Endocrine Regulation of Feto-Placental Growth

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Abstract

Hormones are both growth stimulatory and growth inhibitory in utero. They regulate tissue growth and development by controlling the rates of cell proliferation, apoptosis and differentiation in many fetal tissues. They also signal the level of resources available for intrauterine growth to the fetal tissues and relay back to the placenta the degree of mismatch between the actual fetal nutrient supply and the fetal nutrient demands for growth. They affect intrauterine growth by anabolic and catabolic actions on fetal metabolism and by altering the nutrient transfer capacity and endocrine function of the placenta. By modifying the fetal growth trajectory, hormones have a central role in programming development in utero and in determining the phenotypic outcome of changes in feto-placental growth during adverse intrauterine conditions. This review examines the role of hormones in feto-placental growth with particular emphasis on insulin, the insulin-like growth factors and glucocorticoids.

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Introduction

Size at birth is critical in determining life expectancy. It affects not only neonatal viability but also adult rates of morbidity and mortality. Human epidemiological observations show that the smaller the neonate the less likely it is to survive at birth and more prone it is to developing adult-onset degenerative diseases such as hypertension, coronary heart disease and type 2 diabetes [1]. In experimental animals, natural and experimental restriction of fetal growth is also associated with poor neonatal viability and with postnatal abnormalities in cardiovascular and metabolic function consistent with the human epidemiological data [2]. Taken together, these findings show that changes in the pattern of intrauterine growth have phenotypic consequences for specific tissues and organ systems long after birth. The factors regulating growth in utero, therefore, have an important role in determining adult health and susceptibility to disease.

Manipulation of fetal hormone levels by exogenous administration, drug treatment, gene deletion or by surgical ablation of fetal endocrine glands has shown that a range of different hormones are essential for normal growth and development in utero (table 1). These hormones trigger key developmental events and control the cellular availability of nutrients for fetal growth more generally [3]. They also regulate rates of cell proliferation, apoptosis and differentiation in many fetal tissues [4].

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Table 1. Effects of manipulation of insulin, IGFs and glucocorticoids on fetal and placental growth in late gestation

Hormone	Manipulation	Procedure	Species	Weight, % control		Specific fetal tissue effects
				fetus	placenta	
Insulin	Deficiency	Diabetogenic drug treatment	Sheep	80%	?	Delayed bone ossification
			Rabbit	65%	?	None
			Monkey	85%	?	None
			Rat	92%	?	None
		Pancreatectomy	Sheep	70%	100–110%	Liver, spleen, brain
			Rat	80%	?	Liver, brain
		Gene deletion	Mouse	80%	?	?
		Pancreatic agenesis/neonatal diabetes	Human	70%	?	Emaciated
		Insulin receptor defect	Human	50–80%	?	Emaciated
	Overexposure	Fetal insulin administration	Sheep	100–120%	100%	Increased fat
			Pig	100%	?	Increased fat
			Monkey	135%	?	Increased fat
			Rat	110%	?	Increased fat
		Congenital hyperinsulinaemia	Human	130%	?	Increased fat
		Maternal diabetes	Rat	115%	?	?
			Human	130%	?	Increased fat
IGF-I	Deficiency	*Igf1* gene deletion	Mouse	60%	100%	Skeletal muscle, bone
		Igf1 gene defect	Human	50%	80%	Deafness, microencephaly
		Igf1r gene deletion	Mouse	45%	100%	Skin, bones, respiratory muscles
		Igf1r gene defect	Human	50–80%	?	?
	Overexposure	Fetal IGF-I administration	Sheep	100%	100%	Liver, lungs, heart, kidney, adrenal
IGF-II	Deficiency	*Igf2* gene knockout	Mouse	60%	55%	Diaphragm, skeletal muscle, bones
	Overexposure	Transgenic expression	Mouse	136%	125%	Pancreatic islets
		Igf2r gene deletion	Mouse	140%	140%	Liver, muscle
		H19 gene deletion	Mouse	130%	140%	Liver, muscle
		Igf2 and *H19* gene deletion	Mouse	200%	230%	Liver, heart, kidney
		Beckwith-Wiedemann syndrome	Human	150%	?	Liver, tongue, skeletal muscle
Glucocorticoids	Deficiency	Metyrapone treatment	Sheep	110%	?	Adrenal, kidneys
		Adrenalectomy	Sheep	115%	100%	Liver, lungs, gut
	Overexposure	Maternal glucocorticoid administration	Sheep	80–85%	65–90%	Brain, liver, lungs, heart
			Monkey	90%	75%	?
			Rabbit	75–90%	?	Lungs
			Guinea pig	84%*	?	Brain, liver
			Rat	90–93%	50–60%	Heart, brain, endocrine system
			Human	85%	?	Lungs, gut
			Mouse	81%	93%	?
		Fetal glucocorticoid administration	Sheep	80–100%	100%	Liver, lungs, gut, endocrine systems
		Inhibition of placental 11β-HSD2	Rat	88%	?	?
		11β-HSD2 gene deletion	Mouse	84%	90%	?

