Influence of thyroid hormones and temperature on adipose tissue development and lung maturation

BY MICHAEL E. SYMONDS AND LYNNE CLARKE
School of Animal and Microbial Sciences, The University of Reading, Whiteknights, PO Box 228, Reading RG6 6AJ

Influence des hormones thyroïdiennes et de la température sur le développement du tissu adipeux et la maturation des poumons

RÉSUMÉ

Au cours de la vie périnatale, les interactions entre les apports de nutriments et la situation endocrinienne peuvent avoir des effets prononcés sur le développement des organes. Ces effets non seulement sont cruciaux en ce qu'ils permettent au nouveau-né d'installer une vie indépendante après la naissance à la suite de la séparation d'avec le placenta, mais ils ont aussi des conséquences à long terme sur la santé et la survie. Ces effets se produisent sous la médiation en partie des modifications dans la sécrétion d'hormones thyroïdiennes qui, chez l'agneau, influencent le développement du tissu adipeux aussi bien que des poumons. La montée d'hormones thyroïdiennes après la naissance est nécessaire pour activer pour pleinement la thermogenèse non frissonnante dans le tissu adipeux brun, et celle-ci est réduite après una naissance par césarienne. D'autres facteurs comprenant le poids du corps de la mère et la taille du placenta peuvent aboutir à l'hypothermie de l'agneau, qui semble être due à ce que la thermogenèse frissonnante plutôt que non frissonnante n'a pu être déclenchée. Les hormones thyroïdiennes sont nécessaires pour la maturation des poumons chez le foetus, et dans la vie après la naissance cette influence est déterminée de façon critique par les interactions entre la taille des poumons, la température ambiante et les besoins métaboliques en oxygène.

In species with a functional hypothalamic–pituitary axis at birth, the majority of organs undergo a marked process of maturation during late gestation which are regulated in part by changes in the secretion of a number of hormones, including thyroxine (T_4), triiodothyronine (T_3) and cortisol (see Liggins, 1994; Symonds, 1995*a*). Over this period, interactions between nutrient supply and endocrine status can have a pronounced effect on organ development which are not only crucial in enabling the newborn to establish independent life after birth following separation from the placenta, but can have long-term consequences for health and survival (see Barker, 1994; Symonds *et al.* 1995*a*). To ensure effective adaptation to the cold stimulus of the extra-uterine environment at birth it is essential that both continuous breathing and endogenous mechanisms for increasing heat production are rapidly activated. This necessitates dramatic changes in function of the lungs, which adapt from being fluid filled (see Brace, 1995) to become fully aerated. In addition, internal adipose tissue deposits laid down by lipogenesis (see

Hay, 1995), that undergo a process of maturation resulting in expression and synthesis of the brown adipose tissue (BAT)-specific uncoupling protein (Casteilla *et al.* 1989), rapidly acquire the capacity to produce very large amounts of heat (Symonds, 1995*b*). The rapidity with which these adaptations occur is facilitated by the separation of the newborn from its placenta, thereby removing the inhibitory influences of placental factors such as prostaglandin E_2 (PGE_2) and adenosine (Gunn *et al.* 1993; Ball *et al.* 1995). At the same time, following intense stimulation of the central nervous system and hypothalamic–pituitary axis during labour, large increases in plasma concentrations of stimulatory hormones including catecholamines, cortisol and thyroid hormones ensue (Eliot *et al.* 1981; Silver, 1990; Symonds *et al.* 1994). None of these factors operates in isolation, but they interact depending on their relative concentrations and stage of perinatal development. For example, although PGE_2 infusion into the fetus reduces fetal breathing movements (Kitterman *et al.* 1983) and inhibition of prostaglandin synthesis stimulates breathing (Savich *et al.* 1995), endogenous production of PGE_2 has an important paracrine role in promoting fetal lung maturation (Hume *et al.* 1991, 1996).

