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Symposium on 'Early nutrition and later disease: current concepts, research and implications'

The impact of diet during early life and its contribution to later disease: critical checkpoints in development and their long-term consequences for metabolic health

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Changes in maternal diet at different stages of reproduction can have pronounced influences on the health and well-being of the resulting offspring, especially following exposure to an obesogenic environment. The mechanisms mediating adaptations in development of the embryo, placenta, fetus and newborn include changes in the maternal metabolic environment. These changes include reductions in a range of maternal counter-regulatory hormones such as cortisol, leptin and insulin. In the sheep, for example, targeted maternal nutrient restriction coincident with the period of maximal placental growth has pronounced effects on the development of the kidney and adipose tissue. As a consequence, the response of these tissues varies greatly following adolescent-onset obesity and ultimately results in these offspring exhibiting all the symptoms of the metabolic syndrome earlier in young adult life. Leptin administration to the offspring after birth can have some long-term differential effects, although much higher amounts are required to cause a response in small compared with large animal models. At the same time, the responsiveness of the offspring is gender dependent, which may relate to the differences in leptin sensitivity around the time of birth. Increasing maternal food intake during pregnancy, either globally or of individual nutrients, has little positive impact on birth weight but does impact on liver development. The challenge now is to establish which components of the maternal diet can be sustainably modified in order to optimise the maternal endocrine environment through pregnancy, thus ensuring feto–placental growth is appropriate in relation to an individual's gender and body composition.

Pregnancy: Growth: Lactation: Obesity

There is a complex interrelationship between dietary composition and changes in food intake in women around the perinatal period. This interaction is accompanied by the substantial endocrine changes that are associated with the establishment of pregnancy[1] and concomitant changes in maternal cardiovascular control. The magnitude of adaptation will be dependent on numerous factors including maternal age, parity, fetal number, ethnicity and body composition[2,3]. Ultimately, the effect of the maternal diet on reproductive outcome will be modulated by each of these components, although their relative impact will vary greatly depending on the stage of gestation[4]. One example is the occurrence of morning sickness, which is only experienced by women consuming a Western-style diet and which, in turn, is determined by macronutrient rather than micronutrient intake[5]. It is not uncommon for maternal food intake to decrease at some stage in the first trimester and this reduced intake may be an important

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adaptation that enables changes in maternal body composition to occur through pregnancy whilst ensuring that nutrient flux to the fetus, particularly carbohydrate flux, is maintained[6]. However, it may be the subsequent change in maternal body composition, rather than in dietary intake, that is the key factor determining the magnitude of feto–placental adaptations[7]. This premise could also explain why preterm birth only appears to result when periconceptional nutrient restriction is accompanied by a pronounced reduction in maternal body weight[8,9]. In contrast, micronutrient intake may only be important in determining some of the later effects on reproduction in early pregnancy. Thus to date, vitamin C is the only individual nutrient for which intake has been positively associated with placental weight at term, although its contribution is small (i.e. <5 %)[10].

Dietary challenges during pregnancy: the laboratory *v.* real life

One factor that has a major influence on the interpretation of outcomes from nutritional interventions is whether they are representative of dietary changes seen in human populations. In addition, the extent to which they may have a substantially greater impact on the particular species or breed under examination compared with human subjects must be considered[11]. For example, it has long been established that because of a combination of the large litter size and the short gestation over which fetal growth occurs, protein requirements of the pregnant rat are approximately 30-fold greater than those of larger mammals[12]. Thus, it is not unexpected that, in the rat, reductions in the protein content of the diet, concomitant with an increase in a highly-digestible carbohydrate content, result in fetal growth retardation that can have adverse long-term consequences[13]. However, such adverse effects of protein restriction in large mammals, with a long-length gestation similar to that of human subjects, have yet to be confirmed. Outside the laboratory, in its natural environment, the rat survives on a very diverse diet of different foods that vary in availability through the seasons. This factor could explain why, experimentally, rats can effectively adapt to such apparently large changes in their diet during reproduction. As a consequence, if the same restricted diet fed through lactation is fed to the offspring then no adverse effects on blood pressure are seen in male offspring[14]. Similarly, reducing the amount of food available to the pregnant rat by 50 % through pregnancy has only a transient inhibitory effect on the weight of the offspring that is overcome within 3 d of birth[15]. The offspring subsequently have a reduction in blood pressure as adults despite having a marked deficit in nephron number.