? = Information unknown. * Sex-linked effect. Data from references 2, 3, 10, 11, 14, 20, 31, 33, 37, 38, and 42.

Furthermore, hormones signal the availability of oxygen and nutrients to the developing fetal tissues and, thereby, match the fetal growth rate to the fetal nutrient supply [5]. Hormones, such as insulin, glucocorticoids and the insulin-like growth factors (IGFs), are particularly sensitive to changes in the intrauterine environment and respond to a wide range of metabolic, endocrine and neural stimuli.

In part, their role in regulating fetal growth may be mediated through changes in growth of the placenta, the main interface between the mother and fetus in controlling resource allocation for intrauterine growth [6]. However, compared to the fetus, relatively little is known about the endocrine regulation of placental development. The placenta itself produces hormones, including placen-
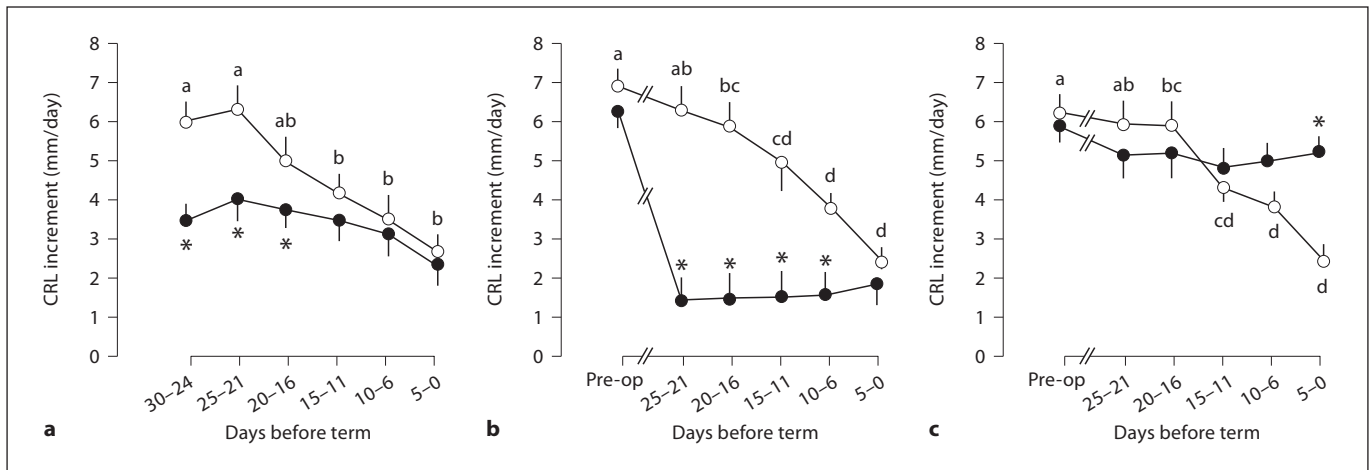
Fig. 1. Mean (±SE) daily CRL increments with respect to days from term in sheep fetuses after **a** hypophysectomy, **b** pancreatectomy and **c** adrenalectomy (all filled symbols) or sham operation (open symbols). In the sham-operated controls, values with different letters are significantly different from each other (p < 0.05, ANOVA). * Significantly different from the corresponding growth rate in the sham-operated controls (p < 0.05, t test). n ≥ 6 fetuses in all groups [data from 7, 12, 32].

tal variants of pituitary hormones like growth hormone (GH) and prolactin, which may influence fetal growth directly or indirectly via maternal metabolic changes and altered partitioning of maternal resources to the fetus [7, 8]. This review examines the role of hormones in regulating feto-placental growth with particular emphasis on the effects of insulin, glucocorticoids and the IGFs.

