5-15-2005

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Topical Review

Investigating the causes of low birth weight in contrasting ovine paradigms

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Intrauterine growth restriction (IUGR) still accounts for a large incidence of infant mortality and morbity worldwide. Many of the circulatory and transport properties of the sheep placenta are similar to those of the human placenta and as such, the pregnant sheep offers an excellent model in which to study the development of IUGR. Two natural models of ovine IUGR are those of hyperthermic exposure during pregnancy, and adolescent overfeeding, also during pregnancy. Both models yield significantly reduced placental weights and an asymmetrically growth-restricted fetus, and display altered maternal hormone concentrations, indicative of an impaired trophoblast capacity. Additionally, impaired placental angiogenesis and uteroplacental blood flow appears to be an early defect in both the hyperthermic and adolescent paradigms. The effects of these alterations in placental functional development appear to be irreversible. IUGR fetuses are both hypoxic and hypoglycaemic, and have reduced insulin and insulin-like growth factor-1 (IGF-1), and elevated concentrations of lactate. However, fetal utilization of oxygen and glucose, on a weight basis, remain constant compared with control pregnancies. Maintained utilization of these substrates, in a substrate-deficient environment, suggests increased sensitivities to metabolic signals, which may play a role in the development of metabolic diseases in later adult life.

(Received 22 December 2004; accepted after revision 14 March 2005; first published online 17 March 2005)
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Impaired fetal nutrient supply and the resulting intrauterine growth restriction (IUGR) continue to cause infant mortality and morbidity affecting 8 and 17% of pregnancies in the developed and developing world, respectively (UNICEF, 2003). The growth-restricted infants that survive the rigours of the neonatal period have a high risk of some serious life-long complications including mental, visual and aural impairment, autism, and cerebral palsy (Hack & Merkatz, 1995). Furthermore, there is now compelling evidence that low birth weight, even within the normal range, is a risk factor for the development of obesity, stroke, diabetes, immune dysfunction and cardiovascular disease in later life (Barker, 1998). Thus it is axiomatic that reducing the incidence of low birth weight and improving the growth trajectory of small preterm infants should be a major research priority with the potential to influence immediate survival and lifelong health of the individual. While many investigators are naturally studying the postnatal sequelae of IUGR we believe that it is equally important to characterize the placental–fetal interactions that underlie developmental programming of later life pathology.

The size and nutrient transfer capacity of the placenta play central roles in determining the prenatal growth trajectory of the fetus (Mellor, 1983; Bell *et al.* 1999; Wallace *et al.* 1999*a*). In the human, abnormalities in placental structure and function are central to many cases of IUGR (reviewed by Regnault *et al.* 2002*a*), and reduced placental volume in mid-pregnancy precedes fetal growth restriction (Thame *et al.* 2004). Exploring the mechanisms underlying placental insufficiency and the consequences for the fetus in human pregnancies is largely impractical, unethical or confounded by poverty, lifestyle and non-compliance issues. Consequently a plethora of animal models have been developed with the pregnant sheep offering distinct advantages over laboratory rodents as clinically relevant paradigms. Relative to the human, these include the ability to study singleton pregnancies, comparable birth weight, similar organogenesis for all major systems, equivalent rates of fetal protein accretion and a similar ratio of maternal : fetal body weight. Furthermore, sheep have a relatively long gestation length and when required the mother and fetus can be catheterized to measure fetal endocrine status, nutrient uptakes and fetal metabolism.

DOI: 10.1113/jphysiol.2004.082032

In sheep, varying degrees of fetal growth restriction can be induced by maternal nutrient restriction, placental embolization with microspheres, surgical limitation of placental implantation sites, umbilical artery ligation, and administration of corticosteroids (reviewed by Anthony *et al.* 2003). However, the aim of this brief review is to compare and contrast the key features of two of the more natural and robust paradigms of placental and fetal growth restriction, namely those produced by exposing pregnant dams to high ambient temperatures and overnourishing the pregnant adolescent ewe.

