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Current perspectives on placental development and its integration with fetal growth

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Survival and development of the conceptus in mammals throughout a prolonged gestation period depends on a variety of factors. These include suppression of luteolysis, and of immunological mechanisms ensuring rejection of foreign tissue as well as the development of mechanisms for exchange of metabolic substrates and waste products between the conceptus and its external environment in the uterine lumen. It has become evident over the last few years that mechanisms for actively regulating these processes begin to develop within the rapidly expanding outer trophectoderm layer of the developing blastocyst even before implantation or development of the complex membrane layers and vascular system linking the embryo with the outer chorionic layer. Fetal growth retardation later in prenatal life may well be consequent on inadequate expression of fetal regulatory mechanisms during these early stages of development.

Nutrition of the conceptus during early development may depend to a large extent on diffusion, but manipulation of the uterine environment by the conceptus has already begun before implantation. Secretion of peptides, steroids and prostaglandins by the trophoblast play important roles in preventing luteolysis, in modifying prostaglandin production within the endometrium and in modifying uterine secretion, but the substances involved and their effects vary greatly between species (Hearn *et al.* 1988; Bazer *et al.* 1989; Thatcher *et al.* 1989). Equally, however, there is evidence that normal development of the embryo during this period also depends on the presence of maternal insulin and metabolite concentrations within the normal range (Travers *et al.* 1989). In both sheep and cattle the secretory proteins include trophoblastin-1, a peptide closely related to the interferons, with anti-viral properties and strong anti-luteolytic activity. The anti-luteolytic activity appears to be mediated through induction of an inhibitor of prostaglandin synthesis within the endometrium. In cattle this inhibitory activity remains high throughout pregnancy and evidence indicates that trophoblastic tissue of the chorion continues to secrete bovine trophoblastin-1 for an extended period (Thatcher *et al.* 1989). In primates, by contrast, the first embryonic signal essential for implantation to occur is the secretion of chorionic gonadotrophin. It is of interest that the secretion of chorionic gonadotrophin by the trophectoderm is dependent on the presence of an intact

inner cell mass, illustrating an early interdependence in function of these two components of the conceptus (Hearn *et al.* 1988). Secretion of peptide and steroid hormones by trophoblast cells does, of course, remain an important function of this outer layer of the conceptus throughout gestation, maintaining pregnancy, whilst manipulating maternal metabolism and the uterine environment to the advantage of the developing conceptus (Heap & Flint, 1982). The enormous increase over recent years in the number of peptides secreted by the placenta and their range of functions (Martal *et al.* 1988), as well as the increased volume of information about better known peptides such as placental somatomammotropin (Chene *et al.* 1988), attests to the significance of this placental function for promoting normal fetal development. The presence of many growth factor receptors on the trophoblast (Blay & Hollenberg, 1989) suggests the conceptus is also responsive to alterations in the uterine environment, but many aspects of these hormonal interactions remain to be elucidated.

Enlargement of the conceptus necessitates the development of more sophisticated mechanisms for substrate acquisition and distribution to the developing embryo. Solutions to this problem are almost as diverse as the species themselves, both in the embryonic structures involved and in the efficiency with which they fulfil these functions. It is not proposed to discuss implantation nor the detailed anatomical considerations of placentation as they have been discussed in detail by numerous earlier texts and reviews (Steven, 1975; Renfree, 1982; Battaglia & Meschia, 1986; Faber & Thornburg, 1986). Suffice it to say that placental attachments between the conceptus and uterine endometrium vary from very diffuse structures where there is no erosion of maternal or fetal tissues, as in the pig, to those where invasion of the endometrium by specialized areas of the trophectoderm leads to direct contact between maternal blood and the exterior surface of the trophectoderm itself, as in the haemochorial placentas of rodents and primates. These differences in placentation and in the arrangement of feto-placental and endometrial vasculature have led to intensive investigation of their functional efficiency for transport of respiratory gases and metabolic substrates (Battaglia & Meschia, 1986; Faber & Thornburg, 1986). As could be expected from the diversity of structural arrangements amongst species, there is considerable variation in the permeability characteristics and transport mechanisms of different placentas, so generalization is difficult. Nevertheless, these characteristics of the trophoblast effectively isolate the developing embryo, other fetal membranes, and their enclosed fluid spaces from unregulated exchange of materials with uterine fluid or maternal blood and are responsible for maintaining the characteristic differences between mother and fetus in circulating concentrations of most blood constituents. Many of the transport processes and cellular structures involved in determining permeability characteristics of the placental membranes remain to be defined for individual species and aspects of this work are considered elsewhere in the symposium.