Growth Stimulatory Hormones

Insulin, thyroid hormones, IGFs and pituitary hormones are all growth stimulatory as removal of these hormones from the fetal circulation retards fetal growth and/or alters development of individual fetal tissues [3]. In fetal sheep, deficiency of these hormones takes effect immediately as growth rate, measured as crown-rump length (CRL) increment, is slowed from directly after ablation of the relevant endocrine gland (fig. 1). In part, the effects of fetal hypophysectomy are the result of multiple endocrine deficiencies as there are changes in the fetal concentrations of IGFs, GH, thyroid hormones and cortisol in hypophysectomised fetuses during late gestation [9]. Generally, the growth stimulatory hormones act as signals of nutrient plenty and rise in concentration in the fetus with increases in the availability of glucose, amino acids and oxygen [5]. Metabolically, they are anabolic, although their specific actions on fetal metabolism and

growth depend on the particular hormone, its concentration and the gestational age of the fetus [10]. In comparison to fetal hormones, relatively little is known about the growth regulatory actions of placentally derived somatomammotrophic hormones, but gene defects in the placental variants of GH and prolactin have little effect on birth weight of the human infant [11].

Insulin
Insulin is an important growth hormone in utero across a range of species (table 1). Its deficiency causes growth retardation (table 1) and, in fetal sheep, reduces growth rate by 50–60% during the last 30–40 days of gestation (fig. 1b). The reduction in fetal growth is uniform with the majority of fetal tissues sharing equally in the growth retardation [12]. In contrast, induction of fetal hyperinsulinaemia has less consistent effects on intrauterine growth (table 1). This may be due, in part, to species differences in body fat content as excessive insulin exposure increases fetal fat deposition in all species studied to date (table 1). Weight gain in response to fetal hyperinsulinaemia is, therefore, greatest in species, like the human, that normally have a high body fat content at birth [13]. In humans, genetic variation in the length of the insulin (INS) gene variable number of tandem repeats (VNTR) on chromosome 11, which is thought to control transcription of the insulin gene, is associated with size at birth with greater birth weights and lengths when the

Table 2. Cell functions stimulated by glucocorticoids in utero

Function	Class of molecule	Specific molecules	Tissues
Receptors	Steroids	Glucocorticoids, mineralocorticoids	Lungs, brain, pituitary, liver
	Proteins	Growth hormone, prolactin, IGF-I, placental lactogen	Liver, adipose tissue, skin
	Peptides	Angiotensin II, vasopressin, ACTH, leptin	Liver, kidney, heart, brain, adrenal
	Amines	Adrenaline, noradrenaline, dopamine	Liver, lungs, brain
Enzymes	Steroids	11β-HSD1&2, 3β-HSD, 17,20-lyase, 17α-hydroxylase, aromatase	Liver, adrenal, placenta
	Eicosanoids	Prostaglandin G/H synthetase	Placenta
	Other hormones	Type I and type III 5′-monoeicodinase, angiotensin-converting enzyme, phenylethanolamino N-methyltransferase	Liver, placenta, lungs, adrenal
	Metabolic	Fatty acid synthetase, argininosuccinate synthetase and lyase, pyruvate carboxylase, glucose-6-phosphatase, fructose diphosphatase, phosphoenolpyruvate carboxykinase, aspartate aminotransferase, glutamate dehydrogenase	Liver, kidney, lungs
	Digestive	Chymosin, amylase, lactase, aminopeptidase	Stomach, pancreas, intestines
	Vasoactive	Renin, endothelial nitric oxide synthetase	Lungs, placenta
Ion channels	Voltage gated	Na^+ channel	Heart
	Ligand gated	Epithelial Na^+ channel	Lungs, kidney
Transporters	Ions	Na^+/K^+ ATPase, Na^+/H^+ exchange	Lungs, kidney
	Water	Aquaporins	Kidney
	Nutrients	Glucose transporters 1, 3 and 4	Placenta, skeletal muscle

Data from references 8 and 29.

class III INS/VNTR genotype is inherited from both parents [11]. In contrast to tissue growth, tissue differentiation during late gestation appears to proceed normally in both hypo- and hyperinsulinaemic fetuses [14]. The primary growth-promoting action of insulin is, therefore, on tissue accretion rather than tissue differentiation.