THYROID HORMONES AND PERINATAL MATURATION

O_2 consumption, lung development and adipose tissue maturation can all be compromised following removal of the fetal thyroid glands during late gestation (Barker *et al.* 1990; Fowden & Silver, 1995; Symonds, 1995*a*). Fetal thyroidectomy results in a reduced rate of lung liquid secretion (Barker *et al.* 1990) which is known to be necessary for pulmonary growth and structural maturation (Moessinger *et al.* 1990). Thyroidectomized fetuses born *per vaginum* at term are able to establish continuous breathing, but their lungs tend to be heavier and have a higher glycogen content (Table 1) that is indicative of a reduction in surfactant synthesis (Rooney *et al.* 1986). Furthermore, a lower lung weight:O_2 consumption ratio that is not accompanied with any difference in breathing frequency, indicates a reduced efficiency of O_2 extraction across the lungs (Table 1). Lung haemoglobin content is also lower in fetal thyroidectomized lambs, indicating a

Table 1. *Effect of fetal thyroidectomy at 127 d of gestation on lung development in neonatal lambs*

(Mean values with their standard errors)

Experimental group	Lung wt (g)		Glycogen content (mmol/g)†		Haemoglobin content (mg/g)		Lung wt: total V_{O_2}		Breathing frequency‡ (breaths/min)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Control (*n* 6)	85	9	2·5**	0·4	71**	5	1·57*	0·42	54	3
TX (*n* 5)	99	7	5·7	0·6	43	4	0·82	0·06	61	7

V_{O_2}, O_2 consumption (ml/min); TX, thyroidectomized.
Mean values were significantly different from those for TX lambs (Student's *t* test): *$P=0·08$, **$P<0·01$.
† mmol Glucose stored as glycogen.
‡ Measured during non-rapid-eye-movement sleep at 15°.

https://doi.org/10.1079/PNS19960048 Published online by Cambridge University Press

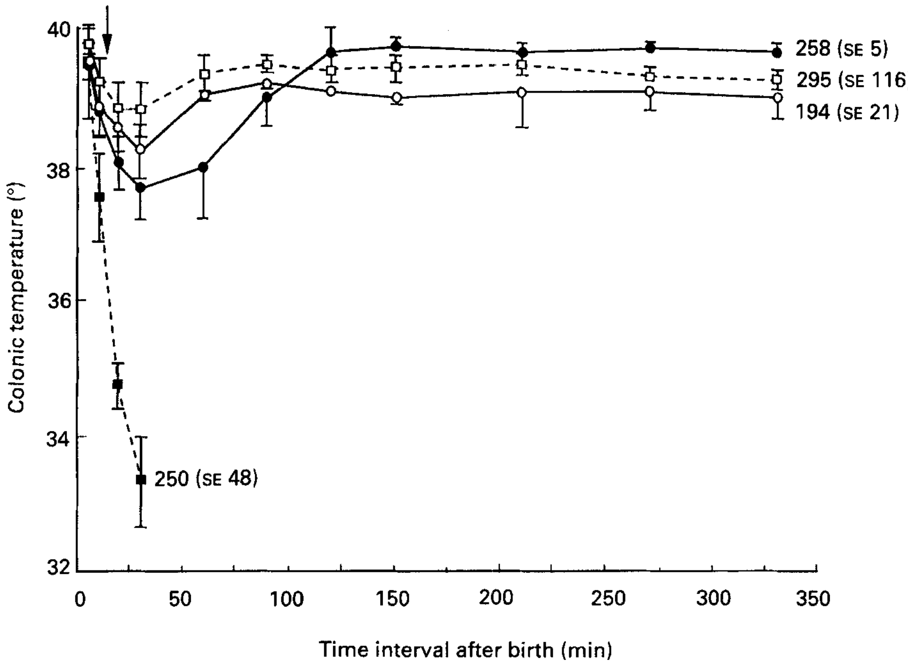

Fig. 1. Effect of ambient temperature on colonic temperature of twin or triplet lambs delivered by caesarean section. Group 1 (■), lambs delivered into 15° ambient temperature which were unable to maintain colonic temperature; group 2 (□), siblings of lambs in group 1 delivered into 30° ambient temperature which were able to maintain colonic temperature; group 3 (●), lambs delivered into 15° ambient temperature which were able to maintain colonic temperature; group 4 (○), siblings of lambs in group 3 delivered into 30° ambient temperature which also maintained colonic temperature. Values shown for each curve are means with their standard errors and represent the thermogenic activity of perirenal adipose tissue as measured from GDP binding to mitochondrial protein (pmol/mg). ↓, Mean time at which all lambs commenced shivering, with the exception of the hypothermic group (■). Points are means with their standard errors represented by vertical bars for five lambs per group.

reduced rate of blood perfusion. Interactions between changes in blood flow and thyroid hormones are known to be important in the control of lung function because induced fetal hyperthyroidism doubles pulmonary blood flow and enhances lung maturation by increasing the width of air spaces (Lorijn *et al.* 1980). In the case of adipose tissue development, T_3 can stimulate transcription of the uncoupling-protein gene in BAT (Rabelo *et al.* 1995) with the result that fetal thyroidectomized lambs possess perirenal adipose tissue with reduced thermogenic activity. These lambs are increasingly reliant on shivering thermogenesis in order to increase O_2 consumption and are at increased risk of becoming hypothermic (Lyke *et al.* 1994; Symonds, 1995*a*).