Establishment of the hyperthermia and overnourished adolescent ewe paradigms

In the hyperthermia paradigm, naturally mated adult ewes are typically exposed to elevated ambient temperature and moderate humidity conditions (40°C for 12 h, 35°C for 12 h at 30–40% relative humidity) for variable periods commencing around day 40 of gestation (Bell *et al.* 1987; Thureen *et al.* 1992; Galan *et al.* 1999). This delay in exposing ewes to hyperthermia avoids the known negative effects of high environmental temperatures on early embryo survival (Bell, 1987). An increase in core body temperature of 0.6–1.0°C within 5–7 days of entering the environmental chamber is associated with the development of a severely growth-restricted fetus (B. de Vrijer, H.L. Galan and T.R.H. Regnault, unpublished data). As early studies showed a marked decrease in appetite following exposure to high temperatures (Alexander & Williams, 1971), the hyperthermic and thermoneutral control ewes are pair-fed to achieve equivalent nutrient intakes throughout gestation.

In direct contrast, the adolescent paradigm is dependent on achieving vastly different maternal nutrient intakes. Single sire semen use and embryo transfer techniques are used to establish singleton pregnancies on day 4 of an induced oestrus cycle in pubertal adolescent ewes of equivalent age, live weight, and body condition score (adiposity). Care is also taken to randomise for recipient dam ovulation rate and the maternity of the embryo (Wallace *et al.* 1997). This approach controls for many of the periconception factors known to influence fetal growth and maximizes the genetic homogeneity of the resulting fetuses. Immediately after embryo transfer, recipient dams are either overnourished (approximately twice maintenance energy requirements) to promote rapid maternal growth leading to obesity or they are fed a control quantity of the same complete diet to maintain normal body adiposity throughout gestation.

Key features

Exposure of a variety of genotypes to high ambient temperatures from the end of the first third of pregnancy onwards results in major placental and fetal growth restriction as assessed during late gestation (Bell *et al.* 1987; Thureen *et al.* 1992; Ross *et al.* 1996) and following caesarian section close to term (Alexander & Williams, 1971; Table 1). Although fetal growth restriction also is evident when hyperthermia is confined to the final third of gestation (Alexander & Williams, 1971), it is less severe than when ewes are exposed during the active placental growth phase (second third of gestation; Alexander & Williams, 1971; Vatnick *et al.* 1991; Galan *et al.* 1999). Thus the development of IUGR in hyperthermic ewes is due to a primary reduction in placental growth during the first half of gestation making it an appropriate model for early onset IUGR in the human.

Perhaps counter-intuitively, overnourishing the adolescent ewe throughout gestation also results in significant placental and fetal growth restriction as assessed during late gestation (Wallace *et al.* 2000, 2002*a*) and following spontaneous delivery at term (Wallace *et al.* 2004; Table 1). It appears that the hierarchy of nutrient partitioning is altered in young rapidly growing sheep to promote the growth of maternal tissues (primarily adipose tissue) at the expense of the nutrient requirements of the gravid uterus. Nutritional switch-over studies demonstrate that the placental and fetal growth trajectories are most sensitive to high maternal intakes during the second two thirds of gestation. Reducing maternal intake from a high to a control level at day 50 of pregnancy stimulates placental growth and enhances pregnancy outcome. In contrast, increasing maternal intake at this time inhibits placental development and fetal growth to the same degree as in continuously overnourished pregnancies (Wallace *et al.* 1999*b*).

Comparison of the relative decrease in fetal cotyledon mass and birth weight at term reveals that the growth of the placenta is more perturbed than that of the fetus in both paradigms with ewes exposed to high temperatures exhibiting the greater degree of IUGR (Table 1). Indeed in the latter model the degree of growth restriction produced is directly related to the degree of hyperthermia induced, which is influenced in turn by the prevailing temperature/humidity and the heat tolerance of the ewe (Alexander & Williams, 1971). In the hyperthermia model, statistically significant differences in placental mass have been detected as early as day 75 of gestation (Vatnick *et al.* 1991) with fetal growth restriction becoming apparent by day 93 (Regnault *et al.* 1999). In addition to placental weight reduction, circulating steroid and protein hormone concentrations are reduced (Bell *et al.* 1989; Regnault *et al.* 1999). In contrast, significant placental growth restriction is not evident until around day 100 in the adolescent paradigm (Wallace *et al.* 1996, 1999*b*), although significant reductions in the proliferation of the fetal trophectoderm have been detected by day 81 of gestation (Lea *et al.* 2005). In the adolescent paradigm these changes in the placental

Table 1. Fetal cotyledon mass and lamb birth weight at or close to term in adult ewes exposed to hyperthermia during the second two thirds of gestation compared with adolescent ewes overnourished throughout gestation