The pregnant animal has a substantial capacity to effectively adapt to changes in the diet that when suddenly imposed at any time in the reproductive process can be well tolerated without any effect on birth weight of the offspring[16]. However, individuals with the same birth weight can exhibit substantial differences in endocrine sensitivity and organ function from birth and throughout later life[17,18]. Moreover, because of the critical periods of organ growth and development from the time of conception through to birth, when approximately 80 % of all cell divisions of the life cycle occur, it is not unexpected that changes in the maternal diet can have longer-term effects on the metabolic and cardiovascular health of the resulting offspring[19]. These responses normally need to be accompanied by a further challenge to that individual's growth capacity as a result of accelerated postnatal growth and/or in the adolescent period of development[20]. At the same time, pronounced adaptations can be found at the cellular level without any gross difference in body composition[18,21], emphasising the need to make relevant tissue measurements of markers of disease progression.

Conception to embryogenesis

Changes in maternal food intake before pregnancy can have marked effects on the conceptus and these effects appear to be dependent on the magnitude of change in maternal body weight[7]. In sheep, therefore, a sudden and maintained reduction in food availability that is sufficient to cause a substantial decline in maternal body weight can result in accelerated maturation of the hypothalamic–pituitary axis of the fetus to the extent that premature birth can occur[22]. Interestingly, this outcome only occurs in approximately 30–40 % of mothers exposed to this nutritional intervention[8,22] and may reflect differences in the maternal catabolic response to chronic food deprivation and/or difference in body composition at the start of the study. For example, in one such study a subgroup of the animals exposed to periconceptional nutrient restriction had a baseline doubling in plasma cortisol[23].

The long-term outcomes of being born to mothers exposed to periconceptional nutrient restriction are very modest and those effects, for example on glucose homeostasis, are inconsistent[24,25]. This outcome contrasts with the effect of maternal nutrient restriction commencing from the time of mating, which has no effect on gestational length, birth weight or glucose homeostasis or on the hypothalamic–pituitary axis of the offspring[26–28]. It does, however, result in a marked leftward shift of the baroreceptor curve relating blood pressure to heart rate[26]. The extent to which this type of adaptation may be exacerbated when these individuals are exposed to an obesogenic environment and become hypertensive[29] clearly warrants further investigation.

Placental development and maturation of the kidney

Adaptations within placental structure, as well as in its endocrine sensitivity, have a pronounced influence on the extent to which changes in the maternal diet may adversely affect fetal growth[30,31]. A reduction in maternal food intake, coincident with uterine attachment and invasion of the fetal trophoblast into the syncitium, reduces placental growth as a consequence of reduced cell proliferation[32]. This outcome is accompanied by raised glucocorticoid action[32], which appears to be a direct response to the reduction in maternal plasma cortisol[16]. At the same time, maternal plasma insulin, thyroid hormones, leptin and insulin-like growth factor-1 are reduced (see Table 1). These adaptations accompany the modest reduction in maternal body weight and the increased plasma NEFA[16]

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Table 1. Summary of the major maternal endocrine changes following exposure to nutrient restriction between 28 d and 80 d of gestation in the sheep (adapted from Bispham *et al.*[16] and Symonds *et al.*[64])

(Values are means with their standard errors for seven sheep per group)

	Control		Nutrient restricted	
Hormone	Mean	SE	Mean	SE
Insulin (ng/ml)	0·69	0·11	0·24***	0·03
Cortisol (nmol/l)	35	4	21*	12
Insulin-like growth factor 1 (nmol/l)	15·8	1·1	10·6*	1·2
Leptin (ng/ml)	11·4	1·8	4·3***	0·8
Thyroxine (nmol/l)	50	5	28***	4

Mean values were significantly different from those for the control diet: *$P<0·05$, ***$P<0·001$.

