Effects of undernutrition and exercise during late pregnancy on uterine, fetal and uteroplacental metabolism in the ewe

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1. Uterine, umbilical and, by difference, uteroplacental net uptakes of oxygen, glucose, lactate and 3-hydroxybutyrate (uterine uptake only) were measured in single-pregnant ewes which were either well-fed throughout, or severely undernourished for 8–20 d during late pregnancy. All animals were studied while standing at rest and then while walking on a treadmill at 0.7 m/s on a $10°$ slope for 60 min.

2. Undernutrition did not significantly affect fetal or placental weights at 143 d gestation but caused a 14% decrease in maternal live weight. Uterine blood flow was decreased by 32% and was associated with a significant decrease in uteroplacental oxygen uptake; neither umbilical blood flow nor fetal O_2 uptake were affected by maternal plane of nutrition. Maternal and fetal hypoglycaemia in underfed ewes was accompanied by 46–63% decreases in uterine, umbilical and uteroplacental net uptakes of glucose, and similar declines in uterine and umbilical glucose/O_2 quotients. Moderate maternal hyperketonaemia was associated with 2.5-fold and 3-fold increases in uterine net uptake of 3-hydroxybutyrate and 3-hydroxybutyrate/O_2 quotient respectively.

3. Exercise caused significant decreases in uterine blood flow in fed and underfed ewes but did not affect uterine or umbilical O_2 uptakes; uterine net glucose uptake increased in most ewes but umbilical uptake was not significantly affected. Umbilical net uptake of lactate was significantly reduced. In underfed ewes, the extent of hyperketonaemia was significantly reduced by exercise.

4. Contrary to earlier proposals, the ovine pregnant uterus is sensitive and adaptable to long- and short-term alterations in maternal energy balance, as achieved by chronic undernutrition and exercise respectively. Thus, the fetus and placenta significantly add to, but do not necessarily have priority over the energy demands of other tissues of the ewe.

Patterns of fetal and uteroplacental energy substrate utilization in the fed, unstressed ewe have been studied in considerable detail (see Battaglia & Meschia, 1978; Meschia *et al.* 1980). The altered states caused by short-term starvation (Schreiner *et al.* 1978; Morriss *et al.* 1980), exercise (Chandler & Bell, 1981; Bell *et al.* 1983) and cold exposure (Thompson *et al.* 1982) have also been described but generally in less detail. In particular, the metabolic sensitivity and adaptability of the placenta under these conditions is poorly understood.

Under pastoral conditions, prolonged undernutrition is more likely to be encountered by the pregnant ewe than is short-term, outright starvation, and can have profound effects on fetal growth, neonatal survival (see Alexander, 1974; Mellor, 1983) and maternal health (see Reid, 1968). Therefore in the present study uterine, umbilical and, by difference, uteroplacental uptakes of oxygen and energy substrates from the maternal circulation were compared in ewes which were either well-fed or severely undernourished during late pregnancy. These indices were also measured during treadmill exercise in each nutrition group to extend our previous observations of uterine and fetal sensitivity to abrupt, natural changes in maternal respiration and metabolism (Chandler & Bell, 1981). Undernutrition caused a substantial decline in uteroplacental but not fetal O_2 uptake, whereas net glucose uptake by both major components of the pregnant uterus was markedly reduced. During exercise, fetal and uteroplacental O_2 consumption was maintained, despite a decrease in uterine blood flow; the accompanying fetal hyperglycaemia was not clearly associated with increased umbilical uptake of maternal glucose. Some of our results have been reported in preliminary communications (Bell *et al.* 1982; Chandler *et al.* 1983).

MATERIALS AND METHODS

Animals and management

Fourteen single-pregnant Merino ewes aged 5–6 years and weighing 31–42 kg at operation were used. Time of mating was detected by colour marks left on ewes by rams fitted with coloured crayons ('Sire-sine', Hortico, Australia). All ewes were inspected daily and date of conception was taken as the first date of crayon marking followed by subsequent failure to mate (Radford *et al.* 1960). Each ewe was housed in an individual metabolism cage and was accustomed to experimental surroundings and procedures, including walking on a moving-belt treadmill, for several weeks before experiment.

