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Early-life programming of livestock metabolism by glucocorticoids

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Review

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Abstract

Adverse environmental conditions during early life are known to determine adult metabolic phenotype in laboratory species and human populations. However, less is known about developmental programming of adult metabolic phenotype in livestock, given their size and longevity compared to laboratory animals. As maternal and/or fetal glucocorticoid (GC) concentrations rise in stressful conditions during pregnancy, GCs may act as a common mechanism linking early-life environmental conditions to the subsequent metabolic phenotype. This review examines prenatal and longer-term postnatal programming of metabolism by early-life GC overexposure in livestock species with a particular emphasis on sheep. It examines the effects of both cortisol, the natural glucocorticoid and more potent synthetic GCs used clinically to treat threatened pre-term delivery and other conditions during pregnancy. It considers the effects of early- life GC overexposure on the metabolism of specific feto-placental and adult tissues in relation to changes in the growth trajectory, other metabolic hormones and in the functioning of the hypothalamic–pituitary–adrenal axis itself. It highlights the role of GCs as maturational and environmental signals in programming development of a metabolic phenotype fit for survival at birth and future homeostatic challenges. However, the ensuing metabolic phenotype induced by early GC overexposure may become inappropriate for the prevailing postnatal conditions and lead to metabolic dysfunction as functional reserves decline with age. Further studies are needed in livestock to establish whether the metabolic outcomes of early-life GC overexposure are sex-linked, more pronounced in old age and inherited transgenerationally in these species.

Introduction

Environmental conditions during early life have been shown to have an important role in determining adult phenotype through experimental studies in animals and epidemiological observations on human populations.[1-3] To date, these studies have tended to concentrate on the postnatal cardio-metabolic consequences of adverse conditions during pregnancy such as malnutrition, obesity and placental insufficiency.[4,5] Since these challenges alter glucocorticoid (GC) exposure *in utero*[6], GCs may act as a common mechanism of early-life programming of adult phenotype. Indeed, GCs are known to have an important role in the developmental programming of cardio-metabolic function in laboratory animals such as adult rodents and guinea pigs.[7-9] However, compared to these animals, there have been fewer studies of programming by early-life GC overexposure in livestock species, despite the ability to study their fetuses *in utero* and their greater similarity to the human developmental and ageing profiles.[10,11] The differing size, lifespan and reproductive characteristics of mammalian species also influences the feasibility with which early-life programming of adult phenotype can be studied (Supplemental Table). This review, therefore discusses GC programming of metabolism primarily in sheep, the most widely used livestock animal for these types of study. It considers the regulation and roles of GCs during normal fetal development and examines the consequences of early-life GC overexposure for metabolism and its control both before and after birth.

Fetal glucocorticoid concentrations

In livestock species such as sheep, cattle, pigs and horses, the primary active GC is cortisol and its circulating concentration in the fetus is lower than maternal values for most of gestation. [12-14] In unstressed sheep, about 80% of the cortisol in the fetal circulation is derived from the mother by transplacental transfer down this concentration gradient until late gestation.[15] During early-mid gestation, fetal cortisol concentrations, therefore, track with maternal values during the normal maternal circadian rhythm and in response to stressors that raise maternal cortisol levels such as undernutrition, hypoxia, transport, isolation and mixing of social groups.[12-16] In part, the fetal

impact of elevated maternal cortisol concentrations during early-mid pregnancy depends on the placental activity of 11-β hydroxysteroid dehydrogenase-2 (11βHSD2) that converts cortisol to its inactive keto-metabolite, cortisone.[17] Placental activity of this enzyme varies between livestock species and is responsive to a range of nutritional and endocrine factors in sheep.[17-19] In human and laboratory species, fetal exposure to maternal GCs also depends, in part, on placental transmembrane ATP-binding cassette (ABC) transporters that minimize access of maternal xenobiotics, steroids and drugs, like the synthetic GCs, to the fetal circulation.[20] However, relatively little is known about these placental efflux transporters in livestock species.

In all livestock species studied to date, the fetal adrenal cortex develops the capacity to secret cortisol in response to adverse intrauterine conditions during late gestation.[6] Fetal cortisol concentrations can then rise independently of maternal values in response to fetal hypoglycaemia and hypoxaemia induced by maternal undernutrition and uterine artery ligation as well as by more specific fetal insults such as placental growth restriction, umbilical cord occlusion and direct insulin-induced hypoglycaemia.[21-28] In sheep, the fetal cortisol response to these types of adversity increases progressively with advancing gestational age.[23,24,26,27] A similar gestational increase in cortisol output in response to hypoglycaemia is seen in the fetal horse over the last month of gestation.[27] The increment in the cortisol response with gestational age is due, in part, to increases in the size, steroidogenic enzymes and adrenocorticotropic hormone (ACTH) receptor abundance of fetal adrenal glands towards term.[29,30] In fetal sheep, there are also developmental changes at the level of the hypothalamus and pituitary that contribute to the increased sensitivity of the whole hypothalamic–pituitary–adrenal (HPA) during late gestation.[29] These gestational changes include increases in the hypothalamic corticotropin-releasing hormone (CRH), pituitary corticotroph abundance of CRH receptor and pro-opiomelanocortin (POMC) and in POMC cleavage to ACTH. These are also increases in fetal concentrations of the more biologically active ACTH isoform towards term.[29,30]

Developmental changes in the fetal HPA axis are also associated with a natural rise in basal fetal cortisol concentrations towards term in the absence of any stressful stimuli in all species studied to date.[6,16,30] This prepartum increment in fetal cortisol is responsible for maturation of a wide range of fetal tissues in preparation for birth.[6,30] It also initiates labour in sheep through effects on placental production of steroids and prostaglandins involved in regulating myometrial contractility.[29-31] The time course and magnitude of the fetal prepartum cortisol surge varies between livestock species. It occurs over the last 10-15% of gestation in fetal sheep and pigs, 2-3% of gestation in fetal cattle but only in last 1-2% of gestation in fetal horses.[12-14] It also occurs later and more rapidly in twin than single sheep fetuses but happens sooner than normal in single fetuses of ewes undernourished in early pregnancy.[22,32] In pigs, littermates are often born with differing patterns of cortisol exposure due to individual variations in the onset, magnitude and speed of the prepartum cortisol surge.[13,33] In full term sheep and pig neonates, cortisol levels peak at birth and then fall rapidly thereafter.[12,33] However, in species like the horse in which the fetal cortisol increment occurs very close to term, neonatal cortisol levels continue to rise in the hours after birth and, in dysmature foals, may remain elevated postnatally for 7 or more days.[34,35] Similarly, in pigs delivering a few days before full term, the neonates have high cortisol levels for up to a week after delivery.[33] When parturition is induced preterm by direct inhibition of placental progestagen synthesis in late gestation, fetal cortisol levels rise rapidly in sheep, pigs and horses to values close to those seen in term delivery and then tend to remain elevated for longer than normal after birth.[31,34,36]