Insulin stimulates fetal growth, in part, by its anabolic effects on glucose and amino acid metabolism [3]. It increases the cellular uptake of these metabolites and enhances the rates of protein synthesis and glucose utilisation in fetal sheep [15, 16]. Fetal glucose and amino acid levels, therefore, fall in response to fetal insulin administration [12, 16]. This maximises the transplacental concentration gradient for glucose and increases facilitated diffusion of glucose across the placenta [15]. The glucose taken up by the fetal tissues is used for both oxidative and non-oxidative processes as CO_2 production and muscle glycogen deposition are both reduced in pancreatectomised sheep fetuses [3]. The rates of fetal glucose utilisation and oxidation are, therefore, related directly to the circulating insulin concentration and growth rate in utero [15].

The effects of insulin on fetal growth do not appear to be mediated via the placenta (table 2). Manipulating fetal insulin concentrations appears to have little effect on glucose consumption or the weight of the ovine placenta [15]. However, for most of late gestation, placental glucose transfer per gram of placenta is reduced in insulin-deficient, pancreatectomised fetuses, probably due to the smaller transplacental glucose concentration gradient rather than a change in the nutrient transfer capacity of the placenta per se [15]. However, there have been few studies of placental transport capacity or nutrient transporter abundance during either fetal insulin deficiency or insulin overexposure in any species. In insulin-deficient diabetic mothers, there is some evidence for changes in expression of glucose and amino acid transporters in human and rodent placentae, but whether this is due to maternal hypoinsulinaemia or hyperglycaemia remains unclear [17]. Manipulation of fetal glucose concentrations is known to alter placental expression of the glucose transporters (GLUTs) in sheep [18], so insulin may have indirect effects on placental GLUT abundance via its glucoregulatory actions in the fetus.

Insulin-Like Growth Factors

Like insulin, the IGFs stimulate growth in utero [19]. Deletion of either the *Igf1* or *Igf2* gene in mice reduces fetal body weight at term and leads to developmental abnormalities in a range of fetal tissues (table 1). Deletion of the *Igf* type 1 receptor responsible for the actions of both IGF-I and IGF-II causes a greater degree of growth retardation than deletion of either *Igf* gene alone [20]. It is also lethal at birth. Mutation of the human *IGF1* gene also produces severe intrauterine growth retardation and leads to failure of postnatal growth [19, 20]. Less is known about the effects of excessive IGF levels in utero. In mice, IGF-II overexpression either locally through imprint relaxation or systemically by deletion of the IGF type 2 clearance receptor *(Igf2r)* leads to macrosomia, specific organomegaly and defects in the heart and kidneys (table 1), which prove fatal at birth [20]. Overexpression of IGF-II in Beckwith-Wiedemann syndrome also causes overgrowth in human infants (table 1). Similarly, in cloned and in vitro produced sheep, increased IGF-II exposure induced by reduced *IGF2R* expression is associated with multiple developmental abnormalities and generalised fetal overgrowth [21]. Administration of IGF-I to normal fetal sheep and monkeys for 10 days in late gestation has little effect on fetal body weight, although it increases the weight of individual fetal tissues [22]. However, when fetal growth is compromised by poor placental perfusion, fetal IGF-I treatment increases body weight in sheep and rabbits [19]. Both IGF-I and IGF-II, therefore, appear to stimulate tissue accretion. However, in several species including humans, body weight is positively correlated to plasma IGF-I but not IGF-II concentrations at birth [19]. Polymorphisms of the human *IGF1*, but not the *IGF2* or *IGF2R* gene are also associated with birth weight in epidemiological studies of large birth cohorts [11]. Since plasma IGF-I concentrations are more responsive to glucose and oxygen levels than IGF-II levels in the fetus [4], IGF-I may act as a nutrient sensor that ensures fetal growth is commensurate with the nutrient supply, while IGF-II provides the constitutive drive to fetal mass accumulation.

