# ENDOCRINE REGULATION OF PLACENTAL PHENOTYPE

**A.L. Fowden[1], A.J. Forhead[1,2], A.N. Sferruzzi-Perri[1], G. J. Burton[1] and O.R. Vaughan[1]**

**[1]Centre for Trophoblast Research,**
**Department of Physiology Development and Neuroscience, University of Cambridge,**
**Cambridge, CB2 3EG, UK**
**and**
**[2]Department of Biological and Medical Sciences, Oxford Brookes University,**
**Oxford, OX3 0BP, UK**

**Key words:** Hormones, transport, placental phenotype

**Short title:** Hormones and placental phenotype

**Address for correspondence:** Abigail L. Fowden
Department of Physiology Development and Neuroscience
University of Cambridge
Downing Street
Cambridge, CB2 3EG, UK
Telephone: 44 (0)1223 333855
Fax: 44 (0)1223 333840
E-mail: alf1000@cam.ac.uk

**ABSTRACT**

Hormones have an important role in regulating fetal development. They act as environmental signals and integrate tissue growth and differentiation with relation to nutrient availability. While hormones control the developmental fate of resources available to the fetus, the actual supply of nutrients and oxygen to the fetus depends on the placenta. However, much less is known about the role of hormones in regulating placental development, even though the placenta has a wide range of hormone receptors and produces hormones itself from early in gestation. The placenta is, therefore, exposed to hormones by autocrine, paracrine and endocrine mechanisms throughout its lifespan. It is known to adapt its phenotype in response to environmental cues and fetal demand signals, particularly when there is a disparity between the fetal genetic drive for growth and the nutrient supply. These adaptive responses help to maintain fetal growth during adverse conditions and are likely to depend, at least in part, on the hormonal milieu. This review examines the endocrine regulation of placental phenotype with particular emphasis on the glucocorticoid hormones. It focuses on the availability of placental hormone receptors and on the effects of hormones on the morphology, transport capacity and endocrine function of the placenta.

## INTRODUCTION

During development, hormones act as environmental cues in regulating tissue growth and differentiation *in utero*. They signal stress levels, temperature, photoperiod and the availability of nutrients and oxygen (1). Towards term, hormones also act as maturational signals in the final processes of tissue differentiation in preparation for delivery (1, 2). By regulating intrauterine development in relation to these cues, hormones determine the phenotype of the offspring and maximise its chances of survival not only during fetal and neonatal life but also onto reproductive age as an adult (3). While hormones control the developmental fate of the resources available to the fetus, the actual supply of nutrients and oxygen to the fetus depends on the placenta. The placenta is known to adapt its transport phenotype to help maintain fetal growth in response to external environmental conditions, such as malnutrition, dietary composition and maternal psychological stresses of restraint, isolation and inappropriate light exposure (4, 5). It is also responds to internal signals of fetal nutrient demands, particularly when there is a mismatch between the placental capacity to supply nutrients and the fetal genetic drive for growth (4, 6). Furthermore, the placenta has endocrine functions itself and can both metabolise and synthesise hormones (1, 2, 7), which influences fetal development directly and indirectly by adapting maternal metabolism in favour of resource allocation to the fetus (8). The placenta is, therefore, exposed to hormones by autocrine, paracrine and endocrine mechanisms from early in development. However, compared to the fetus, less is known about the role of endocrine signals in placental development (2). This review, therefore, examines the endocrine regulation of placental phenotype. It places particular emphasis on the glucocorticoids because these hormones act as both environmental and maturational signals and affect growth and differentiation of many tissues known to be programmed during intrauterine development (1, 4). It does not consider the role of hormones in human trophoblast invasion or in the control of placental blood flow more generally.

## PLACENTAL HORMONE RECEPTORS

Hormones can influence placental phenotype either directly via specific receptors on various cell types forming the placenta or indirectly by inducing physiological changes in the fetus

and/or mother, such as alterations in nutrient availability or placental blood flow. The placenta has receptors for a wide range of circulating hormones, including those it produces, from early in development in several species (Table 1). In humans, it also expresses receptors for opioid, neuro-, growth regulatory and vasoactive peptides that are produced endogenously to act locally (7). Receptor expression can be ubiquitous or restricted to specific zones or cell types within the placenta (20, 31, 37, 41, 45, 51, 52, 56, 64). Their abundance may also be sex-linked (9, 14, 26, 69). Multiple isoforms of certain hormone receptors exist in the placenta and can be expressed selectively or differentially in the different placental tissues (9, 31, 42, 46, 55, 69). Some of the variants appear to be unique to the placenta and not every isoform identified in the placenta is expressed in every individual (7, 9, 70). In term human placenta, for instance, there are 5 isoforms of the glucocorticoid receptor (GR) in the endothelium but 12 different variants in the trophoblast, which are differentially expressed in male and female infants (9). Consequently, by late gestation when most fetal endocrine glands are functional (1), the placenta has the necessary receptors to respond to a range of hormones in both the fetal and maternal circulations.

With increasing gestational age, there are changes in placental abundance and spatial localisation of several hormone receptors including those for insulin, angiotensin, estrogens, glucocorticoids, adiponectin, leptin and the thyroid hormones (14, 30, 31, 49-51, 58-61, 68). Some of these developmental changes are isoform specific (31, 49, 58, 61, 68, 70). In the human placenta, localisation of the insulin receptor (IR) changes with gestational age from presence primarily in the syncytiotrophoblast facing the maternal circulation in the first trimester to expression predominantly in the placental endothelial cells facing the fetal circulation at term (37). In contrast, the increase in placental GR abundance between mid and late gestation is more widespread, although the magnitude of the increment may vary regionally depending on species (11, 15, 49, 69-73). In rats, for instance, the ontogenic increase in GR is more pronounced in the labyrinthine zone (Lz) responsible for nutrient transfer than in the junctional zone (Jz), the morphologically distinct region with endocrine functions (73). These spatio-temporal changes in placental hormone receptor abundance indicate that hormones are likely to have a significant role in normal placental development

and that the relative importance of fetal versus maternal endocrine signals may change as the metabolic demands of pregnancy increase with fetal growth towards term.

Placental hormone receptor abundance is also responsive to external environmental conditions (4). There are changes in placental abundance of GR, IR, IGFR1 and Ob-R when maternal nutritional state is altered by diabetes or dietary manipulation of calorie, macro- and/or micronutrient intake during pregnancy in experimental animals (11, 12, 38, 40, 74-76). In part, these nutritionally-induced changes in hormone receptor expression may reflect the concomitant alterations in the endocrine environment as direct experimental manipulation of maternal hormone concentrations, particularly of the glucocorticoids, alters placental expression of several hormone receptors including AT2R, Ob-Ra, Ob-Re, FP, EP2, IGF1R and GR itself (17, 33, 49, 57, 69, 77, 78). In addition, clinical complications of human pregnancy that alter placental blood flow or the circulating concentrations of hormones and metabolites, such as gestational diabetes, intrauterine growth restriction (IUGR) and pre-elampsia, are associated with changes in placental expression of a range of hormone receptors including AT1R, GR, GHR, IGF-1R, OB-R, AR and IR (9, 30, 37, 79-82). Taken together, these observations indicate that hormone receptor abundance in the placenta can vary with gestational age, sex of the offspring and with a range of environmental cues of fetal and maternal origin. In turn, this will influence the effects that hormones can have on the morphological, transport and endocrine phenotype of the placenta.

