

Fetal undernutrition – programming for metabolic syndrome?

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A world wide series of epidemiological studies has shown that poor intrauterine growth is associated with an increased prevalence of cardiovascular disease, non insulin dependent diabetes mellitus and metabolic syndrome in adult life. It has been postulated that a reduced intrauterine nutrient supply perturbs fetal growth and concomitantly alters or programs the structure and function of developing systems. There are a range of pathophysiological factors which may result in a perturbation or restriction of fetal growth which include gene defects, chromosomal abnormalities, poor placental function, maternal smoking, maternal alcohol or drug abuse and altered maternal substrate concentrations. The mechanisms by which these factors alter the pattern of fetal growth vary and the physiological adaptations of the fetus to these stimuli will depend on their nature, timing and intensity. The physiological adaptations of the fetus to an adverse intrauterine environment are in turn clearly important in determining the immediate and longer term consequences for the health and well being of the fetus, newborn and adult. Whilst restriction of placental function and maternal undernutrition may each affect fetal growth, there may be important differences in the fetal neuroendocrine and physiological adaptations to these stimuli which result in different outcomes for the fetus and adult. A range of experimental animal models have been used to investigate the fetal adaptations to restriction of placental function. Ligation of the uterine artery in the guinea pig or rat, embolisation of the uterine or umbilical circulation or restriction of placental growth from the beginning of pregnancy in the ewe each result in fetal hypoxaemia, hypoglycaemia and fetal growth restriction. Plasma catecholamine concentrations are increased in the placentally restricted (PR) fetal lamb throughout late gestation. Whilst covariate analysis reveals that there is a similar and inverse relationship between arterial PO_2 and noradrenaline in normally grown and PR fetal sheep, the relationship between fetal arterial PO_2 and adrenaline is different in control and PR animals and experimental data suggest that there is a profound dissociation of the effects of chronic hypoxaemia on noradrenaline and adrenaline synthesis within the developing sympathoadrenal system of the PR fetus. This dissociation may have significant physiological consequences in the perinatal period and may also be important in the context of the early origins of cardiovascular disease if the changes persist through adult life. PR also has a differential impact on the pituitary-adrenal axis in the late gestation sheep fetus. Whilst PR did not alter plasma concentrations of ACTH during the last 15d gestation, it was associated with an increase in fetal adrenal weight and in plasma cortisol concentrations in late pregnancy. There is also an increase in the expression of the mRNA levels of the 11 β hydroxysteroid dehydrogenase Type 1 enzyme (11BHS-D-1) in the liver of the PR fetus in late gestation. 11BHS-D Type 1 acts as a reductase in the fetal liver to convert cortisone to cortisol and thus hepatocytes may be exposed to increased cortisol in the PR fetus. Whether maternal undernutrition also results in fetal glucocorticoid exposure depends on whether the maternal pituitary-adrenal axis is stimulated by maternal hypoglycaemia and on the timing and magnitude of the fetal hypoglycaemia induced by the maternal undernutrition. Exposure of the fetus to increased circulating glucocorticoid concentrations after either PR or maternal nutrient restriction is important for the maturation of the respiratory, gastrointestinal and cardiovascular systems and for neonatal survival. There is also evidence supporting an interaction between prenatal glucocorticoid exposure and the renin-angiotensin system (RAS) in the programming of adult hypertension after either placental or maternal nutrient restriction. Placental restriction and maternal nutrient restriction also affect kidney growth and development. Finally we have also recently demonstrated that circulating leptin concentrations are positively related to leptin mRNA expression in fetal adipose tissue in fetal sheep during late gestation and found evidence that leptin can act as a signal of adiposity in fetal life. Alterations in the synthesis, secretion or actions of fetal leptin in response to changes in fetal nutrient supply may play an important role in the early programming of adult obesity. In summary, there are a range of fetal neuroendocrine, cardiovascular and metabolic adaptations which ensure the fetus survives the challenge of an acute or chronic reduction in its substrate supply during late gestation. There is also growing evidence, however, that it is the pathophysiological consequences of these prenatal adaptive responses which result in the association between poor fetal growth and the features of the metabolic syndrome in adult life.

Key words: fetus, nutrition, cardiovascular