Paradigm	No. of ewes	Fetal cotyledon mass (g)	Lamb birth weight (g)
[$]Maternal hyperthermia			
Control	12	150 ± 19.5^{a}	3457 ± 82^{a}
Treated	14	48 ± 6.9^{b}	1732 ± 148^{b}
% decrease from control		68	50
[§]Maternal hyperthermia*			
Control	26	357 ± 22.2^{a}	3247 ± 84^{a}
Treated	29	149 ± 14.8^{b}	1586 ± 155^{b}
% decrease from control		58	51
[#]Overnourished adolescent			
Control	85	137 ± 4.4^{a}	5136 ± 88^{a}
Treated	97	74 ± 2.6^{b}	3650 ± 111^{b}
% decrease from control		45	29

Values are mean ± S.E.M. [$] Recalculated from two hyperthermic studies reported in Alexander & Williams (1971); [§]recalculated from four hyperthermic studies, Thureen *et al.* (1992), Ross *et al.* (1996), Anderson *et al.* (1997) and Regnault *et al.* (2003); [#]data from nine studies reviewed in Wallace *et al.* (2004). [§]Fetal cotyledon mass is replaced in this data set by total placental weight. Within models, a and b significantly different at $P < 0.001$.

growth trajectory do not markedly alter fetal growth until the final third of gestation (Wallace *et al.* 2000, 2002*a*). In common with the majority of human IUGR cases, growth restriction in both of these ovine paradigms affects the body weight more than the body length, resulting in a low ponderal index (weight/×length (100)^{3}). Furthermore, while growth of the brain also is somewhat restricted, its growth is preserved relative to that of the rest of the body and particularly the abdominal organs, resulting in an increased brain : liver weight ratio (Thureen *et al.* 1992; Regnault *et al.* 1999; Wallace *et al.* 2002*a*).

IUGR in the overnourished adolescent ewe is characterized by a consistent but significant reduction in mean gestation length of approximately 3 days, with viable lambs being born as early as day 135 of gestation (mean gestation length = 145 days in control ewes; Wallace *et al.* 1996, 2004). Data for gestation length in ewes exposed to hyperthermia are somewhat equivocal and confounded by litter size and the small numbers of ewes with accurate mating dates (Yeates, 1953; Shelton & Huston, 1968), as well as more recent studies not allowing these pregnancies to go to term (Regnault *et al.* 2003). Nevertheless some singleton-bearing ewes exposed to hyperthermia do deliver a few days earlier than their thermoneutral counterparts (Alexander & Williams, 1971). Placental insufficiency resulting in fetal hypoxia and hypoglycaemia during late gestation (detailed below) may accelerate the maturation of the fetal hypothalamic–pituitary–adrenal axis, which is central to the initiation of parturition. In support of this concept, both paradigms are characterized by an increase in relative fetal adrenal gland weight in the IUGR fetuses (Alexander & Williams, 1971; Wallace *et al.* 2004), but cortisol concentrations, at least in the adolescent ewe paradigm, are equivalent in IUGR and control fetuses (mean ± S.E.M., 30.4 ± 2.51 and 25.2 ± 2.21 ng ml^{-1}, $n = 15$ and 17 per group, respectively; J.M. Wallace, R.P. Aitken and J.S. Milne, unpublished data). In the hyperthermia model, the relationship with fetal cortisol concentrations appears more complex. In a study of 15 control and 10 IUGR pregnancies, there appears to be a sex-by-treatment interaction, where only male IUGR fetuses displayed elevated cortisol concentrations (female ($n = 5$), 4.7 ± 0.60 ng ml^{-1} and male ($n = 5$), 24.4 ± 9.39 ng ml^{-1}; T.R.H. Regnault, R.B. Wilkening and R.V. Anthony, unpublished data). However, this elevation may be influenced by the degree of fetal hypoxaemia, fetal glycaemia and fetal lactate concentrations, requiring further definition of the severity of growth restriction as has recently been reported (De Vrijer *et al.* 2004) to understand the fetal cortisol response in hyperthermia-induced IUGR. Both IUGR paradigms have been associated with increased neonatal mortality (Shelton *et al.* 1968; Wallace *et al.* 1996), but with appropriate neonatal husbandry the majority of the low birth weight neonates should survive making them appropriate models for developmental programming.