## HORMONES AND PLACENTAL MORPHOLOGY

Changes in trophoblast invasion and in the size and morphology of the definitive placenta have been observed in response to experimental manipulation of both maternal and fetal hormone concentrations (2, 4, 7). These studies have tended to focus on the glucocorticoids and insulin-like growth factors because of their known effects on fetal growth (83, 84). Maternal glucocorticoid administration during the last third of gestation leads to reduced placental weight in a wide range of species including monkeys, sheep, rabbits, rodents and human infants (4, 83, 85, 86). The degree of placental growth restriction depends on the type of glucocorticoid administered, the dose and duration of treatment and the gestational

age at both treatment and assessment (85, 86). The growth inhibitory effects are more pronounced with administration of synthetic than natural glucocorticoids and when glucocorticoid overexposure occurs in mid to late gestation than close to term (87, 88). In rodents, placental growth is also restricted to a greater extent by continuous than intermittent maternal treatment, irrespective of the exact route of glucocorticoid administration (86, 88). Furthermore, growth restriction of the rodent placenta occurs in response to local overexposure to glucocorticoids induced by reducing the activity of placental 11β-hydroxysteroid dehydrogenase-2 (11βHSD2), the enzyme that normally converts active glucocorticoids to their inactive metabolites (89, 90). In contrast, overexposure of the placenta to glucocorticoids via the fetal circulation appears to have less severe effects on placental growth, although this may relate, partially, to treatment later in gestation (91, 92).

These changes in placenta size and/or weight are accompanied by more specific alterations in placental morphology. In sheep, glucocorticoids affect the gross morphology of the placenta whether given maternally or fetally (86). In particular, there is a reduced number of everted placentomes without a change in total number, which leads to an altered frequency distribution of the different placentome types with potential consequences for glucose transport (91). Glucocorticoid treatment of either the mother or fetus in late gestation also reduces the numbers of binucleate cells (BNC) in the ovine placentomes (91, 92). These cells migrate from the fetal trophectoderm across the feto-maternal junction to form a syncytium with the maternal epithelium. They also produce progesterone and placental lactogen that influence maternal metabolism and tissue growth. Changes in BNC frequency and migration induced by glucocorticoid overexposure may, therefore, alter the morphological remodelling of the placenta and the maternal adaptations to pregnancy with consequences for resource allocation to the fetus.

In several species, there are changes in the surface area of the placenta in response to manipulating placental exposure to the glucocorticoids and IGFs (2, 4, 86). In rodents, maternal treatment with natural and synthetic glucocorticoids decreases the volume and surface area of the Lz trophoblast, particularly when treatment coincides with the main period of placental development (14, 49, 57, 69, 87, 88, 90-92). These changes are coupled

with a decrease in placental vascularity and *Vegf* expression, which can persist or reverse after cessation of treatment depending on the gestational age at time of overexposure (14, 69, 87, 88, 93-96). Similarly, there are reductions in the Lz volume and fetal vascularity of the mouse placenta locally overexposed to glucocorticoids by deletion of the *11βHsd2* gene (90). Reduced vascularity of the fetal villi has also been observed in term placenta of asthmatic women treated clinically with high doses of glucocorticoids during pregnancy (97). In mice, high doses of synthetic glucocorticoids have been shown to lead to placental necrosis and increased expression of several apoptotic genes (94). In contrast to the glucocorticoids, IGFs increase placental size, Lz volume and vascularity in mice and guinea pigs (6, 39). The IGFs also decrease the thickness of the interhemel membrane between the maternal and fetal circulations (6). However, the extent to which these hormonally induced changes in placental morphology and vascularity lead to altered placental blood flow still remains unclear as blood pressure is often elevated in response to glucocorticoid administration (85, 86). Nevertheless, changes in placental size and morphology with the endocrine milieu will alter the placental capacity for transfer of oxygen and nutrients to the fetus.

## HORMONES AND PLACENTAL NUTRIENT TRANSPORT

Using both *in vivo* and *in vitro* experimental methods, a wide range of different hormones have been shown to alter placental uptake and/or transplacental transfer of glucose and amino acids (Table 2). In some instances, these changes are associated with altered placental abundance of the transporters required for active transport of amino acids or facilitated diffusion of glucose from mother to fetus (Table 2). Much less is known about the endocrine regulation of placental lipid transport, although environmental factors such as maternal obesity and gestational diabetes can influence placental abundance and activity of the fatty acid transfer proteins involved in fetal uptake of fatty acids (131, 132). The hormonally induced changes in trophoblast surface area, thickness and vascularity will also influence the passive diffusion properties of the placenta and, hence, transport by simple diffusion of oxygen and waste products like urea and carbon dioxide (2, 5). In addition, both the glucocorticoids and the IGFs are known to alter placental production of the fetal

metabolic substrate, lactate, and its distribution between the uterine and umbilical circulations (91, 117, 118). Furthermore, fetal cortisol infusion has been shown to increase glucose consumption by the ovine placentomes, thereby limiting the proportion of uterine glucose uptake that is passed onto the fetus (91). Thus, hormones affect placental delivery of nutrients to the fetus not only by altering the morphological and functional characteristics of the actual transport processes but also by actions on the production and consumption of nutrients by the placenta *per se*.

Not all hormonal actions on placental nutrient delivery are direct. Some are mediated indirectly by physiological actions in the mother and fetus or by effects on energy availability for active transport or on the sodium concentration gradient used to drive secondary active, sodium-coupled amino acid transport (133). For example, the inhibitory effect of angiotensin II on sodium dependent MeAIB transport in human placental villous fragments appears to be mediated by AT-1R induced down-regulation of $Na^+$-$K^+$ ATPase activity that maintains the transcellular sodium concentration gradient (130). With simple or facilitated diffusion, the hormonal effects on transport may be the result of alterations in placental blood flow or the transplacental concentration gradients driving net transfer. For instance, insulin administration to pregnant ewes lowers maternal glucose levels and reduces facilitated diffusion of maternal glucose to the fetus in proportion to the decrease in the transplacental concentration gradient (111). Thus, insulin appears to have little direct effect on the placental capacity for glucose transport *per se* in sheep in late gestation with no changes in placental glucose transporter (GLUT) abundance or glucose partitioning in the short term (111, 112, 132). Similarly, insulin has no effect on glucose uptake by villous fragments of term human placenta *in vitro* (122). When insulin infusion is more prolonged in pregnant ewes *in vivo*, there are changes in placental GLUT expression in line with the reduced glucose transport, although whether these changes are the consequence of the sustained hyperinsulinaemia or of the concomitant hypoglycaemia still remains unclear (111, 112, 134). However, in rats, short term insulin infusion in euglycaemic conditions has been shown to increase placental glucose uptake at day 19 of pregnancy but not closer to term (114). In *in vitro* studies, insulin has been shown to increase amino acid uptake by villous fragments of term human placenta after periods of between 2-24h in culture (110, 122, 130). These actions of insulin and IR localisation suggest that insulin may be involved in

the growth and remodelling of the placenta from early in gestation and, particularly, the placental vasculature nearer to term (37). However, like the brain, uptake and utilisation of glucose by the placenta appears to be insulin insensitive, despite the presence of insulin receptors (Table 1), which probably relates to the lack of insulin-sensitive glucose transporters, GLUT4, in the placenta (135).