Despite the diversity in structure and function between species, measurements of placental size and its relation to fetal weight, both at term and earlier, indicate the efficiency with which this specialized exchange organ meets the demands placed on it by growth of fetal tissues. Variations between species in placentation do not appear to result in significant differences in the success of prenatal development. For example, the relationships between placental and fetal weights in the pig, a species with a diffuse epitheliochorial placenta (Michael *et al.* 1983), are very similar to those observed in the rabbit, a species with a discoid haemochorial placenta (Bassett, 1986), despite these very

dissimilar methods of placentation. The importance of the placenta in this relationship has been highlighted by the almost universal clinical assumption that small placental size is the major determinant of intrauterine growth retardation (IUGR) in human infants. Certainly, investigations of the relationships in experimental animals have provided strong support for this view (Alexander, 1974). Correlations between placental weight and infant size at birth are high in all species investigated, while investigations in guinea-pigs (Myers *et al.* 1982), pigs (Michael *et al.* 1983) and in rabbits (Duncan, 1969; Bassett, 1986) indicate that similarly close relations exist earlier in gestation. Measurements of uterine blood flow to the placenta show that this increases more rapidly than placental weight with increasing gestational age (Bruce & Abdul-Karim, 1973; Rosenfeld, 1984), but within groups of animals at a similar gestational age blood flow to the placental discs in anaesthetized rabbits (Duncan, 1969) and conscious guinea-pigs (Myers *et al.* 1982; Jones & Parer, 1983) is also closely related to placental size. Flow per unit weight also increases with placental size, so within litters, larger placentas are hyperperfused relative to smaller ones. Umbilical flow to the placenta also increases relative to placental weight with gestational age (Rosenfeld, 1984), but there is no detailed information about the way uterine and umbilical flows alter relative to one another as placental size varies within litters in polytocous species. However, Saintonge & Rosso (1981) showed that placental transfer of methyl glucose and α-aminoisobutyric acid to the fetus was proportional to placental size, suggesting some matching of flows on the two sides of the placenta.

Experimental production of IUGR by a variety of methods, including uterine artery ligation, removal of uterine caruncles before mating, severe maternal undernutrition, prolonged heating or embolization of the uterine vasculature, all lead to reduction in both placental and fetal growth and in extreme cases to fetal death (Creasy *et al.* 1972; Alexander, 1974; Robinson *et al.* 1979; Mellor & Murray, 1981; Lafeber *et al.* 1984; Harding *et al.* 1985; Mellor, 1985; Bell *et al.* 1989). By contrast, reduction in fetal number of rabbits on day 9 of gestation and of rats on day 14 leads to fetal and placental hypertrophy (Fletcher *et al.* 1982; Ogata & Finley, 1988).