Maternal endocrine and metabolic status

The partitioning of glucose, oxygen and amino acids between the dam and her gravid uterus are orchestrated by a number of endocrine hormones of maternal, placental and fetal origin. The circulating concentrations of many

Table 2. Comparison of maternal endocrine and metabolic changes in adult ewes exposed to hyperthermia compared with overnourished adolescent ewes

Hormone/metabolite	Hyperthermia IUGR	Overnourished adolescent IUGR
Progesterone	Decreased	Decreased
Placental lactogen	Decreased	Decreased
Prolactin	Increased*	Increased
Insulin	No change	Increased
IGF-1	Decreased	Increased
Growth hormone	nd	Decreased
Thyroid hormones	Decreased/no change	Increased
Cortisol	Decreased/no change	No change
Leptin	nd	Increased
Glucose	No change	Increased

nd, not determined. Original data in Bell *et al.* (1989); Regnault *et al.* (1999); Wallace *et al.* (1999*b*, 2000, 2001); Matsuzaki *et al.* (2004) and T.R.H. Regnault and J.M. Wallace, unpublished data. *During exposure to hyperthermia only.

of these maternal and placental hormones have been documented in both paradigms (Table 2) and may operate by influencing maternal or placental metabolism, placental growth, uteroplacental blood flows and nutrient transport functions. Limited space precludes a detailed discussion of the putative role of each hormone, but comparatively it is clear that the alterations in the somatotrophic hormones in the overnourished adolescent dams primarily reflect the high maternal feed intakes in this group. Thus the elevated insulin and IGF-1 concentrations promote maternal tissue synthesis, primarily of adipose tissue, and this in turn is associated with elevated leptin concentrations. While this does not preclude a role for these hormones in the development of placental and fetal growth restriction, it does indicate that their role may be confined to the rapidly growing adolescent. In contrast, both paradigms are characterized by low circulating progesterone and placental lactogen concentrations *versus* high prolactin levels. While in both paradigms the former may partially reflect the reduction in placental mass, particularly during the final third of pregnancy, the changes in these hormones are also detected during the first two thirds of gestation (Regnault *et al.* 1999; Wallace *et al.* 2001, 2003*a*). This implies altered trophoblast function as early as 55 days gestation, possibly via reduced trophoblast cell migration (Regnault *et al.* 1999), and these effects continue until near term (135 days gestation, T.R.H. Regnault, R.B. Wilkening and R.V. Anthony, unpublished data). Similarly reduced trophoblast endocrine function and mass have been reported in human IUGR (see Regnault *et al.* 1999 for original references). The significance of the elevated maternal prolactin concentrations in both paradigms (Regnault *et al.* 1999; Matsuzaki *et al.* 2004) is unknown and associations between prolactin and IUGR have not been detected in the human (Nieto-Diaz *et al.* 1996). Although it is tempting to suggest that the increase in prolactin may be a response to physiological stress, this is unlikely as maternal cortisol concentrations are not elevated relative to control pregnancies in either paradigm (Wallace *et al.* 2000; T.R.H. Regnault, unpublished data).

Placental development and uteroplacental blood flows

Absolute placental and fetal nutrient requirements are at a maximum in late pregnancy. It is not surprising therefore that positive correlations between placental and fetal weights become progressively stronger as birth approaches (Bell *et al.* 1999). During the final third of pregnancy, uteroplacental blood flows increase markedly to keep pace with fetal growth (Molina *et al.* 1991). Increased vascular resistance and reduced uteroplacental blood flows are used as predictors of high-risk human pregnancies and are strongly associated with intrauterine growth restriction (Coleman *et al.* 2000; Rigano *et al.* 2001; Harrington *et al.* 2004). Similarly, in both of our ovine paradigms, absolute uterine and umbilical blood flows are attenuated in late pregnancy, as is fetal weight-specific umbilical flow (Bell *et al.* 1987; Thureen *et al.* 1992; Wallace *et al.* 2002*a*). In the hyperthermia model, any reduction in absolute uterine blood flow appears to segregate to only the most severely growth-restricted pregnancies (sFGR), and not with more moderate growth restriction (mFGR; de Vrijer *et al.* 2004). Furthermore, relative uterine blood flow (per 100 g placenta) is actually increased regardless of the severity of growth restriction (Regnault *et al.* 2003; de Vrijer *et al.* 2004), indicating that maternal supply of nutrients to the placenta is not rate limiting during late gestation in this paradigm. It is axiomatic that the factors which influence placental vascular development and angiogenesis during the first half of pregnancy set the trajectory for these later haemodynamic changes. Indeed, in the hyperthermia model, placental expression of several angiogenic growth factors and their receptors (VEGF, PlGF, Ang-1, Ang-2, VEGFR-1, VEGFR-2 and Tie-2) varies depending on gestational age and the time frame relative to hyperthermic exposure (see Regnault *et al.* 2002*b*, 2003 for review of these data). Furthermore, these changes in developmental gene expression are associated with alterations in placental vascular architecture such as loss of terminal villi as demonstrated by Doppler velocity waveforms indicative of increased placental vascular resistance (Regnault *et al.* 2002*a*; Galan *et al.* 2005). All of these parameters mirror placental insufficiency in human IUGR. While the currently available information for the adolescent paradigm is much less detailed, attenuated expression of several placental angiogenic growth factors (VEGF, Ang-1, Ang-2 and eNOS), has recently been reported in overnourished dams studied