During early life, endogenous increases in cortisol concentrations can, therefore, occur in two main ways: first, by enhanced transplacental transfer of cortisol from the mother due to maternal stress or decreased placental 11βHSD2 activity and, secondly, by increased activity of the HPA axis in the fetus or neonate. Activation of the HPA axis can occur either (i) as part of the normal sequence of developmental events preceding delivery at term or (ii) as a response to adverse conditions either *in utero* or during adaptation to extrauterine life when delivery occurs before full term. In addition to the circulating GC concentration, the degree of fetal GC exposure also depends on the plasma level of corticosteroid-binding globulin (CBG) and the tissue abundance of the various ABC efflux transporters, GC and mineralocorticoid receptors and 11βHSD isoforms.[19,20,29,30] These factors control availability of free cortisol in the fetal circulation for uptake into the cells and the efflux of cortisol from the cells back into the blood.[20,29] The receptors bind cortisol and enable its genomic and non-genmic actions within the cell, while the two 11βHSD isoforms metabolism cortisol to its inactive metabolite cortisone (11βHSD2) and vice versa (11βHSD1), decreasing and increasing intracellular availability of cortisol, respectively.[18,19,29] All these factors vary developmentally, between tissues and with environmental conditions in a species-specific manner.

GCs, therefore, act as both environmental and maturational signals during intrauterine development to maximize the chances of surviving before and after birth. Consequently, exogenous administration of synthetic GCs is widely used to treat pregnant women threatened with pre-term labour to improve viability of their neonates should delivery occur.[37] In sheep, cows and horses, maternal administration of synthetic GCs at high doses during late gestation also improves neonatal viability after induction of pre-term delivery.[38-40] Both natural and synthetic GCs have, therefore, been used to study early-life GC programming experimentally.

Prenatal metabolic effects of glucocorticoid exposure

The metabolic effects of GC exposure before birth depend on its timing in gestation, its duration and on whether exposure is of maternal or fetal origin.[16] The effects can also differ between overexposure to natural cortisol and the more potent synthetic GCs used clinically.[29] Compared to cortisol, synthetic GCs, like dexamethasone and betamethasone, only bind to the GC receptors (GR) and are poorly metabolized by 11βHSD2.[19,29] Consequently, synthetic GCs cross the placenta from mother to fetus more readily than cortisol.[6-8]

Uteroplacental and fetal metabolism

The relative contribution of different nutrients to feto-placental metabolism varies between species but glucose is the principal metabolite in all livestock species studied to date including sheep, cows, pigs and horses.[41] In late gestation, short-term (<24h) infusions of cortisol or dexamethasone directly into fetal sheep have little apparent effect on the fetal uptake of glucose.[16,17] However, when fetal cortisol concentrations are raised within the physiological range by direct infusion for 5 days, fetal glucose uptake decreases by 30% per kg of fetus.[42,43] Similar reductions in fetal glucose uptake are seen in response to physiological

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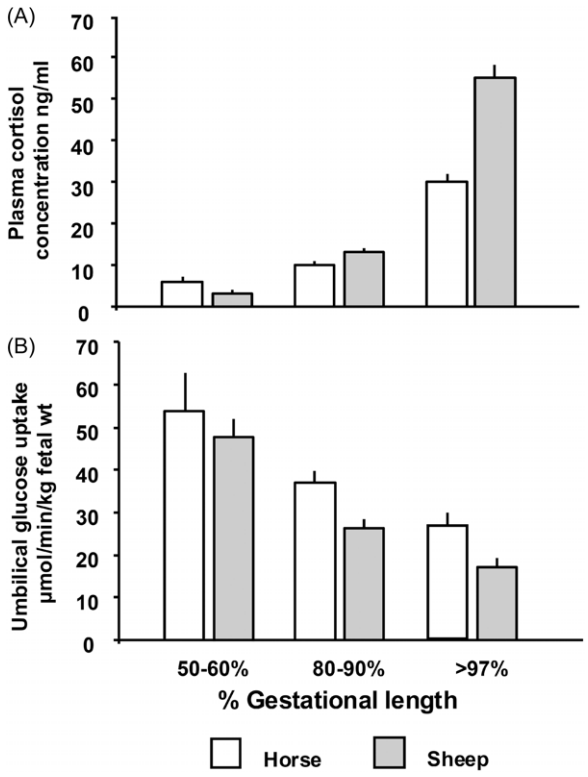

Figure 1. Mean values (±SEM) of (A) plasma cortisol concentrations and (B) the rate of umbilical glucose uptake in fetal sheep (filled columns) and horses (open columns) with respect to the stage of gestation (term: sheep, ≥ 145 days, horse approx. 335 days). Data from references.[23,45-47]

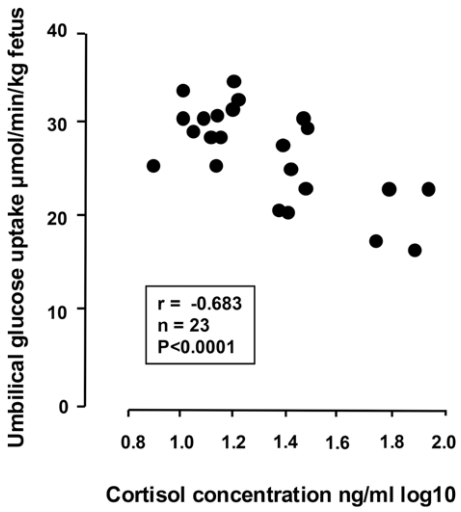

Figure 2. Relationship between the plasma cortisol concentration and the rate of umbilical glucose in fetal sheep during late gestation in 11 separate published studies, references.[23,25,42-44,48-53] Data points are the mean values for each group of fetuses with respect to their mean cortisol concentration caused by fetal cortisol infusion, placental growth restriction or by the natural prepartum increment in fetal cortisol towards term. (All animals≥130 days, term≥145 days). Statistical analysis was carried out using sigma-stat (Statistical software version 3.5; San Jose, CA, USA).

increments in the maternal cortisol concentration for 5 days during the same period of late pregnancy.[44] Weight specific rates of fetal glucose uptake also decrease as fetal cortisol levels rise naturally during the prepartum period in sheep and horses (Fig 1). In addition, when data are combined from the several ovine studies in which fetal cortisol concentrations are raised either exogenously or endogenously, there is an inverse correlation between umbilical glucose uptake per kg fetus and the fetal cortisol concentration during late gestation, irrespective of the mechanism by which cortisol concentrations is increased (Fig 2).