The IGFs act at several stages of the cell cycle and affect cell proliferation, differentiation, maintenance, regeneration and apoptosis [19]. Both IGF-I and IGF-II are mitogens in a range of different mesenchymal cells, although their relative potencies differ with cell type. They also stimulate cell differentiation in fetal muscle, bone, brain and adrenal cells, particularly during late gestation when terminal differentiation is occurring in preparation for extrauterine life [4, 14]. In part, these effects on differentiation are due to apoptosis of fetal cells and their replacement with adult cell types. The IGFs, therefore, have specific developmental effects on individual tissues as well as stimulating general somatic growth in utero. They also have anabolic effects on fetal metabolism [3, 19]. Administration of IGF-I to fetal sheep and rats can stimulate fetal glucose utilisation, although to a lesser extent than insulin [15, 16]. In rat fetuses, this effect may reflect IGF-I stimulated up-regulation of tissue GLUT abundance [20]. Treatment with IGF-I also reduces amino acid levels, protein catabolism and the oxidative use of amino acid carbon in fetal sheep [16, 23]. Consequently, urea production decreases and amino acid accretion increases in these fetuses. The net result is that protein synthesis increases in the whole body and in individual tissues like the liver and skeletal muscle when fetal IGF-I levels are raised [16, 22]. The primary growth-promoting action of IGF-I, therefore, appears to be on protein and amino acid kinetics.

The actions of the IGFs on fetal growth may be mediated, in part, via changes in placental growth (table 2). In particular, IGF-II has an important role in regulating growth of the definitive hemochorial placenta in rodents [24]. It acts by paracrine and endocrine mechanisms to stimulate growth of all zones of the rodent placenta. Deletion of the *Igf2* gene in either all feto-placental tissues (complete *Igf2* null) or in the labyrinthine trophoblast specifically (*Igf2P0* null) reduced placental weight by 30–50% near term (table 2). Conversely, increasing IGF-II exposure by imprint relaxation or deletion of the *Igf2r* gene causes placentomegaly with placental weight more than doubling in the fetuses with the highest IGF-II exposure (table 2). IGF-II also stimulates the migration and invasiveness of human extravillous trophoblast and is strongly expressed in invasive trophoblast tissues during early placental development in several species [25]. In addition to regulating placental size, IGF-II influences placental morphology [24]. In the complete *Igf2* null placenta, there are fewer invasive giant trophoblast and glycogen cells during early development and a 50% reduction in the average number of cells in the labyrinthine and junctional zones in late gestation [26]. The weight and morphological changes are less pronounced in the *Igf2P0* null placenta, but there is still a 50% reduction in the surface area and a 30% increase in the thickness of the labyrinthine exchange barrier that, together, lead to a 60% reduction in the theoretical diffusion capacity of these placentae [24]. Indeed, passive diffusion of solutes is reduced by 30–40% in the *Igf2P0* placenta in vivo [27, 28]. The *Igf2* gene, therefore, appears to regulate the number, size and type of cells present in the placenta.

In contrast to IGF-II, IGF-I appears to have little effect on placental size (table 2). Neither deletion of the *Igf1*

gene nor intrafetal IGF-I treatment affects placental weight [20]. However, IGF-I does appear to alter placental nutrient transfer. Administration of IGF-I to fetal sheep increases placental glucose consumption and decreases placental production and delivery of lactate to the umbilical circulation [23]. It also reduces placental clearance of glucose and the amino acid analogue, methylaminoisobutyric acid (MeAIB). Since placental urea clearance, a marker of simple diffusion was unaffected by fetal IGF-I treatment [23], expression of glucose and amino acid transporters in the ovine placenta may be IGF-I sensitive. IGF-II has been shown to affect expression of a range of nutrient transporters in human and murine placentae [24]. There is decreased abundance of the System X$^-$AG, System Y+ and System A amino acid transporters in the complete *Igf2* null placenta, which is associated with a 25% reduction in the transplacental transport of MeAIB [24, 27, 29]. In contrast, the *Igf2P0* placenta transfers 30–60% more glucose and MeAIB per gram than the wild-type placenta and up-regulates expression of GLUT3 and the SNAT4 isoform of System A amino acid transporters [29]. Since the fetal tissues continue to express *Igf2* in the *Igf2P0* mutant but not in the complete *Igf2* null, placental and fetal *Igf2* must interact in the control of placental nutrient transfer. This interplay enables the placenta to respond to the fetal nutrient demands for growth and helps maintain fetal growth for as long as possible when placental growth is compromised. The IGFs, therefore, affect growth of fetal tissues not only directly but also indirectly through changes in the placental capacity to deliver nutrients to the fetus. Changes in the relative proportions of different nutrients supplied to the fetus may be as important as the absolute quantity of nutrients available in programming intrauterine development.

