Mending a growth-restricted fetal heart: should we use glucocorticoids?

Ryan J. Hodges1,2 & Euan M. Wallace1,2

1Maternal Fetal Medicine, Monash Medical Centre, Southern Health, Victoria, Australia and 2Department of Obstetrics and Gynaecology, The Ritchie Centre, Monash Institute of Medical Research, Southern Clinical School, Monash University, Victoria, Australia

Clinical and experimental studies suggest that the growth-restricted fetus at increased risk of impaired cardiovascular function that likely contributes to both increased mortality rate and in survivors, to cardiovascular dysfunction apparent in childhood and later life. Fetal growth restriction is also associated with a high risk of preterm birth. Accordingly, the growth-restricted fetus is more likely than average to receive antenatal glucocorticoids to accelerate lung maturation in preparation for birth. However, glucocorticoids are powerful regulators of vascular tone and antenatal glucocorticoid administration to the intrauterine growth restriction (IUGR) fetus results in systemic cardiovascular changes that are not observed in the healthy normal grown fetus. These responses to glucocorticoids may disturb the IUGR fetus’ ability to appropriately compensate to placental insufficiency. Indeed is it possible that in the setting of severe IUGR exogenous glucocorticoids are detrimental rather than beneficial to the fetus?

Keywords: betamethasone, fetal growth restriction, glucocorticoids, IUGR, placental insufficiency

Introduction

Intrauterine growth restriction (IUGR) defines a fetus that is failing to reach its genetic growth potential. While management of the pregnancy per se and decisions regarding timing of birth may be challenging enough for the attending obstetrician, it is becoming increasingly appreciated that events in utero, particularly adverse events such as IUGR, may program the fetus for lifelong morbidities [1]. The well established recognition that IUGR is associated with increased perinatal mortality and morbidity [2,3], accounting for the majority stillbirths not associated with congenital abnormality [4,5], underpins the need for timely diagnosis and careful management of the growth-restricted fetus. Much effort has been expended in describing the sequence of changes in the deteriorating growth-restricted fetus to allow safe prolongation of pregnancy [6]. However, these observational studies and assessments of different management protocols, such as the GRIT trial [3], are focused on outcomes at the very near horizon – that is perinatal/neonatal survival and morbidity. The recognition that IUGR is associated with important longer-term ill-health, particularly with cardiovascular disease [7], merits the skilled attending obstetrician extending his/her outcome horizons. For example, IUGR is associated with significant myocardial dysfunction evident in infancy [8], hypertension [8,9], diabetes [10], and eventually obesity and ischaemic heart disease in adulthood culminating in heightened premature mortality [8,11,12]. It is time to ask whether the care we provide to the unborn growth-restricted fetus sets it up for a life of ill-health and whether changes to our care could decrease subsequent adult burdens of disease.

Once IUGR is confirmed in a preterm pregnancy, current management strategies are centered on close fetal Doppler surveillance followed by timely administration of exogenous glucocorticoids and planned delivery. However, glucocorticoids are potent regulators of feto-placental blood flow and recent reports suggest their administration to IUGR fetuses result in profound haemodynamic alterations that may unravel the fetal compensatory mechanisms underpinning their ongoing survival. In this review, we introduce the hypothesis that glucocorticoids may in fact be detrimental, rather than beneficial, to the preterm growth-restricted fetus. We consider the necessary adaptive cardiovascular changes that occur in utero in response to worsening placental insufficiency, review recent insights into in utero cardiac assessment in IUGR fetuses and then examine the cardiovascular effects of glucocorticoids, questioning the appropriate-ness of this intervention in this population. We will argue novel strategies of fetal assessment and thresholds for delivery may be required if we are to improve both the care of these pregnancies and the longer-term health outcomes for survivors.

Glucocorticoids and preterm delivery: the *sine qua non* of modern obstetric care?

