NUTRITION–ENVIRONMENT INTERACTIONS IN PREGNANCY

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INTRODUCTION

Pregnancy represents a state of potential conflict between the mother and the products of conception which may not only determine the survival of mother and fetus (Haig, 1993) but can have a profound influence on long term health and future reproductive capacity of each (Barker, 1994). In this respect the extent to which maternal reproductive performance is limited can depend on a number of factors including current nutrition, quantity of endogenous energy reserves, availability of a compatible partner, as well as the mother's and/or grandmother's past nutritional history (Lumey, 1992). During pregnancy a female's ability to maintain or increase her own body tissue reserves while at the same time meeting the increasing energy requirements for placental and fetal growth not only determine size at birth but can also determine an individual's susceptibility to disease in later life (Godfrey & Barker, 1995). The close relationship between birth weight and mortality rate (Scriver, 1995; Fig. 1) emphasizes the need to optimize fetal growth and therefore nutrition throughout gestation (Harding & Johnston, 1995).

MATERNAL NUTRITION AND REPRODUCTIVE PERFORMANCE

Both high (twice maintenance) and low (half maintenance) levels of feed intake can compromise the establishment of pregnancy and/or embryo survival in domestic species (Robinson, 1990). It has been suggested that some of these effects may be mediated *via* changes in peripheral progesterone concentrations which can have a strong influence on fertility in sheep (Parr *et al.* 1987; Fig. 2). Mean plasma progesterone concentrations, for example, on days 8–14 after mating may determine pregnancy rates. In order to maximize conception rates progesterone levels should be above a threshold value of 2 ng/ml (Parr *et*

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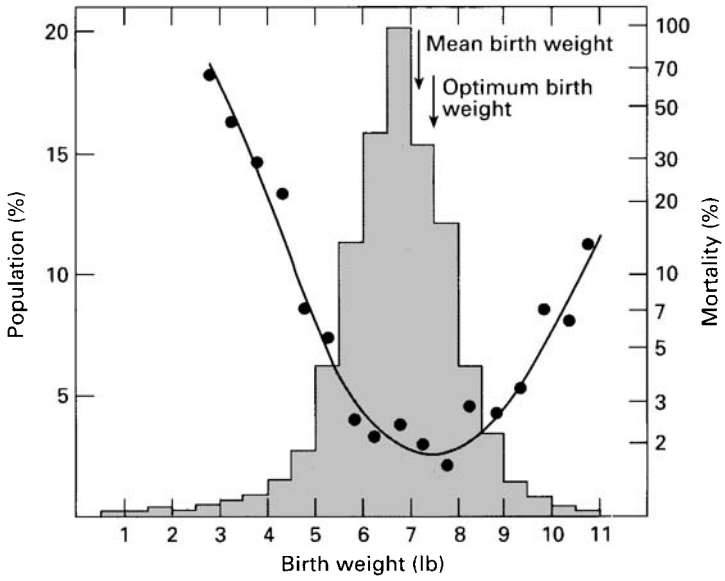

Fig. 1. Relationship between infant birth weight and mortality rates. (Reprinted with permission from Cavalli-Sforza & Bodmer, 1971, p. 613.)