Growth Inhibitory Hormones

The main growth inhibitory hormones in utero appear to be the glucocorticoids, although other hyperglycaemic hormones, such as glucagon and the catecholamines, have been shown to influence fetal metabolism and the biochemical composition of specific fetal tissues [4]. These hormones act as signals of nutrient insufficiency and rise in concentration in response to fetal hypoxaemia and hypoglycaemia [5]. Catecholamines have been shown to reduce the gain in body weight and limb length in fetal sheep during late gestation in association with a reduced fetal muscle mass [30]. However, these effects can be abolished by preventing the fall in fetal insulin concentrations induced by catecholamine treatment [30]. The actions of the catecholamines are, therefore, not directly growth inhibitory but rather the indirect consequence of withdrawing a growth stimulus. Glucocorticoids, on the other hand, appear to have more direct actions on the pattern of fetal growth and differentiation, particularly close to term.

Glucocorticoids

Administration of glucocorticoids to either the mother or the fetus during late gestation leads to fetal growth retardation in several species including humans (table 1). Total body weight and the weight of most individual fetal tissues are reduced in proportion by these treatments [14]. The degree of fetal growth retardation depends on the dose and specific glucocorticoid used, the frequency and route of its administration and on the sex and gestational age of the fetus [4]. Body weight is also reduced in rat fetuses overexposed to glucocorticoids as a result of inhibiting placental 11β-hydroxysteroid dehydrogenase type 2, the enzyme that converts active glucocorticoids to their inactive metabolites [31]. This increases the transplacental transfer of bioactive glucocorticoids from the maternal to fetal circulations down the normal concentration gradient. In sheep, infusion of cortisol into pre-term fetuses reduced CRL increment by 50% to a value similar to those seen in older fetuses close to term [32]. Conversely, preventing the fetal cortisol surge towards term by fetal adrenalectomy or metyrapone treatment tends to increase fetal body weight near term and abolishes the normal prepartum decline in fetal growth rate observed over the last 10–15 days before term (fig. 1c). Glucocorticoids are, therefore, responsible for the natural decrease in growth towards term and, probably, also contribute to the growth retardation associated with adverse intrauterine conditions, such as undernutrition and hypoxaemia, which raise glucocorticoid concentrations in utero.

Glucocorticoids stimulate differentiation of a wide range of fetal tissues including the liver, lungs, gut, skeletal muscle and adipose tissue [14]. They induce morphological and functional changes in these tissues and activate many of the biochemical processes which have little or no function in fetal life. They affect not only tissues essential for neonatal survival but also those involved in more long-term adaptations to extrauterine life. At the cellular level, glucocorticoids alter receptors, enzymes, ion channels and transporters (table 2). They also change expression of various growth factors, cytoskeletal proteins, myelination, binding proteins, clotting factors, gap

and tight junction proteins and of various components in intracellular signalling pathways involved in growth, such as the mTOR pathway [14, 17, 31]. Together, these glucocorticoid-induced alterations in cell physiology combine to produce integrated changes in function at the systems level. Glucocorticoids, therefore, act to switch the cell cycle from tissue accretion to tissue differentiation in preparation for delivery. However, if this switch occurs prematurely due to stress-induced glucocorticoid overexposure, the normal pattern of intrauterine growth will be altered and inappropriate tissue development may occur for the stage of gestation with long-term consequences for tissue function much later in life. Glucocorticoids can, therefore, programme tissues in utero and, by signalling nutrient restriction, may also mediate the programming effects of nutritional and other environmental challenges during pregnancy [33].