Feeding. Ewes were brought indoors at 80–100 d gestation and were given daily 800–1200 g lucerne (*Medicago sativa*) chaff (metabolizable energy (ME) content approximately 9 MJ/kg) according to body-weight and gestational age until surgery, usually at 115–120 d gestation. All ewes were allowed to eat *ad lib.* for 2 d following surgery, during which most animals re-attained pre-surgery intakes. Seven ewes were then given 1000–1200 g lucerne chaff/d ('fed' group) while the remaining seven were given 350 g lucerne chaff/d ('underfed' group) until 143 d gestation, when all ewes were slaughtered. In both groups the daily ration was given in twelve equal portions at two-hourly intervals, with *ad lib.* access to water and a mineralized salt block (Cheetham Salt, Geelong, Australia).

Surgery. Surgery was performed on four fed and seven underfed ewes at 115–120 d gestation, and at 101–111 d on the remaining three fed ewes. Ewes were fasted for 24 h before general anaesthesia, induced by intravenous injection of thiopentone sodium (Pentothal, Abbott Laboratories, Kurnell, Australia) and maintained with halothane (Fluothane, ICI, Villawood, Australia) – oxygen mixtures given in closed-circuit through an endotracheal tube. The uterine vein draining the pregnant horn of the uterus and the common umbilical vein were catheterized as described by Meschia *et al.* (1969) and the fetal abdominal aorta as described by Chandler & Bell (1981). Catheters were also inserted into the fetal posterior vena cava via a recurrent tarsal vein and into the maternal abdominal aorta via a saphenous artery. Post-operative care of animals and maintenance of catheter patency were as described previously (Chandler & Bell, 1981).

Experimental procedure

Experiments were done on fed ewes at least 7 d after surgery, when they were at 108–140 d gestation, and on underfed ewes at 10–22 d after surgery, when they had been underfed for 8–20 d and were at 125–141 d gestation. Where possible, several studies per animal were attempted, with an interval of at least 1 week between studies. Ewes were killed at 143 d gestation for dissection and weighing of the pregnant uterus and its contents.

On the morning of study the ewe was given one-twelfth of its normal daily ration at 09.00 hours and was placed on the stationary treadmill. Infusion of antipyrine into the fetal posterior vena cava for measurement of umbilical and uterine blood flows (see p. 627) commenced at about 09.45 hours. Blood samples were simultaneously drawn from the maternal aorta and uterine vein (each 5 ml), fetal aorta and common umbilical vein (each 1·2 ml) at about 10.40, 10.50 and 11.00 hours.

The ewe then commenced walking (0·7 m/s, 10° slope) and the above sampling routine was repeated at about 11.40, 11.50 and 12.00 hours. Exercise and antipyrine infusion then ceased.

Blood samples for measurement of O_2 content were stored anaerobically in glass syringes on ice before analysis within 1 h of sampling. Samples for metabolite analysis were stored on ice in capped, heparinized syringes before being deproteinized with zinc sulphate–barium hydroxide (for glucose and antipyrine analysis) or perchloric acid (for lactate and

3-hydroxybutyrate analysis), or centrifuged at 2000 *g* and 4° to separate plasma (for free-fatty acid analysis). Plasma and neutralized, deproteinized extracts from whole blood were stored at −20° before analysis within 3 months.