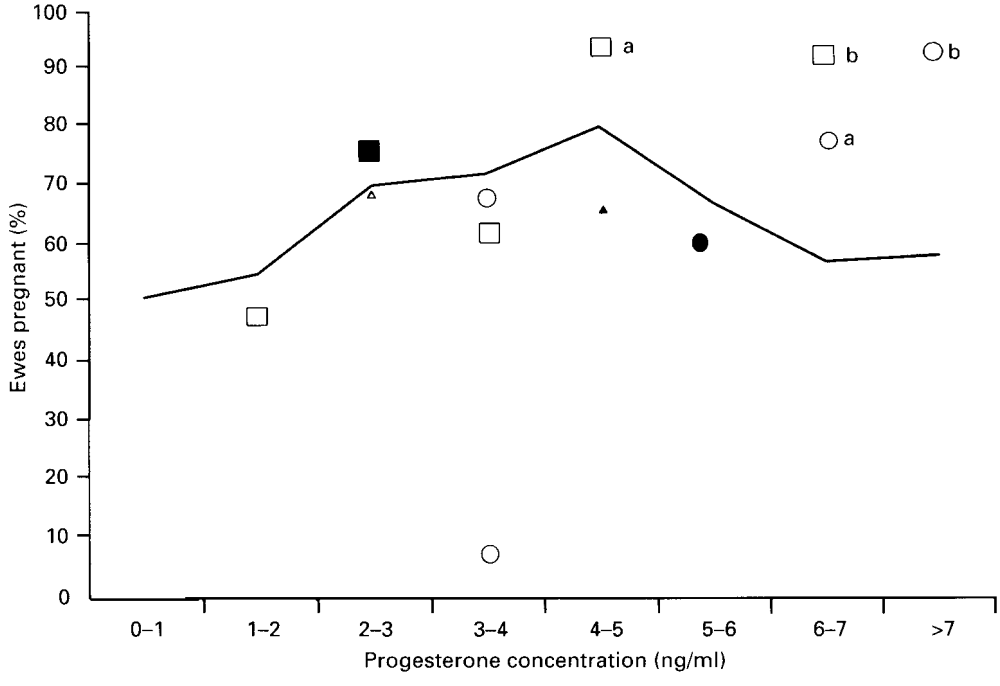

Fig. 2. Relationship between peripheral progesterone concentrations measured 8–14 days after mating and nutrient intake and pregnancy in sheep. ○, 25–50% maintenance; △, 100% maintenance; □, 150–200% mainenance. Closed symbols are ewes treated with an intrauterine device containing 340 mg progesterone. a, ewes treated with 100 μg prostaglandin F_{2a} analogue; b, ewes treated with 650 i.u. pregnant mare serum gonadotrophin. Adapted from Abecia *et al.* (1994); Parr *et al.* (1987); Rhind *et al.* (1989*a*, *b*) and Wallace *et al.* (1994).

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al. 1987). Exogenous progesterone treatment of ewes fed at a high nutritional level raises plasma progesterone concentrations above this value and results in a 50% increase in pregnancy rate. In ewes fed at maintenance or below, in which progesterone levels are above 2 ng/ml, exogenous administration has no influence on pregnancy rates (Parr *et al.* 1987; Fig. 2). The mechanisms by which increased food intake lowers circulating progesterone concentrations remain in doubt but could include an enhanced rate of progesterone clearance by the gut and liver (Parr, 1992) or a reduction in mean luteinizing hormone pulse frequency and concomitant lowering in plasma progesterone concentrations (Rhind *et al.* 1989*a*).

Recent studies have questioned the extent to which alterations in maternal progesterone profiles mediate nutritional influences on reproduction (Wallace *et al.* 1994; Abecia *et al.* 1995). It must be noted that in both studies progesterone levels in all ewes were above the critical threshold value of 2 ng/ml (Fig. 2). In experiments conducted by Wallace *et al.* (1994) plasma progesterone concentrations were high in all ewes which had been treated with 650 i.u. of pregnant mare's serum gonadotrophin, so it may not be unexpected that maternal nutrition had no effect on embryo development. The absence of any influence of feed intake on luteinizing hormone secretion, follicle growth or the capacity of corpora lutea to secrete progesterone, in studies by Abecia *et al.* (1995), could similarly be predicted, as plasma progesterone concentrations were identical (3·06 ng/ml) between groups. Despite this similarity in reproductive hormonal profiles and ovulation rates the proportion of ewes fed at a low level that became pregnant was small (8% compared with 62% in the high fed group). These findings strongly indicate the involvement of alternative nutritionally regulated hormones in controlling reproduction.