CAESAREAN SECTION DELIVERY AND ADAPTATION AT BIRTH

Caesarean section delivery near to term can compromise the newborn's ability to adapt to the extra-uterine environment which is partly the result of significant reductions in the post-partum surges in thyroid hormones and catecholamines, but not cortisol (Symonds

Table 2. *Comparison of maternal body weight, placental weight and metabolic status between ewes which produced lambs that adapted or failed to adapt to caesarean section delivery into a cool ambient temperature of 15° (see Fig. 1)*

(Mean values with their standard errors)

	Maternal body wt (kg)		Placental wt (g): Fetal cotyledons		Placental wt (g): Maternal caruncles and membranes		Total fetal wt (kg)		Maternal plasma concentration†: Glucose (mM)		Maternal plasma concentration†: 3-Hydroxy-butyrate (mM)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Adapted (*n* 5)	68·0*	3·9	435	46	1280*	79	8·54*	0·22	2·77	0·30	1·93	0·17
Failed (*n* 4)	56·0	2·2	365	43	831	163	7·35	0·44	3·08	0·18	1·75	0·90

Mean values were significantly different from those for the failed group (Student's *t* test): $*P<0{\cdot}05$.
† Mean values from jugular venous samples taken hourly between 09.00–17.00 h at 140 d of gestation.

et al. 1994, 1995*a*). Infants and lambs born following caesarean section near to term have a reduced capacity for non-shivering thermogenesis (Christensson *et al.* 1993; Symonds *et al.* 1994, 1995*a*); this capacity is even further reduced following premature birth. Premature birth is also associated with failure to restore plasma thyroid hormone concentrations and with compromised lung function (Clarke *et al.* 1996). The ambient temperature into which caesarean-section-delivered lambs are born has a marked effect on the magnitude of decline in body temperature, as well as the rate at which body temperature is restored and the thermogenic activity of BAT (Fig. 1).

Irrespective of delivery temperature lambs born by caesarean section are increasingly dependent on shivering thermogenesis in order to increase heat production (Clarke *et al.* 1994), although this is an inefficient method of thermoregulation due to an increase in air movement around the animal which increases rate of heat loss (Alexander, 1979). The importance of shivering thermogenesis in preventing hypothermia in newborn lambs is illustrated by the finding that near-term lambs, delivered by caesarean section into a cool ambient temperature, which fail to shiver, have an appreciably greater decline in body temperature (Fig. 1) and in some cases exhibit respiratory failure. These lambs possess BAT with a thermogenic activity in the normal range, although there is considerable variation between individuals. On average, BAT thermogenic activity tends to be lower than that of their siblings delivered into the warm which shiver and are able to restore body temperature (Fig. 1). One factor which appears to determine if lambs delivered by caesarean section into a cool ambient temperature effectively adapt is maternal body and placental weights which are both significantly lower for these lambs (Table 2). Women with a body weight below normal at conception are at increased risk of producing low-birth-weight infants (Abrams & Laros, 1986). Similarly, ewes which lose 10% of body weight 2 months before conception are more likely to have slowly-growing fetuses (Harding *et al.* 1992*a*). The extent to which these effects are linked to altered placental function, particularly changes in blood flow (Reynolds & Redmer, 1995) remain unexplored, although it has been suggested that irrespective of nutrient intake, almost two-thirds of the variance in fetal weight is accounted for by changes in placental weight (Mellor, 1983). The extent to which this can reduce fetal nutrition and growth or development of specific organs remains in doubt (see Robinson & Symonds, 1995).