In part, the effects of hormones on nutrient transfer depend on their route of administration and on whether measurements are made during or after ending treatment. Short term infusion of IGF-I increased placental lactate production when given maternally but not fetally while, conversely, umbilical uptake of glucose is increased with fetal but not maternal administration in the sheep (117, 118). In both sheep and mice, glucocorticoid overexposure during late gestation reduces placental transport of glucose and amino acids during the period of overexposure, irrespective of its duration, method of induction, or the type of glucocorticoid involved (Figure 1). In contrast, after glucocorticoid treatment, transport of glucose and amino acids by the growth restricted mouse placenta tends to increase compared to age matched controls, although the precise response appears to depend on the interval between ending treatment and measuring transport (Figure 1). In part, the up-regulated nutrient transport seen after treatment may reflect an increased demand for nutrients from the growth restricted fetus once the glucocorticoid has cleared from the tissues. Indeed, increased placental nutrient transport, particularly of the amino acids, is also seen when there is a disparity between the placental capacity to supply nutrients and the fetal nutrient demands for growth, irrespective of whether this mismatch is induced nutritionally or genetically (4, 6).

When all the mouse transport data at day 19 of pregnancy are combined, irrespective of the period of corticosterone treatment, there is a significant inverse correlation between maternal corticosterone concentrations and placental MeAIB transport (87). This is consistent with the concept that there is a dynamic balance in resource allocation between the mother and fetus that is responsive to environmental conditions (4, 8). By reducing placental size and nutrient transport, increased maternal glucocorticoids levels spare nutrients for maternal use during stressful periods and, by limiting fetal growth, further reduce the nutritional demands on the mother if the stress is prolonged. Conversely, when

maternal stress and glucocorticoid levels are low, more maternal nutrients can be diverted to the gravid uterus, particularly when there is an increased demand signal from fetuses growth restricted below their genetic potential by earlier periods of adverse environmental conditions.

## HORMONES AND PLACENTAL ENDOCRINE FUNCTION

The placenta produces a wide range of hormones including sex steroids, eicosanoids, glycoprotein and peptide hormones, some of which are unique variants of pituitary hormones (1, 7). Secretion of several of these is sensitive to the endocrine milieu and, particularly, to the glucocorticoids (Table 3). Increasing placental exposure to glucocorticoids *in vivo* in late gestation has been shown to increase placental production of $PGE_2$ and estrogen, and reduce secretion of placental lactogen, leptin, IGF-I and the family of prolactin hormones depending on the specific species (Table 3). In rodents, these changes are often Jz specific (93, 147). Similarly, glucocorticoids have been shown to alter secretion of leptin, placental GH, hCG and $PGE_2$ by human villous fragments and trophoblast cell lines *in vitro* (Table 3). In most species studied to date, glucocorticoid-induced changes in placental hormone production form part of the normal sequence of prepartum maturational events that ensure fetal maturation is co-ordinated with the onset of labour and lactation (1, 151). However, changes in placental hormone production induced by glucocorticoids earlier in gestation as a result of stressful conditions can have adverse consequences for fetal development, maternal recognition of and metabolic adaptation to pregnancy as well as for lactation. Indeed, in mares, preterm changes in placental progestagen production induced by stress or more direct glucocorticoid administration are associated with prepartum running of milk, poor colostrum production at birth and failure of foals to thrive postnatally if they are not given supplementary immunoglobulins (152).

The placental endocrine phenotype depends not only on the production of hormones but also on their metabolism. In several species including rodents, sheep and humans, the placenta inactivates glucocorticoids and prostaglandins, thereby reducing their circulating and placental bioavailability. In turn, the inactivating enzymes are responsive to hormones (1, 2, 83). Both progesterone and cortisol have been shown to regulate placental activity of

11βHSD2 and prostaglandin dehydrogenase (PGDH), the enzymes responsible for inactivating glucocorticoids and prostaglandins, respectively (83, 85). However, the specific response of these placental enzymes to hormonal signals depends on species, gestational age, duration of treatment and maternal nutritional state (2, 83, 149).

## CONCLUSIONS

Hormones in the fetal and maternal circulations have an important role in determining placental phenotype (Figure 2). They signal fetal wellbeing and maternal environmental conditions to the placenta, respectively. In turn, placental hormones signal resource availability to the fetus and fetal nutrient demands to the mother based on the genetic drive and current mass of the fetus (Figure 2). The placenta integrates all these hormonal signals and adapts its phenotype to optimise resource allocation between the mother and growing fetus with respect to both fetal and maternal fitness. The hormonally-induced adaptations can be either short lived to allow a rapid response to environmental change or persist to transmit memories of earlier events to the fetus later in development. Endocrine regulation of placental phenotype, therefore, provides a unifying mechanism for determining the phenotype of the offspring that develops from the genotype inherited at conception. However, little is yet known about the specific cellular and molecular pathways in the placenta that sense the hormonal signals and then mediate the adaptive responses. Nor is it clear whether hormones alter the placental epigenome, although epigenetic modifications in the placenta occur during normal development and growth restriction as well as in several other clinical complications of human pregnancy (6, 153, 154).

## ACKNOWLEDGEMENTS

We would like to thank the many members of the Department of Physiology, Development and Neuroscience who have contributed to discussions and helped with our own studies cited here. We are also grateful for financial support from the BBSRC, Horserace Betting Levy Board, the Wellcome Trust and the Centre for Trophoblast Research at the University of Cambridge.

**FIGURE LEGEND**

**Figure 1:** Effects of glucocorticoids during and after treatment on placental transport of glucose and amino acids in sheep and mice during late gestation. In sheep, placental glucocorticoid overexposure was increased by fetal intravenous treatment with either for cortisol for 5 days (Cort, hatched columns) or dexamethasone for 24h (Dex, grey columns) and measurements of transport made during the final hours of treatment. In mice, placental overexposure was induced either to the synthetic glucocorticoid, dexamethasone (Dex, grey columns) by maternal administration for 5 days or to the natural glucocorticoid, corticosterone (Cort, hatched columns), by deletion of the *11ϐhsd2* gene or maternal corticosterone administration for 5 days. In the mice, transport measurements were made either during overexposure (during treatment) alone and/or after cessation of treatment (after treatment with the timing indicated as + days from ending treatment). All values are expressed as % of that in the control animals (open columns).
* significantly different from control by the statistical analyses used in the relevant study.
Data from references 87, 88, 90, 91, 101-103, 106 and 107.

**Figure 2:** A schematic diagram showing the role of hormones in regulating placental phenotype with respect to balancing maternal resource availability with fetal resource demands for optimal intrauterine growth.