Thyroid hormones play an active role in terminating the breeding season in sheep (see Adam & Robinson, 1994) but the extent to which they can alter reproductive performance is not known. The quantity and energy content of food consumed is a major factor determining thyroid status in non-pregnant individuals (Dauncey, 1990). During late pregnancy energy intake is a primary factor determining plasma thyroid hormone concentrations in sheep (Symonds, 1995*a*), but it is not known if this influences conception. Studies in women have shown that maternal thyroid status or presence of thyroid microsomal antibodies is a primary factor determining whether pregnancy is maintained or aborted (Maruo *et al.* 1992; Roberts *et al.* 1996). Interactions between maintenance of pregnancy and thyroid hormones appear to be linked, in part, to an ability to increase circulating concentrations during early pregnancy. The importance of this adaptation is emphasized by the finding that thyroid hormones stimulate production of a number of placental hormones, including chorionic gonadotrophin, placental lactogen, progesterone and oestradiol-17β (Mauro *et al.* 1991). This response is confined to the early part of gestation and not observed near to term. Taken together these findings indicate that thyroid hormones play a primary role in maintaining the function of the differentiated trophoblast over a period in which growth and metabolic requirements are high (Robinson & Symonds, 1995). Furthermore, daily thyroxine treatment of rats throughout pregnancy enhances placental and fetal growth (Spencer & Robinson, 1993). Interactions between maternal nutrition, thyroid hormones and fertility may, however, be limited to underfed individuals.

Excess maternal nutrition in rats at the time of conception can result in a marked increase in teratogenesis due to enhanced oxidative stress (Wentzel *et al.* 1995). These effects may be linked with alterations in maternal insulin secretion, as it has been shown in women and rats that congenital malformations are induced early in diabetic pregnancies (Eriksson *et al.* 1989; Fraser, 1994). Interactions between insulin secretion, plasma glucose concentrations and nutritional manipulation of ovulation have been demonstrated in sheep (Downing *et al.* 1995). Following chronic glucose infusion there is a compensatory

reduction in feed intake as the plasma glucose concentration increases from 2·5 mM to above 10 mM and the insulin concentration rises from the basal value ($\simeq$ 0·4 μg/l) to 5 μg/l. Under these conditions a modest 20% rise in ovulation rate is observed suggesting that insulin, because of its role in regulating cell growth and metabolism, can mediate some of the ovulatory responses to nutritional stimuli (Downing *et al.* 1995). The full extent to which reproductive gonadotrophic hormones as opposed to metabolic regulatory hormones such as insulin, insulin-like growth factors (IGF), thyroid hormones or growth hormone mediate nutritionally induced alterations in fertility remains to be clarified. Additional factors that must be considered in such experiments are the long term consequences on fetoplacental growth as well as postnatal viability.

THE MATERNAL ENVIRONMENT AND PLACENTAL GROWTH

Placental weight is known to peak at around mid gestation in sheep compared with late gestation in women (Hay & Wilkening, 1994) and if placental growth is restricted (i.e. to less than half of normal weight) subsequent fetal growth is markedly reduced (Owens *et al.* 1995). Recent studies have shown that significant alterations in maternal macro- or micronutrient status are associated with an enhancement of placental weight or volume which does not appear to be accompanied by increased fetal growth. In the case of gross nutritional effects on placental growth, long term periods of energy restriction before or after mating of sheep, leading to a pronounced loss of maternal body weight, result in an enhancement of placental weight (McCrabb *et al.* 1991; Robinson *et al.* 1994). It has yet to be determined if this is a response to undernutrition *per se* or due to concomitant changes in maternal energy metabolism associated with mobilization of body fat reserves as observed after underfeeding in late pregnancy (Symonds & Lomax, 1990). In unshorn sheep, feeding at one-third of predicted energy requirements for 5–21 d during late pregnancy halves the rate of maternal glucose production (Leury *et al.* 1990). Twin bearing ewes can adapt to this situation by decreasing their metabolism without any change in total rate of fat oxidation, thereby increasing the contribution of non-esterified fatty acid oxidation to total heat production (Symonds *et al.* 1989). Nitrogen metabolism can also be enhanced (Faichney & White, 1987) which could be particularly important during pregnancy in women for whom urea salvage may be an important maternal adaptation in order to maintain fetal nitrogen supply (Forrester *et al.* 1994).

Effects of maternal nutrition on placental and fetal growth can be influenced by increased or decreased nutrient intake at different stages of pregnancy. This point is emphasized by studies on 538 women from the Southampton area which indicate that a high carbohydrate or fat intake in early pregnancy suppresses placental growth, especially if combined with a low dairy protein intake in late pregnancy (Godfrey *et al.* 1996; Table 1).