Measurements

Uterine and umbilical blood flows were measured by the antipyrine steady-state diffusion method (Meschia *et al.* 1967). Blood concentration of antipyrine was measured by the method of Brodie *et al.* (1949), as modified by Chandler (1983). Blood haemoglobin (Hb) and oxyhaemoglobin saturation (S_{O_2}) were measured with an automatic, direct-reading photometer (OSM2, Radiometer A/S, Copenhagen, Denmark) calibrated with sheep's blood. Blood O_2 content (ml/l) was calculated as: Hb (g/l) × S_{O_2} × 1·34. Blood glucose was analysed by the glucose oxidase (*EC* 1.1.1.34) method of Bergmeyer & Bernt (1974); lactate by the lactate dehydrogenase (*EC* 1.1.1.27) method of Gutmann & Wahlefeld (1974); 3-hydroxybutyrate by the 3-hydroxybutyrate dehyrogenase (*EC* 1.1.1.30) method of Williamson & Mellanby (1974); and plasma free fatty acids (FFA) by a modification of the microtitration method of Patterson (1963), using a microtitrator (Dosimat E535, Metrohm, Herisau, Switzerland) and thymol blue as an indicator.

Calculations

Net fluxes of O_2, glucose, lactate and 3-hydroxybutyrate from the uterine circulation to the pregnant uterus were calculated as the product of uterine blood flow and the maternal arterial–uterine venous concentration difference. Net fluxes of O_2, glucose and lactate from the placenta to the fetus were calculated as the product of umbilical blood flow and the umbilical venous–fetal arterial concentration difference. Net uteroplacental uptake or release of O_2, glucose and lactate were calculated as the difference between the net uterine and net umbilical rates of exchange (Meschia *et al.* 1980).

Statistics

The significances of the effects of exercise were assessed by the paired *t* test. Effect of undernutrition on resting absolute values and on exercise-induced changes from resting values were assessed by the unpaired *t* test. Where more than one study was done per animal, the values were averaged before calculation of means, standard errors and *t* values.

RESULTS
Maternal, fetal and placental weights

Mean live weight in fed ewes increased by almost 3 kg (8%) during the period of study whereas, in the underfed ewes, it decreased by more than 5 kg (14%), so that the underfed animals were significantly lighter than the fed animals at 143 d (*P* < 0·01) (Table 1). Neither fetal nor placental weights at 143 d were significantly affected by maternal nutrition; although four of six fetuses in the underfed group were lighter than the smallest fetus from a fed ewe (3·11 kg), the remaining two were heavier than 4 kg.

Uterine and umbilical blood flows

The mean, resting value for uterine blood flow was 30% lower in underfed than in fed ewes (*P* < 0·001); umbilical blood flow was unaffected by maternal nutrition (Table 2). The mean ratio, uterine:umbilical blood flow in those ewes in which both were measured simultaneously was significantly reduced (*P* < 0·01) from 3·3 (SE 0·4) in the fed group to 1·6 (SE 0·1) in the underfed group.

During exercise, mean resting uterine flow decreased by 18 and 28% in fed (*P* < 0·01)

Table 1. *Maternal and fetal body-weights (kg) and placental weight (g)† in well-fed and underfed ewes*

(Values are means with their standard errors for six sheep in each group‡)

	Gestational age (d)	Fed		Underfed		Effect of nutrition
		Mean	SE	Mean	SE	
Ewe	120	35·24	1·33	38·97	1·12	NS
	143	38·00	0·42	33·68	1·23	**
Fetus	143	3·58	0·14	3·28	0·32	NS
Placenta	143	371	27	334	29	NS

NS, not significant.
** $P < 0.01$.
† Weight of whole placentomes, including fetal cotyledon and maternal caruncle.
‡ Values unavailable for one ewe in each group.