Metabolic investigations indicate that experimentally produced small fetuses, like IUGR infants, have low plasma glucose and insulin concentrations, may be hypoxaemic and have numerous other metabolic and endocrine alterations indicative of severe undernourishment (Robinson *et al.* 1979, 1980; Jones & Robinson, 1983; Lafeber *et al.* 1984; Harding *et al.* 1985; Owens *et al.* 1987*a*,*b*), whilst the larger fetuses from litter-reduced rabbits and rats (Fletcher *et al.* 1982; Ogata & Finley, 1988) have elevated insulin concentrations. As already indicated, small placental size results in a reduction in uterine blood flow to the placenta, so placental transport and delivery of both oxygen and glucose to the fetus are reduced (Owens *et al.* 1987*a*,*b*). Despite these changes, consumption of O_2 by the gravid uterus and fetus per kg tissue mass were comparable with those of control lambs because of an increase in extraction. Glucose utilization in the fetus per kg tissue, also, was not different from that of control fetal lambs, due to increased extraction. However, glucose consumption in the uteroplacenta, both absolutely and per kg tissue, was decreased and there was a greatly increased output to the fetus of lactate, which could not be accounted for by glucose utilization. Glucose was apparently being disproportionately diverted to the fetus, at the expense of the placenta.

All these investigations seem to indicate that small placental size limits fetal growth. However, when the effects of fetal undernutrition on the relative growth of individual

tissues and organs are examined, marked differential effects, not simply a consequence of the allometric nature of growth, are found (Robinson & McDonald, 1979). Surprisingly, considering its location on the supply line between mother and fetus, the reduction in placental growth rate in naturally small fetal rabbits is as great or greater than that in any of the fetal somatic organs or tissues (Bassett, 1986). At each gestational age studied the proportional reduction in placental size is as great or greater than that in the fetal liver and considerably more than that of the fetal body as a whole, while the reduction in growth of the fetal brain is substantially less than that of other organs. Alternatively, looking at the observations from a different viewpoint, it may be that with increasing substrate supply to the conceptus proportionately more is available to support growth of the placenta and liver relative to that of other tissues, such as the brain. The reasons for such changes in distribution of nutrient use are likely to be complex.

Examination of the relative retardation of placental growth and that of other tissues in experimentally growth-retarded fetuses of other species show similar effects on the relative growth of placenta and brain. Irrespective of whether fetal growth has been retarded by ligatures on one uterine artery (guinea-pigs; Lafeber *et al.* 1984), severe reduction of uterine caruncle number before mating (sheep; Harding *et al.* 1985; Mellor, 1985; Owens *et al.* 1986), by undernutrition during mid-gestation (sheep; Mellor & Murray, 1981) or by hyperthermia during the second half of gestation (sheep; Alexander, 1974; Bell *et al.* 1989), brain growth is retarded significantly less than the body as a whole, while the growth of the placenta, like that of the liver, is proportionately more retarded and it would appear that, despite the diverse methods used to reduce fetal growth, the pattern of changes in fetal development are much the same. It should be noted, however, that these relationships obtain even though there is considerable evidence for attempts by the placenta to compensate for the experimental limitation imposed on its functional development as, for example, in the carunclectomy preparation, where the size of cotyledons which develop may be substantially greater than normal (Alexander, 1974; Robinson *et al.* 1979; Harding *et al.* 1985).

Perhaps most surprisingly, similar changes in the relative proportions of placenta and other tissues also occur in sheep where growth retardation has been induced by repeated microsphere injection into one uterine artery during the last 6 weeks of gestation (Creasy *et al.* 1972), well after the time when the ovine placenta is normally considered to have reached its maximum weight. In this preparation, not only is fetal growth reduced, but the weights of cotyledons in both control and embolized horns of the uterus and total placental weight are reduced more than fetal body-weight, while fetal brain weight is little altered from normal (Clapp *et al.* 1982; Charlton & Johengen, 1987). Interestingly, Charlton & Johengen (1987) also showed that nutritional supplementation of embolized fetuses by continuous intravenous infusion of a glucose–amino acid mixture can maintain normal growth of the fetus. Placental weight in these supplemented embolized fetuses was actually greater than that of controls. These studies are important since they show placental tissue weight, like fetal growth, is actively maintained by the rate of nutrient delivery into the fetal circulation and imply that even in the embolized preparation gaseous exchange across the placenta may not be the first rate-limiting factor for normal development of the conceptus.