Human studies have indicated that placental volume at 18 weeks of gestation is negatively correlated with maternal haemoglobin and ferritin concentrations in blood (Wheeler, 1994). At term, the ratio of placenta weight to birth weight is highest in those mothers in whom lowest haemoglobin concentrations were recorded during pregnancy, an association that is amplified if mean cell volume falls by more than 6 fl (Godfrey, 1994). These relationships are of increasing interest given their strong correlation with adult disease (Barker & Sultan, 1995). It must be noted that the extent to which relationships of this kind are linked to maternal iron deficiency remain in doubt as a variety of other factors including maternal smoking and number of pregnancies are also associated with enhanced placental volume (Howe, 1994). Importantly the functional significance of low maternal haemoglobin concentrations in pregnancy remains in doubt as a recent survey has indicated

Table 1. *Relationship between nutrient intake during early and late pregnancy and placental and birth weights in women. Adapted from Godfrey* et al. *(1996)*

	Unit change	Decline in placental weight (g)	Decline in birth weight (g)
Early pregnancy			
Energy	log Kcal increase	38	134
Carbohydrate	log g increase	49	165
Fat	log g incrase	27	101
Late pregnancy*			
Dairy protein[1]	g decrease	1·4	—
Mean protein[1]	g decrease	—	3·1

* After taking account of carbohydrate intake in early pregnancy.

that when maternal haemoglobin does not fall below 105 g/l there is a 5–7-fold higher incidence of low birth weights and preterm births (Steer *et al.* 1995).

ENVIRONMENTAL INFLUENCES ON MATERNAL METABOLISM DURING PREGNANCY

During the final weeks of gestation the mother's ability to supply glucose to the developing fetus is one key factor regulating fetal growth. Transfer of glucose across the placenta is dependent on maternal arterial plasma glucose concentration (Hay, 1995). In sheep, several days of underfeeding, sufficient to induce maternal hypoglycaemia, can dramatically decrease fetal growth rate (Mellor, 1983). Conversely, intragastric infusion of glucose and amino acids into fetuses of underfed ewes can restore growth rates to those observed in well fed ewes (Charlton & Johengen, 1985; Table 2). The potential benefits to the fetus of maternal nutrient supplementation remain in doubt although some studies have shown enhanced fetal weight or neonatal survival (see Table 2). The extent to which such strategies are adopted in the future must be carefully considered. This point is emphasized by the observation that maternal glucose supplementation over this final week of pregnancy in underfed ewes (60% of energy requirements) at a level equal to endogenous glucose production can result in a reduction in postnatal survival and also a postnatal decline in insulin secretion (Clarke *et al.* 1996).

Interactions between acute and chronic regulation of maternal glucose production and fetal growth have been highlighted by studies indicating that fetal thyroid microsomal antibodies persist even when 'optimal' maternal glucose control is maintained by thrice daily insulin injections in women (Roversi *et al.* 1979). Exogenous insulin administration cannot mimic the *in vivo* situation, so very high postprandial glucose concentrations in maternal plasma are likely to be reflected in the fetus, thereby stimulating fetal insulin secretion (Fraser, 1994). A similar situation is observed following chronic cold exposure of pregnant sheep (Thompson *et al.* 1982) but owing to the ewe's ability to alter insulin sensitivity (Symonds *et al.* 1988) hyperglycaemia does not ensue (Symonds *et al.* 1986). Lambs born to underfed ewes exposed to cold have an enhanced ability to maintain body temperature and growth during postnatal life (Symonds *et al.* 1990, 1992). The level of maternal nutrition appears to play a primary role in mediating some of these responses as cold exposure induced by winter shearing of well fed ewes (100% of total energy requirements) which remain normoglycaemic during late gestation (Symonds, 1995*a*, *b*) does not enhance lamb birth weight (Symonds *et al.* 1993).