Table 2. *Effects of undernutrition and exercise on uterine and umbilical blood flows (ml/min)*

(Values are means with their standard errors, with no. studies and no. sheep in parentheses)

	Fed				Underfed				Effect of nutrition	
	R		ΔE		R		ΔE		R	ΔE
	Mean	SE	Mean	SE	Mean	SE	Mean	SE		
Uterine	1851	122	−328**	87	1292	137	−361*	100	***	NS
		(10, 7)				(9, 7)				
Umbilical	803	100	−40	28	771	137	−94	108	NS	NS
		(10, 6)				(6, 5)				

R, rest; ΔE, change with exercise; NS, not significant.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

and underfed ($P < 0.05$) ewes respectively (Table 2). The absolute exercise-induced decrement (ml/min) in uterine blood flow was not affected by plane of nutrition. Umbilical blood flow decreased during exercise in eight of ten experiments on fed ewes, and in four of six experiments on underfed ewes, but the mean decrease was not significant in either group.

Uterine, umbilical and uteroplacental O_2 uptakes

Uterine O_2 uptake tended to be lower in underfed than in fed ewes ($P < 0.1$). Since umbilical O_2 uptake was little affected by maternal nutrition, most of the decline in uterine consumption was due to a substantial reduction in uteroplacental O_2 uptake ($P < 0.01$) (Table 3).

In fed ewes, exercise caused a 20% increase in maternal arterial O_2 concentration ($P < 0.01$) (Table 3), which was almost entirely due to increased haemoglobin concentration. A similar but less consistent effect was observed in underfed ewes. Fetal arterial O_2 concentration tended to decline during exercise in each group, due entirely to decreased S_{O_2}; the decrease was significant ($P < 0.01$) when data from fed and underfed ewes were pooled.

Uterine O_2 uptake and its partition between the fetus and uteroplacental tissues were unchanged during exercise (Table 3); decreases in uterine blood flow (Table 2) were

Table 3. *Effects of undernutrition and exercise on maternal and fetal arterial blood concentrations, and on uterine, umbilical and uteroplacental uptakes of oxygen*

(Values are means with their standard errors, with no. studies and no. sheep in parentheses)

| | Fed | | | | Underfed | | | | Effect of nutrition | |
| | R | | ΔE | | R | | ΔE | | | |
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	R	ΔE
Arterial O_2 concentration (ml/l):										
Ewe	100·1	3·7	+22·1**	5·4	102·5	7·0	+16·0	7·7	NS	NS
		(11, 7)				(6, 5)				
Fetus	88·8	3·1	−9·0	4·5	87·1	7·2	−22·3	8·4	NS	NS
		(14, 7)				(6, 5)				
Oxygen uptake (ml/min):										
Uterine	33·4	1·5	+1·4	2·4	26·2	3·7	+2·5	6·4	NS	NS
		(10, 7)				(6, 5)				
Umbilical	22·7	3·1	+0·8	0·7	20·9	2·5	+2·5	2·9	NS	NS
		(8, 5)				(5, 5)				
Utero-placental	16·7	2·3	+0·6	2·3	5·9	1·5	+0·2	4·3	**	NS
		(6, 5)				(5, 5)				

R, rest; ΔE, change with exercise; NS, not significant.
** $P < 0.01$.

completely compensated by concomitant increases in uterine extraction of maternal arterial blood O_2.

Glucose metabolism

Undernutrition caused significant decreases in maternal and fetal blood glucose concentrations (both $P < 0.001$), which were accompanied by 46–63% decreases in mean uterine ($P < 0.05$), umbilical ($P < 0.05$) and uteroplacental ($P < 0.05$) net uptakes of glucose (Table 4). In ewes in which uterine and umbilical uptakes were measured simultaneously the fractional partition of glucose taken up by the uterus between the fetus and uteroplacental tissues was not significantly altered by undernutrition. Thus, the fetus and uteroplacental tissues of fed ewes received 31 (SE 3)% and 69 (SE·3)% of uterine glucose respectively, while corresponding values in underfed ewes were 34 (SE 9)% and 66 (SE 9)% respectively. The decreased net uptakes of glucose by the uterus and fetus in undernourished ewes were associated with significant decreases (each approximately 45%) in mean uterine ($P < 0.05$) and umbilical ($P < 0.001$) glucose/O_2 quotients (Table 4).