In current clinical practice, identification of IUGR requires an astute clinical diagnosis, perhaps aided by customized clinical examination charts [13] and complemented by careful ultrasound-based fetal surveillance. This surveillance is usually based on Doppler ultrasound assessment of the feto-placental circulation (e.g. uterine artery, umbilical vessels, middle cerebral artery and ductus venosus), and on biophysical ultrasound assessments of acute fetal well-being. It is hoped that such a strategy will allow the pregnancy to continue “safely” for as long as possible while being able to detect, in a timely manner, the progression from fetal compensation to decompensation secondary to worsening hypoxaemia [6]. Such progression triggers early delivery of the fetus, often at a very preterm gestation, which delivers the compromised fetus out of harms from a failing placenta into intensive care. For these preterm babies, antenatal maternal glucocorticoid administration is routine [14,15]. After all, multiple randomized controlled trials (RCTs) and systematic reviews of those RCTs have shown that antenatal glucocorticoid administration is routine [14,15]. After all, multiple randomized controlled trials (RCTs) and systematic reviews of those RCTs have shown that antenatal glucocorticoid...
administration accelerates fetal lung maturation and reduces respiratory distress syndrome (RDS), necrotizing enterocolitis, intraventricular haemorrhage and neonatal mortality in those babies born before 34 weeks’ gestation [16]. However, none of this extensive literature specifically addresses the value of antenatal glucocorticoids in the IUGR fetus; an evidence gap acknowledged during the NIH sponsored conference on antenatal corticosteroid prescribing [17]. Indeed, recently Torrance and his colleagues [18] highlighted that the literature on antenatal corticosteroid therapy in IUGR pregnancies is sparse; identifying no specific RCTs or only trials in which IUGR fetuses were excluded. Results from observational studies are mixed with little evidence that antenatal glucocorticoids decrease the incidence of RDS or mortality in babies with IUGR [19–21]. This is important because, as discussed later, there are experimental data that raise concerns that antenatal glucocorticoid administration may cause harm in the IUGR fetus. Put simply, it is uncertain if the benefits that exogenous glucocorticoids confer to the appropriately grown preterm fetus also apply to their IUGR counterparts, or whether such treatments are deleterious.

**New insights into fetal cardiovascular adaptations to hypoxia**

The IUGR fetus adapts to restricted substrate availability through preferential redistribution of oxygenated blood to its brain, heart and adrenals, sacrificing perfusion and associated growth and function of other organs [22]. This manifests clinically as small for gestational age on palpation of symphysis-fundal height. On ultrasound, there is fetal asymmetry due to a reduced abdominal circumference reflecting inadequate hepatic storage of glycogen, a reduction in resistance to blood flow of the middle cerebral artery pulsatility index, maintaining cerebral blood flow (so-called “head sparing” effect) and decreased amniotic fluid volume owing to reduced renal perfusion [22]. Such a protective response is thought to be important for the heart because, characteristically, the IUGR fetus is hypertensive and has an increased after-load secondary to increased placental vascular resistance. This increased resistance is observed as absent or reversed end-diastolic flow in the umbilical artery (UA AREDF) [15], reflecting significantly impaired placental perfusion and an increased likelihood of fetal hypoxia [23,24]. The increased after-load and hypertension in turn result in ventricular hypertrophy [25] and an associated increased cardiac metabolic demand in an environment of reduced oxygen availability. In this setting, a “hypertensive cardiomyopathy”, secondary to impaired myocardial perfusion and fetal decompensation, may result [26]. Alterations to the pulsatility index of the ductus venous (absent or reversal of the a wave), umbilical vein and grossly vasodilated coronary vessels ultimately reflect increasing myocardial dysfunction, principally decreasing ventricular function [27,28].

Monitoring these fetal haemodynamic changes remains clinically challenging. Determining the optimum timing of delivery is even more. This is in part due to the limitations of small observational studies of various Doppler measurements and the difficulties extrapolating this information for one’s individual practice. While the evidence for the utility of umbilical artery (UA) Doppler is very good, the level of evidence for other Doppler surveillance parameters is less strong and randomized trials are awaited [29].