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Table 2. *Examples of fetal or maternal nutrient supplementation which have increased fetal body weight or neonatal survival*

Species	Nutrient supplemented	Dose	Stage of pregnancy	Birth weight				Low birth weight (%)		Responses	Ref.
				Controls		Supplemented					
				Mean	SE	Mean	SE	Controls	Additional Supplemented		
Sheep	Fetal glucose	15–25 g/kg daily	115–137 days	3·28	0·24	3·86*	0·16	—	—	45% increase in internal fat depots	Stevens *et al.* (1990)
Women	Maternal energy	1·95 MJ/d	27–40 weeks	3·19	0·23	3·30	0·24	12·9[a]	9·5	Children taller at 5 years	Kardjati *et al.* (1988) Kusin *et al.* (1992)
Women	Maternal oxygen	55% O_2 at 8 l/min	1 week between 26–34 weeks	1·00	0·13	1·07	0·13	63[b]	47	Perinatal death reduced from 63 to 29%	Battaglia *et al.* (1992)
Women	Maternal zinc	25 mg/d	19–40 weeks	3·09	0·73	3·24*	0·67	12·7[a]	7·8	0·7 cm larger head circumference	Goldenberg *et al.* (1995)

Significant differences between control and supplemented: *, $P < 0·05$.
[a] Low birth weight < 2·5 kg.
[b] Low birth weight < 1·0 kg.

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It should be noted that chronic fetal hyperglycaemia can result in suppression of insulin secretion (Carver *et al.* 1995), and may explain why birth weight is decreased in some diabetic pregnancies (Gestation and Diabetes in France Study Group, 1991). Alterations in maternal glucose metabolism following exercise, which can increase insulin sensitivity (Henriksson, 1995), could explain why birth weight is 315 g lower in mothers who perform regular vigorous exercise (more than 4 sessions per week) during pregnancy (Bell *et al.* 1995). Maternal insulin secretion can be further modulated by previous dietary history as an increased insulin response to intravenous glucose persists after weight loss in obese women with polycystic ovarian syndrome (Holte *et al.* 1995).

MATERNAL INFLUENCES ON FETAL BODY PROPORTIONS

For any group of non-obese females of similar body weight, although maternal weight gain through pregnancy is positively correlated with infant birth weight (Abrams & Laros, 1986) significant changes in birth weight distribution may not be fully identified. In order to obtain a more accurate assessment of growth restriction the use of an individualized birth weight ratio is required. This should give a measure of the difference between actual birth weight and a predicted value calculated from the relative contributions of gestation, maternal weight and height, infant sex, parity and ethnic origin (Sanderson *et al.* 1994). By the use of these criteria an increased number of infants are classified as being small with abnormal ponderal indices and skinfold thickness. In addition more of these infants exhibit abnormal fetal heart rate patterns, and require operative delivery for fetal distress and neonatal resuscitation.

The importance of determining whether fetal growth restriction is symmetrical or asymmetrical has been emphasized by an increasing body of epidemiological evidence from England (Barker, 1994) and more recently Sweden (Leon *et al.* 1996; Lithell *et al.* 1996). These investigations have indicated that a primary risk factor for a number of adult cardiovascular diseases, including coronary heart disease, hypertension and diabetes, is the relationship between birth weight and body proportions (Barker, 1994). Two particular types of babies have been identified as being most at risk, either those that are long and thin (i.e. indicative of reduced adipose deposition) following reduced growth during mid gestation (Barker *et al.* 1993), or those that are short for weight due to poor growth, particularly that of the liver (Gruenwald, 1974), in late gestation. Clearly the extent to which alterations in maternal weight or fat distribution around conception or later contribute to asymmetric fetal growth will continue to be a major research focus. Despite asymmetric fetal growth restriction occurring more often than the symmetrical kind (Owens *et al.* 1995) the primary stage or stages of fetal development which contribute to this problem have yet to be determined. It is of particular interest to note that premature infants of low birth weight (but unspecified body proportions) do not exhibit higher blood pressure during childhood (Lucas & Morley, 1994). This raises the possibility that preterm delivery of the growth retarded fetus could be beneficial by removing it from an adverse maternal and/or placental environment.