386

387

388

389 **REFERENCES**


390 1 Fowden AL, Forhead AJ. Hormones as epigenetic signals in developmental
391 programming. Exp Physiol 2009; 94:607-625.
392 2 Fowden AL, Sferruzzi-Perri AN, Coan PM, Constancia M, Burton GJ. Placental efficiency
393 and adaptation: Endocrine regulation. J Physiol 2009; 587:3459-3472.
394 3 Lewis RM, Cleal JK, Hanson MA. Review: Placenta, evolution and lifelong health.
395 Placenta 33 Suppl A. Trophoblast Research 2012; 26:S28-S32.
396 4 Vaughan OR, Sferruzzi-Perri AN, Coan PM, Fowden AL. (2012). Environmental
397 regulation of placental phenotype: implications for fetal growth. Reprod Fert Develop
398 2012; 24:80-96.
399 5 Lager S, Powell TL. Regulation of nutrient transport across the placenta. J Pregnancy
400 2012; doi:10.1155/2012/179827.
401 6 Fowden AL, Coan PM, Angiolini E, Burton GJ, Constancia M. Imprinted genes and the
402 epigenetic regulation of placental phenotype. Prog Biophy Mol Biol 2011; 106:281-
403 288.
404 7 Petraglia F, Florio P, Torricelli M. Placental endocrine function. In Knobil and Neill's
405 Physiology of reproduction. 3rd edition 2006; pp 2847-2897 Editor-in-Chief: JD Neill.
406 Elsevier Inc. St Louis USA.
407 8 Fowden AL, Moore T. Maternal-fetal resource allocation: co-operation and conflict.
408 Placenta 2012; 33 Suppl. 2:e11-e15.
409 9 Saif Z, Hodyl HE, Tuck AR, Butler MS, Osei-Kimah, Clifton VL. The human placenta
410 expresses multiple glucocorticois receptor isoforms that are altered by fetal sex,
411 growth restriction and maternal asthma. Placenta 2014; 33:260-268.
412 10 Flint AP, Burton RD. Properties and ontogeny of the glucocorticoid receptor in the
413 placenta and fetal lung of the sheep. J Endocrinol 1984; 103:31-42.
414 11 Gnanalingham MG, Williams P, Wilson, V, Bispham J, Hyatt MA, Pellicano A, Budge H,
415 Stephensen T, Symonds ME. Nutritional manipulation betweem early and late
416 gestation: effects on uncoupling protein-2, glucocorticoid sensitivity, IGF-I receptor
417 and cell proliferation but not apoptosis in the ovine placenta. Reproduction 2007;
418 134:675-623.
419 12 Kanitz E, Otten W, Tuchscherer M, Grabner M, Brussow K-P, Rehfeldt C, Metges CC.
420 High and low protein: carbohydrate dietary ratios during gestation alter maternal-fetal
421 cortisol regulation in pigs. PLoS One 2012; 7:e52748.
422 13 Waddell BJ, Benediktsson R, Brown RW, Seckl JR. Tissue specific messenger ribonucleic
423 acid expression of 11β-hydroxysteroid dehydrogenase types 1 and 2 and the
424 glucocorticoid receptor within rat receptor suggests exquisite local control of
425 glucocorticoid action. Endocrinol 1998; 139:1517-1523.
426 14 O'Connell BA, Moritz KM, Roberts CT, Walker DW & Dickinson H. The placental
427 response to excess maternal glucocorticoid exposure differs between male and female
428 conceptus in spiny mice. Biol Reprod 2011; 88:1040-1047.
429 15 Spiers HJL, Seckl JR, Brown RW. Ontogeny of glucocorticoid receptor and 11β-
430 hydroxysteroid dehydrogenase type 1 gene expression identifies potential critical

periods of glucocorticoid susceptibility during development. J Endocrinol 2004; 181:105-116.

16 Hirasawa G, Takeymama J, Sasano H, Fukushima K, Suzuki T, Muramatu Y, Darnet AD, Kaneko C, Hiwatashi N, Toyota T, Nagura H, Krozowski ZS. 11Beta-hydroxysteroid dehydrogenase type 11 and mineralocorticoid receptor in human placenta. J Clin Endocrinol Metab 2000; 85:1306-1309.

17 Jensen EC, Rochette M, Bennet L, Wood CE, Gunn AJ, Keller-Wood M. Physiological changes in maternal cortisol do not alter expression of growth-related genes in ovine placenta. Placenta 2010; 31:1064-1069.

18 Kneussl ES, Ances IG, Albrecht ED. A specific cytosolic estrogen receptor in human term placenta. Am J Obstet Gynecol 1982; 144:803-809.

19 Khan-Dawood FS, Dawood MY. Estrogen and progesterone receptor and hormone levels in human myometrium and placenta in term pregnancy. Am J Obstet Gynecol 1984; 150:501-505.

20 Abd-Elnaeim MMM, Derar IR, Wilsher S, Allen WR, Leiser R, Schular G. Immunohistochemical localization of oestrogen receptors α and β, progesterone receptor and aromatase in the equine placenta. Reprod Dom Anim 2009; 44:312-319.

21 Leung ST, Reynolds TS, Wathes DC. Regulation of oxytocin receptor in the placentome capsule throughout pregnancy in the ewe: the possible role of oestradiol receptor, progesterone receptor and aromatase. J Endocrinol 1998; 158:173-181.

22 Guerne JM, Stutinsky F. Estradiol and progesterone binding in rabbit placenta during gestation. Horm Metab Res 1978; 10:548-553.

23 Younes MA, Besch NF, Besch PK. Estradiol and progesterone binding in human term placental cytosol. Am J Ostet Gynecol 1981; 141:170-174.

24 Miller BG, Tassell R, Stone GM. Growth of the endometrium and cotyledons during pregnancy in the ewe: rates of protein secretion and synthesis and nuclear and cytosol steroid hormone receptor levels. J Endocrinol 1983; 96:137-146.

25 Ogle TF Characteristics of high affinity progesterone binding to rat placental cytosol. Endocrinol 1980; 106:1861-1866.

26 McCormick PD, Pazel AJ, Spelberg TC, Coulam CB. Evidence for an androgen receptor in human placenta Am J Obstet Gynecol 1981; 140:8-13.

27 Khatri P, Hoffman B, Schuler G. Androgen receptor is widely expressed in bovine placenta and up-regulated during differentiation of bovine trophoblast giant cells. Placenta 2013; 34:416-423.

28 Sun M, Maliqueo M, Benrick A, Johansson J, Shoa R, Hou L, Jansson T, Wu X, Stener-Victorin E. Maternal androgen excess reduces placental and fetal weights, increases placental steroidogenesis, and leads to long term health effects in their female offspring. Am J Physiol 2012; 303:E1373-E1385.

29 Banovac K, Ryan EA, O'Sullivan MJ. Triiodothyronine ($T_3$) nuclear binding sites in human placenta and decidua. Placenta 1986; 7:543-549.

30 Kilby MD, Verhaeg J, Gittoes N, Somerset DA, Clark PMS, Franklyn JA. Circulating thyroid hormone concentrations and placenta thyroid hormone receptor expression in normal human pregnancy and pregnancy complicated by intrauterine growth restriction. J Clin Endocrinol Metab 1998; 83:2964-2971.

31 Leonard AJ, Evans IM, Pickard MR, Bandopadadhyay R, Sinha AK, Ekins RP. Thyroid hormone receptor expression in rat placenta. Placenta 2001; 22:352-359.

32 Unlugedik E, Alfraidy N, Holloway A, Lye S, Bocking A, Challis, J, Gibb W. Expression

and regulation of prostaglandin receptors in the human placenta and membranes at term and preterm. Reprod Fert Develop 2010; 22:796-807.