Most recently, fetal echocardiography has been used to study cardiac function in IUGR fetuses and may provide more specific insights into the underlying pathophysiology of cardiac dysfunction compared with the more traditional and surrogate feto-placental Dopplers [4,8,30–34]. Such studies have revealed evidence of subclinical cardiac injury early in the disease process—an injury that is progressive [4]. Specifically, the IUGR fetus displays increased early-to-late-diastolic filling ratios (E:A) and prolonged isovolumic relaxation time (IVRT), reflecting impaired diastolic function on both sides of the heart. A prolonged isovolumic contraction time (IVCT) and shortened ejection time (ET) measures reflect impaired systolic function [4]. A modified myocardial performance index [MPI = (IVCT + IVRT)/ET], a Doppler derived “measure” of combined systolic and diastolic performance, is abnormally increased in the IUGR fetus and has a linear correlation with haemodynamic severity evident on UA Doppler (positive end-diastolic flow, absent and reversed EDF) [35,36]. As with the fetal Doppler studies of flow velocity waveforms, and indeed in combination with these, MPI measurements have been used to predict perinatal death. The MPI in combination with DV PI proved a better predictor of perinatal death than either parameter alone [36]. This is relevant as contemporary decisions regarding delivery thresholds currently rest significantly on the DV [37].

In addition to assessing flow of blood, Doppler ultrasound can be used to assess tissue motion. Recently, tissue Doppler imaging (TDI) has been used to provide an assessment of myocardial motion. In IUGR, studies of myocardial TDI have confirmed systolic and diastolic dysfunction [30,38,39], revealed as lower systolic and diastolic myocardial velocities in mitral and tricuspid annulus, higher mitral E/A’ ratio and higher mitral, tricuspid and septal myocardial performance indices [38]. TDI has been used to identify subclinical cardiac dysfunction in a proportion of small near-term fetuses, consistent with a diagnosis of IUGR rather than constitutional small for gestational age [40]. Accordingly, there is hope that such techniques may prove useful to differentiate a constitutionally small fetus from a growth-restricted one requiring early delivery, especially in late gestation when feto-placental Doppler studies become less reliable.

If experimental studies in animal models of IUGR accurately reflect human IUGR then they suggest that cardiac dysfunction associated with fetal growth restriction may persist lifelong. For example, chick embryos exposed to hypoxia develop cardiomyopathy and pump failure, mediated, at least in part, through increased vascular endothelial growth factor (VEGF) expression, which persists into adulthood [41]. In adults, models of IUGR fetuses have demonstrated chronic cardiopulmonary dysfunction, including cardiomyopathy, poor diastolic function, increased left ventricular mass, pulmonary hypertension and an increased susceptibility to ischaemia/reperfusion (IR) injury [7,41]. These experimental observations are consistent with the epidemiological data underpinning the developmental origins of health and disease, or so-called Barker Hypothesis [42] that first linked the in utero environment underpinning the developmental origins of health and disease, or so-called Barker Hypothesis [42] that first linked the in utero environment with adult disease risk. More recently, attention has also focused on cardiovascular outcomes more proximate to pregnancy than late adult health outcomes. It would appear, perhaps not surprisingly, that IUGR is associated with cardiac dysfunction in childhood. Children who were growth-restricted as a fetus have a different cardiac shape to healthy children. This results in a decreased stroke volume necessitating, in turn, an increased heart rate to maintain adequate cardiac output. They have higher blood pressure than children with a normal birth weight and overall they suffer subclinical chronic systolic and diastolic dysfunction [8]. Of additional concern, aortic wall thickening is greater than normal in both IUGR fetuses and children who had been IUGR compared to those who were appropriately grown [43]. This
may be important as aortic wall thickness is a marker of future atherosclerotic disease risk [43].