MATERNAL BODY SIZE AND NEWBORN BIRTH WEIGHT

Maternal body weight and/or glucose status can have a large influence not only on birth weight (Abrams & Laros, 1986) but also on the incidence of fetal macrosoma (Hill *et al.* 1995; Fig. 3). This interaction appears to be partly dependent on level of maternal feed intake during early pregnancy in conjunction with the mother's ability to maintain or

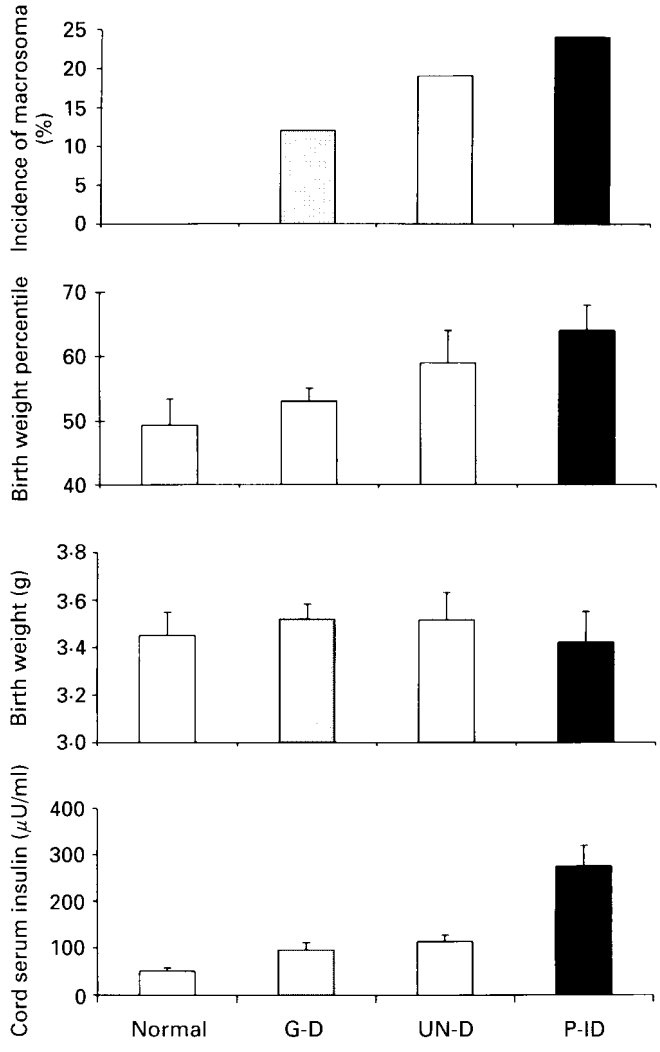

Fig. 3. Relationship between maternal glucose status, infant birth weight and incidence of fetal microsomal antibodies. Adapted from Hill *et al.* (1995). G-D, gestational diabetes; UN-D, previously undiagnosed diabetes; P-ID, progestational insulin-dependent diabetes.

increase her body fat deposits over this period. For example, studies using sheep of similar age have shown that, when ewes are underfed between 30 and 90 d of gestation in order to cause a 12% decline in body weight, then weight at mating accounts for 78% of the variance in lamb birth weight (Russel *et al.* 1981). In well fed ewes that maintain body weight no value was attributable to the impact of maternal mating weight on lamb birth weight.

In studies on women, any relationships between maternal weight and neonatal outcome may be obscured by the wide age range of women recruited, as older women (> 35 years) have an elevated risk of stillbirth (Raymond *et al.* 1994). A recent study from Finland has shown that young nulliparous women (< 20 years) are more likely to be thin and produce low birth weight infants, while older multiparous women (> 35 years) tend to have larger