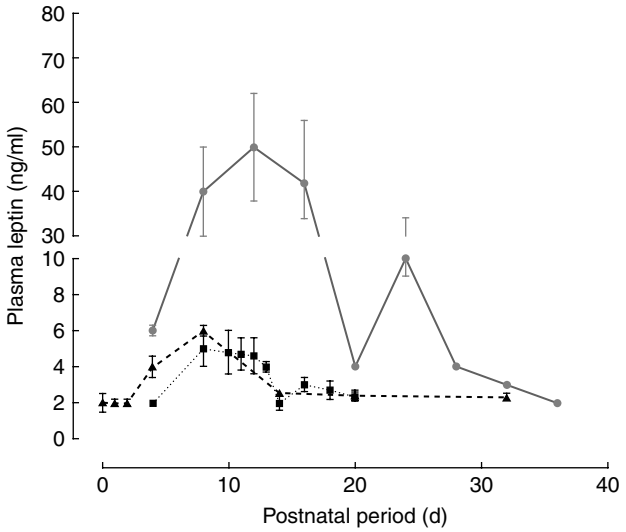

Fig. 1. Comparison of the changes in plasma leptin after birth in mice (—●—)[65], rats (···■···)[45] and sheep (- -▲- -)[43]. Values are means with their standard errors represented by vertical bars for six to eight animals per time point.

that may be important, in conjunction with the reduction in maternal plasma insulin, in maintaining the concentration of glucose[16,33], which is the main metabolic substrate required by the fetus. Conversely, increasing the amount of feed consumed by the mother from calculated requirements to *ad libitum* has very little effect on fetal growth through gestation[34,35], and at term gestation fetal fat mass can even be reduced[35].

To date, all organs and mechanisms that have been examined in the adult offspring born to nutrient-restricted mothers appear to be re-set following exposure to this targeted nutritional intervention. However, adaptations that may place in the offspring at increased risk of later adult disease are not seen until individuals are subsequently exposed to an obesogenic environment[18,21,36]. This outcome is most notable in the kidney in which there is a marked attenuation of both cellular stress and inflammatory responses[18]. These responses contrast with other pathways, including apoptosis and glucocorticoid action, that may initially protect the kidney from glomerulersclerosis[29]. It is likely that with age the cardiovascular health of these offspring will deteriorate more rapidly[21] and that they will therefore be at increased risk of CVD[37]. Indeed, there is further indirect evidence to support this outcome, as if these offspring become obese they show an exacerbated increase in blood pressure with age compared with those born to control-fed mothers[37]. Ultimately, these offspring exhibit all the symptoms of the metabolic syndrome including raised plasma TAG, hyperinsulinaemia, hyperleptinaemia and leptin resistance together with ectopic lipid deposition[21,29,36].

Fetal and neonatal growth, leptin and maturation of the hypothalamic–pituitary axis

There are substantial differences between both species and nutritional models in the development of a number of organ systems that relate to their critical windows of development. Such differences are also found in the hypothalamic–pituitary axis, which primarily matures after birth in rodents compared with the final third of gestation in sheep and human subjects[11]. The importance of this profound difference between species, primarily linked to maturation at birth, has a substantial impact on the magnitude of leptin surge at birth and therefore its relative influence on postnatal growth and development, as summarised in Fig. 1. In small mammals leptin has a primary role in regulating brain development after birth[38]; there is currently no evidence of comparable effects in large mammals.

In the sheep leptin administration to either the preterm fetus (10 d before birth)[39] or to the neonate[40] has very limited effects on metabolism, which are confined to brown adipose tissue. Interestingly, in the sheep the amount of leptin required to induce the effects that follow an approximately 5–10-fold rise in plasma leptin is 10-fold greater in the fetus[39] compared with the neonate[40] (i.e. 0·48 mg/kg body weight *v.* 0·04 mg/kg body weight). In the fetal sheep the administration of leptin results in a stability in uncoupling protein 1[39], whereas after birth an increase in body temperature is accompanied by an accelerated loss of uncoupling protein 1[40]. Leptin also promotes the loss of uncoupling protein 2 from the lung[41] and pancreas[42] but not adipose tissue[41], although whether this response is a direct effect or is mediated by the concomitant reduction in plasma cortisol remains to be established. These findings emphasise the comparatively modest effects of administering a physiological dose of leptin to a species with a mature hypothalamic–pituitary axis and in which there is an immediate reduction in plasma leptin[43] at birth, as is also seen in the human neonate[44]. It is in marked contrast to the rat in which plasma leptin increases 1 week after birth[45] and parallels the postnatal recruitment of non-shivering thermogenesis[46]. In neonatal rats a much higher amount of leptin has been used, i.e. 2·5 mg/kg body weight, and a pronounced divergence in effect is observed between males[47] and females[48]. This difference is not unexpected given the greater amount of fat present in

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females[49] across species[50], which is usually reflected in higher plasma leptin in females compared with males[49,51]; a difference that is present from birth in both sheep[40] and human subjects[52].