While maternal and fetal cortisol exposure appear to have similar effects on umbilical glucose uptake in fetal sheep, their effects on uteroplacental glucose metabolism and the supply of lactate to the fetus differ.[42-44] Uteroplacental glucose consumption per kg placenta increases with fetal but not maternal cortisol treatment while uteroplacental lactate production rises with maternal but not fetal treatment.[43,44] This leads to an increase in fetal lactate delivery with maternal but not fetal treatment, despite the similar decrements in umbilical glucose uptake with the two routes of placental cortisol overexposure. Fructose is also produced and used oxidatively by ovine uteroplacental and fetal tissues and its fetal concentration rises with maternal but not fetal hypercortisolaemia.[42-44] In part, these differences in carbohydrate handling appear to relate to the direction and/or degree of the transplacental GC gradient. Longer term maternal infusions of cortisol for 30 days in late pregnancy are known to alter amino acid metabolism and biosynthesis in the term ovine placenta using multiomics analyses.[54] In addition, both maternal and fetal GC administration have been shown to affect fetal amino acid uptake and catabolism with increased proteolysis and/or reduced protein synthesis by the fetus, depending on the origin, timing and duration of the GC overexposure in late gestation.[55] Significant feto-placental shuttling of nutrients, therefore, occurs in response to raised cortisol levels, whether of maternal or fetal origin, and appears to reflect altered enzyme activities and nutrient transporter abundance in tissues like the placenta and fetal liver.[17,51,55]

In normoxic conditions, the fetal and uteroplacental rates of oxygen consumption vary little with variations in either fetal or maternal cortisol concentrations,[42-44] although the oxidative substrates used for energy production alter with the cortisol-induced changes in the type and origin of substrates available to the tissues.[56] For example, the increase in urea production seen in fetal sheep in response to maternal cortisol infusion suggests that amino acids become a more prominent fetal oxidative fuel as the umbilical supply of glucose declines.[57] Other substrates like the volatile fatty acids (VFAs) also make a contribution to fetal oxidative metabolism and carbon accumulation in ruminants, compared to other livestock species with hind gut fermentation.[58] However, little is known about the effects of GCs on the fetal supply or utilization of VFAs in ruminants.

Collectively, these observations suggest that ovine feto-placental metabolism adapts to maternal hypercortisolaemia by diverting glucose into lactate and possibly fructose as well as altering fetal amino acid provision and metabolism. This diversifies the fetal carbon supply and allows the fetus more options for carbon utilization during maternal stressful conditions. In contrast, when fetal cortisol levels rise independently of maternal levels, ovine uteroplacental tissues use more glucose on a weight specific basis and transfer less to the fetus. There is also an increase in the fetal to placental glucose and pyruvate clearance when cortisol level rise in response to stressful concentrations on either side of the placenta.[43,44,59] This suggests that, in certain circumstances, the fetus may prioritise placental glucose requirements over its own needs to ensure survival of the placenta on which its own survival *in utero* depends.[43,59]

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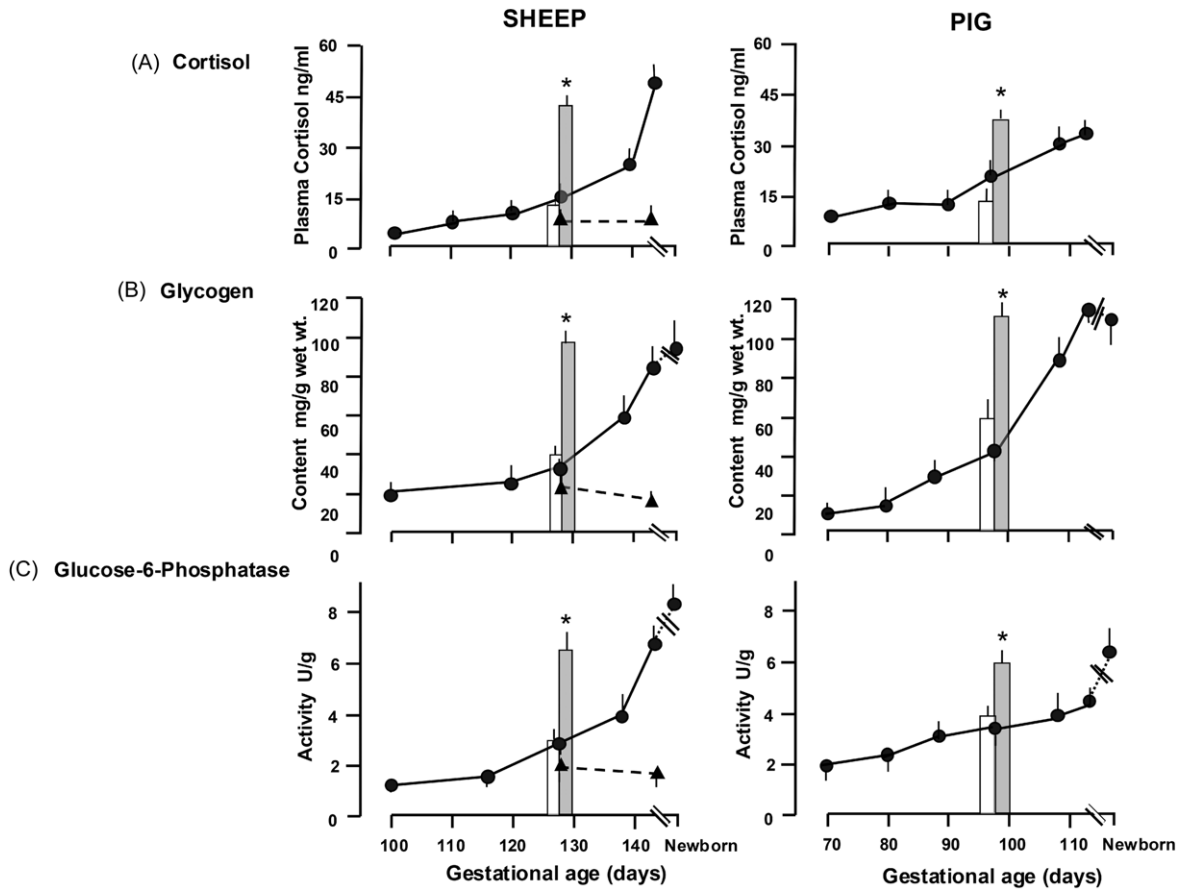