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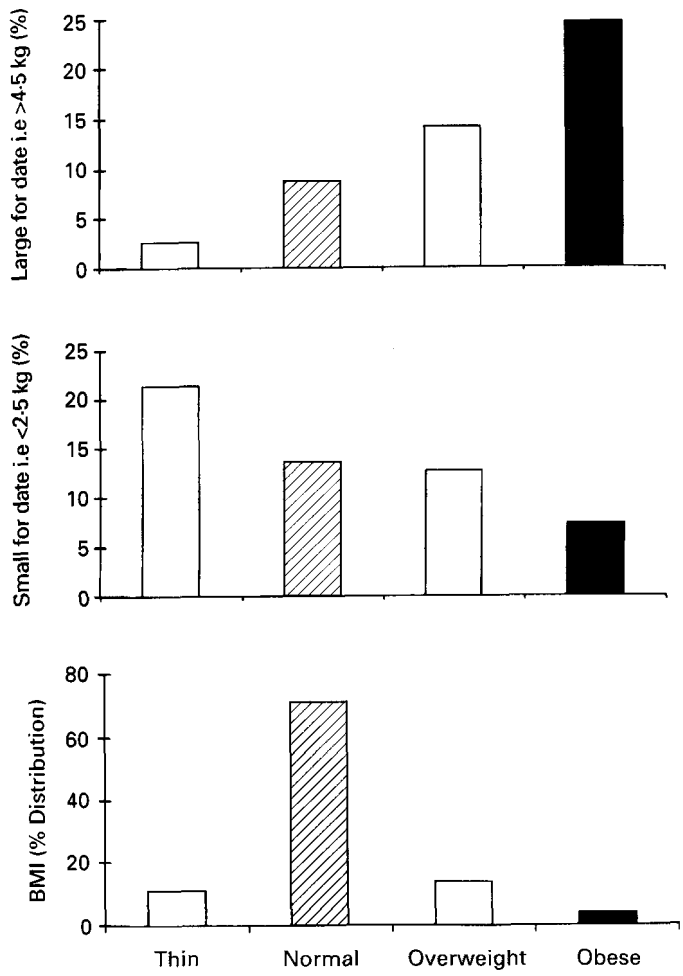

Fig. 4. Relationship between body mass index (BMI) distribution and incidence of small or large for dates infants in pregnancies with antenatal complications. Adapted from Lumme *et al.* (1995).

infants and increased incidence of births by Caesarean secretion (Lumme *et al.* 1995; Fig. 4). Relationships between maternal body mass index and infant birth weight are not greatly influenced by antepartum complications (i.e. gestational diabetes, hypertension or pre-eclampsia), although the incidence of smoking is higher in thin women compared with other groups (28·4 *v.* 21·3 %; Lumme *et al.* 1995). Smoking can reduce placental growth and increase the incidence of placental abruption and placenta praevia (Meyer & Tonascia, 1977; Callan & Witter, 1990). The influence of maternal nutrition on relationships between maternal age, intrauterine growth retardation, smoking and gestational age remain to be fully explained (Raymond *et al.* 1994).

One factor that could provide an important link between compromised fetoplacental growth and maternal nutrition is the mother's ability to alter circulating concentrations of IGF-1 and IGF-binding protein (IGFBP-1) during pregnancy. Fetal size and growth during the third trimester are closely related to umbilical venous blood concentrations of IGF-1 at term (Spencer *et al.* 1995). IGFBP-1 levels in maternal circulation are negatively

Table 3. *Umbilical vein plasma hormone and metabolite concentrations from lambs delivered by Caesarean section born to heavy (≥ 60 kg) or light (≤ 55 kg) ewes*

(Values are means with their standard errors)

		Glucose (mM)		Lactate (mM)		NEFA (mM)		T_3 (nM)		T_4 (nM)		Cortisol (ng/ml)		IGF-1 (ng/ml)	
	n	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Heavy	5	3·23	1·26	5·13	0·24	0·12	0·06	1·03*	0·30	275*	47	75	6	223	50
Light	5	4·48	2·79	4·36	0·26	0·05	0·04	0·50	0·24	208	26	62	12	180	43

Significantly different from lambs born to light ewes as assessed by Students *t* test: $^*P < 0{\cdot}05$.
T_3, triiodothyronine; T_4, thyroxine.
NEFA, non-esterified fatty acids.
IGF, insulin-like growth factor.

correlated with maternal weight, birth weight and placental weight and are highest in women that produce small-for-gestational-age babies (Hills *et al.* 1996). Adaptations of this type may result in reprogramming of the IGF-1 axis after birth, thereby resulting in children of low birth weight developing higher IGF-1 concentrations than expected for weight and height, in association with a higher risk of elevated blood pressure in later life (Fall *et al.* 1995). A failure to realize growth potential *in utero* further increases the risk of raised blood pressure in adult life if this is accompanied by adult obesity (Leon *et al.* 1986).