Thus, it would appear that some of the fetal adaptive changes made in response to oxygen and substrate restriction, itself secondary to placental insufficiency, changes that may serve the fetus well in utero, protecting vital organs and ensuring survival, likely lead to various cardiovascular morbidities both in early childhood and in adult life. While the excess burden of post-neonatal morbidity may be the price that the fetus has to pay for perinatal survival, we should question whether any clinical interventions we impose perinatally may add to the long term burdens and so consider whether perceived short-term gains, if any, outweigh longer-term losses. Specifically, we wonder whether the administration of glucocorticoids in preparation for preterm delivery may trigger further haemodynamic changes that lead to decompensation in an already compromised IUGR fetus. If this is so, then perhaps we should revisit the administration of antenatal glucocorticoids in the setting of severe IUGR, particularly if they do not confer acute benefit to the IUGR fetus in the same way they do to the normally grown fetus.

Cardiovascular implications of intrauterine growth restriction and glucocorticoids

In the normal, healthy fetus glucocorticoids are known to induce significant cardiovascular changes. For example, in healthy fetal sheep maternal glucocorticoid administration, akin to that used clinically, results in transient increases in peripheral and cerebral vascular resistance [44]. This is associated with hypertension [45,46] and mild hypoxaemia [47]. Similar effects have been observed in the fetal baboon suggesting that they are also likely to happen in the human fetus [48].

Glucocorticoids may be also detrimentally affecting the fetal coronary vasculature [36]. Exogenous glucocorticoids increase coronary artery angiotensin (AT1) receptor expression leading to exaggerated ATII-mediated vasoconstriction. Of note, however, these findings were in near term ovine fetuses. It is not known whether this effect also occurs in the preterm fetus. Consistent with these experimental findings, some clinical studies have shown that antenatal glucocorticoids are associated with increased blood pressure neonatally and in later childhood [49–51]. Reassuringly though, Dalziel et al. [52] recently reported a 30-year follow-up of children who had been exposed to antenatal betamethasone use in the world’s first RCT of antenatal glucocorticoids [53]. In that follow-up study, there were no apparent differences in blood pressure but there were a slight increase in insulin resistance in individuals whose mothers had received betamethasone prior to delivery compared to individuals whose mothers had not. However, in this cohort only 15% of the individuals had a birth weight less than the 10th percentile and only 5% of them had been born at less than 30 weeks gestation. While detailed data are not available, these birth demographics suggest that the majority of individuals had not been an IUGR fetus. Therefore, it remains unclear whether there are additional longer-term cardiovascular sequelae for very preterm IUGR fetuses who receive glucocorticoids and further follow-up studies are required.

This is particularly important because the haemodynamic effects of glucocorticoids in the IUGR fetus are quite different to those in the healthy, well-grown fetus. In contrast to the vasoconstriction effects induced by exogenous glucocorticoids in the healthy fetus, in pregnancies complicated by IUGR and absent end-diastolic flow in the UA, maternal administration of betamethasone is associated with a transient return of UA end-diastolic flow and widespread Doppler waveform changes in the fetal circulation suggestive of generalised vasodilatation [54–56]. This effect is seen in the majority, though not all, fetuses and persists, on average, for 2–3 days [54–57]. While the precise mechanisms underlying these unexpected transient systemic fetal haemodynamic changes are unclear, in vitro placental perfusion and umbilical cord studies have shown that glucocorticoids vasodilate the placental vasculature and the umbilical cord [58,59].

In the context of the circulatory adaptations that the IUGR fetus has to make to protect cardiac and cerebral perfusion, such vasodilatation in response to betamethasone may be harmful. Using an experimental ovine model of fetal growth restriction, we recently confirmed the two very different haemodynamic responses to betamethasone administration in normally grown and IUGR fetuses and identified key cardiac differences [60]. Systemic vascular resistance increased in the normally grown fetal sheep following betamethasone, just as in humans, and reduced cardiac output and blood flow to most organs, including the heart and brain. Indeed, this may be the mechanism underlying altered heart rate variability, and reduced fetal movements and breathing induced by exogenous glucocorticoids [61–63]. In contrast, in the IUGR fetus betamethasone administration significantly increased cardiac output and increased blood flow to all major organs, including the brain. This finding is presumably due to widespread glucocorticoid induced vasodilatation, reducing after-load and increasing cardiac output. Indeed, cerebral blood flow more than doubled in IUGR fetuses, consistent with the clinical observation of decreased MCA PI on Doppler ultrasound [56] in the IUGR human fetus. Of particular concern, at least in sheep fetus, these sudden and dramatic increases in cerebral blood flow are associated with increased cerebral oxidative stress and evidence of brain injury [64]. The potential to cause, rather than prevent neuropathology in the IUGR fetus with antenatal glucocorticoid administration is clear. Reassuringly, the limited follow-up human data published to date suggests that antenatal glucocorticoids are still neuroprotective in the IUGR fetus [21]. Nonetheless, the limitations of that study oblige ongoing caution.