Figure 3. Mean values (±SEM) of (A) plasm cortisol concentrations, (B) hepatic glycogen content and (C) hepatic glucose-6-phosphatase activity in fetal sheep and pigs with respect to gestational age to term (filled circles), after preterm fetal infusion of either saline (open columns) or cortisol (filled columns) for 5-6 days and in fetal sheep after adrenalectomy (filled triangles). * significantly greater value than in saline infused fetuses ($P < 0.01$, *t*-test). Data from references.[60,61]

Tissue specific metabolic effects

A wide range of fetal tissues, in addition to the placenta, are affected metabolically by rising fetal cortisol levels including the liver, skeletal and cardiac muscle, adipose tissue and gastrointestinal tract as well as several endocrine axes involved in controlling metabolism.[16,55] In fetal sheep and pigs, cortisol increases the hepatic glycogen content and the activity of glucose-6-phosphatase (G6P), the final enzyme in both the gluconeogenic and glycogenolysis pathways of glucose production (Fig 3). In fetal sheep, GCs also increase phosphoenolpyruvate carboxykinase (PEPCK) activity which controls gluconeogenesis from lactate and amino acids.[61] In addition, the hepatic activity of lactate dehydrogenase and specific aminotransferases involved in gluconeogenesis increase in response to elevated cortisol concentrations.[44,61] Similarly, dexamethasone administration to pregnant ewes in late gestation increases the hepatic glycogen content and G6P activity in the fetal liver.[62] Increases in hepatic glycogen content and enzyme activities also occur when fetal cortisol concentrations rise naturally towards term in fetal sheep, pigs and horses[60,61,63] and are prevented in fetal sheep when the prepartum cortisol surge is abolished by fetal adrenalectomy (Fig 3). Moreover, increases in the glycogen content and glucogenic enzymes activities are seen in the fetal kidney with increased GC exposure in fetal sheep, pigs and horses.[60-63]

In line with the gestational rise in fetal glucogenic capacity, endogenous glucose production rises naturally towards to term in fetal sheep and is positively related to the cortisol concentration during the prepartum period and in response to intrauterine stress and fetal growth restriction in late gestation.[23,51,64] Conversely, when cortisol increments are prevented in fetal sheep by adrenalectomy, glucose production does not occur in response to maternal fasting close to term, despite normal fetal circulating catecholamine concentrations.[49] More specifically, hepatic glucose production from lactate and amino acids has been shown to be activated in fetal sheep by short term GC exposure close to term, although not earlier in gestation when hepatic glycogen storage and gluconeogenic enzyme activities are still low.[55,65] The role of GCs in regulating hepatic glucose production during late gestation is amplified by their actions in increasing hepatic abundance of both the β-adrenoreceptors which bind catecholamines and the enzyme 11βHSD1 which increases availability of cortisol from cortisone.[16,43,60,66] Collectively, these findings suggest that GCs first increase the fetal glucogenic capacity before activating endogenous glucose production *per se*. This will maintain a glucose supply to key fetal tissues as the weight specific rate of umbilical glucose uptake declines towards term and then ceases at birth.

In skeletal muscle, direct cortisol infusion into fetal sheep for 5 days in late gestation increases the content and respiratory capacity of the mitochondria in a manner that depends on the specific oxidative substrate and muscle studied.[56] Similar increases in muscle oxidative phosphorylation (OXPHOS) capacity are also seen in fetal sheep as cortisol concentrations rise naturally towards term and are abolished by fetal adrenalectomy.[56,67] This cortisol

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induced upregulation of muscle OXPHOS capacity is associated with changes in the mitochondrial abundance of specific electron transfer system (ETS) and adenine translocator proteins. [56,67] However, longer term cortisol administration to pregnant ewes in late gestation reduces the mitochondrial OXPHOS transcriptomics of fetal cardiac and skeletal muscle, consistent with sustained reductions in the fetal nutrient supply.[68] Fetal cortisol also regulates the relative proportions of the slow twitch (oxidative) and fast twitch (more glycolytic) fibres in specific skeletal muscles.[56] Since OXPHOS produces more ATP per molecule of glucose utilized than glycolysis, changes in the proportion of the different muscle fibres has implications for whole body energetics and metabolic phenotype.[56] In addition, there are changes in glucose transporter abundance in certain fetal muscles GC overexposed during late gestation, with an increase in the insulin-responsive transporter (GLUT4) and a relative reduction in insulin-unresponsive GLUT1, thereby allowing insulin to assume tighter glucoregulatory control of metabolism postnatally.[69]

Like fetal liver and muscle, there are also GC induced changes in the metabolic profile of fetal adipose tissue and the gastrointestinal tract during late gestation.[16,55] In sheep near term, both fetal cortisol infusion and maternal dexamethasone administration increase the abundance of mitochondrial ETS, uncoupling and voltage dependent anion channel proteins in fetal perirenal adipose tissue, in line with the need for non-shivering thermogenesis at birth.[70,71] Similarly, in fetal pigs and sheep, specific pancreatic, stomach and small intestine enzymes involved in postnatal digestion increase in activity in response to pre-term fetal cortisol infusion and the natural prepartum rise in cortisol concentrations.[33,72] GC exposure during late gestation, therefore, affects the metabolic characteristics of many somatic tissues with important consequences for the nutrient demands for both intrauterine growth and the onset of new functions essential for neonatal survival.

Other metabolic hormones

Not all the metabolic outcomes of increased GC exposure are likely to be due directly to the GCs as fetal availability of several other metabolic hormones are affected in these circumstances.[16,55] In late gestation fetal sheep, GCs regulate the circulating concentrations of tri-iodothyronine (T_3), adrenaline, insulin-like growth factor-1 (IGF1), leptin and ovine placental lactogens (oPL), all of which have metabolic actions *in utero*.[55,73] For instance, fetal cortisol infusion and maternal dexamethasone administration are known to reduce the number of binucleate cells producing oPL in the placenta and lower maternal and fetal oPL concentrations.[73,74] Indeed, the changes in placental oPL availability may mediate, in part, the effects of GCs on umbilical glucose uptake as recent studies have shown that reducing placental oPL protein abundance directly using RNAi technology lowers umbilical glucose uptake at any given maternal-fetal glucose concentration gradient.[75] In late gestation GCs increase adrenaline, IGF1 and leptin availability in fetal sheep.[55] Adrenaline can stimulate fetal glucose production while IGF1 has organ specific effects on glucose and amino acid utilization in fetal sheep[23,53,76]. Fetal leptin affects growth and development of a range of fetal tissues including the lungs, pancreatic β cells and bones in addition to its potential role in programming appetite regulation.[77,78]