PLACENTAL DEVELOPMENT AND NEONATAL SURVIVAL

Sheep are characterized as possessing a cotyledonary placenta which develops from the maternal caruncles of which a constant percentage (70–80) develop into fetal cotyledons and placental growth is normally complete at mid-gestation (Alexander, 1964). Experimental restriction of placental growth following removal of endometrial caruncles (Robinson *et al.* 1979) or maternal heat stress (Bell *et al.* 1989) both result in a marked reduction in fetal nutrient supply and, therefore, fetal growth. The fetus is able to alter the partition of available nutrients by changes in its somatotrophic axis, although this ability is dependent on adequate glucose supply (Oliver *et al.* 1993). Maternal undernutrition between 100 and 124 d of gestation (Bauer *et al.* 1995) or placental restriction (Kind *et al.* 1995) both result in fetal hypoglycaemia, 17% lighter fetuses and a 30% decline in liver weight, although maternal undernutrition causes a greater reduction in fetal plasma insulin-like growth factor-I and insulin concentrations than restriction of placental size. Both these experimental manipulations may be expected to compromise newborn viability, although this has only been established in the case of fetuses born to caruncIectomized ewes (Harding *et al.* 1985).

One factor which may determine fetal nutrient supply is the extent to which energy requirements between fetal and maternal components of the placenta alter with gestational age. It is noticeable that *in vitro* O_2 consumption is approximately 2-fold higher in the maternal compared with fetal components of the sheep placenta at 75 d of gestation (Vatnick & Bell, 1992). This ratio declines up to term, in parallel with the large increase in fetal glucose demands which are met in part by developmental changes in placental glucose transfer capacity (Molina *et al.* 1991). The extent to which these adaptations could be linked has not been established, although growth and metabolism of the fetal liver appear to be closely related to the ability of the placenta to supply nutrients (Vatnick & Bell, 1992). The poor viability in caesarean-section-delivered lambs (Fig. 1) in which maternal, but not fetal components of the placenta are reduced (Table 2), in the absence of any maternal metabolic abnormalities could be the result of prolonged nutrient limitation and compromised development, as observed following experimental placental restriction (Harding *et al.* 1985).

AMBIENT TEMPERATURE AND LUNG MATURATION

Animal studies have shown that during postnatal and juvenile life changes in ambient temperature, within the normal operant range in which an individual is reared, can have a large impact on growth and development. In carefully-conducted experiments for which food intake has remained constant it is clear that thyroid hormones play a key role in the partitioning of energy necessary for growth and development of many tissues, including skeletal muscle, liver and adipose tissue (Dauncey, 1990; Darby *et al.* 1996; Dauncey & Gilmour, 1996). Some of these effects have been observed in hand-reared lambs for which rearing at a cool ambient temperature of 10–15° (CR) delays both the postnatal decline in plasma thyroid hormone concentrations and the extent to which the

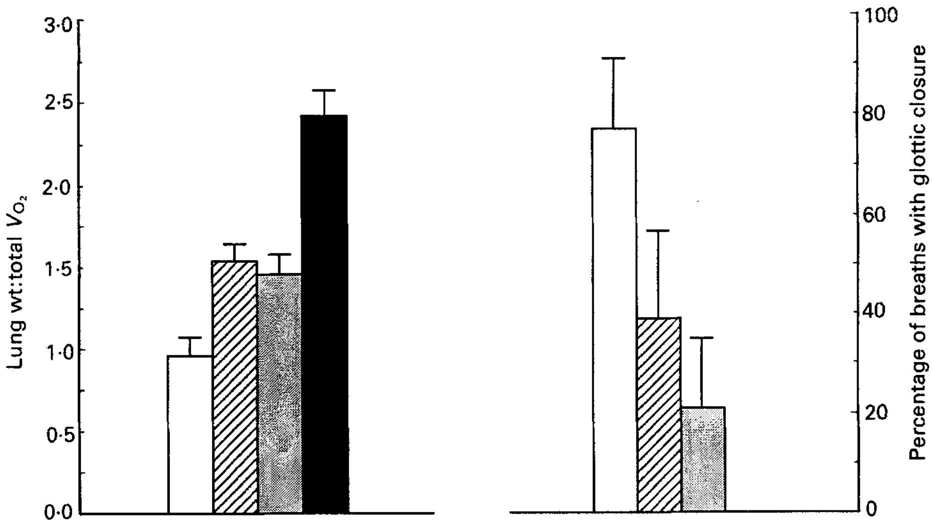

Fig. 2. Relationship between lung weight:whole-body oxygen consumption (V_{O_2}) and the mean percentage of breaths exhibiting expiratory laryngeal braking during non-rapid-eye-movement sleep between 28 and 30 d of age in lambs reared in a warm environment of 25° and given methimazole at a dose of 50 mg/kg body weight per d (■) or milk alone (▨), or at a cool ambient temperature of 10–15° and given methimazole (▩) or milk alone (□). Values are means with their standard errors represented by vertical bars. Laryngeal braking was not observed in lambs reared at 25° and given methimazole. (Adapted from Symonds *et al.* 1995*b*, 1996.)