Table 3. Umbilical blood flow, fetal nutrient uptakes and fetal arterial nutrient concentrations in relation to fetoplacental mass at day 130–135 of gestation in two ovine paradigms of intrauterine growth restriction

Paradigm	Hyperthermia		Adolescent	
	Control	Study	Control	Study
Fetal weight (g)	3435 ± 150^a	1989 ± 252^b	4670 ± 196^a	3072 ± 266^b
Placental weight (g)	388 ± 47^a	191 ± 29^b	386 ± 34^a	209 ± 23^b
Umbilical blood flow (ml min $^{-1}$)	728 ± 106^a	288 ± 49^b	869 ± 84^a	585 ± 63^b
Umbilical glucose uptake (μmol min $^{-1}$)	97 ± 6.6^a	49 ± 7.8^b	206 ± 25^a	120 ± 13^b
Umbilical glucose uptake per kg fetus (μmol min $^{-1}$ kg^{-1})	31.7 ± 2.2	29.4 ± 1.7	45.2 ± 4.3	40.3 ± 2.2
Umbilical oxygen uptake (μmol min $^{-1}$)	1180 ± 100^a	710 ± 140^b	1637 ± 239^a	1030 ± 101^b
Umbilical oxygen uptake per kg fetus (μmol min $^{-1}$ kg^{-1})	340 ± 10	330 ± 30	357 ± 41	350 ± 17
Umbilical nitrogen uptake (mg N day $^{-1}$)*	3781 ± 403^a	1108 ± 103^b	4206 ± 586^a	2176 ± 177^b
Umbilical nitrogen uptake per kg fetus (mg N day $^{-1}$ kg^{-1})*	1037 ± 110	680 ± 62	962 ± 120	805 ± 98
Fetal arterial plasma glucose (μmol ml $^{-1}$)	1.16 ± 0.02^a	0.68 ± 0.05^b	1.32 ± 0.05^a	0.90 ± 0.10^b
Fetal arterial blood oxygen content (μmol ml $^{-1}$)	2.47 ± 0.1^a	1.58 ± 0.3^b	3.0 ± 0.3^a	2.1 ± 0.2^b
Fetal arterial plasma insulin (μU ml $^{-1}$)	39.9 ± 2.23^a	23.15 ± 3.5^b	17 ± 2.0^a	10 ± 1.48^b

Data from Regnault *et al.* (2003); Wallace *et al.* (2000, 2002*a*,*b*, 2003*b*); and *T.R.H. Regnault, B. de Vrijer, F.C. Battaglia, G. Meschia and R.B. Wilkening, unpublished data. Within paradigms means with different superscripts are significantly different ($P < 0.05$ to $P < 0.001$).