33 Palliser HK, Hirst JJ, Ooi, GT, Rice GE, Dellios NL, Escalona RM, Parkington HC, Young IR. Prostaglandin E and F receptor expression and myometrial activity at labour in the sheep. Bio Reprod 2005; 72: 937-943.

34 Berndt S, Blacher S, Munaut C, Delilleux, Perrier d'Hauterive S, Huhtaniemi I, Evian-Brion D, Noel A, Fournier T, Foidart JM. Hyper-glycosylated human chorionic donadotrophin stimulates angiogenesis through TGF-β receptor activation. FASEB J 2013; 27:1309-1321.

35 Cabrera-Sharp V, Read JE, Richardson S, Kowalski AA, Antczak DF, Cartwright JE, Mukherjee A, de Mestre AM. SMAD1/5 signaling in the early equine placenta regulates trophoblast differentiation and chorionic gonadotrophin secretion. Endocrinol 2014;en20132116.

36 Posner BI. Insulin receptors in human and animal placental tissue. Diabetes 1974; 23:209-217.

37 Hiden U, Glitzner E, Hartmann M, Desoye G. Insulin and the IGF system in the human placenta of normal and diabetic pregnancies. J Anat 2009; 215:60-68.

38 Sferruzzi-Perri AN, Vaughan OR, Haro M, Cooper WN, Musial B, Charalambous M., Pestana D, *et al.* An obesogenic diet during mouse pregnancy modifies maternal nutrient partitioning and the fetal growth trajectory. FASEB J 2013; 27:3928-3937.

39 Sferruzzi-Perri AN, Owens JA, Pringle KG, Robinson JS, Roberts CT. Maternal insulin-like growth factors–I and –II acts via different pathways to promote fetal growth.Endocrinol 2006; 147:3344-3555.

40 Cisse O, Fajardy I, Dickes-Coopman A, Moitrot E, Montel V, Deloof S, Rousseaux J, *et al.* Mild gestational hyperglycaemia in rat induces fetal overgrowth and modultes placental growth factors and nutrient transporter expression. PLoS One 2013; 8:e64251.

41 Tabarelli M, Kofler R, Berger P, Wick G. Placental Hormones: II. Immunofluorescence studies of the localization of prolactin/placental lactogen- and human chorionic gonadotrophin-receptors in human and rat placenta. Placenta 1983; 4:389-396.

42 Maaskant RA, Bogic LV, Gilger S, Kelly PA, Bryant-Greenwood GD. The human prolactin receptor in the fetal membranes, decidua and placenta. J Clin Endocrinol Metab 1996; 81:396-405.

43 Frasor J, Gaspar CA, Donnelly KM, Gibori G, Fazleabas AT. Expression of prolactin and its receptor in the baboon uterus during the menstrual cycle and pregnancy. J Clin Endocrinol Metab 1999; 84:3344-3350.

44 Freemark M, Nagano M, Edery M, Kelly PA. Prolactin receptor expression in the fetal rat. J Endocrinol 1995; 144:285-292.

45 Bodner J, Ebenbichler CF, Wlk HJ, Muller-Holzner E, Stanzi U, Gander R, Huter O, Patsch JR. Leptin receptor in human term placenta: in situ hybridization and immunohistochemical localization. Placenta 1999; 20:677-682.

46 Green AE, O'Neil JS, Swan KF, Bohm RP, Ratterree MS, Henson MC. Leptin receptor transcripts are constitutively expressed in placenta and adipose tissue with advancing baboon pregnancy. Proc Soc Exp Bio Med 2000; 223:362-366.

47 Ashworth CJ, Hoggard N, Thomas L, Mercer JG, Wallace JM, Lea RG. Placental leptin. Rev Reprod 2000; 5:18-24.

48 Dall'Aglio C, Ploisca A, Boiti C, Ceccarelli P. Immunolocalization of leptin and its receptor in the placenta of cats. Acta Histochem 2012; 114:719-722.
49 Smith JT, Waddell BJ. Leptin receptor expression in the rat placenta: Changes in Ob-Ra, Ob-Rb and Ob-Re with gestational age and suppression by glucocorticoids. Biol Reprod 2002; 67:1204-1210.

50 Hoggard N, Hunter L, Lea RG, Trayburn P, Mercer JG. Ontogeny of the expression of leptin and its receptor in the murine fetus and placenta. Brit J Nutr 2000; 83:317-326.
51 Caminos JE, Nogueiras R, Gallego R, Bravo S, Tovar S, Garcia-Caballero T, Casanueva FF, Dieguez C. Expression and regulation of adiponectin and receptor in human and rat placenta. J Clin Endocrinol Metab 2005; 90:4276-4286.
52 Klempt M, Bingham B, Breier BH, Baumbach WR, Gluckman PD. Tissue distribution and ontogeny of growth hormones receptor messenger ribonucleic acid and ligand binding to hepatic tissue in the mid gestation sheep fetus. Endocrinol 1993; 132:1071-1077.
53 Lacroix M-C, Devinoy E, Cassy S, Servely J-L, Vidaud M, Kann G. Expression of growth hormones and its receptor in the placental and feto-maternal environment during early pregnancy in sheep. Endocrinol 1999; 140:5587-5597.
54 Clifton VL, Owens PC, Robinson PJ, Smith R. Identification and characterization of a corticotrophoin-releasing hormone receptor in human placenta. Eur J Endocrinol 1995; 133:591-597.
55 Florio P, Franchini A, Reis FM, Pezzani I, Ottaviani E, Petraglia F. Human placenta, chorion, amnion and decidua express different variants of corticotrophin-releasing factor receptor messenger RNA. Placenta 2000; 21:32-37.
56 Hiden U, Bilban M, Knofler M, Desoye G. Kisspeptins and the placenta: regulation of trophoblast invasion. Rev Endocr Metab Disord 2007; 8:31-39.
57 Mark PJ, Jones ML, Lewis JL, Waddell BJ, Smith JT. *Kiss1* and *Kiss1r* mRNA expression in the rat placenta: Changes with gestational age and regulation by glucocorticoids. Placenta 2013; 34:657-662.
58 Lin LS, Roberts Vj, Yen SS. Expression of human gonadotrophin-releasing hormone receptor gene in the placenta and its functional relationship to human chorionic gonadotrophin secretion. J Clin Endocrinol Metab 1995; 80:580-585.
59 Cooper AC, Robinson G, Vinson GP, Cheung WT, Broughton-Pipkin F. The localization and expression of the renin-angiotensin system in the human placenta throughout pregnancy. Placenta 1999; 20: 467-474.
60 Zheng J, Vagnoni KE, Bird IM, Magness RR. Expression of basic fibroblast growth factor, endothelial mitogenic activity, and angiotensin II type-1 receptors in the ovine placenta during the third trimester of pregnancy. Biol Reprod 1997; 56:1189-1197.
61 Koukoulas I, Mustafa T, Douglas-Denton R, Wintour EM. Angiotensin II receptor (type 1 and 2) expression peaks when placental growth is maximal in sheep. Am J Physiol 2002; 283:R972-R982.
62 Nielsen AH, Winther H, Dantzer V, Poulsen K. High densities of angiotensin II subtype 2 (AT2) receptors in the porcine placenta and fetal membranes. Placenta 1996; 17:147-153.
63 McArdle AM, Denton KM, Maduwegedura D, Moritz K, Flower RL, Roberts CT. Ontogeny of placental structural development and expression of the renin-angiotensin system and 11beta-HSD2 genes in the rabbit. Placenta 2009; 30:590-598.