thermogenic activity of BAT is lost (Symonds *et al.* 1995*b*; Darby *et al.* 1996). A combination of higher plasma thyroid hormone concentrations and enhanced thermogenic activity of BAT results in higher rates of O_2 consumption in CR lambs compared with their twins reared at a warm ambient temperature of 25° (WR). Surprisingly, at 1 month of age CR lambs possess less total lung mass, but are able to compensate for the greater metabolic demands for O_2 by increasing the recruitment of laryngeal braking of expiratory air flow (Symonds *et al.* 1995*b*). This mechanism is an example of the Hering-Breuer lung inflation reflex which has been repeatedly observed in infants over the first year of life (Rabbette *et al.* 1994). In lambs, laryngeal braking becomes prominent after the second week of life when O_2 consumption and breathing frequency have both declined from the very high rates observed soon after birth (Andrews *et al.* 1991*a*). Laryngeal braking is important in maintaining breathing rhythm and lung volume (Andrews *et al.* 1991*b*), although its recruitment is reduced in lambs born to chronically-underfed ewes (Symonds *et al.* 1993) in which fetal lung growth can be restricted (Symonds *et al.* 1995*a*).

Postnatal growth of the lung appears to be particularly sensitive to alterations in plasma thyroid hormone concentrations because at 1 month of age lung weight is negatively correlated with plasma T_4 concentration (Symonds *et al.* 1995*b*). This interaction persists following daily administration of the drug methimazole which inhibits thyroid hormone synthesis, although this effect is reduced in CR lambs (Symonds *et al.* 1994). Methimazole treatment does, however, reduce O_2 consumption (Symonds *et al.* 1995*b*), but lung weight:total O_2 consumption ratio remains greater in CR lambs and the recruitment of laryngeal braking is not observed in WR lambs receiving methimazole

(Fig. 2). Taken together, these findings suggest that an important factor which can influence the recruitment of expiratory laryngeal braking is the interrelationship between lung size and whole-body O_2 demands, and it is only when these reach a critical level that laryngeal braking is exhibited. This mechanism, therefore, appears to serve a dual role in preventing a decline in blood gas status under normoxic conditions (Andrews *et al.* 1991*a*) as well as maintaining lung volume.

In conclusion, changes in the rate of production of inhibitory and stimulatory factors can have a marked influence on perinatal development and postnatal survival. These effects can be altered dramatically depending on the level of maternal and fetal nutrition or route of delivery. Concomitant changes in adipose tissue development and/or lung maturation can persist into juvenile or adult life (Barker *et al.* 1991; Symonds *et al.* 1992, 1993). It is also becoming apparent that the consequences of alterations in maternal nutrition during pregnancy on fetal development may not manifest themselves until subsequent pregnancies or generations (Lumey, 1992; McCrabb *et al.* 1992). Placental growth appears to play a pivotal role in mediating some of these effects, which cannot be overcome by simply increasing the level of feed intake at a later stage of gestation (Faichney & White, 1987; Newnham *et al.* 1991) and which can further compromise development and maturation (Harding *et al.* 1992*b*; L. Clarke, D. C. Andrews, M. A. Lomax and M. E. Symonds, unpublished results).

The authors would like to thank the Wellcome Trust and BBSRC for their financial support.

REFERENCES

Abrams, B. S. & Laros, R. K. (1986). Pre-pregnancy weight, weight gain and birth weight. *American Journal of Obstetrics and Gynecology* **154,** 503–509.

Alexander, G. (1964). Studies on the placenta of the sheep *(Ovis aries L.)*. Placental size. *Journal of Reproduction and Fertility* **7,** 289–305.

Alexander, G. (1979). Cold thermogenesis. In *International Review of Physiology – Environmental Physiology III*, vol. 20, pp. 43–155 [D. Robertson, editor]. Baltimore: University Park Press.