Similarly, the actions of GCs on fetal gluconeogenic and OXPHOS capacity are mediated, in part, by the fetal thyroid hormones and upregulation of the tissue deiodinases producing the more biologically active T_3 from circulating thyroxine.[79,80] Thyroidectomy of fetal sheep impairs the normal prepartum increments in both mitochondrial density and OXPHOS capacity in skeletal muscle and the glycogen content and gluconeogenic enzyme activities in the liver.[67,81,82] It also prevents activation of endogenous glucose production by the fetus in response to maternal fasting in late gestation.[48] However, pre-term T_3 infusion is less effective than cortisol at increasing hepatic glycogen content in fetal sheep.[82] This suggests that the actions of T_3 in mediating the effects of cortisol also depend on concomitant changes in other circulating factors and/or cellular pathways, such as tissue thyroid hormone receptor abundance.[82] Feto-placental hormones, therefore, interact widely in controlling feto-placental metabolism through actions on the development of the fetal endocrine axes *per se*.[16,29,55] Indeed, in fetal sheep, pre-term GC overexposure influences functioning of the HPA axis.[6,29] Depending on timing of the overexposure, there are alterations in fetal HPA stress responsiveness and the trajectory of the normal prepartum cortisol surge together with molecular changes at all levels of the axis from the brain to tissue GR abundance.[83-86]

Intrauterine growth

In sheep, maternal but not fetal treatment with synthetic GC during the last third of gestation reduces fetal body weight with symmetrical reductions in the weight of most fetal organs.[87] By birth, lamb body weight is reduced by 10 to 30% in ewes receiving synthetic GCs in late gestation but not with treatment before 80 days pregnancy.[88] The degree of prenatal growth restriction is more pronounced when maternal synthetic GC treatment is closer to term, longer in duration and at higher doses.[87-89] Similarly, maternal dexamethasone treatment in late gestation reduces piglet birthweight and the height but not the weight of newborn foals.[90,91] In contrast, treatment of ewes with cortisol for 30 days before term has little effect on lamb body weight but increases the rate of stillbirth.[92] In sows in late gestation, ACTH-induced increments in maternal cortisol increase birthweight of their piglets with no effect on stillbirth rates.[93] With shorter maternal or direct fetal cortisol infusions of ≤ 10 days duration in late gestation, there is also little effect on lamb body weight before or at birth, despite reductions in the fetal growth rate measured as the increment in girth or crown-rump length.[57,94] Growth of fetal bone and specific somatic tissues may, therefore, be affected differentially by prenatal GC overexposure. The differing intrauterine growth trajectories seen with the various GC dosing regimens are, therefore, likely to reflect the specific alterations in a range of factors including feto-placental nutrient handling, concentrations of other metabolic hormones and tissue expression of receptors, transporters and growth factors like the IGFs, in addition to variations in the size and/or gross morphology of the placenta.[16,17,30,55,76]

Postnatal metabolic effects of glucocorticoid exposure in early life

The initial studies of early-life programming in farm animals focused on postnatal growth and body composition with respect to animal welfare, productivity and food production.[95-97] More recently, livestock studies have broadened to cover developmental programming of metabolism and other physiological systems both by direct experimental manipulation of GC levels and by adverse environmental conditions that raise fetal cortisol levels naturally.[98-100] In the studies directly manipulating GC

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Table 1. Postnatal metabolic outcomes of prenatal glucocorticoid overexposure in livestock. (dGA = days gestational age, dPN = days postnatal age)

	Species	Age at treatment	Postnatal age at study	Postnatal outcomes	Reference
Maternal treatment					
Dexamethasone	Sheep	26-28 dGA	4 years	Improved glucose tolerance and first phase insulin secretion in males. No Δ insulin sensitivity	101
		26 -28 dGA	5 years	No Δ Glucose tolerance No Δ insulin sensitivity of glucose and amino acid metabolism ↓ insulin suppression of lipolysis	102
		67-68 dGA	5 years	No Δ Glucose tolerance No Δ insulin sensitivity of glucose and amino acid metabolism	102
		103-105 dGA	2.5-3.5 years	Glucose intolerance Reduced insulin secretion	103
		138-140 dGA	Neonate	Increased UCP1 and VDAC protein in adipose tissue	70
	Horse	270-276 dGA	2 weeks	No Δ glucose tolerance or β-cell response to glucose or arginine	91
			12 weeks	No Δ glucose tolerance or β-cell response to glucose ↓ β-cell response to arginine	
Betamethasone	Sheep	104, 111, 118 & 125 dGA	6 months	↑ early insulin response to glucose ↑ insulin:glucose ratio ↓ Insulin sensitivity	89
			1 year	Fasting hyperglycaemia and hyperinsulinaemia Increased insulin response to glucose	104
		104, 111, 118 & 125 dGA	2 years	↑basal insulin concentration and insulin:glucose ratio No effect on the insulin or glucose responses during glucose tolerance test	105
			3 years	↑basal insulin:glucose ratio No effect on the insulin or glucose responses during glucose tolerance test ↑ hepatic glucose-6-phatase activity	
Cortisol	Sheep	26-28 dGA	4 years	Fasting hyperglycaemia and hyperinsulinaemia in males ↑ Second phase insulin secretion to glucose No Δ glucose tolerance or insulin sensitivity	101
		115 dGA- term	Newborn	Altered cardiac amino acid and TCA metabolism ↑ Cardiac insulin signalling pathways ↓ Cardiac glucose and glycerophospholipid metabolic pathways	106 107
			10-12 days	↑ Basal glucose levels ↓ Basal insulin levels ↑ Insulin sensitivity	108
	Pig	81-100 dGA	6 months	↓ Lean mass ↑ Fat deposition	109
Fetal/Neonatal Treatment					
Dexamethasone	Pig	3 dPN	6 dPN	↑ intestinal alanine uptake	110
		1 dPN	83 days	↑ Body weight with no Δ in back fat or muscle areas	111
Betamethasone	Sheep	104, 111. 118 & 125 dGA	6 months	↑ Early insulin response to glucose	89
			1 year	↓ Glucose level in early phase of glucose tolerance test. No change in insulin concentrations Increased insulin sensitivity	89 104
			2 & 3 years	No effect on basal glucose or insulin concentrations No Δ glucose tolerance	105
Cortisol	Sheep	125-130 dGA	10 months	No Δ glucose tolerance or insulin sensitivity Muscle specific decreases in ETS complexes and increases in fat OXPHOS capacity	112 113
ACTH	Horse	1-5 dPN	2 & 12 weeks	No Δ glucose tolerance or insulin sensitivity ↑ early phase insulin secretion to glucose but not arginine	114
			1 & 2 years	No Δ glucose tolerance, insulin secretion or insulin sensitivity Muscle specific alteration in insulin receptor abundance	115

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exposure during early life, there are species-specific alterations in postnatal glucose tolerance, insulin secretion and sensitivity, mitochondrial function, hepatic gluconeogenic capacity and in body composition and adiposity, which depend on the timing, type, duration and route of experimental GC overexposure (Table 1).