64 Burson JM, Aquilera G, Gross KW, Sigmund CD. Differential expression of angiotensin receptor 1A and 1B in mouse. Am J Physiol 1994; 267:E260-E267.
65 McQueen J, Kingdom JC, Jardine AG, Connell JM, Whittle MJ. Vascular angiotensin II and atrial natriuretic peptide receptors in normal and growth retarded human placentae. J Endocrinol 1990; 126:341-347.

66 Apodac CC, Moore KH, Rossignol TM, Pierce B, Matej LA, Hume RL, Calhoun BC. Localization of messenger ribonucleic acid for adrenomedullin and adrenomedullin receptor in the human placenta in normal pregnancies and pregnancies complicated by oligohydramnios. Am J Obstet Gynecol 2000; 183:1213-1219.
67 Hayashi KG, Hosoe M, Sakumoto R, Takahashi T. Temporo-spatial expression of adrenomedullin and its receptor in the bovine placenta. Reprod Biol Endocrinol 2013; 11:62.doi:10.1186/1477-7827-11-62.
68 Li L, Tang F, O WS. Co-expression of adrenomedullin and its receptor component proteins in the reproductive system of the rat during gestation. Reprod Biol Endocrinol 2010; 8:130.doi:10.1186/1477-7827-8-130.
69 Cuffe JS, O'Sullivan, Simmons DG, Anderson ST, Moritz KM. Maternal corticosterone exposure in the mouse has sex-specific effects on placental growth and mRNA expression. Endocrinol 2012; 153:5500-5511.
70 Iwashita M, Evans MI, Catt KJ. Characterization of a gonadotrophin-releasing hormone receptor site in term placenta and chorionic villi. J Clin Endocrinol Metab 1986: 62: 127-133.
71 Speeg KV, Harrison RW. The ontogeny of the human placental glucocorticoid receptor and inducibility of heat-stable alkaline phosphatase. Endocrinol 1979; 104: 1364-1368.
72 Root B, Abrassart J, Myers DA, Monau T, Ducsay CA. Expression and distribution of glucocorticoid receptors in the ovine fetal adrenal cortex: effects of long term hypoxia. Reprod Sci 2008; 15:517-528.
73 Mark PJ, Augustus S, Lewis JL, Hewitt D, Waddell BJ. Changes in the placental glucocorticoid barrier during rat pregnancy: Impact on placental corticosterone levels and regulation of progesterone. Biol Reprod 2009; 80:1209-1215.
74 Korgan ET, Acar N, Sati L, Kipmen-Korgan D, Ozen A, Unek G, Ustenel I, Demir R. Expression of glucocorticoid receptor and glucose transporter-1 during development in the diabetic rat.
75 Jiang X, Yan J, West AA, Perry CA, Malysheva OV, Devapatia S, Pressman E, *et al.* Maternal choline intake alters the epigenetic state of the fetal cortisol-regulating genes in humans. FASEB J 2012; 26:3563-3574.
76 Ueda H, Nakai T, Konishi T, Tanaka K, Sakazaki F, Min KS. Effects of zinc deficiency and supplementation on leptin and leptin receptor expression in pregnant mice. Biol Pharm Bull 2014; 37:581-587.
77 Bloomfield FH, van Zijl PL, Bauer MK, Phua HH, Harding JE. Effect of pulsatile growth hormone administration to the growth-restricted fetal sheep on somatotrophic axis gene expression in fetal and placental tissues. Am J Physiol 2006; 291:E333-E339.
78 Whittle WL, Holloway AC, Lye S, Challis JR, Gibb W. The pattern of glucocorticoid and estrogen receptors may explain differences in steroid dependency of intrauterine prostaglandin production at parturition in sheep. J Soc Gynecol Investig 2006; 13;506-511.

79 Li X, Shams M, Zhu J, Khalig A, Wilkes M, Whittle M, Barnes N, Ahmed A. Cellular localizartion of AT1 receptor mRNA and protein in normal placenta and its reduced expression in intrauterine growth restriction. Angiotensin II stimulates the release of vasorelaxants. J Clin Invest 1998; 101:442-454.

80 Uzelac PS, Li X, Lin J, Neese LD, Lin L, Nakajima ST, Bohler H, Lei Z. Dysregulation of leptin and testosterone production and their receptor expression in the human placenta with gestational diabetes mellitus. Placenta 2010; 31:581-588.

81 Grissa O, Yessoufou A, Mrisak I, Hichami A, Amoussou-Guenou D, Grissa A, Djrolo F *et al.* Growth factor concentrations and their placental mRNA expression are modulated in gestational diabetes mellitus: possible interactions with marcosomia. BMC Pregnancy & Childbirth 2010; 10:7.

82 Mistry HD, Kurlak LO, Broughton-Pipkin F. The placental renin-angiotensin system and oxidative stress in pre-eclampsia. Placenta 2013; 34:182-186.

83 Harris A, Seckl JR. Glucocorticoids, prenatal stress and the programming of disease. Horm Behav 2011; 59:279-289.

84 Sferruzzi-Perri AN, Owens JA, Pringle KG, Roberts CT. The neglected role of insulin-like growth factors in the maternal circulation regulating fetal growth. J Physiol 2011; 589:7-20.

85 Fowden AL, Ward JW, Wooding FBP, Forhead AJ. Developmental programming of the ruminant placenta. In Reproduction in Domestic Rum*inants* 2010 Eds: Lucy MC, Pate JL, Smith MF, Spencer TE. pp 41-57. Nottingham University Press.

86 Vaughan OR, Forhead AJ, Fowden AL. Glucocorticoids and placental programming. In The Placenta and Human Developmental Programming 2011 Eds: Burton GJ, Barker DJP, Moffett A, Thornburg KL. pp 175-186. Cambridge University Press, Cambridge.

87 Vaughan OR, Sferruzzi-Perri AN, Fowden AL. Maternal corticosterone regulates nutrient allocation to fetal growth in mice. J Physiol 2012; 590:5529-5540.

88 Vaughan OR, Sferruzzi-Perri AN, Coan PM, Fowden AL. Adaptations in placental phenotype depends on the route and timing of maternal dexamethasone administration in mice. Biol Reprod 2013; 89:80.doi:10.1095/biolreprod.113.109678.

89 Lindsay RS, Lindsay RM, Edwards CR, Seckl JR. Inhibition of 11-beta-hydroxysteroid dehydrogenase in pregnant rats and the programming of blood pressure in the offspring. Hypertension 1996; 27:1200-1204.

90 Wyrwoll CS, Seckl JR, Holmes MC. Altered placental function of 11β-hydroxysteroid dehydrogenase 2 knockout mice. Endocrinol 2009; 150:1287-1293.

91 Ward JW, Wooding FPB, Fowden AL. Ovine feto-placental metabolism. J Physiol 2004; 554:529-541.

92 Braun T, Li S, Moss TJ, Newnham JP, Challis JR, Gluckman PD, Slododa DM. Maternal betamethasone administration reduces binucleate cell number and placental lactogen in sheep. J Endocrinol 2007; 194:337-347.