Glucocorticoids are both anabolic and catabolic in utero, but their predominant effect is catabolic [3]. They stimulate glycogen accumulation in the fetal liver and muscle yet simultaneously increase the activity of hepatic gluconeogenic enzymes [14]. Glucocorticoids, therefore, activate endogenous glucose production by the fetus. They also decrease fetal protein accretion by enhancing proteolysis rather than reducing protein synthesis [34]. These changes are accompanied by alterations in inter-organ amino acid kinetics and the relative contribution of different amino acids to oxidative metabolism of the fetus [35]. These catabolic actions will restrict tissue accretion in the fetus.

The actions of glucocorticoids on fetal growth are mediated, in part, by changes in the placenta (table 1). In sheep, rats, mice and non-human primates, administration of synthetic glucocorticoids during late gestation reduces placental weight (table 1). In most of these species, the effect on the placenta is greater than that on the fetus (table 1). The effect on the ovine placenta was also more pronounced with maternal than fetal glucocorticoid administration which may account for the greater degree of intrauterine growth restriction (IUGR) seen with maternal treatment (table 1). In mice, maternal dexamethasone administration decreases placental expression of a number of genes involved in cell division and increases apoptosis of trophoblast cells [36]. Together, these observations indicate that placental growth retardation may be the primary cause of the IUGR induced by synthetic glucocorticoids. On the other hand, manipulation of natural glucocorticoid levels within the physiological range in fetal sheep appears to have little effect on placental weight, although there are alterations in placental morphology

[32, 37]. This may have consequences for nutrient transfer as placental efficiency, measured as grams fetus produced per gram placenta, is increased after maternal glucocorticoid treatment in sheep, rats and non-human primates, despite the reduction in placental mass [38].

Glucocorticoids have been shown to affect expression of the primary glucose transporters, GLUT1 and GLUT3, in human and rat placentae [38]. These effects appear to depend on the dose and duration of glucocorticoid treatment and/or on the degree of ensuing IUGR. Short-term exposure to glucocorticoids appears to reduce GLUT1 and GLUT3 abundance in rat and human placenta, while more long-term exposure associated with IUGR more than doubles expression of these transporters in rat placenta during late gestation [6]. In sheep, fetal cortisol infusion increases placental glucose consumption and reduces placental delivery of glucose to the fetus [36]. Similarly, there are changes in the placental handling and fetal delivery of lactate and certain amino acids in response to glucocorticoid treatment of either the mother or fetus [35, 39]. However, to date, there have been few studies of the effects of glucocorticoids on amino acid transporters in the placenta of any species.

In addition to effects on placental nutrient transfer, glucocorticoids alter the production and metabolism of hormones by the placenta [38]. For instance, the cortisol-induced reduction in binucleate cell numbers will alter delivery of placental lactogen into the maternal circulation with consequences for the partitioning of nutrients between the maternal and fetal tissues [6]. Glucocorticoids also alter the placental activity of a range of enzymes involved in the synthesis and inactivation of steroids, eicosanoids and thyroid hormones (table 2). Depending on gestational age, these actions may have beneficial effects on maintaining pregnancy and diverting maternal nutrients for fetal use yet, simultaneously, have detrimental effects on tissue programming with adverse sequelae long after birth [4]. In particular, the actions of glucocorticoids on placental 11β-HSD2 activity are likely to have widespread effects on fetal development by altering glucocorticoid exposure of both the fetal and uteroplacental tissues [31].

