

Fetal Nutrition And Growth

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ABSTRACT

Fetal nutrition is the main regulator of fetal growth in late gestation. However the influence of maternal nutrition on fetal growth is also dependent on the relative efficiency of the fetal supply line, the timing and balance of changes in maternal nutrition, and the indirect effects of altered maternal nutrition on fetal endocrine status and substrate balance.

KEY WORDS : Nutrition, fetal growth, placenta

Cross breeding and embryo transplant experiments in a variety of animal species have clearly demonstrated that size at birth is largely determined by the maternal uterine environment, with the parental genotype having a relatively small influence(1). Fetal growth in late gestation is normally limited by maternal size and her capacity to supply nutrients to her fetus; a phenomenon known as maternal constraint. Thus fetal growth in late gestation is normally regulated by fetal nutrient supply(2). This principle of the nutritional regulation of fetal growth is relatively easily demonstrated in animal species. In pregnant sheep, maternal undernutrition in late gestation results in prompt slowing of fetal growth, and fetal growth resumes with maternal refeeding(3,4). However such a relationship is more difficult to demonstrate in human pregnancy. There are case reports of women with severe undernutrition for medical reasons resulting in impaired fetal growth which is at least partially reversed by improving maternal nutrition status(5,6). Nevertheless, in general the relationship between maternal nutrition and fetal growth is difficult to demonstrate in human pregnancy.

This difficulty in demonstrating a direct relationship between maternal nutrition and fetal growth relates largely to the very indirect relationship between maternal nutrition and fetal nutrition. The mammalian fetus grows at the end of a long and sometimes precarious "supply line", linking maternal diet at one end with fetal tissue nutrient uptake at the other(7). The supply line includes maternal diet, maternal metabolism and endocrine status, uterine and umbilical blood flows and placental transfer capacity and metabolism. Relatively large changes in maternal nutrition may have little impact on fetal nutrition if the capacity of the fetal supply line allows a large margin of safety for fetal growth. Conversely,

common clinical causes of impaired fetal growth in well nourished populations such as maternal hypertension associated with reduced uterine blood flow, or placental infarcts resulting in reduced placental transfer capacity, may severely limit fetal nutrient supply without a corresponding change in maternal nutrition. Much confusion and debate in the literature has arisen from failure to make this distinction between maternal nutrition and fetal nutrition, in the regulation of fetal growth.

The indirect relationship between maternal nutrition and fetal growth is further confused by the influence of the timing and balance of maternal nutrient intake on fetal growth. Much of the work on nutrient balance has come from human studies. Although randomised controlled trials of maternal dietary supplements have shown relatively little effect on birthweight, supplements with a relatively high proportion of calories provided as protein actually result in reduced mean birth weight(8,9). Similarly, in a relatively well nourished population, the combination of high carbohydrate intake in early pregnancy and low protein intake in late pregnancy, was shown to be associated with reduced birthweight, low ponderal index and reduced placental weight(10,11). The proportions of protein and carbohydrate in a woman's diet in pregnancy have also been shown to influence both placental size and the blood pressure of the adult offspring(12).

There is also increasing evidence that maternal nutrition around the time of conception is particularly critical in the regulation of fetal growth. We have shown in sheep that maternal undernutrition from 60 days before, until 30 days after mating, results in fetuses that grow relatively slowly in utero in late gestation. These slowly growing fetuses are relatively resistant to the effects of late gestation maternal undernutrition on fetal growth(3,4). They also continue to grow slowly until delivery and half of them deliver prematurely(13). Lambs are thin at birth but do not have reduced total birthweight (13). It is not clear what specific time in the periconceptual period is critical for this effect. Maternal weight before pregnancy is an important influence on birth size in women, but it is not yet clear to what extent improved maternal nutrition in early pregnancy may influence birth size independent of nutritional status at pregnancy onset.

Although it is clear from experimental data that nutrition influences fetal growth in late gestation, the mechanisms by which this occurs are far from clear. It appears superficially logical to assume that nutrient limitation to the fetus at a given stage of development is likely to inhibit growth of organs that are growing rapidly at that time. However simple limitation of substrates to growing organs leading to reduction in size of those organs is an inadequate explanation. For example, maternal protein restriction in pigs results in reduced fetal weight and length at mid-gestation at a time when the fetus is extremely small and fetal protein requirements for growth are unlikely to have been limiting(14). Similarly, maternal undernutrition in either early or late gestation in sheep, leading to fetal undernutrition and limited nutrient supply to growing organs, cannot explain our experimental findings that the size of the heart and kidneys is increased rather than decreased(15,16).

Nutritional influences on fetal growth may also be mediated by nutritional regulation of fetal endocrine status. The major hormones regulating fetal growth in late gestation appear to be insulin and insulin-like growth factors (IGFs)(17,18). These regulate fetal nutrient uptake and distribution of nutrients within the fetus. In turn, they are all regulated by fetal nutrient supply(19,20). Thus reduced glucose supply to the fetus results in reduced circulating insulin and IGF concentrations and consequently in reduced fetal growth. Improved nutrient supply to the fetus results in increased insulin and IGF concentrations, redistribution of fetal nutrients and reduced protein breakdown leading to fetal growth. In this way, fetal growth is tightly linked to nutrient supply. Such a linkage is clearly essential if the fetal demand is not to exceed maternal capacity to supply nutrients to her conceptus.

One of the hallmarks of impaired fetal growth is altered fetal body proportions. In clinical practice, this is often reflected in relative sparing of head size with loss of subcutaneous tissue. Such altered body proportions have widely been assumed to reflect altered blood flow distribution within the fetus as a result of chronic hypoxia. While such redistribution clearly does occur, it is also clear from human as well as animal studies that many poorly growing fetuses are not hypoxaemic in utero, although head sparing can be readily demonstrated(21). Indeed, if fetal growth restriction is induced by feed restriction in sheep, there is relative head sparing with impaired fetal growth but no evidence of hypoxia(4).

There are several other nutritional mechanisms that may allow relative preservation of brain growth in the substrate limited fetus. Glucose uptake into many

tissues is mediated by insulin, and fetal insulin secretion is regulated by glucose and amino acid supply. However, glucose uptake into the brain does not require insulin. Thus reduced supply of glucose and amino acids to the fetus will reduce circulating insulin concentrations and reduce glucose uptake into peripheral tissues such as muscle. The limited glucose supply available is thus spared for uptake into tissues which do not require insulin for glucose uptake such as the brain.

An altered balance of substrates available to the fetus may also influence fetal body proportions. Undernutrition in women increases the supply of ketones to the fetus(22) and the fetal brain has been shown to preferentially take up and oxidise ketones(23,24). Similarly, during undernutrition in pregnant sheep, supply of lactate to the fetus from the placenta is maintained. The fetal heart will preferentially utilise lactate as an oxidative fuel(25). Thus altered body proportions at birth, and particular relative preservation of brain and heart size, may reflect altered distribution of fetal cardiac output in utero. However they may also reflect complex metabolic adaptations to limited fetal nutrient supply including an altered hormone environment and altered substrate availability.

It is clear that fetal nutrition is a critical regulator of fetal growth in late gestation. However the influence of maternal nutrition on fetal growth is also dependent on the relative efficiency of the fetal supply line, the timing and balance of changes in maternal nutrition, and the indirect effects of altered maternal nutrition on fetal endocrine status and substrate balance.

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