Andrews, D. C., Symonds, M. E. & Johnson, P. (1991*a*). Thermoregulation and the control of breathing during NREM sleep in the lamb. *Journal of Developmental Physiology* **16,** 27–36.

Andrews, D. C., Symonds, M. E. & Johnson, P. (1991*b*). The interaction of the upper airway and thermometabolism on respiratory rhythm during NREM sleep in the developing lamb. *Journal of Developmental Physiology* **16,** 37–43.

Ball, K. T., Gunn, T. R., Power, G. G., Asakura, H. & Gluckman, P. D. (1995). A potential role for adenosine in the inhibition of nonshivering thermogenesis in the fetal sheep. *Pediatric Research* **37,** 303–309.

Barker, D. J. P. (1994). *Mothers, Babies and Disease in Later Life.* London: BMJ Publishing Group.

Barker, D. J. P., Godfrey, K. M., Fall, C., Osmond, C., Winter, P. D. & Shaheen, S. O. (1991). Relation of birth weight and childhood respiratory infection to adult lung function and death from obstructive airways disease. *British Medical Journal* **303,** 671–675.

Barker, P. M., Strang, L. B. & Walters, D. V. (1990). The role of thyroid hormones in maturation of the adrenaline-sensitive lung liquid reabsorptive mechanism in fetal sheep. *Journal of Physiology* **424,** 473–485.

Bauer, M. K., Breier, B. H., Harding, J., Veldhuis, J. D. & Gluckman, P. D. (1995). The fetal somatotropic axis during long term maternal undernutrition in sheep: evidence of nutritional regulation in utero. *Endocrinology* **136,** 1250–1257.

Bell, A. W., McBride, B. W., Slepetis, R., Early, R. J. & Currie, W. B. (1989). Chronic heat stress and prenatal development in sheep: 1. Conceptus growth and maternal plasma hormones and metabolites. *Journal of Animal Science* **67,** 3289–3299.

Brace, R. A. (1995). Progress towards understanding the regulation of amniotic fluid volume: Water and solute fluxes in and through the fetal membranes. *Placenta* **16,** 1–18.

Casteilla, L., Champigny, O., Bouillaud, F., Robelin, J. & Ricquier, D. (1989). Sequential changes in the expression of mitochondrial protein mRNA during the development of brown adipose tissue in bovine and ovine species. *Biochemical Journal* **257**, 665–671.

Clarke, L., Bird, J. A., Lomax, M. E. & Symonds, M. (1996). Effect of β_3-adrenergic agonist (Zeneca D7114) on thermoregulation in near-term lambs delivered by cesarean section. *Pediatric Research* (In the Press).

Clarke, L., Darby, C. J., Lomax, M. A. & Symonds, M. E. (1994). Effect of ambient temperature during the 1st day of life on thermoregulation in lambs delivered by cesarean section. *Journal of Applied Physiology* **76**, 1481–1488.

Christensson, K., Siles, C., Cabrera, T., Belaustequi, A., De La Fuente, P., Largercrantz, H., Puyol, P. & Winberg, J. (1993). Lower body temperatures in infants delivered by caesarean section than vaginally delivered infants. *Acta Paediatrica Scandinavica* **82**, 128–131.

Darby, C. J., Clarke, L., Lomax, M. A. & Symonds, M. E. (1996). Brown adipose tissue and liver development during early postnatal life in hand-reared and ewe-reared lambs. *Reproduction, Fertility and Development* (In the Press).

Dauncey, M. J. (1990). Thyroid hormones and thermogenesis. *Proceedings of the Nutrition Society* **49**, 203–215.

Dauncey, M. J. & Gilmour, R. S. (1996). Regulatory factors and the control of muscle development. *Proceedings of the Nutrition Society* **55**, 543–559.

Eliot, R. J., Klein, A. H., Glatz, T. H., Nathanielsz, P. W. & Fisher, D. A. (1981). Plasma norepinephrine, epinephrine and dopamine concentrations in maternal and fetal sheep during spontaneous parturition and in premature sheep during cortisol-induced parturition. *Endocrinology* **108**, 1678–1682.

Faichney, G. J. & White, G. A. (1987). Effects of maternal nutritional status on fetal and placental growth and on fetal urea synthesis in sheep. *Australian Journal of Biological Sciences* **40**, 365–377.