When a comparatively high dose of leptin is administered to neonatal rats a substantial loss of body weight only results in female pups exhibiting pronounced intrauterine growth retardation and also exposed to the additional stress of cross-fostering (not adopted for controls)[48]. Indeed, selective cross-fostering could be a major factor in determining the apparent opposite effects of leptin between nutritional groups in a number of outcomes, including changes in gene expression and methylation relating to glucocorticoid action in the adult liver[53]. In males leptin has little effect on body weight[47], possibly because these offspring were still growing at the end of the study (i.e. 170 d after birth) when no 'protective effect' of early leptin administration was apparent. In females the change in total fat mass is not however accompanied by a reduction in plasma leptin[48]. Furthermore, whether adaptations in the amount of ectopic fat accumulation occur is currently unknown and is clearly important because it is critical in determining the magnitude of adverse metabolic outcomes[54]. Given the pronounced differences in maturation at birth and the interaction between fat mass, leptin and gender outlined earlier, the extent to which such effects from using pharmacological amounts of leptin to prevent adverse body composition in the neonate are relevant to the clinical situation remains in doubt.

Increased maternal fat intake and compromised fetal growth

One current concern is the rise in obesity[55], particularly its increased incidence in women of child-bearing age[56]. Macrosomic newborns of obese women have an increased amount of body fat[57]. However, consistent observations have yet to be produced, as many confounding effects, particularly gender, have yet to be clarified. Indeed, in a recent study of nulliparous obese women in the UK 19 % of women had small-for-dates infants compared with 13 % producing large-for-dates offspring[58]. In mice increasing the amount of dietary fat alone or in combination with other carbohydrates has no effect on birth weight. However, if this dietary intervention is commenced several weeks before pregnancy and is accompanied by increased energy intake, then maternal body weight is raised and subsequent changes in offspring feeding behaviour are observed[59]. In the case of non-human primates doubling fat availability in the diet, primarily at the expense of protein content, actually reduces fetal weight[60], with approximately 50 % of the subjects being resistant to the effects of the high-fat diet on insulin secretion (and the accompanying increase in maternal body weight). Irrespective of the maternal response, in the fetus there is a consistent effect on hepatic gene expression of enzymes involved in gluconeogenesis, in conjunction with raised hepatic TAG content. This adaptation persists up to 6 months after birth, although the difference is greatly reduced after birth, and as the hepatic TAG content remains lower than in the fetus is not indicative of a disease-like state. Interestingly, the effects seen on hepatic genes are not translated to changes in protein abundance. This outcome is not unexpected as fetal glucose production is only normally activated after birth[61]. It may be that raised hepatic gene expression reflects a non-permanent response to the nutritional stress[62] imposed on the mother. This finding is also in accord with the effect of feeding a low-protein high-carbohydrate diet to rodents through pregnancy, which promotes glucocorticoid receptor abundance in a range of fetal tissues including the liver[63].

In the non-human primate study described earlier it was found that placing the mothers back onto the control diet after 4 years alleviates the effects of maternal consumption of a high-fat low-protein diet[60]. However, hepatic TAG content in the fetus remain above control values in those mothers no longer consuming the high-fat low-protein diet. Furthermore, non-human primates have very low body fat, which explains the near undetectable plasma leptin in the fetus (approximately 0·5 ng/ml). As their maximal fat mass, recorded at 3 months of age, is only approximately 5 % body weight they do not exhibit signs of obesity or metabolic compromise. It would, of course, be highly informative to know how food intake changed with age and through each pregnancy in these studies[60].

Conclusion

In conclusion, changes in maternal diet throughout pregnancy and during the lactation period will modify the mother's endocrine status and can have pronounced effects on the growth and development of the conceptus that are dependent on the stage of gestation of exposure. Increasing evidence links the perinatal dietary environment to cardiometabolic disease development in adulthood. Critically, an increased understanding of these processes and the relative contributions of individual components of the diet to the endocrine status of both the mother and resulting offspring will be important in improving the long-term health of the population.

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