Exercise caused significant increases in maternal arterial blood glucose concentrations in both fed and underfed ewes and in fetal glucose in the underfed group; absolute changes in maternal and fetal glycaemia were not significantly affected by nutrition (Table 4). Uterine net uptake of glucose increased variably during exercise, in eight of nine studies on fed ewes ($P < 0.1$) and in six of seven studies on underfed ewes ($P < 0.05$). Accompanying mean increases in umbilical and uteroplacental net uptakes were also variable and not statistically significant at either level of feeding. Uterine and umbilical glucose/O_2 quotients tended to increase during exercise in fed and underfed ewes but this effect was statistically significant only for the uterine quotient in underfed ewes ($P < 0.05$) (Table 4).

Lactate metabolism

In fed ewes, exercise caused a 3-fold increase in mean maternal blood lactate concentration ($P < 0.01$) and a 45% increase in mean fetal concentration ($P < 0.001$) (Table 5). In the

Table 4. *Effects of undernutrition and exercise on maternal and fetal arterial blood concentrations, and on uterine, umbilical and uteroplacental net uptakes and oxygen quotients of glucose*

(Values are means with their standard errors, with no. studies and no. sheep in parentheses)

	Fed				Underfed				Effect on nutrition	
	R		ΔE		R		ΔE			
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	R	ΔE
Arterial glucose concentration (mmol/l):										
Ewe	2·52	0·08	+1·23* (9, 7)	0·47	1·48	0·19	+1·24 (7, 6)	0·21	***	NS
Fetus	0·74	0·05	+0·32 (9, 5)	0·18	0·26	0·05	+0·47* (6, 5)	0·14	***	NS
Net uptake (μmol/min):										
Uterine	227	35	+76 (9, 7)	49	122	25	+60* (7, 6)	23	*	NS
Umbilical	84	18	+16 (8, 5)	8	39	7	+39 (6, 5)	16	*	NS
Utero-placental	167	24	+67 (7, 5)	64	62	28	+14 (6, 5)	35	*	NS
Glucose/oxygen quotient:†										
Uterine	0·97	0·14	+0·34 (9, 7)	0·18	0·53	0·09	+0·17* (6, 5)	0·04	*	NS
Umbilical	0·48	0·03	+0·11 (7, 5)	0·09	0·27	0·06	+0·20 (6, 5)	0·13	***	NS

R, rest; ΔE, change with exercise; NS, not significant.

* $P < 0.05$; *** $P < 0.001$.

† $\dfrac{\text{Glucose uptake } (\mu\text{mol/min}) \times 6}{\text{Oxygenuptake } (\mu\text{mol/min})}$.

Table 5. *Effect of exercise on maternal and fetal blood concentrations, and on net uterine, umbilical and uteroplacental metabolism of lactate*

(Values are means with their standard errors, with no. studies and no. sheep in parentheses)

	Rest		Change with exercise	
	Mean	SE	Mean	SE
Arterial lactate concentration (mmol/l):				
Ewe	0·95	0·21	+2·00** (13, 7)	0·45
Fetus	1·63	0·33	+0·74*** (13, 6)	0·10
Net uptake (μmol/min):				
Uterine	−59	55	+121 (10, 7)	114
Umbilical	176	30	−85* (8, 5)	25
Uteroplacental	−154	102	+150 (7, 5)	197

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 6. *Effects of undernutrition and exercise on maternal arterial plasma concentration of free fatty acids (FFA), and on arterial blood concentration and net uterine metabolism of 3-hydroxybutyrate (3HB)*