Fowden, A. L. & Silver, M. (1995). The effects of thyroid hormones on oxygen and glucose metabolism in the sheep fetus during late gestation. *Journal of Physiology* **482**, 203–213.

Gunn, T. R., Ball, K. T. & Gluckman, P. D. (1993). Withdrawal of placental prostaglandins permits thermogenic responses in fetal sheep brown adipose tissue. *Journal of Applied Physiology* **74**, 998–1004.

Harding, J. E., Jones, C. T. & Robinson, J. S. (1985). Studies on experimental growth retardation in sheep. The effects of a small placenta in restricting transport to and growth of the fetus. *Journal of Developmental Physiology* **7**, 427–442.

Harding, J. E., Liu, L., Evans, P., Oliver, M. & Gluckman, P. (1992*a*). Intrauterine feeding of the growth retarded fetus: can we help? *Early Human Development* **29**, 193–197.

Harding, J. E., Owens, J. A. & Robinson, J. S. (1992*b*). Should we try to supplement the growth retarded fetus? A cautionary tale. *British Journal of Obstetrics and Gynaecology* **99**, 707–710.

Hay, W. W. (1995). Metabolic interrelationships of placenta and fetus. *Placenta* **16**, 19–30.

Hume, R., Conner, C. & Gilmour, M. (1996). Lung maturation. *Proceedings of the Nutrition Society* **55**, 529–542.

Hume, R., Kelly, R., Cossar, D., Giles, M., Hallas, A., Gourlay, M. & Bell, J. (1991). Self-differentiation of human fetal lung organ culture: The role of prostaglandins PGE_2 and $PGF_{2\alpha}$. *Experimental Cell Research* **194**, 111–117.

Kind, K. L., Owens, J. A., Robinson, J. S., Quinn, K. J., Grant, P. A., Walton, P. E., Gilmour, R. S. & Owens, P. C. (1995). Effect of restriction of placental growth on expression of IGFs in fetal sheep: relationship to fetal growth, circulating IGFs and binding proteins. *Journal of Endocrinology* **146**, 23–34.

Kitterman, J. A., Liggins, G. C., Fewell, J. E. & Tooley, W. H. (1983). Inhibition of breathing movements in fetal sheep by prostaglandins. *Journal of Applied Physiology* **54**, 687–692.

Liggins, G. C. (1994). The role of cortisol in preparing the fetus for birth. *Reproduction, Fertility and Development* **6**, 141–150.

Lorijn, R. H. W., Nelson, J. C. & Longo, L. D. (1980). Induced fetal hyperthyroidism: cardiac output and oxygen consumption. *American Journal of Physiology* **239**, H302–H307.

Lumey, L. H. (1992). Decreased birthweights in infants after maternal in utero exposure to the Dutch famine of 1944–1945. *Paediatric and Perinatal Epidemiology* **6**, 240–253.

Lyke, S. J., Bird, J. A., Lomax, M. A., Shepherd, D. A. L. & Symonds, M. E. (1994). Effect of fetal thyroidectomy on thermoregulation in newborn lambs. *Proceedings of the Nutrition Society* **53**, 213A.

McCrabb, G. J., Egan, A. R. & Hosking, B. J. (1992). Maternal undernutrition during mid-pregnancy in sheep: variable effects on placental growth. *Journal of Agricultural Science* **118**, 127–132.

Mellor, D. J. (1983). Nutritional and placental determinants of fetal growth rate in sheep and consequences for the newborn lamb. *British Veterinary Journal* **139**, 307–324.

Moessinger, A. C., Harding, R., Adamson, T. M., Singh, M. & Kun, G. T. (1990). Role of lung liquid fluid in growth and maturation of the fetal sheep lung. *Journal of Clinical Investigation* **86,** 1270–1277.

Molina, R. D., Meschia, G., Battaglia, F. C. & Hay, W. W. (1991). Gestational maturation of placental glucose transfer capacity in sheep. *American Journal of Physiology* **261,** R697–R704.

Newnham, J. P., Kelly, R. W., Patterson, L. & James, I. (1991). The influence of maternal undernutrition in ovine twin pregnancy on fetal growth and Doppler flow-velocity waveforms. *Journal of Developmental Physiology* **16,** 277–282.