at mid-gestation (day 81; Redmer *et al.* 2005) prior to any reduction in placental mass. Indeed, impaired placental angiogenesis and uteroplacental blood flow may be an early defect in both the hyperthermia and adolescent paradigms. A rapid fall in uteroplacental blood flow was reported following exposure to hyperthermia during mid-pregnancy and persisted throughout the 20 day treatment period (Alexander *et al.* 1987). Likewise uterine blood flow (measured using a Transonic flow probe) in the artery supplying the gravid uterine horn was 170 ± 38 *versus* 386 ± 37 ml min^{-1} in overnourished adolescent ($n = 4$) compared with control ($n = 5$) intake groups, respectively, at day 90 of gestation. Furthermore, irrespective of treatment group, uterine flow at day 90 of gestation was positively correlated ($r = 0.677$, $P < 0.05$) with fetal weight at term (J.M. Wallace, M. Matsuzaki, J.S. Milne and R.P. Aitken, unpublished data). Irrespective of whether these early changes in blood flow are a cause or consequence of decreased placental metabolism and growth, the negative implications for the fetus appear to be permanent. The available information indicates that fetuses of ewes exposed to hyperthermia are relatively unresponsive to maternal nutrient supplementation in late pregnancy (Shelton *et al.* 1968). Similarly, switching previously overnourished adolescent ewes to a low nutrient intake from day 90–130 of gestation results in fetal growth restriction equivalent to that of continuously overnourished dams (3538 ± 133 and 3593 ± 192 g, respectively) and significantly lower than the moderate-intake control group (4465 ± 120 g, $n = 10$ per group; D.A. Redmer and J.M. Wallace, unpublished data).

Impaired nutrient supply and fetal growth

In late gestation, the growth-restricted fetuses of both the hyperthermic and overnourished adolescent paradigms are hypoxic and hypoglycaemic compared with the normally growing fetuses from their respective control groups (Thureen *et al.* 1992; Wallace *et al.* 2002*a*,*b*; Regnault *et al.* 2003; Table 3). In addition, fetal insulin and IGF-1 concentrations are low while lactate concentrations are elevated. We have used chronically instrumented pregnancies to address whether these alterations in fetal nutrient/endocrine status reflect defects in uteroplacental nutrient uptake, metabolism or transport of essential nutrients. Attenuated umbilical (fetal) uptakes of glucose, oxygen and amino acids have been documented in both paradigms (Table 3). However, all umbilical nutrient uptakes are normal when expressed on a fetal-weight-specific basis implying that fetal cellular metabolism is preserved at the expense of body growth (see below). Altered uteroplacental metabolism is not the cause as uteroplacental glucose and oxygen consumption together with uteroplacental lactate production are attenuated in proportion to the observed decrease in placental mass in both paradigms (Bell *et al.* 1987; Wallace *et al.* 2002*a*). However, the

paradigms do differ with respect to placental glucose transport capacity. Glucose clamp procedures have been used to assess placental glucose transport over a range of steady-state maternal–fetal transplacental plasma glucose concentration gradients. Comparison of the resulting glucose transport curves relative to the normal control pregnancies demonstrates that absolute placental glucose transport is reduced by approximately 64 and 47% in the hyperthermic and overnourished adolescents, respectively (Thureen *et al.* 1992; Wallace *et al.* 2002*b*). However, when expressed per kilogram of placenta, weight-specific glucose transport is relatively normal in the overnourished adolescent pregnancies but remains significantly attenuated in the hyperthermic animals. This difference in weight-specific placental glucose transport in the two paradigms is commensurate with the lack of effect of maternal nutrition on the expression of placental GLUT-1 and -3 in adolescent dams (Wallace *et al.* 2004) compared with the reduced expression of GLUT-1 (S.W. Limesand, T.R.H. Regnault, R.V. Anthony and W.W. Hay Jr, unpublished data), and -8 (Limesand *et al.* 2004) in hyperthermic pregnancies at both day 90 and 135 of gestation, and reduced GLUT-3 at 135 days (S.W. Limesand, T.R.H. Regnault, R.V. Anthony and W.W. Hay Jr, unpublished data). In spite of the dissimilarity with respect to placental glucose transport function, the currently available data suggest a similar fetal response to the decreased ability of the placenta to supply glucose. In both cases, fetal glucose utilization remains at normal levels per fetal weight, resulting in increased fetal glucose extraction and a decrease in fetal glucose and insulin concentrations (Table 3). The nature of the adaptive mechanisms that maintain fetal-weight-specific glucose utilization are currently being evaluated and may involve increased insulin sensitivity and/or enhanced glucose tolerance. Such information is required if we are to evaluate the appropriateness of nutritional strategies aimed at improving the growth trajectory of these fetuses prior to or following delivery. Increases in insulin action and glucose tolerance prenatally also may have implications, as yet untested, for the development of metabolic disease in later life (the metabolic syndrome or Syndrome X). The 'Thrifty Phenotype' hypothesis, for example, assumes that up-regulation of metabolic and/or hormonal capacity is a natural response to nutrient and anabolic hormone deficit, allowing the organism to regain growth following periods of undernutrition. However, if this increased metabolic capacity persists, it might prove detrimental when a surfeit of nutrients is available later in the organism's life. Obesity, insulin resistance, pancreatic failure and diabetes are therefore possible long-term adverse consequences (Hales & Barker, 2001).