(Values are means with their standard errors, with no. studies and no. sheep in parentheses)

| | Fed | | | | Underfed | | | | Effect of nutrition | |
| | R | | ΔE | | R | | ΔE | | | |
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	R	ΔE
FFA concentration (mmol/l)	0·86	0·09	+1·05*** (8, 6)	0·11	1·94	0·29	+0·94** (7, 6)	0·21	**	NS
3HB concentration (mmol/l)	0·60	0·04	+0·12 (9, 6)	0·07	2·12	0·30	−0·40** (5, 4)	0·06	***	***
3HB uterine uptake (μmol/min)	40	6	+4 (9, 6)	7	99	22	−10 (5, 4)	37	*	NS
3HB/oxygen quotient†	0·12	0·02	+0·01 (9, 6)	0·02	0·33	0·06	−0·08 (5, 4)	0·05	**	NS

R, rest; ΔE, change with exercise; NS, not significant.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

† $\dfrac{\text{3HB uptake } (\mu\text{mol/min}) \times 4.5}{\text{O}_2 \text{ uptake } (\mu\text{mol/min})}$.

majority of trials, exercise caused a reversal of the net uterine release of lactate, usually seen in resting ewes, to a net uptake, and of the usual uteroplacental net production of lactate to a net consumption; these trends were highly variable and not statistically significant. However, there was a significant 48% decline in mean umbilical net uptake of lactate ($P < 0.05$) (Table 5).

Lactate metabolism was not studied in underfed ewes.

FFA and 3-hydroxybutyrate metabolism

In resting, undernourished ewes, mean arterial plasma FFA level was more than double that in fed ewes ($P < 0.01$), while mean blood 3-hydroxybutyrate concentration was increased almost 4-fold ($P < 0.001$). The latter was associated with significant increases in uterine net uptake of 3-hydroxybutyrate ($P < 0.05$) and in the uterine 3-hydroxybutyrate/O_2 quotient ($P < 0.01$) (Table 6). There was a highly significant correlation between arterial concentration and uterine O_2 quotient of 3-hydroxybutyrate (r 0.878, $P < 0.001$).

Exercise caused significant increases in arterial plasma FFA concentrations in fed ($P < 0.001$) and underfed ($P < 0.01$) ewes, the increment being about 1 mmol/l in each case (Table 6). In fed ewes, 3-hydroxybutyrate concentrations were not significantly affected by exercise, but the elevated resting levels in underfed ewes were decreased by 19% ($P < 0.01$) (Table 6).

DISCUSSION

Effects of undernutrition

The energy intake of our fed ewes (270 kJ ME/d per kg live weight) was approximately that recommended for single-pregnant ewes during late pregnancy (Agricultural Research Council, 1980). Changes in live weight between 120 and 143 d gestation (Table 1) and maternal arterial concentrations of glucose (Table 4), FFA and 3-hydroxybutyrate (Table 6) satisfy the criteria for nutritional adequacy proposed by Russel et al. (1967) and Mellor (1983). The severity of undernutrition in our 'underfed' group (0.3–0.4 recommended ME intake) was reflected in the substantial loss of maternal live weight over the period of study. Surprisingly, this was not associated with a significant reduction in fetal body-weight at 143 d. In view of previous observations on larger groups of ewes (see Alexander, 1974; Mellor, 1983), this may be attributable more to a lack of statistically adequate numbers than to the lack of an effect on individual fetal growth rates. Also, the difference in maternal live weight at 120 d between subsequently fed and underfed ewes was almost significant (Table 1); it is known that initial body-weight and condition can influence later effects of undernutrition on lamb birth weight (Russel et al. 1981). Because of uncertainty about fetal growth rates, particularly in underfed ewes, fetal metabolic indices in the present paper have not been expressed in terms of fetal weight. Nevertheless, the ability of some severely undernourished ewes to produce a relatively large (> 4 kg) fetus at the expense of their own body stores of energy and possibly, protein, is impressive.

