Abstract

This article reviews the effects that maternal nutrition can produce in the fetus through leptin and other components of the fetal endocrine system, both immediately and in the long-run. Early, but not late, maternal overnutrition increases fetal plasma leptin and adipose tissue mass, while early, but not late, maternal undernutrition causes fetal hypoinsulinemia and hypoleptinemia and postnatal hyperphagia, obesity, hyperinsulinemia, and hyperleptinemia. Because many adult diseases seem to be pre-programmed *in utero*, this field has the potential to be very beneficial to society.

Introduction

The developing fetal endocrine system can adjust in response to maternally induced changes in its intrauterine environment. Depending on the nature and duration of the stress, the fetal endocrine system and growth development may alter permanently and may be responsible for diseases such as hypertension, obesity, and insulin insensitivity in adulthood (1). This review will look at the effects that maternal nutrition can have on the fetus and its endocrine system and the role that the protein leptin plays in mediating this. Unless otherwise stated, this article focuses on the sheep; sheep make an ideal human model because the fetal sheep shows similar metabolic responses to the human fetus, undergoes a relatively long gestation, and can be manipulated easily (1, 10).

Leptin plays a role in metabolic regulation

The 16 kDa protein leptin acts as an adiposity signal in the adult. It indicates nutritional status and responds to excess energy by depressing appetite and increasing glucose and fat

metabolism (2). Leptin levels rise after food consumption in response to increases in plasma glucose and insulin and help indicate satiety (12). This product of the *ob* gene acts primarily through brain receptors to modulate hypothalamic control of food intake and sympathetic stimulation of energy expenditure (5). Various tissues express some level of leptin, but the most significant source is adipose tissue (4). Leptin additionally suppresses the orexigenic peptide neuropeptide Y and its mRNA (Neuropeptide Y stimulates hyperphagia and subsequent obesity in the adult and amniotic fluid swallowing as ingestive behavior in the fetus) (5). Leptin levels also correlate with the amount of body fat. As food intake increases and introduces excess energy into the body, lipogenesis is stimulated and the newly synthesized adipose tissue secretes additional leptin (4). The fetal hypothalamus also expresses leptin receptors, suggesting that leptin may also play a role in fetal metabolic regulation (9).

Maternal overnutrition in early to mid pregnancy increases plasma leptin, leptin mRNA expression, and fat deposition in the fetus

In normal fetal development, leptin mRNA expression in adipose tissue peaks in the second half of gestation and then undergoes a decline (5). Circulating levels of leptin reflect the amount of leptin mRNA expression in fetal adipose tissue (3), although in humans the placenta may also contribute to plasma leptin levels (5). Maternal pigs that were overfed during the second quarter of pregnancy produced offspring with increased levels of plasma leptin and leptin mRNA in adipose tissue (7). Two explanations have been proposed for this observation. Although a recent study was unable to detect leptin receptor in the ovine placenta (11), an earlier study reported placental leptin receptors, leading to the suggestion that these receptors mediated the direct uptake of maternal leptin into fetal blood (2, 4). Alternatively, induced maternal hyperglycemia, by continuous glucose infusion, causes fetal hyperglycemia and mild fetal

hyperinsulinemia. After 14 days of hyperglycemia, the fetus showed a significant increase in leptin mRNA expression in adipose tissue (5). Likewise, induced maternal hypoglycemia, by continuous insulin infusion, produces fetal hypoglycemia and subsequent hypoinsulinemia as well as a sharp decline in leptin mRNA expression in fat around the time when hypoinsulinemia begins to appear (5). Further experiments showed that hyperglycemia with an insulin clamp – to test the effects of glucose independently of insulin – did not affect leptin mRNA expression while hyperinsulinemia with a glucose clamp did produce a rapid increase in leptin mRNA levels in white adipose tissue (5). The results from these experiments indicate that hyperglycemia produces an increase in leptin mRNA only by inducing hyperinsulinemia and has no direct effect itself. Maternal overnutrition leading to maternal and fetal hyperglycemia may therefore also act in this manner to mediate increased fetal leptin concentration.