93 Ain R, Canham LN, Soares MJ. Dexamethasone-induced intrauterine growth restriction impacts the placental prolactin, insulin-like growth factor-II and Akt signalling pathway. J Endocrinol 2005; 185:252-263.

94 Baisden B, Sonnes S, Joshi RM, Ganapathy V, Skekhanat PS. Antenatal dexamethasone treatment leads to changes in gene expression in a murine late placenta. Placenta 2007; 28:1082-1090.

95 Hewitt DP, Mark PJ, Waddell BJ. Glucocorticoids prevent the normal increase in placental vascular endothelial growth factor expression and placental vascularity

during late gestation. Endocrinol 2006; 147:5568-5574.
96 Burton PJ, Waddell BJ. 11 Beta-hydroxysteroid dehydrogenase in the rat placenta: developmental changes and the effects of altered glucocorticoid exposure. J Endocrinol 1994; 143:505-513.
97 Mayhew TM, Jenkins H, Todd B, Clifton VL. Maternal asthma and placental morphometry: effects of severity, treatment and fetal sex. Placenta 2009; 29:366-373.
98 Jones HN, Ashworth CJ, Page KR, McArdle HJ. Cortisol stimulates system A amino acid transport and SNAT2 expression in human placental cell line (BeWo). Am J Physiol 2006; 291:E596-E603.
99 Speake PF, Glazier JD, Greenwood SL, Sibley CP. Aldosterone and cortisol acutely stimulate $Na^+/H^+$ exchanger activity in the syncytiotrophoblast of the human placenta: Effect of sex. Placenta 2010; 31:289-294.
100 Audette MC, Greenwood SL, Sibley CP, Jones CJ, Challis JR, Matthews SC, Jones RL. Dexamethasone stimulates placental system A transport and trophoblast differentitation in term villous explants. Placenta 2010; 31:97-105.
101 Milley JR. Fetal substrate uptake during increased ovine fetal cortisol concentration. Am J Physiol 1996; 271:E186-E191.
102 Timmerman M, Teng C, Wilkening RB, Fennessey P, Battaglia FC, Meschia G. Effect of dexamethasone on fetal hepatic glutamine-glutamate exchange. Am J Physiol 2000; 278: E839-E845.
103 Barbera A, Wilkening RB, Teng C, Battaglia FC, Meschia G. Metabolic alterations in the fetal hepatic and umbilical circulations during glucocorticoid-induced parturition in sheep. Pediatr Res 1997; 41:242-248.
104 Langdown ML, Sugden MC. Enhanced placental GLUT1 and GLUT3 expression in dexamethasone-induced fetal growth restriction. Mol Cell Endocrinol 2001; 185:109-117.
105 Wyrwoll CS, Kerrigan D, Holmes MC, Seckl JR, Drake AJ. Altered placental methyl donor transport in the dexamethasone programmed rat. Placenta 2012; 33:220-223.
106 Vaughan OR, Fifher HM, Sferruzzi-Perri AN, Fowden AL. Exogenous corticosterone administration increases materno-fetal glucose transport in the mouse in late pregnancy. Proceeding of the Physiological Society. ISSN 1749-6187. Proc 37th IUPS 2013; PCN344.
107 Audette MC, Challis JR, Jones RL, Sibley CP, Matthews SC. Antenatal dexamethasone treatment in midgestation reduces system A mediated transport in the late-gestation murine placenta. Endocrinol 2011; 152:3561-3570.
108 Sathishkumar K, Ellis R, Chinnathambi V, Gaott A, Hankins GD, Yallampalli C. Prenatal testosterone-induced fetal growth restriction is associated with down regulation of rat placenta amino acid transport. Reprod Bio Endocrinol 2011; 9:110.doi:10,1186/1477-7827-9-110.
109 Kagawa N, Saito Y, Nagao T. Early to middle gestational exposure to diethylstilbestrol impairs the development of the labyrinth zone in mouse placenta. Congenit Anom (Kyoto) 2014; 54:116-119.
110 Karl PI, Alpy KL, Fisher SE. Amino acid transport by the cultured human placental trophoblast: effects of insulin on AIB transport. Am J Physiol 1992; 262:C834-C839.
111 Aldoretta PW, Carver TD, Hay WW. Ovine uteroplacental glucose and oxygen metabolism in relation to chronic changes in maternal and fetal glucose

concentrations. Placenta 1994; 15:753-764.

112 Das UG, Sadiq HF, Soares MJ, Hay WW, Devaskar SU. Time-dependent physiological regulation of rodent and ovine placental glucose transporter (GLUT-1) protein. Am J Physiol 1998; 272:R339-R347.

113 Hay WW, Meznarich HK, Sparks JW, Battaglia FC, Meschia G. Effect of insulin on glucose uptake in near-term fetal lambs. Proc Soc Exp Biol Med 1985; 178:557-564.

114 Leturque A, Ferre P, Burnol AF, Kande J, Maulard P, Girard P. Glucose utilization rates and insulin sensitivity in vivo in tissues of virgin and pregnant rats. Diabetes 1986; 35:172-177.

115 Kniss DA, Shubert PJ, Zimmerman PD, Landon MB, Gabbe SC. Insulin-like growth factors: Their regulation of glucose and amino acid transport in placental trophoblasts isolated from first-trimester chorionic villi. J Reprod Med 1994; 39:249-256.

116 Karl PI. Insulin-like growth factor-I stimulates amino acid uptake by the cultured human trophoblast. J Cell Physiol 1995; 165:83-88.

117 Liu L, Harding JE, Evans PC, Gluckman PD. Maternal insulin-like growth factor-I infusion alters feto-placental carbohydrate and protein metabolism in pregnant sheep. Endocrinol 1994; 135:895-900.

118 Harding JE, Liu L, Evans PC, Gluckman PD. Insulin-like growth factor-I alters feto-placental protein and carbohydrate metabolism in fetal sheep. Endocrinol 1994; 134: 1509-1514.

119 Bloomfield FH, van Zijl PL, Bauer MK, Harding JE. A chronic low dose infusion of insulin-like growth factor I alters placental function but does not affect fetal growth. Reprod Fert Dev 2002; 14: 393-400.

120 Sferruzzi-Perri AN, Owens JA, Standen P, Taylor RL, Robinson JS, Roberts CT. Early pregnancy maternal endocrine insulin-like growth factor I programs the placenta for increased functional capacity throughout gestation. Endocrinol 2007; 148:4362-4370.

121 Sferruzzi-Perri AN, Owens JA, Standen P, Taylor RL, Heinemann, Robinson JS, Roberts CT. Early treatment of the pregnant guinea pig with IGFs promotes placental transport and nutrient partitioning near term. Am J Physiol 2006; 292:E668-E676.

122 Ericsson A, Hamark, Jansson N, Johansson BR, Powell TL, Jansson T. Hormonal regulation of glucose and system A amino acid transport in first trimester placental villous fragments. Am J Physiol 2004; 288:R656-R662.

