Animal Studies of the Effects of Early Nutrition on Long-Term Health

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Epidemiological studies over the last 20 years have shown that low birthweight is associated with increased risk of a variety of common chronic adult diseases[1]. Since maternal undernutrition was a well-recognized cause of reduced birthweight, it was hypothesized that undernutrition before birth would lead to permanent changes in growth and development, thus increasing the risk of later disease. Prenatal nutrition therefore provided the likely link between reduced birthweight and later health outcomes [1]. Numerous experimental studies in animals have supported the observations in humans, demonstrating that changes in nutrition in early life can indeed lead to altered growth and development, and also to the associated long-term health outcomes. However, they have also demonstrated that the causal pathways are more complex than originally envisaged.

Animal studies have demonstrated the important distinction between maternal nutrition, fetal nutrition, and fetal growth. The fetus grows at the end of a long supply line, comprising not only maternal nutrition, but also uterine and umbilical blood flows, as well as placental transport and metabolism [2]. Interference with steps along this supply line commonly results in growth restriction, since fetal nutrition is the key regulator of fetal growth. However, changes in maternal nutrition do not always result in altered fetal growth, and can affect offspring health independent of size at birth.

Macronutrients in the maternal diet are important determinants of growth and development of the offspring. Many animal studies show that maternal protein restriction has deleterious effects on offspring health [3]. However, the balance of macronutrients, including the quality and quantity of dietary fat, can also affect outcome. There is also an
interaction between pre- and postnatal diets. The negative effects of maternal protein restriction are magnified by a postnatal high-fat diet, while some of the adverse effects of a maternal high-fat diet are ameliorated by continuation of this diet after birth [3]. There are also many examples of specific micronutrients in the maternal diet that influence physiology of the offspring, including minerals (e.g. iron, calcium, and zinc) and specific amino acids such as taurine and glycine.

Importantly, the effects of undernutrition in utero may vary depending on the timing, severity and duration of the nutritional insult [3]. Numerous studies, particularly in sheep, have highlighted the importance of nutrition in the periconceptional period. Mild periconceptional undernutrition alters fetal growth trajectory, metabolism and endocrinology in late gestation [3], and some of these changes persist after birth, with implications for long-term health. For example, accelerated pancreatic maturation in the fetus after periconceptional undernutrition is associated with impaired glucose tolerance in adulthood [4]. Similarly, accelerated maturation of the hypothalamic-pituitary-adrenal axis in the fetus [2] is associated with suppressed activity of this axis after birth, which is sex specific and becomes more marked with increasing age (fig. 1).

The mechanisms underlying these observed effects of early nutrition on long-term health are complex. They include not only altered growth and development of specific organs such as the kidney and pancreas, but also altered placental function, and exposure to altered

![Fig. 1. Cortisol response to an AVP + CRH challenge in male and female sheep at 4, 10 and 18 months of age. Grey bars represent offspring of periconceptionally undernourished ewes, and black bars the offspring of normally nourished ewes. * p < 0.05 for nutrition effect.](https://example.com/cortisol-graph.png)
metabolic and endocrine environments in utero. For example, periconceptional undernutrition in sheep prevents the development of the normal physiological insulin resistance of pregnancy, which in turn is related to fetal growth (fig. 2). Similarly, maternal nutrition influences the glucocorticoid environment in which the embryo and fetus develop, and the consequent effects on hypothalamic-pituitary-adrenal axis development in the offspring may explain many of the later effects on adult health [2, 3]. Animal studies have provided an important contribution to our understanding of how nutritional quality and quantity in early life are critical in determining growth, development and disease risk in later life.

**References**