, 87]. We have been trying to answer that concern using an experimental fetal sheep model of IUGR [94]. We have shown that maternal betamethasone administration in pregnancies complicated by IUGR causes a significant increase in fetal cardiac output [21] due to both an increased fetal heart rate [11] and possibly an increased stroke volume. This increased cardiac work is matched with increased coronary blood flow and results in an increase in blood flow to all other major organs, including the brain, adrenals, kidneys and placenta [21]. None of this occurs in healthy fetuses. As described above, in the healthy fetus glucocorticoid administration leads to decreased, not increased, blood flow. What is not yet clear is whether the profound cardiovascular effect of exogenous glucocorticoids in the IUGR fetus reflects a primary effect on the heart or, probably more likely, a response to decreased systemic vasculature resistance secondary to widespread vasodilatation, particularly in the placenta. It is certainly possible that there are direct effects on the heart. Glucocorticoids have been shown to increase nitric oxide synthase (NOS) activity and nitric oxide-mediated dilatation in fetal coronary arteries [33]. This mechanism could explain the increased coronary blood flow following betamethasone but it wouldn’t explain increased flow to other organs unless the increased myocardial perfusion improved depressed myocardial function [84] and thereby increased stroke volume and systemic perfusion. However, that increased coronary artery flow was only observed in growth restricted fetuses and not in well grown fetuses [21] suggests that either this is not the primary mechanism or that NOS is not normally inducible in the healthy fetus. Enhanced NOS activity could be the mechanism underlying the IUGR fetus’ ability to centralize blood flow to its heart (and brain). If this was the case then it may be more readily able to respond to further glucocorticoid induction of NOS. This certainly warrants investigation. Indeed, the molecular and cellular mechanisms underlying the differential vascular responses to glucocorticoids in the IUGR fetus have not yet been addressed in any detail at all. Whether the vascular mechanisms that lead to hypertension in the well grown fetus [31-38, 39, 40] are simply absent in the IUGR fetus or whether there are other changes that override these merit clarification. In this regard, the glucocorticoid effects on the placental vasculature [85, 90, 91] seem the most likely mechanism leading to increased fetal cardiac output. This would also explain a lack of effect in the well-grown fetus whose placenta is already maximally vasodilated and thus unable to respond to glucocorticoids [90]. Given that the majority of the fetal cardiac output is to the placenta, a sudden decrease in placental resistance, not thought possible until the original description of the effects of betamethasone on umbilical artery Doppler signals [85], would be expected to greatly reduce fetal cardiac after-load thereby improving ventricular contractility, stroke volume and cardiac output. Whether this sequence of events actually happens has not yet been reported but preliminary studies in our centre suggest that this is the case.

Whatever the mechanism(s) there are clearly fundamental differences in the responses of the IUGR and well-grown fetus to excess glucocorticoids, with the former displaying widespread vasodilatation, resulting in a 350% increase in coronary blood flow and a 150% in cerebral blood flow, and increased cardiac output whereas the well-grown fetus demonstrates peripheral vasoconstriction and no change in blood flow to major organs [21]. Importantly, these experimental observations closely mimic what is seen clinically where the IUGR fetus responds to antenatal glucocorticoids by increasing placental, renal, and cerebral blood flow [85-89, 92, 93, 95, 96] indicative of systemic vasodilatation, whereas the well-grown fetus shows no response [86]. Three of these clinical studies [89, 95, 96] reported neonatal outcomes from these pregnancies. All three studies showed that the IUGR fetuses who did not respond to glucocorticoid exposure with altered fetoplacental Doppler flows – about a third of fetuses overall – did less well neonatally, more likely requiring ventilation support and longer ventilation [89, 95] and more likely to die [96]. The most likely explanation for this observation is that the fetuses who did not respond to steroids were beginning to decompensate and had impaired cardiac reserve [80]. Unfortunately, because all fetuses had received betamethasone antenatally, the design of the studies did not permit an assessment of whether the IUGR-specific haemodynamic effects of exogenous glucocorticoids were harmful or not. In this regard, detailed assessment of brain histology following betamethasone administration may offer some insights.

**Glucocorticoid Effects on the IUGR Brain**

There are scant data, either experimental or clinical, that specifically examine the consequences of antenatal glucocorticoid administration on the developing brain of the IUGR fetus. The limited evidence available suggests that the differential cerebrovascular response to synthetic glucocorticoids in the IUGR fetus – that is a doubling of cerebral blood flow – may injure the developing fetal brain. As described above, IUGR human and sheep fetuses demonstrate cerebral vasodilatation and increased cerebral blood flow following maternal betamethasone administration, an effect not observed in well-grown fetuses [11, 21, 86]. This is potentially important because in IUGR fetal sheep, the degree of rebound cerebral vasodilatation is correlated with the presence of lipid peroxidation products within the brain. Indeed, the increased cerebral blood flow following glucocorticoid administration in the IUGR fetus is associated with evidence of excessive lipid peroxidation and an increase in apoptotic neuronal cell death [21]. Therefore, it is possible that exogenous glucocorticoids may be harmful, rather than protective, to the IUGR fetal brain. However, before concluding that exogenous glucocorticoids should not be administered to the IUGR fetus, careful consideration of all available evidence is important for a number of reasons. First, it is clear that further specific studies are required, both human and animal, to better understand the consequences of altered haemodynamic response within the IUGR brain, compared to the well-
grown fetal brain following synthetic glucocorticoids. In particular, functional follow-up studies are required. Second, if the cerebral vasoconstrictor response to antenatal glucocorticoid in the well-grown fetus represents a protective mechanism against preterm intraventricular haemorrhage, is this vascular response lost in the IUGR fetus? While the review by Torrance and colleagues [16] certainly finds no protective effect of antenatal glucocorticoids with respect to the incidence of intraventricular hemorrhage (IVH) in IUGR fetuses neither does it find that the incidence of IVH is elevated in glucocorticoid-exposed IUGR babies. This is reassuring. Further, at least one longer-term neurodevelopmental follow-up study of human IUGR babies suggests that antenatal steroids are overall beneficial [97]. Finally, as discussed above, the observation that exogenous glucocorticoids acutely alter cardiac function in the IUGR fetus requires further and more complete evaluation. Until then, clinicians should continue to recommend the administration of exogenous glucocorticoids to all women likely to give birth before 34 weeks’ gestation. In pregnancies complicated by IUGR the attending clinicians should be mindful that such an intervention may alter fetal and neonatal haemodynamics, albeit only acutely.

SUMMARY

Over recent years, clinical and experimental studies have highlighted that the well-grown and growth-restricted fetus display quite different hemodynamic responses to antenatal glucocorticoids. Whereas antenatal glucocorticoids induce transient mild systemic vasoconstriction and minimally reduced cardiac output in the healthy well-grown fetus, the IUGR fetus responds with widespread vasodilatation and increased blood flow to all major organs including the brain and heart, most likely secondary to placental vasodilatation. Whether these effects are beneficial or harmful to the already compromised IUGR fetus remains under investigation. In the meantime, the haemodynamic response of the IUGR fetus to exogenous glucocorticoids can be used as part of the assessment for timing of delivery.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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