123 Tung E, Roberts CT, Heinemann GK, de Blasio MJ, Kind KL, van Wettere WHEJ, Owens JA, Gatford KL. Increased placental nutrient transporter expression at mid gestation after maternal growth hormone treatment of pigs: A placental mechanism for increased fetal growth. Bio Reprod 2012; 87:1-8.

124 Harding JE, Evans PC, Gluckman PD. Maternal growth hormone treatment increases placental growth diffusion capacity but not fetal or placental growth in sheep. Endocrinol 1997; 138:5352-5358.

125 Jansson N, Greenwood SL, Johansson BR, Powell TL, Jansson T. Leptin stimulates the activity of the system A amino acid transporter in human placental villous fragments. J Clin endocrinol Metab 2003; 88:1205-1211.

126 Bond H, Dilsworth MR, Baker B, Cowley E, Requena Jumenez A, Boyd RDH, Husain SM, Ward BS, Sibley CP, Glazier JD. Increased maternofetal calcium flux in parathyroid hormone-related protein-null mice. J Physiol 2008; 586:2015-2025.

127 Jones HN, Jansson T, Powell TL. Full length adiponectin attenuates insulin signaling

and inhibits insulin-stimulated amino acid transport in human primary trophoblast cells. Diabetes 2010; 59:1161-1170

128 Rosario FJ, Schumacher MA, Jiang J, Kanai Y, Powell TL, Jansson T. Chronic maternal infusion of full-length adiponectin in pregnant mice down-regulates placental amino acid transporter activity and expression and decreases fetal growth. J Physiol 2012; 590:1495-1509.

129 Giovannelli A, Greenwood SL, Desforges M, Sibley CP, Petraglia F. Corticotrophin-releasing factor and urocortin inhibits System A activity in term placental villous explants. Placenta 2011; 32:99-101.

130 Shibata E, Powers RW, Rajakumar A, von Versen-Hoynck F, Gallaher MJ, Lykins DL, Roberts JM, Hubel CA. Angiotensin II decreases system A amino acid transporter activity in human placental villous fragments through AT1 receptor activation. Am J Physiol 2006; 291:E1009-E1016.

131 Duttaroy AK. Transport of fatty acids across the human placenta: A review. Prog Lipid Res 2009; 48:52-61.

132 Cetin I, Parisi F, Berti C, Mando C, Gesoye G. Placental fatty acid transport in maternal obesity. J DoHAD 2012; 3:409-414.

133 Cleal JK, Glazier JD, Ntani G, Crozier SR, Day PE, Harvey NC, Robinson SM *et al.* facilitated transporters mediate net efflux of amino acids to the fetus across the basal membrane of the placental syncytiotrophoblast. J Physiol 2011; 589:987-997.

134 Das UG, He J, Ehrhart RA, Hay WW, Devaskar SU. Time-dependent physiological regulation of ovine placental GLUT-3 glucose transporter protein. Am J Physiol 2000; 279:R2252-R2261.

135 Wooding FPB, Burton GJ Comparative Placentation. Cambridge University Press.

136 Ringler GE, Kallen CB, Strauss JF. Regulation of human trophoblast function by glucocorticoids: dexamethasone promotes increased secretion of chorionic gonadotrophin. Endocrinol 1989; 124:1625-1631.

137 Coya R, Gualillo O, Pineda J, Garcia MC, Busturia MA, Aniel-Quiroga A, Martul P, Senaris RM. Effect of cyclic 3',5'-adenosine monophosphate, glucocorticoids, and insulin on leptin messenger RNA levels and leptin secretion in cultured human trophoblast. Biol Reprod 2001; 65:814-819.

138 Riley SC, Greer IA, Schembri LA, Challis JR. Dexamethasone inhibits basal and stimulated prostaglandin E2 output from human placental cells by inhibition of prostaglandin H synthase. Gynecol Obstet Invest 1992; 33:85-89.

139 Zeck W, Widberg C, Maylin E, Desoye G, Lang U, McIntyre D, Prins J, Russell A. Regulation of placental growth hormone secretion in a human trophoblast model – the effects of hormones and adipokines. Pediatr Res 2008; 63: 353-357.

140 Wilson EA, Jaward MJ. Stimulation of human chorionic gonadotrophin secretion by glucocorticoids. Am J Obstet Gynecol 1982; 142:344-349.

141 Kauppila A, Tuimala R, Yikorkala O, Reinila M, Ylostalo P. Placental steroid synthesis from DHES during dexamethasone therapy. Obstet Gynecol 1979; 54:39-42.

142 Marinoni E, Korebritis C, Di Lorio R, Cosmi EV, Challis JR. Effect of betamethasone in vivo on placental corticotrophin-releasing hormones in human pregnancy. Am J Obstet Gynecol 1998; 178:770-778.

143 Lange AP, Anthonsen H. Serum levels of human placental lactogen during and after prenatal dexamethasone therapy. Acta Obstet Gynecol Scand 1980; 59:111-114.

144 Izhar M, Pasmanik M, Marcus S, Shemesh M. Dexamethasone inhibition of cyclooxygenase expression in bovine term placenta. Prostaglandins 1992; 43: 239-254.
145 Anderson AB, Flint AP, Turnbull AC. Mechanism of action of glucocorticoids in induction of ovine parturition: effect on placental steroid metabolism. J Endocrinol 1975; 66:61-70.

146 McClaren WJ, Young IR, Wong MH, Rice GE. Expression of prostaglandinG/H synthase 1 and 2 in ovine amino and placenta flowing glucocorticoid-induced labour onset. J Endocrinol 1996; 151:125-135.
147 Whittle WL, Holloway AC, Lye SJ, Gibb W, Challis JRG. Prostaglandin production at the onset of ovine parturition is regulated by both estrogen-independent and estrogen-dependent pathways. Endocrinol 2000; 141:3783-3791.
148 Sugden MC, Langdown ML, Munns MJ, Holness MJ. Maternal glucocorticoid treatment modulates placental leptin and leptin receptor expression and materno-fetal leptin physiology during late pregnancy, and elicits hypertension associated with hyperleptinaemia in the early-growth-retarded adult offspring. Eur J Endocrinol 2001; 145:529-539.
149 Lee J-Y, Park SJ, Kim SH, Kim MH. Prenatal administration of dexamethasone during early mouse pregnancy negatively affects placental development and function in mice. J Anim Sci 2012; 90:4846-4856.
150 Rak-Mardyla A, Gregoraszczuk EL. Effect of pituitary growth hormone and insulin-like growth factor type-I on proliferation, apoptosis and hormone secretion of the placental cell line JEG-3. Gynecol Endocrinol 2010; 26:302-306.
151 Whittle WL, Patel FA, Alfraidy N, Holloway AC, Fraser M, Gyomorey S, Lye SJ, *et al.* Glucocorticoid regulation of human and ovine parturition: the relationship between fetal hypothalamic-pituitary-adrenal axis activation and intrauterine prostaglandin production. Biol Reprod 2001; 64:1019-1032.
152 Ousey JC. Hormone profiles and treatments in the late pregnant mare. Vet Clin North Am Equine Pract 2006; 22:727-747.
153 Rugg-Gunn PJ. Epigenetic features of the mouse trophoblast. Reprod Biomed Online 2012; 25:21-30.
154 Novakovic, Saffrey R. DNA methylation profiling highlights the unique nature of the human placental epigenome. Epigenetics 2010; 2:627-638.