Indeed, there is a paucity of information on the consequences of poor *in utero* growth in these two paradigms on postnatal growth, body composition and metabolism. Growth rates of low birth weight lambs from overnourished adolescent dams initially lag behind those of control offspring, but by 6 months of age, live weights are equivalent (Da Silva *et al.* 2001). Late gestation growth-restricted fetuses from overnourished dams have a relatively higher fat mass per kilogram body weight (Matsuzaki *et al.* 2004). Whether this relative increase in adiposity persists postnatally currently is unknown but an increase in central adiposity has been reported in low birth weight human infants and may provide a link between prenatal growth restriction and subsequent

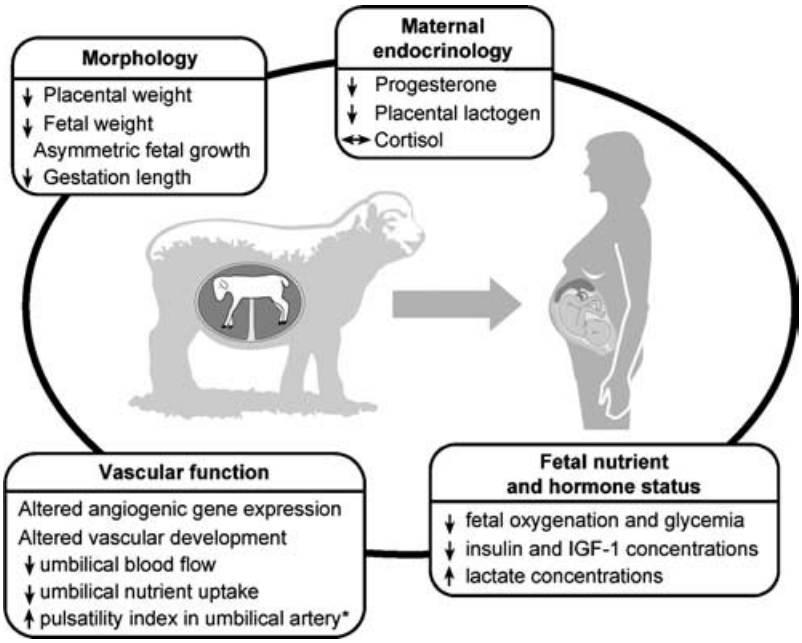

Figure 1. Features common to placentally mediated fetal growth restriction in the human and in two contrasting ovine paradigms, namely the hyperthermic adult and the overnourished adolescent sheep
* Human and hyperthermic ewes only.

obesity (Yajnik *et al.* 2003). The recent observation of a central appetite-regulatory neural network in the normally growing late gestation sheep fetus with the potential to respond to altered fetal nutrient supply may also be pertinent (Muhlhausler *et al.* 2004) in that it provides a means whereby prenatal programming of the neuro-endocrine hypothalamus may influence postnatal body weight regulation.

Conclusion

The timing and severity of IUGR in the human is highly variable (Anthony *et al.* 2003) and we readily accept that no one animal model will completely replicate the sequence of events which leads to an individual pregnancy being compromised. Nevertheless, the available evidence suggests that these two ovine paradigms mirror many of the central features of human IUGR associated with placental insufficiency (Fig. 1). Clearly the hyperthermia paradigm mimics early onset severe IUGR while the adolescent paradigm mimics a more modest, later onset form of the disorder. Exposing overnourished adolescent ewes to elevated environmental temperatures may provide an intriguing new paradigm not withstanding the practical difficulties associated with maintaining high dietary intakes during the hyperthermia treatment.

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Acknowledgements

Financial support from the Scottish Executive Environment and Rural Affairs Department (J.M.W.) and National Institutes of Health (HD20761, DK28794, HD42815, HD41505 and DK52138; T.R.H.R., S.W.L., R.V.A. and W.W.H. Jr) is gratefully acknowledged.