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Nutritional Approaches to Breaking the Intergenerational Cycle of Obesity

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Abstract

The link between poor maternal nutrition and an increased burden of disease in the subsequent generations has been widely demonstrated in both human and animal studies. Historically, the nutritional challenges experienced by pregnant and lactating women were largely those of insufficient calories and severe micronutrient deficiencies. More recently however, Western societies have been confronted with a new nutritional challenge; that of maternal obesity and excessive maternal intake of calories, fat and sugar. The exposure of the developing fetus and infant to this obesogenic environment results in an increased risk of obesity and metabolic disease later in life. Furthermore, this increased caloric intake often occurs in conjunction with micronutrient deficiency, which may further exacerbate these programming effects. In light of the current epidemic of obesity and metabolic disease, attention has now turned to identifying nutritional interventions for breaking this intergenerational obesity cycle. In this review, we discuss the approaches that have been explored to date, and highlight the need for further research.

Key words: maternal nutrition, pregnancy, fetal programming, obesity, micronutrients

Introduction

A world-wide series of epidemiological and experimental animal studies has provided compelling evidence that the nutritional environment experienced before birth and early infancy has a central role in determining the long-term health of individuals (McMillen & Robinson, 2005). As a result, maintaining an appropriate maternal nutrient supply during pregnancy and lactation is of central importance for optimising the development of the fetus and neonate. For the developing fetus and breast-fed infant, the maternal diet is the sole source of nutrition, and must therefore supply all of the necessary macro- and micro-nutrients to support the growth and development of tissue and organ systems. As a consequence, inappropriate maternal nutrition during these critical periods of development has the potential to impact negatively on the long-term health of the children.

The importance of maternal nutrition for supporting growth and development has been recognised for decades. The devastating effects of sub-optimal maternal nutrition on fetal and infant growth are perhaps illustrated most clearly by the effects of severe deficiencies of key micronutrients (Zlotkin 2011). Rickets was once a relatively common childhood disorder resulting from maternal Vitamin D deficiency, and spina bifida a neural tube disorder is caused by insufficient maternal folate intake during the critical period of development of the nervous system in the first trimester of pregnancy (Park, 1940; De Wals *et al.*, 2007; Zlotkin 2011). Recognition of the origin of these disorders led to wide-spread interventions to correct these deficiencies in the maternal diet and, as a result, these once common disorders have been virtually eliminated in the developed world (Park, 1940; De Wals *et al.*, 2007).

Whilst overt maternal nutrient deficiencies are no longer commonplace, modern Western countries are facing a new nutritional challenge, that of maternal obesity and caloric excess,

sometimes in conjunction with micronutrient deficiency(Kaidar-Person *et al.*, 2008). The exposure of individuals to this 'obeseogenic environment' before birth and in early infancy has been shown to increase their propensity to obesity and its associated metabolic disorders in child and adult life, thereby creating an intergenerational cycle of obesity and metabolic disease (Catalano, 2003; Catalano & Ehrenberg, 2006; Rkhzay-Jaf *et al.*, 2012). The purpose of this review is to explore our current understanding of the early life origins of obesity and to discuss potential nutritional strategies for breaking the intergenerational obesity cycle.

The Global Epidemic of Obesity and Metabolic Disease

The incidence of obesity and metabolic disease continues to increase across the globe. According to the most recent figures released by the WHO, the worldwide prevalence of obesity nearly doubled between 1980 and 2008. In 2008, more than 1.4 billion adults (20 years and older) were overweight and, of these, over 200 million men and nearly 300 million women were obese (WHO, 2012). The obesity epidemic has extended to the world's children, and in 2012 more than 40 million children under the age of five were classified as overweight (WHO, 2012). In addition to the direct impact of overweight and obesity on physical and mental health, these conditions are also associated with a number of co-morbidities, in particular type 2 diabetes (T2DM) and cardiovascular disease, which further reduce the quality of life of these individuals (Bray, 2004). The rising prevalence of obesity and its associated metabolic disorders places a considerable economic burden on the health care budgets of governments in developed and developing countries (Daviglus *et al.*, 2004; WHO, 2012). In this context, there has been a growing recognition of the need to develop effective strategies for obesity prevention, and attention has turned to the role of the early nutritional environment as a modulator of obesity risk and a potential window of opportunity for intervention.

Maternal Obesity and Overnutrition: A Growing Obstetric Challenge

The obesity epidemic has spread to include women from all age groups, including women of reproductive age, and this has resulted in a dramatic rise in the number of women entering pregnancy overweight or obese. In 2000, around 30% of women entering pregnancy in the US and Australia were classified as overweight or obese (Callaway *et al.*, 2006; Catalano & Ehrenberg, 2006). More recent figures have suggested that this figure may now be even higher, and that over 50% of women were overweight or obese when presenting for their first antenatal appointment (Athukorala *et al.*, 2010; Dodd *et al.*, 2011c). On the basis of these figures, we would therefore expect that at least half of all infants born in developed countries are exposed to maternal overweight or obesity before birth.

This increasing prevalence of maternal overweight and obesity has implications for the long-term health of children. Mothers who are overweight or obese during their pregnancy have an increased risk of pregnancy complications, caesarean delivery and infant morbidities (Dodd *et al.*, 2011a). The infants are also more likely to be born at greater than the 90th centile for their gestational age or macrosomic (>4000g), largely as a result of increased fat deposition (Catalano, 2003). Importantly, these infants are not only heavier at birth, but go on to be at increased risk of obesity and type 2 diabetes during childhood and adulthood (Catalano & Ehrenberg, 2006; Rkhzay-Jaf *et al.*, 2012). This has therefore created an intergenerational cycle of obesity and metabolic disease, which has been identified in numerous populations across the globe. More recent studies have attempted to quantify the magnitude of the effect; population-based studies in both Pima Indians and multi-ethnic populations in the US have identified maternal obesity and diabetes during pregnancy as the strongest risk factor for the development of type 2 diabetes in the offspring, accounting for 40% and 47% respectively of the type 2 diabetes cases in these populations (Dabelea *et al.*, 1998; Dabelea *et al.*, 2008).