An increased predisposition to neonatal complications in offspring from low body weight mothers is not confined to women as similar interactions have been observed in sheep. Twin or triplet bearing ewes, which maintain an average body weight of 55 kg (i.e. 'light' ewes) throughout pregnancy and exhibit an appreciable decline in body fat stores during the final month of gestation, have reduced placental mass and produce smaller lambs than 'heavy' ewes (> 60 kg) that maintain constant fat reserves (Symonds & Clarke, 1996). Importantly, lambs delivered near to term by Caesarean section from light ewes are at increased risk of becoming hypothermic and may exhibit respiratory failure when delivered into a cool ambient temperature. These symptoms may be linked to the significantly lower plasma triiodothyronine and thyroxine concentrations observed in cord blood at term as all other hormones and metabolites measured were similar between groups (Table 3). Triiodothyronine is known to be necessary for growth, development and maturation of the majority of fetal organs and its concentration in fetal circulation is reduced following placental insufficiency (Symonds, 1995*a*). The importance of normal thyroid function after birth for thermoregulation in lambs has been emphasized from studies involving vaginally delivered lambs which had been thyroidectomized at 127 days of gestation (Schermer *et al.* 1996). Over the first day of life these lambs had a decreased ability to effect non-shivering thermogenesis in brown adipose tissue and increased incidence of hypothermia. In contrast, umbilical cord injection of a physiological dose of triiodothyronine or thyrotrophin releasing hormone immediately before cord cutting can improve thermoregulation in lambs delivered by Caesarean section (Lyke *et al.* 1995; Heasman *et al.* 1996). It is therefore important to consider the impact of any nutritional or environmental strategies aimed at improving maternal or fetal health in relation to potential changes in thyroid hormone secretion (Symonds, 1995*b*).

MATERNAL BODY WEIGHT AND DISEASE IN PREGNANCY

Although recent research has emphasized the potential constraints on fetal growth associated with maternal thinness, it is established that being overweight increases both the incidence of large infants (Lumme *et al.* 1995) and a mother's risk from complications associated with pregnancy (Drife, 1986). Hypertension and diabetes are the most prevalent and may represent an overcompensation by maternal physiological and metabolic regulatory systems in response to conflicting metabolic demands between maternal tissues and products of conception. In this respect the relatively high incidence of hypertensive disorders in pregnancy (1 in 7–10 for first pregnancies) suggests that this is not always a condition that must have an adverse outcome for mother and fetus (Broughton Pipkin, 1995). It could be that, as in the case of diabetes, hypertension in pregnancy represents compensatory mechanisms which were once advantageous in terms of maximizing efficiency of substrate utilization by mother and fetus when food availability was limited and have adverse consequences only when dietary intake is excessive or unrestricted (Robinson & Johnston, 1995). Alterations in food selection and levels of consumption associated with western lifestyles could explain in part why overweight women are at much greater risk from pregnancy related complications which can be exacerbated if excessive weight is gained during early pregnancy (Drife, 1986).

PERSPECTIVES

The potential impact of female development from embryonic stages to adulthood on the health and wellbeing of future generations has been clearly identified (Barker, 1994). In this context a primary strategy for decreasing the incidence of birth complications, ranging from the need for delivery by Caesarean section (Robinson *et al.* 1994) to immature organ function appears to reside in an increased understanding of nutritional and related factors (e.g. thyroid hormones; Symonds, 1995*a*, *b*) which promote female growth, development and maturation. In respect of human health such knowledge has the potential not only to decrease complications during pregnancy but also to give long term benefits by reducing the incidence of cardiovascular disease during adulthood. These problems may be greatly exacerbated by nutritional/psychological difficulties associated with urbanization (Hoek *et al.* 1995) and by anorexia in juvenile and young mature females (Hill, 1993) as well as the continued persistence of smoking during pregnancy (Raymond *et al* 1994). An increased global awareness of such interactions has a far greater potential to reduce infant and adult morbidity and mortality than specific nutrient supplements aimed at females during pregnancy.

The authors would like to acknowledge the financial support of The Wellcome Trust, the Biotechnology and Biological Sciences Research Council and the Ministry of Agriculture, Fisheries and Food.

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Printed in Great Britain