Metabolism

The effects of prenatal GC overexposure on adult glucose tolerance and insulin sensitivity in sheep appear to be less pronounced than in rodents, guinea pigs or human populations.[2,4,7,116] This is consistent with adult ruminants being less dependent on glucose metabolism than simple monogastric animals or monogastric, hind gut fermentors.[41,117] However, pre-weaning lambs are purely monogastric and depend more heavily on glucose as a metabolic substrate than adult sheep.[41,117] There is, therefore, a natural decline in glucose tolerance, relative insulin secretion and insulin sensitivity with ageing in sheep, irrespective of the prenatal environmental or endocrine conditions, as they switch to using VFA and free fatty acids as more prominent primary sources of energy.[118]

After prenatal GC overexposure in late gestation, juvenile (pre-pubertal) sheep and horses have improved glucose-stimulated insulin secretion compared to controls irrespective of the type or route of GC administered (Table 1). There is also increased insulin sensitivity in neonatal and juvenile sheep after maternal GC treatment (Table 1), which may reflect persisting upregulation of muscle GLUT4 expression *in utero*.[69] By 3 years of age, there is little, if any, effect of fetal or maternal treatment with betamethasone in late gestation on ovine glucose tolerance or insulin sensitivity, although basal hyperinsulinaemia is seen after maternal betamethasone treatment in the older offspring (Table 1). In contrast, treatment of ewes with dexamethasone in late gestation is associated with glucose intolerance and reduced insulin secretion in the 2-3 year-old offspring and in their subsequent progeny.[103] In horses, short-term maternal administration of dexamethasone in late gestation had no effect on glucose tolerance or glucose-stimulated insulin secretion in the foals 2 weeks after birth but reduced their β cell response to arginine 10 weeks later.[91] When synthetic GCs are given to ewes early in pregnancy or directly to the fetus late in gestation, there are only minor effects on glucose tolerance or insulin sensitivity in their postnatal offspring compared to maternal treatment (Table 1). There is also little evidence for altered metabolism of substrates other than glucose with either early or late gestation overexposure to synthetic GCs, although insulin is less effective at suppressing lipolysis in adult sheep after maternal dexamethasone treatment in early pregnancy.[102]

In growth restricted lambs that had high endogenous cortisol concentrations during late gestation due to placental restriction by pre-pregnancy carunclectomy, glucose-stimulated insulin secretion and whole-body insulin sensitivity are impaired 1 month after birth but are normalized at 1 year of age.[119,120] Similarly, in sheep at 10 months, there are no changes in insulin secretion or sensitivity after direct intrauterine infusion of cortisol during late gestation.[112] In addition, in newborn foals, a short period of neonatal cortisol overexposure induces only minor increases in glucose-stimulated insulin secretion during the suckling period with no persisting effects on glucose tolerance, insulin secretion or insulin sensitivity at weaning or in early adulthood.[114,115] However, there were muscle specific differences in insulin receptor abundance in adult horses 2 years after neonatal cortisol overexposure, which may affect insulin sensitivity later in life.[115] Collectively, these observations suggest that early-life overexposure to cortisol may be less effective at programming glucose-insulin dynamics in later life than the synthetic GCs.

Tissue specific metabolic effects

Prenatal GC overexposure is known to alter the postnatal metabolome of ovine liver, heart, skeletal muscle and adipose tissue.[58,105,106,112] In addition to changes in expression of the muscle GLUT transporters and insulin receptors[69,121], there are also alterations in the abundance of mitochondrial ETS complexes, OXPHOS capacity and uncoupling proteins in a range of postnatal ovine tissues after prenatal GC overexposure in late gestation induced either experimentally or by adverse intrauterine conditions.[70,107,113] The upregulation of the hepatic glucogenic capacity induced in fetal sheep by early GC overexposure also persists into adult life with sustained increases in key gluconeogenic enzyme activities.[62,66,105] In contrast, the cortisol-induced changes in muscle fibre composition in fetal sheep did not persist into early adulthood.[113] However, the changes in gut structure and enzyme activity induced by early GC overexposure are associated with altered intestinal nutrient uptake postnatally.[72] For instance, treatment of newborn pigs with synthetic GCs advances postnatal development of intestinal amino acid uptake by at least 4 weeks.[110] The tissue specific changes in nutrient handling induced by early-life GC overexposure alter the balance of nutrients available for glycolytic and oxidative metabolism postnatally with implications for heat and energy production essential for pre-weaning survival.

Other Metabolic Hormones

In addition to pancreatic β cell function (Table 1), early-life GC exposure alters postnatal activity of several other endocrine axes involved in regulating metabolism. Basal concentrations of T_3 and IGF-I are lower than control values in young sheep after prenatal GC overexposure.[88,122] Similarly, leptin concentrations are suppressed in sucking calves for 2 weeks after giving cortisol for the first 24h after birth.[123] In contrast, in juvenile sheep, postnatal levels of leptin are elevated or unaffected by prenatal GC overexposure depending on its cause.[88,124] Basal ACTH and cortisol concentrations, and the sensitivity of the HPA axis to stressful stimuli and exogenous CRH/ACTH administration, are also altered following prenatal GC overexposure in sheep, pigs and horses after birth (Table 2). In general, prenatal GC overexposure tends to increase pituitary-adrenal responses pre-weaning but leads to adrenal hypo-responsiveness in older animals, particularly after maternal treatments later in gestation (Table 2). These changes are accompanied by molecular alterations at all levels of the HPA axis as well as in adrenal morphology (Table 2). In both sheep and pigs, there is a relative expansion of adrenal medullary cells at the expense of the cortex after prenatal cortisol overexposure[93,110]. Furthermore, there are changes in plasma CBG and in tissue abundance of the GC receptors in adult sheep following prenatal overexposure to synthetic GCs, which will influence the overall metabolic outcomes of the programmed HPA activity.[85,86,93,126,127] Indeed, the relative hypo-responsiveness of the adult HPA axis after prenatal GC overexposure may reduce the risk of developing dysfunctional glucose-insulin dynamics with ageing. However, collectively, the changes in postnatal endocrine function induced by prenatal GC overexposure are likely to influence postnatal growth and body composition.