The consequences of these amplified plasma leptin levels are uncertain, but may have one of two opposing effects. Because leptin represses neuropeptide Y function, increased leptin may decrease fetal amniotic fluid intake, affecting gastrointestinal tract development, and promote energy reducing behaviors in the neonate (5). Conversely, fetal leptin may actually make fetal insulin more sensitive to glucose usage, stimulating cell growth, and may also be mitogenic itself, leading to fetal body weight gain (5). It remains undetermined which leptin response predominates in the fetus and neonate and requires further investigation for clarification.

Independently of any leptin-mediated effects, glucose directly promotes moderate fetal fat mass deposition. Insulin does not produce the same effects, indicating that glucose acts through the insulin-independent glucose transporter GLUT 1, and not the insulin-dependent transporter GLUT 4 (8). Remarkably, leptin and fat mass increases do not manifest if the mother is only overfed in late pregnancy, after the final stage of rapid fetal growth (9).

Early maternal undernutrition predisposes offspring to obesity and cardiovascular disease

Restriction of maternal diet early in pregnancy has been strongly linked to an increase in obesity, heart disease, and hypertension. The specific mechanisms that produce this effect are still unclear, but seem to involve interactions between leptin, glucose, and insulin like growth factors (IGF) I and II (11). Offspring born to mothers that were temporarily under nutrient restriction early in pregnancy are larger and have more adipose tissue mass and increased levels of IGF-I and IGF-II mRNA and growth hormone receptor mRNA in the liver. These hormones may act cooperatively to alter gluconeogenesis permanently, and up-regulation of the IGF receptors may stimulate adipose tissue growth, which may increase the risk for future obesity (1, 11). Under the same conditions, ewes exhibit lower circulating leptin; since maternal and fetal leptin levels correspond positively, one would expect fetal leptin levels to be lower also, although this was not observed in this study (11). Severe maternal undernutrition can also lead to fetal hypoglycemia and hypoinsulinemia, which depresses fetal leptin levels, as discussed previously. In rats, juvenile offspring of mothers that were undernourished throughout pregnancy present hyperphagia, hyperinsulinemia, hyperleptinemia, hypertension, and obesity, metabolic deficiencies suggested to be induced *in utero* (6). The persistence of hyperphagia, hyperinsulinemia, and hyperleptinemia points to both leptin and insulin resistance since normally high levels of insulin and leptin would depress appetite. High caloric diets greatly magnified these phenomena (6). Although none of the ovine studies examined offspring at juvenile stage, it is reasonable to believe that they would show similar symptoms. In the offspring of undernourished mothers, low ovine fetal leptin levels would also cause postnatal hyperphagia and aggravate the pre-programmed metabolic abnormalities.

As with overnutrition, undernutrition in late gestation differs from that in early or mid gestation. Moderate nutrient deprivation late in pregnancy causes maternal glucose to decrease while maternal and fetal leptin do not change (10, 11). This can be partially explained by the level of nutrient deprivation in the studies. Undernutrition initially stimulates adaptations to maintain the fetal glucose supply such as a decrease in maternal insulin sensitivity, and if the undernutrition is moderate enough then these maternal metabolic actions compensate adequately for the fetus and leptin levels remain steady (10). Additionally, the notable difference between the time-dependent effects of maternal nutrition, with respect to both overnutrition and undernutrition, may be due to greater fetal glucose requirements at the end of gestation (11).