Reevaluating our current management strategies

In modern perinatal practice, much effort is rightly directed at improving the detection and surveillance of the IUGR fetus with the aims of trying to optimise the timing of delivery – a balance between fetal maturity and fetal well-being – to afford the best short- and long-term outcomes for the baby. At present, there is uncertainty regarding the most useful marker(s) to trigger timing of delivery. In that regard, the European Trial of Umbilical and Fetal Flow (TRUFFLE) that is currently underway is addressing timing of delivery based on ductus venosus Doppler ultrasound or computerized cardiotocography. Appropriately, neurodevelopmental outcomes the key endpoints. This is based on the very reasonable premise that delivery before the onset of severe hypoxia may decrease neonatal and longer-term morbidity, in particular neurodevelopmental delay. However, as we have learnt from the Growth Restriction Intervention Trial (GRIT) [2] and its recent follow up [2,65], neurological change, like cardiovascular remodeling described earlier, likely occurs early and continues as the fetus adapts. If this is so, timing of delivery, on its own, may have less of a protective effect than once previously thought [66].

Perhaps a different approach, at least while we currently continue to give glucocorticoids, would be to assess the fetal response to a glucocorticoid challenge. Two out of three IUGR fetuses with UA AREDF display a transient return in diastolic flow following betamethasone. Once delivered, this cohort of babies has better neonatal respiratory outcomes, requires less assisted
ventilation, less duration of ventilation and less supplemental oxygen than those fetuses that did not display a haemodynamic response to steroids [67]. Most recently, this group has also shown to have a delayed onset of cardiotocograph abnormalities necessitating delivery [68]. This suggests that IUGR fetuses (or placenta) who fail to “respond” to glucocorticoids may represent pregnancies with longer standing and/or more severe placental insufficiency. In this regard, persistent AREDF following betamethasone may require even more intensive fetal surveillance or even be a novel useful trigger for early delivery.

Nevertheless, irrespective of the results of TRUFFLE, or similar trials, we will still be no closer to matching optimized fetal surveillance, whichever method(s) prove the most valuable, with any effective antenatal therapeutic interventions. Rather, such “protective” therapies must necessarily wait until the baby is in the hands of the neonatologist. Thus, despite intensive (and expensive) surveillance, the growth-restricted fetus continues to be exposed to oxidative stress and the attendant risks of cardiac and neurological injury until delivery. Whilst magnesium sulfate is gaining popularity as a fetal neuroprotectant [69], the IUGR fetus may once again fall victim to meta-analysis, as it did with glucocorticoids, with no specific randomized trial addressing efficacy and safety in this population. It is therefore crucial, we believe at the minimum, to evaluate more formally the merit of our only current therapeutic, glucocorticoids, in the setting of IUGR. On this basis, we join the chorus of others calling for new randomised trials to address this question [17,18].

Conclusion
The IUGR fetus employs a range of cardiovascular adaptations to maintain oxygen delivery and ensure survival, while antenatal administration of glucocorticoids to pregnant women at risk of preterm delivery is unquestionably one of the greatest advances in modern obstetric care. There is accumulating clinical and experimental evidence that it has profoundly different effects on fetoplacental blood flow in the growth-restricted fetus from the normal fetus. Whether these blood flow changes are beneficial or detrimental to the IUGR fetus is not yet known, but this fetal response requires much closer scrutiny than simple observation and merits attending clinical teams to be cautiously aware of the potential to cause harm.

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References