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Table 2. Postnatal outcomes of prenatal glucocorticoid overexposure on the HPA axis in livestock. (dGA = days gestational age, dPN = days postnatal age)

	Species	Age at treatment	Postnatal age at study	Postnatal outcomes	Reference
Maternal treatment					
Dexamethasone	Pig	99 & 100 dGA	67 days	↑ Basal ACTH and cortisol concentrations ↑ ACTH response to hypoglycaemia	90
	Sheep	40-42 dGA	31 days	↓ cortisol response to tail docking in females.	125
			7 months	↓ ACTH and cortisol responses to CRH in females Sex-linked changes in hypothalamic GR, pituitary POMC, adrenal ACTH receptors & adrenal steroidogenic enzymes	126
		103-105 dGA	2.5-3.5 years	Elevated basal cortisol concentrations Slower ACTH-induced cortisol response Blunted ACTH response to CRH/AVP	127
Betamethasone	Sheep	80 dGA	42 ± 3 days	↑ ACTH and cortisol response to hypotension	128
		104, 111, 118 & 125 dGA	12 weeks	↓ Hypothalamic CRH and AVP ↓ Pituitary POMC ↓ Adrenal StAR & 11βHSD2	85
			6 months & 1 year	No Δ basal ACTH or cortisol concentrations No Δ ACTH response to CHR/AVP No Δ Cortisol responses to ACTH	129
			2 years	No Δ basal ACTH or cortisol concentrations ↑ ACTH response with normal cortisol response to CRH/AVP ↓ Adrenal ACTH sensitivity	130
			3 years	↑ Basal ACTH concentration ↓ Basal cortisol concentration Normal ACTH response to ACTH with ↓ cortisol response to CRH/AVP ↓ Adrenal ACTH sensitivity	
Cortisol	Pig	81-110 dGA	6 weeks & 6 months	Reduced salivary cortisol response to ACTH Increased novelty-induced locomotion	109, 131,132
ACTH	Pig	47-79 dGA	Newborn	↓ CBG concentration No Δ cortisol concentration	93
		85-107 dGA	28 dPN	No Δ CBG or cortisol concentrations	
			Newborn	↓ CBG concentration No Δ cortisol concentration ↓ Adrenal medullary cell number	
			28 dPN	No Δ CBG or cortisol concentrations ↓ Relative adrenal weight	
Fetal/Neonatal Treatment					
Betamethasone	Sheep	104, 111. 118 & 125 dGA	6 months	No Δ basal ACTH or cortisol concentrations No Δ ACTH or cortisol response to CHR/AVP	129
			1 year	No Δ basal ACTH or cortisol concentrations ↓ ACTH response but normal cortisol response to CRH/AVP ↑ Adrenal ACTH sensitivity	
			2 years	↓ Basal ACTH concentration Trend to reduced basal cortisol concentration ↓ ACTH response to CRH/AVP No change in stimulated cortisol: ACTH response ratio	130
			3 years	No Δ in basal or stimulated ACTH or cortisol concentrations.	
Cortisol	Sheep	125-130 dGA	10 months	↓ Adrenal ACTH sensitivity Adrenal hypo-responsiveness to hypoglycaemia ↓ Relative area of adrenal cortex	112
ACTH	Horse	1-5 dPN	3weeks	↑ Basal cortisol concentrations No Δ adrenal sensitivity to ACTH	133 134
			13 weeks	No Δ basal or ACTH stimulated cortisol concentrations	
			1 year	No Δ basal ACTH or cortisol concentrations ↑ ACTH response with no Δ cortisol response to hypoglycaemia. No Δ cortisol response to exogenous ACTH	
			2 years	No Δ basal ACTH or cortisol concentrations ↑ ACTH and cortisol responses to hypoglycaemia. No Δ cortisol response to exogenous ACTH	

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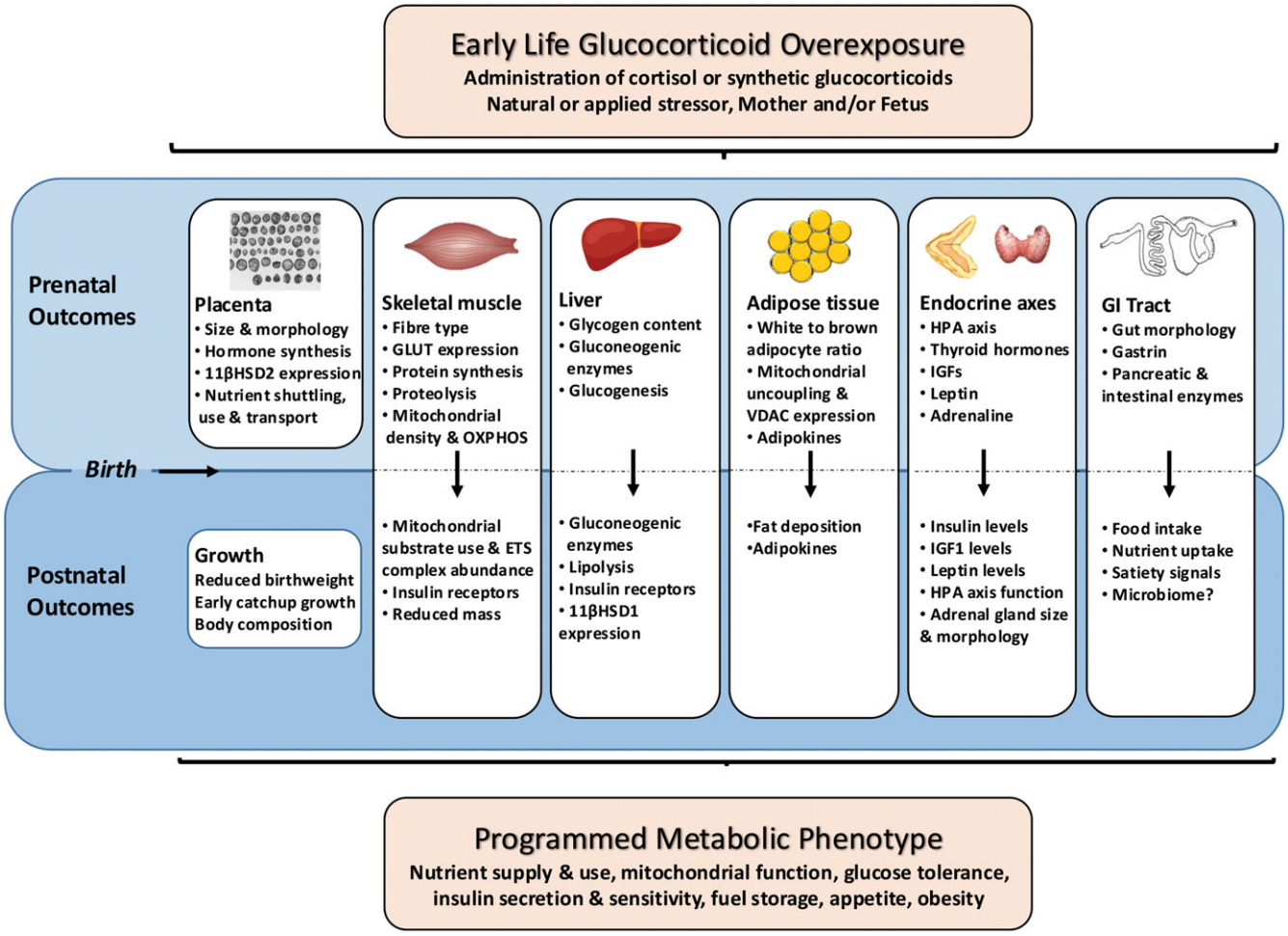