Conclusion

A consensus on the exact effects of maternal nutrition on offspring endocrine systems and future health remains to be determined, but some key points in the current field have been identified. Excessive or limited maternal nutrition most likely induces metabolic changes *in utero*, largely through leptin, with significant health and endocrinological consequences resulting from this "fetal programming." In particular, maternal undernutrition has been linked to offspring at increased risk of obesity, cardiovascular disease, hypertension, etc. Additionally, the timing of the maternal nutrition disturbance is significant, with the greatest fetal effects seen as a result of early to mid maternal over- or undernutrition. The implications this field has for society are vastly importance since cardiovascular and obesity-linked diseases cost billions of dollars a year. With the knowledge that so many adult diseases probably derive from metabolic problems initiated in gestation, devoting more resources to pre-natal course could be immensely more cost-efficient and disease preventive in the long run.

References

1. Symonds, M.E., Budge, H., Stephenson, T., McMillen, I.C.
(2001) Fetal endocrinology and development – manipulation and adaptation to long-term nutritional and environmental challenges.
Reproduction 121:853-862.

2. Yuen, B.S.J., Owens, P.C., McFarlane, J.R., Symonds, M.E., Edwards, L.J., Kauter, K.G., McMillen, I.C.
(2002) Circulating leptin concentrations are positively related to leptin messenger RNA expression in the adipose tissue of fetal sheep in the pregnant ewe fed at or below maintenance energy requirements during late gestation.
Biology of Reproduction 67: 911-916.

3. Yuen, B.S.J., McMillen, I.C., Symonds, M.E., Owens, P.C.
(1999) Abundance of leptin mRNA in fetal adipose tissue is related to fetal body weight.
Journal of Endocrinology 163: R11-R14.

4. Thomas, L., Wallace, J.M., Aitken, R.P., Mercer, J.G., Trayhurn, P., Hoggard, N.
(2001) Circulating leptin during ovine pregnancy in relation to maternal nutrition, body composition and pregnancy outcome.
Journal of Endocrinology 169:465-476.

5. Devaskar, S.U., Anthony, R., Hay, W.
(2002) Ontogeny and insulin regulation of fetal ovine white adipose tissue leptin expression.
Am J Physiol Regulatory Integrative Comp Physiol 282: R431-R438.

6. Vickers, M.H., Breier, B.H., Cutfield, W.S., Hofman, P.L., Gluckman, P.D.
(2000) Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition.
Am J Physiol Endocrinol Metab 279: E83-E87.

7. Ekert, J.E., Gatford, K.L., Luxford, B.G., Campbell, R.G., Owens, P.C.
(2000) Leptin expression in offspring is programmed by nutrition in pregnancy.
Journal of Endocrinology 165:R1-R6.

8. Mühlhäusler, B.S., Roberts, C.T., Yuen, B.S.J., Marrocco, E., Budge, H., Symonds, M.E., McFarlane, J.R., Kauter, K.G., Stagg, P., Pearse, J.K., McMillen, I.C.
(2003) Determinants of fetal leptin synthesis, fat mass, circulating leptin concentrations in well-nourished ewes in late pregnancy.
Endocrinology 144:4947-4954.

9. Mühlhäusler, B.S., Roberts, C.T., McFarlane, J.R., Kauter, K.G., McMillen, I.C.
(2002) Fetal leptin is a signal of fat mass independent of maternal nutrition in ewes fed at or above maintenance energy requirements.
Biology of Reproduction 67: 493-499.

10. Erhardt, R.A., Bell, A.W., Boisclair, Y.R.
(2002) Spatial and developmental regulation of leptin in fetal sheep.
Am J Physiol Regulatory Integrative comp Physiol 282: R1628-R1635.

11. Bispham, J., Gopalakrishnan, G.S., Dandrea, J., Wilson, V., Budge, H., Keisler, D.H., Pipkin, F.B., Stephenson, T., Symonds, M.E.
(2003) Maternal endocrine adaptation throughout pregnancy to nutritional manipulation: consequences for maternal plasma leptin and cortisol and the programming of fetal adipose tissue development.
Endocrinology 144: 3575-3585.

12. Thompson, M.P.
(1996) Meal-feeding specifically induces obese mRNA expression.
Biochem Biophys Res Commun; 224: 332-337.