In the present study, undernutrition for 8–20 d was characterized by substantial reductions in uterine blood flows and uteroplacental O_2 consumption but little or no effect on umbilical O_2 uptake. In general, these observations are consistent with separate reports of decreased uterine blood flow and O_2 uptake (Morriss et al. 1980), but no significant effect on umbilical O_2 uptake (Boyd et al. 1973; Lemons & Schreiner, 1983) in ewes starved completely for several days. The nature of the association between uteroplacental O_2 uptake and uterine blood flow in chronically-underfed ewes is not clear. In the short term, uterine blood flow does not appear to be sensitive to local metabolic factors (Greiss et al. 1972; Makowski et al. 1973), nor is uteroplacental O_2 uptake significantly affected by changes in uterine blood flow (Wilkening & Meschia, 1983). In the long term, however, it remains

possible that adaptive changes in placental metabolism, such as appear to have occurred during underfeeding, may indeed influence uterine, and particularly placental, perfusion.

Undernutrition resulted in the development of maternal hypoglycaemia, FFA mobilization and moderate hyperketonaemia, as described in numerous early reports on the metabolic characteristics of the undernourished, pregnant ewe (see Reid, 1968). It was once considered that these metabolic changes, which in severe cases can lead to ketoacidosis and death, were due to the conceptus having first priority on available nutrients, especially glucose, to the detriment of the mother (e.g. Barcroft, 1946; Reid, 1968). However, the present results, together with those of Hay *et al.* (1983) for the starved, hypoglycaemic ewe, indicate that, contrary to earlier proposals, the fetus and uteroplacental tissues respond to maternal hypoglycaemia by markedly decreasing their demands on the maternal glucose supply. Thus, Hay *et al.* (1983) showed that the partition of maternal glucose between maternal tissues and the pregnant uterus was essentially unaltered by starvation. The sensitivity of the uteroplacental tissues to maternal glycaemia is particularly notable, because these tissues account for about 70% of uterine glucose uptake in well-fed ewes (Meschia *et al.* 1980; Hay *et al.* 1983; present results, Table 4).

The potential contribution of glucose to uterine oxidative metabolism was reduced during undernutrition to about 50% of that in fed ewes, and it is likely that the moderate (20–30%) contribution of acetate (Chandler & Bell, 1981) declined even more markedly. At least some of the shortfall in oxidizable substrate appears to have been made up by increased uterine uptake of 3-hydroxybutyrate, corroborating a recent observation on starved, pregnant ewes (Pethick & Lindsay, 1982). In the latter, as in the present study, the uterus of fed ewes took up modest amounts of 3-hydroxybutyrate, sufficient to account for about 12% of O_2 consumption, and the uterine 3-hydroxybutyrate/O_2 quotient was closely related to arterial 3-hydroxybutyrate concentration in fed and underfed animals. Pethick & Lindsay (1982) did not measure the rate of uterine uptake of 3-hydroxybutyrate but estimated that, in fasted ewes, it might account for about 25% of the total ketones entering the bloodstream. This agrees closely with our own prediction for chronically undernourished ewes, based on direct measurements of uterine uptake and estimation of 3-hydroxybutyrate entry rate from its regression on arterial concentration (Pethick & Lindsay, 1982). Thus, from the mean arterial concentration of 2·12 mmol/l (Table 6) we estimated an entry rate of 0·66 mmol/kg per h, which in our animals would correspond to about 390 μmol/min. The observed mean uterine uptake of 99 μmol/min (Table 6) is about 25% of this predicted value. As discussed by Pethick & Lindsay (1982), most of this 3-hydroxybutyrate was probably metabolized by the uteroplacental tissues, because umbilical net uptake of ketones was negligible, even in hyperketonaemic ewes (Morriss *et al.* 1974).

During undernutrition, the pattern of fetal, as well as of uterine substrate utilization was altered, as indicated by the marked decrease in the umbilical glucose/O_2 quotient. We did not measure fetal uptake or utilization of nutrients other than glucose in underfed ewes. However, other evidence suggests that in starved and chronically underfed ewes, increased fetal amino acid catabolism may substitute for a declining glucose supply (Simmons *et al.* 1974; Faichney, 1981). It also appears that fetal gluconeogenesis, normally insignificant in the fed ewe, may increase when the availability of exogenous glucose is markedly reduced (Hay *et al.* 1984*b*).