Oliver, M. H., Harding, J. E., Breier, M. H., Evans, P. C. & Gluckman, P. D. (1993). Glucose but not amino acids regulates plasma insulin-like growth factor (IGF)-1 concentrations in fetal sheep. *Pediatric Research* **34,** 62–65.

Rabbette, P. S., Fletcher, M. E., Dezateux, C. A., Soriano-Brucher, H. & Stocks, J. (1994). Hering-Breuer reflex and respiratory system compliance in the first year of life – a longitudinal study. *Journal of Applied Physiology* **76,** 650–656.

Rabelo, R., Schifman, A., Rubio, A., Sheng, X. & Silva, J. E. (1995). Delineation of thyroid hormone-responsive sequences with a critical enhancer in the rat uncoupling protein gene. *Endocrinology* **136,** 1003–1013.

Reynolds, L. P. & Redmer, D. A. (1995). Utero-placental vascular development and placental function. *Journal of Animal Science* **73,** 1839–1851.

Robinson, J. J. & Symonds, M. E. (1995). Whole-body fuel selection: reproduction. *Proceedings of the Nutrition Society* **54,** 283–299.

Robinson, J. S., Kingston, E. J., Jones, C. T. & Thorburn, G. D. (1979). Studies on experimental growth retardation in sheep: the effect of removal of endometrial caruncles on fetal size and metabolism. *Journal of Developmental Physiology* **1,** 379–398.

Rooney, S. A., Gobran, L. I. & Chu, A. J. (1986). Thyroid hormone opposes some glucocorticoid effects on glycogen content and lipid synthesis in developing fetal rat lung. *Pediatric Research* **20,** 545–550.

Savich, R. D., Guerra, F. A., Lee, C-C. H. & Kitterman, J. A. (1995). Effect of inhibition of prostaglandin synthesis on breathing movements and pulmonary blood flow in fetal sheep. *Journal of Applied Physiology* **78,** 531–538.

Silver, M. (1990). Prenatal maturation, the timing of birth and how it may be regulated in domestic animals. *Experimental Physiology* **75,** 285–307.

Symonds, M. E. (1995*a*). Pregnancy, parturition and neonatal development: interactions between nutrition and thyroid hormones. *Proceedings of the Nutrition Society* **54,** 329–343.

Symonds, M. E. (1995*b*). Metabolism and growth during neonatal and postnatal development. In *The Fetus and Neonate*, vol. 3, *Growth*, pp. 117–135 [M. A. Hanson, J. A. D. Spencer and C. H. Rodeck, editors]. Cambridge: Cambridge University Press.

Symonds, M. E., Andrews, D. C., Buss, D. S., Clarke, L. C., Darby, C. J., Johnson, P. & Lomax, M. A. (1995*b*). Environmental effects on thermoregulation and breathing patterns during early postnatal development in hand-reared lambs. *Experimental Physiology* **80,** 779–792.

Symonds, M. E., Andrews, D. C., Buss, D. S., Clarke, L. & Lomax, M. A. (1996). Influence of rearing temperature on lung development following methimazole treatment of postnatal lambs. *Experimental Physiology*. (In the Press).

Symonds, M. E., Bird, J. A., Clarke, L., Gate, J. J. & Lomax, M. A. (1995*a*). Nutrition, temperature and homeostasis during perinatal development. *Experimental Physiology* **80,** 907–940.

Symonds, M. E., Bryant, M. J., Clarke, L., Darby, C. J. & Lomax, M. A. (1992). Effect of maternal cold exposure on brown adipose tissue and thermogenesis in the neonatal lamb. *Journal of Physiology* **455,** 487–502.

Symonds, M. E., Clarke, L. & Lomax, M. A. (1994). The regulation of neonatal metabolism and growth. In *Early Fetal Growth and Development*, pp. 407–419 [R. H. T. Ward, S. K. Smith and D. Donnai, editors]. London: RCOG Press.

Symonds, M. E., Lomax, M. A., Andrews, P. C. & Johnson, P. (1993). Effect of the prenatal maternal environment on the control of breathing during non-rapid-eye-movement sleep in the developing lamb. *Journal of Developmental Physiology* **19,** 43–50.

Vatnick, I. & Bell, A. W. (1992). Ontogeny of fetal hepatic and placental growth and metabolism in sheep. *American Journal of Physiology* **263,** R619–R623.

Printed in Great Britain