In an earlier presentation (Bassett, 1986) it was proposed that differences in the relative growth of the placenta and other fetal tissues could most readily be explained by regulation of placental growth from within the body of the fetus, rather than by

autonomous local regulation. Possible ways in which this might be achieved include regulation of nutrient and hormone concentrations in the blood supplied to the placenta via the umbilical circulation as well as changes in the rate of umbilical blood flow.

Variations in fetal and placental size in normal and litter-reduced fetal rabbits are closely correlated with fetal plasma insulin concentrations (Fletcher *et al.* 1982), while decreased fetal plasma insulin is associated with experimental growth retardation (Robinson *et al.* 1980; Lafeber *et al.* 1984; Harding *et al.* 1985). However, while administered insulin may increase both fetal and placental weights (Susa *et al.* 1979; Fletcher & Bassett, 1986*a*), neither fetal pancreatectomy (Fowden *et al.* 1986), nor fetal streptozotocin administration (Fletcher & Bassett, 1986*b*) resulted in a reduction in placental size proportionate to the reduction in fetal weight. Despite the documentation of insulin receptors in placental tissue (Blay & Hollenberg, 1989) and stimulatory effects of insulin on the protein synthetic rate in ovine placental cotyledons (Horn *et al.* 1983), direct effects of insulin on placental glucose metabolism remain uncertain. There is compelling evidence that it has no effect on placental glucose utilization or transfer to the fetus, although it does influence these processes indirectly, through its effects on glucose uptake within fetal tissues (Hay & Meznarich, 1988; DiGiacomo & Hay, 1989).

The possibility, important for fetal control of placental function, that substrate utilized to support placental metabolism may be derived from the umbilical arterial supply, rather than from substrate derived directly from the mother by active uptake at the brush border, is supported by the finding of ^{14}C:^{3}H ratios in fetal plasma lactate and fructose which were not significantly different from those in fetal plasma glucose, but which differed greatly from those in maternal plasma glucose, during infusions of [U-^{14}C]glucose into fetal lambs and of [6-^{3}H]glucose into their mothers (Bassett *et al.* 1985). The ovine placenta is poorly permeable to lactate and fructose so the ^{14}C:^{3}H values in these metabolites in fetal plasma give a good indication of the glucose pool from which they are derived, as glucose ^{14}C:^{3}H values within maternal and fetal compartments differ greatly. Since fructose is evidently synthesized exclusively in the placenta and lactate is a major product of placental glucose metabolism, these observations imply that virtually all the glucose metabolized by the fetal placenta is derived from the umbilical arterial supply and suggest there may be some compartmentation of glucose transport and oxidative metabolism within the organ. Additional evidence that this somewhat unlikely conclusion may be correct has been provided by several more recent investigations of glucose utilization in the uteroplacenta of the sheep. Gu *et al.* (1987) reported that about two-thirds of the glucose removed from the fetal circulation was taken up by the placenta and that most of this was returned to the fetus as lactate or fructose, labelling patterns indicating that there was little mixing with glucose derived from the mother. However, as dual labelling of maternal and fetal pools was not used this conclusion should be treated with some reservation. None the less, the observations are indicative of extensive utilization by the placenta of glucose from the fetal pool. Far stronger support is provided by the recent studies of DiGiacomo & Hay (1990) and Hay *et al.* (1990) which show that uteroplacental glucose utilization is 'primarily placental, i.e. tissues having direct access to glucose molecules carried by the umbilical circulation' and that its rate is proportional to the fetal plasma glucose concentration and not to that of the mother, irrespective of the concentration gradient across the placenta. These studies do not provide evidence for the source of the glucose utilized, but it is significant that rates of uteroplacental glucose utilization are directly comparable with rates of glucose utilization

from the fetal circulation observed in earlier studies when the maternal–fetal difference was abolished (Simmons *et al.* 1979). The possibility that a substantial amount of the glucose utilized by the placenta might be derived from glucose in the umbilical circulation was discussed by Meschia *et al.* (1980), but further stringent validation of this has not been reported.