Figure 4. Summary diagram of pre- and post-natal metabolic outcomes of early life glucocorticoid overexposure in specific tissues that lead to altered growth and a programmed metabolic phenotype. GI = gastrointestinal, 11βHSD = 11β-hydroxysteroid dehydrogenase, GLUT = glucose transporter, VDAC = voltage dependent anion channel, IGFs = insulin like growth factors (Data from references [6,30,55,60,61] and Table 1 & 2).

Postnatal growth

Low birthweight neonates of ewes, sows and mares treated with synthetic GCs in late gestation often undergo catch-up growth after birth.[109,111,120,127,135-137] Offspring body weight tends to be normalized by the time of weaning or puberty. Similar postnatal increases in the fractional growth rate are also seen in growth restricted lambs that had high endogenous cortisol concentrations during late gestation due to placental restriction induced by pre-pregnancy carunclectomy.[119,120] In part, the catch-up growth probably reflects the increased insulin secretion and the changes in tissue insulin receptors and mitochondrial function seen in early postnatal life (Table 1). It may also reflect postnatal alterations in appetite and feeding behaviour as increased sucking frequency and more rapid intake of the food ration are observed in low birthweight lambs and piglets following prenatal GCs over-exposure.[124,131,135,137] In both piglets and lambs, the increased postnatal growth rate is associated with increased fat deposition and a reduced relative lean or muscle mass by young adulthood.[109,119,137,138] Together, the GC-induced changes in postnatal appetite regulation and fat deposition may eventually lead to more pronounced insulin resistance and glucose intolerance in aged ruminants as occurs in other species.

Conclusions

The combined metabolic changes in the feto-placental tissues induced by GC exposure contribute to switching tissues from growth to differentiation important for survival both in adverse intrauterine conditions and during the transition to extrauterine life (Fig 4). With elevated maternal GC levels, the metabolic changes tend to slow fetal growth, thereby reducing the fetal demand for maternal resources in stressful conditions while maintaining a basic supply of nutrients to the fetus. While this strategy aids survival *in utero*, it can lead to fetal growth restriction if the adverse conditions and GC exposure are prolonged, particularly in late gestation when the fetus is normally growing most rapidly in absolute terms. When fetal cortisol levels rise either naturally towards term or are due to fetal stresses in late gestation, feto-placental metabolism is directed away from fetal growth towards tissue differentiation and fuel storage in preparation for delivery. However, these late gestational rises in fetal cortisol concentrations can also affect placental hormone synthesis with consequences for the onset of labour dependent on species.[29,31] Collectively, the effects of cortisol maximize the chances of neonatal survival by preparing the somatic tissues for the loss of the continuous placental nutrient supply while

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simultaneously facing the new postnatal energy demands for breathing, glucoregulation, locomotion, heat production and digestion.[30]

The GCs induced metabolic changes *in utero* not only improve the chances of survival to delivery but also optimize development of a metabolic phenotype fit for the homeostatic challenges after birth. However, by inducing a premature switch from tissue growth to differentiation *in utero*, early GC overexposure can have adverse metabolic consequences later in life (Fig 4). By reducing cell number, altering cell composition and/or inducing functional changes in key metabolic tissues (Fig 4), the ensuing metabolic phenotype may be inappropriate for the prevailing postnatal conditions. In turn, this can lead to metabolic dysfunction later in life, particularly as functional reserves decline with ageing. The adult metabolic outcomes of early-life GC overexposure, therefore, depend not only on the developmental changes induced *in utero* but also on the conditions encountered postnatally.

Collectively, the current studies on livestock suggest that prenatal GC overexposure has milder effects on adult glucose metabolism than in laboratory species and human populations. In part, this may be due to the underlying dietary and metabolic differences between species and the concentration of studies on a ruminant species (Tables 1 and 2) . It may also reflect the comparative youth of the livestock species studied relative to their natural lifespans (Supplemental Table 1). However, in line with other species[7-9,116], early-life GC exposure alters postnatal growth, body composition and endocrine function of livestock, which could have more pronounced metabolic effects in the longer term (Table 1 & 2). Further studies are, therefore, needed on livestock to determine whether metabolic dysfunction becomes more pronounced with age and involves metabolic substrates other than glucose. Whether the GC programmed changes in metabolism are sex-linked and inherited trans-generationally also remains unclear in livestock species.[10,87,123,137] There is also little information about the effects of early-life GC overexposure of livestock on their subsequent fertility and reproductive performance.[10,139] Nevertheless, like other animals, there is a fine balance between the beneficial effects of GCs in ensuring survival of livestock species to reproductive age and the potentially more detrimental metabolic outcomes in later adulthood. As climatic conditions change with rising temperatures and more variable rainfall, there will be new environmental challenges to livestock homeostasis including heat stress and forage availability and quality.[99,139,140] As programming signals, GCs are, therefore, likely to become increasingly important determinants of adult metabolic phenotype in the coming years not only for livestock but also for all other species inducing human populations worldwide.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2040174425000091.

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