Interactions between Hormones

Growth inhibitory and growth stimulatory hormones interact extensively in the control of feto-placental growth (fig. 2). Insulin up-regulates tissue expression and circulating concentrations of IGF-I, while IGF-I reduces cir-
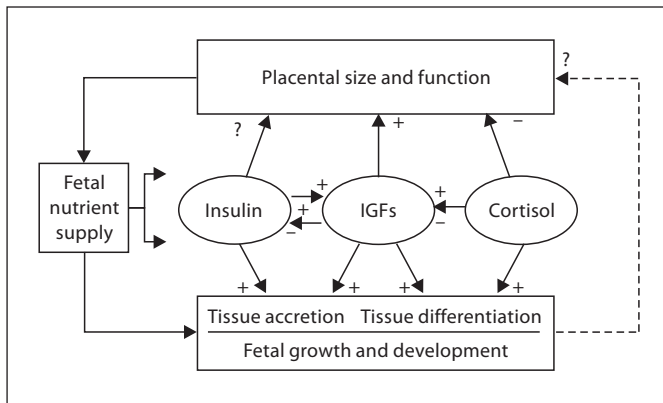
Fig. 2. Schematic diagram showing the actions and interactions of insulin, insulin-like growth factors and glucocorticoids in the control of feto-placental growth and development during late gestation. Solid arrows = Known actions; dashed lines = uncertain actions; + = stimulatory effect; – = inhibitory effect; ? = unknown effect.

culating insulin levels in the fetus [19]. The latter action may explain the lack of a body weight increment in IGF-I-treated sheep fetuses [22]. These two hormones can also interact with each other's receptors, although they appear to use distinct intracellular signalling pathways, even when stimulating common processes, such as protein synthesis [16]. Insulin secretion is also affected by IGF-II [19]. In mouse fetuses, transgenic expression of IGF-II increases the size of the pancreatic islets by preventing the normal wave of developmental apoptosis that occurs in β cells as pancreatic *Igf2* gene expression declines towards term [40]. The IGFs are, therefore, a major influence on pancreatic β-cell mass and the capacity for insulin secretion in the fetus. In addition, insulin and IGF-I regulate production of the insulin-like binding proteins which can both enhance and impede delivery of the IGFs to the insulin and IGF type 1 receptors [19].

Glucocorticoids also interact with both insulin and the IGFs developmentally. Glucocorticoids suppress β-cell development and reduce the insulin content of fetal rat pancreas in culture [14]. Although glucocorticoids appear to have little effect on insulin secretion once the pancreas has formed, the lack of a prepartum decline in growth rate in the pancreatectomised fetuses despite a normal fetal cortisol surge suggests that the growth inhibitory effect of cortisol in late gestation may be due, in part, to suppression of the actions of insulin (fig. 1b). Glucocorticoids also affect expression of IGF-I and IGF-II in the placenta and other fetal tissues, such as the liver, skeletal muscle and

adrenal, in a tissue-specific manner [3, 19]. In fetal ovine adrenals, cortisol decreases *IGF2* gene expression, which is associated with cytodifferentiation of the adrenal cortex and activation of the enzymes involved in cortisol synthesis [41]. Consequently, there may be a local regulatory loop operating between adrenal cortisol and IGF-II that ensures an exponential rise in cortisol secretion and, hence, tissue maturation in the period immediately before delivery. In fetal sheep, this prepartum rise in cortisol is known to initiate a switch from GH-independent paracrine production of IGFs in utero to GH-dependent production of endocrine IGF-I characteristic of the adult hepatocytes [10, 14]. It is also down-regulates IGF-II expression in fetal ovine liver and skeletal muscle [4, 10]. Glucocorticoids, therefore, lead to the perinatal transition from IGF-II to IGF-I as the predominant growth regulatory IGF [10]. Premature activation of these switches by glucocorticoid exposure early in gestation may be responsible for the changes in growth trajectory and tissue programming observed in these circumstances.

Conclusions

Hormones have an essential role in feto-placental growth [7]. They act directly on the fetal tissues to regulate tissue accretion and differentiation and indirectly via the placenta to alter the fetal nutrient supply and bioavailability of key growth regulatory hormones (fig. 2). They act as both maturational and epigenetic signals, optimising fetal growth in relation to the prevailing intrauterine conditions and ensuring the maximum chances of survival at birth. More specifically, hormones signal the general level of resource available for growth to the fetal tissues and, probably also, the degree of mismatch between the actual fetal nutrient supply and the fetal growth demands to the placental tissues (fig. 2). By modifying the fetal growth trajectory and the placental capacity to support intrauterine growth, particularly during adverse intrauterine conditions, hormones have a central role in programming development and determining the phenotypic outcome of changes in the pattern of feto-placental growth.

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