However, while these observations have important implications for the integrated control of fetal and placental glucose metabolism, the measurements of Owens *et al.* (1987*b*) indicate that placental utilization of glucose in hypoglycaemic growth-retarded fetal lambs may be inadequate to support placental lactate and fructose production. Indeed, further unpublished observations of Kind and Robinson, cited by Robinson (1989), indicate substantial conversion of alanine and branched-chain amino acids from the fetus to lactate in the placenta. Our own measurements of lactate specific activity during labelled glucose infusions (Bassett *et al.* 1985) were also consistent with the conclusion that a substantial amount of the lactate in fetal blood (about 35%) may be derived from substrates other than glucose, though not necessarily in the placenta. In addition, observations of DiGiacomo & Hay (1990) show that, although uteroplacental glucose consumption falls during fetal hypoglycaemia, O_2 consumption does not alter and they postulate the existence of a reciprocal relationship between placental glucose oxidation rate and that of other substrates such as placental glycogen, amino acids, or lactate. It will obviously be important to determine whether the alternative substrates are derived from maternal or fetal plasma. It is noteworthy, however, that fetal hypoinsulinaemia is associated with increased plasma α-amino acid-nitrogen concentrations and that insulin infusion will decrease their concentration (Fowden *et al.* 1986), though there appears to be no information about effects of insulin on placental amino acid uptake from the fetal circulation.

All these observations are strongly indicative of integrated control of placental and fetal somatic oxidative metabolism through differences in tissue responses to insulin and perhaps other hormones, whose concentrations alter as nutrient availability to the conceptus changes. They suggest, however, that it may be very difficult to overcome the limitation imposed on fetal growth by a small placenta through manipulation of maternal nutrition or blood supply to the uterus. The very severe limitation on transfer of glucose and amino acids to the conceptus imposed by the small placenta also appear to preclude this approach. On the other hand, it is evident that the placentas of small fetuses are relatively underperfused by maternal blood and there may be some possibility of overcoming this limitation pharmacologically. The prevention of fetal growth retardation by fetal infusion of glucose and amino acid mixtures after uterine embolization in late pregnant sheep (Charlton & Johengen, 1987) suggests an alternative way in which the limitation may possibly be overcome, but wider application must undoubtedly wait until it is clear that placental O_2 transfer really is not a limiting factor and that fetal growth retardation resulting from inadequate placental growth far earlier in development can also be counteracted.

A question of greater long-term significance, perhaps, is the nature of the mechanism by which the conceptus determines the extent of the initial expansion in the vascular network of the endometrium around the site of implantation. It is evident from observations on polytocous species that differences in fetal growth throughout gestation are, to a large extent, determined by early events probably associated with implantation. The fact that reduction in fetal number around this time can result in larger fetuses with

bigger placentas in the rabbit (Fletcher *et al.* 1982) and up to 14 d, but not later, in the rat (Ogata & Finley, 1988), and that substantial compensatory growth can occur in individual cotyledons after carunclectomy in sheep (Alexander, 1974; Harding *et al.* 1985), though there is no similar compensatory placental development in remaining conceptuses after fetal loss later in gestation, suggests there is a critical time window during which the conceptus is able to bring about the changes in the uterine wall necessary to support the development of a larger placenta and a higher rate of fetal growth subsequently. Recent observations on changes in angiogenic activity within the uterine caruncles and cotyledonary tissue throughout gestation in sheep are consistent with this view (Millaway *et al.* 1989). The identity of the angiogenic factors involved and mechanisms by which their production is regulated remain to be defined before any possibility of placental manipulation can be contemplated.

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