Effects of exercise

The exercise-induced decrease in uterine blood flow, previously observed by others using a variety of methods (Clapp, 1980; Chandler & Bell, 1981; Lotgering *et al.* 1983*a*; Hohimer *et al.* 1984), was not associated with any change in uterine or umbilical O_2 uptake, as also reported by Clapp (1980). This is consistent with recent evidence that during short-term reductions in uterine blood flow, fetal O_2 uptake is not impaired until the decrement in

perfusion exceeds 50% (Wilkening & Meschia, 1983). The decline during exercise in fetal arterial O_2 content (Clapp, 1980; Chandler & Bell, 1981; Lotgering *et al.* 1983*b*; present study) would appear to be the price paid by the fetus in order to maintain umbilical O_2 extraction in the face of a decrease in placental O_2 supply.

The present study has not fully resolved the origin of the fetal hyperglycaemia during maternal exercise, observed in this and our previous studies (Chandler & Bell, 1981; Bell *et al.* 1983). Changes during exercise in umbilical and uteroplacental net uptakes of glucose were variable. Nevertheless, in most animals, the increase in fetal arterial glucose concentration was clearly not associated with a major increase in umbilical net glucose uptake. Alternative explanations include decreased fetal glucose utilization or hepatic glycogenolysis, or both, in response to hypoxaemia. Both of these have recently been shown to account for the fetal hyperglycaemia which develops during the more severe hypoxaemia induced by maternal hypoxia (Jones *et al.* 1983). It is notable that the pattern of change in fetal plasma insulin concentration before, during and after maternal exercise (Bell *et al.* 1983) qualitatively resembles that occurring before, during and after maternal hypoxia (Jones *et al.* 1983). This pattern is consistent with unchanged or depressed glucose utilization during hypoxaemia, followed by enhanced utilization during the recovery phase.

Exercise also caused highly variable changes in uterine and umbilical net exchanges of lactate. However, it is evident that the moderate increase during exercise in fetal blood lactate concentration (Chandler & Bell, 1981; Bell *et al.* 1983; Lotgering *et al.* 1983*b*; present study, Table 5) was not caused by increased uptake from the placenta. In fact, umbilical net uptake of lactate was significantly decreased because umbilical venous levels remained unchanged, while umbilical arterial levels increased. Presumably, fetal endogenous lactate production was moderately increased through increased rates of tissue glycolysis, stimulated by concurrent elevation of blood glucose and depression of blood O_2.

Several interesting features of glucose and ketone metabolism emerged from the responses of undernourished ewes to exercise. In particular, these ewes retained an apparently unimpaired capacity for glycogenolysis, as judged from the rapid and sustained increase in maternal blood glucose; in absolute terms this was at least as great as that in exercising well-fed ewes. Under these conditions, the uterus was able to increase significantly its glucose uptake and glucose/O_2 quotient, despite the presumably pressing demands of a number of non-pregnant maternal tissues, especially exercising muscles. This may have been assisted by the lack of dependence of uterine glucose uptake on maternal plasma insulin levels (Hay *et al.* 1984*a*), assuming that the latter were minimal in underfed, exercising ewes. Finally, maternal arterial 3-hydroxybutyrate concentration was significantly reduced by exercise, possibly via a decrease in hepatic ketogenesis due to increased availability of glucose and TCA cycle intermediates, or increased peripheral utilization of 3-hydroxybutyrate, particularly in exercising muscle (Jarrett *et al.* 1976; A. R. Bird and A. W. Bell, unpublished results). This suggests that moderate levels of exercise may be beneficial in preventing the onset of uncontrolled hyperketonaemia, ketoacidosis and pregnancy toxaemia in undernourished ewes under field conditions.

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