The risk of type 2 diabetes in populations exposed to diabetes *in utero* remains higher even when the effects of maternal body fat mass are controlled for, suggesting that there are independent effects of maternal diabetes and high maternal glucose levels on the systems which control fat deposition and insulin sensitivity (Dabelea *et al.*, 2008).

The description of this intergenerational cycle of obesity in human populations world-wide, has led to the search for the underlying biological mechanisms which drive it and these studies have implicated maternal nutrition as a critical player. In these studies, maternal overweight or obesity is associated with increases in the concentrations of key nutrients, in particular glucose, in the maternal circulation (Catalano *et al.*, 2003). Glucose is the principal substrate for fetal growth, and is delivered to the fetus down a transplacental glucose gradient from the maternal circulation (Fowden, 1995). Therefore, increased maternal glucose concentrations result in an increased delivery of glucose to the developing fetus. This stimulates insulin production by the fetal pancreas and leads to excess fetal growth and fat deposition (Metzger, 1991) as well as increased infant weight at birth **(Figure 1)**. In addition to the effects on growth, exposure to excess glucose and fat (particularly saturated fat) also influences gene expression in developing tissues and thereby produce permanent changes in their structure and function (Armitage *et al.*, 2004).

The Biological Mechanisms

An increasing number of studies in animal models have attempted to explore the biological mechanisms through which maternal overweight and overnutrition increase the susceptibility to obesity in the offspring (Armitage *et al.*, 2004; McMillen *et al.*, 2009). These studies have provided evidence that exposure to an excess nutrient supply before birth, particularly glucose and saturated fat, acts on a number of the key systems involved in the regulation of

appetite, fat deposition and insulin sensitivity, reducing the capacity of an individual to maintain energy balance and glucose homeostasis in postnatal life. While animal studies have provided important insights into the biological mechanisms of developmental programming, there are differences between animals and humans in the timing of organ development, placental nutrient transfer and maternal/fetal metabolism which need to be considered when extrapolating these findings to humans. There is also a need to consider how the treatment applied to the animals relates to the human experience. By way of example, exclusively high-fat diets have been widely used in rodent studies of developmental programming, but are have been shown to be a less robust model for studying human metabolic disease compared to the model in which animals are fed a cafeteria diet (Sampey *et al.*, 2011). Whilst it is not clear whether all the mechanisms identified in animals also operate in humans, the phenotype of offspring born following maternal nutritional perturbations are comparable between humans and many different animal models, suggesting that the process of fetal programming is common to a wide range of species (Ozanne, 2001; Armitage *et al.*, 2004).

The appetite-regulating neural network is located in the arcuate nucleus of the hypothalamus. This network has been well-described in a number of species, and consists of neurons which contain neuropeptides that act to either stimulate (e.g Neuropeptide Y, NPY and Agouti-related peptide, AGRP) or inhibit (e.g. Proopiomelanocortin, POMC and Cocaine-amphetamine regulated transcript, CART) food intake (Williams *et al.*, 2001). The network is chiefly regulated by the adipocyte-derived hormone, leptin, whose receptor is expressed on the neurons within the appetite-regulating network. Leptin binding acts to reduce the expression of appetite-stimulating neuropeptides and increase the expression of appetite-inhibitors, thereby potently reducing feeding behaviour (Williams *et al.*, 2001) (Baskin *et al.*, 2001). The major period of development of this network is before birth (in humans and large

mammals) and in the early postnatal period (in rats and mice). Importantly, exposure to an increased nutrient supply during the development of this network results in impaired appetite regulation in postnatal life (Grove & Smith, 2003) (Muhlhausler *et al.*, 2004). In sheep, lambs exposed to maternal overnutrition during the second half of pregnancy consume more milk during the immediate postnatal period and are fatter at one month of age than their control counterparts (Muhlhausler *et al.*, 2006). Importantly, these lambs are no longer able to appropriately regulate their appetite in response to an increase in food intake, and this appears to be a consequence of reduced expression of the leptin receptor in the appetite-regulating centre (Muhlhausler *et al.*, 2006). Similar dysregulation of appetite and persistent hyperphagia are also reported in rodent offspring who are born to mothers fed on high-fat, high-sugar diets during pregnancy and lactation, or exposed to overnutrition as a result of small-litter rearing in the early postnatal period (Plagemann *et al.*, 1999; Kirk *et al.*, 2009).

In addition to effects on food intake, there is also evidence that prenatal exposure to high-fat and high-sugar diets results in alterations to food preferences (Bayol *et al.*, 2007; Teegarden *et al.*, 2009; Ong & Muhlhausler, 2011). In our laboratory, we have shown that offspring of rat dams fed a high fat, high sugar cafeteria diet during pregnancy and lactation exhibit an increased preference for fat compared to offspring of dams fed a standard rodent diet, when provided with free access to a cafeteria diet after weaning (Ong & Muhlhausler, 2011). Perinatal exposure to the cafeteria diet was also associated with altered development of the central reward pathway in the offspring, which could account for the increased propensity towards overconsumption of palatable foods (Ong & Muhlhausler, 2011).

In the case of adipose tissue, studies in both rodents and large animal models have reported that maternal obesity and hyperglycemia are associated with increased mRNA expression

(Muhlhausler *et al.*, 2007) and activity (Kasser *et al.*, 1981; Benkalfat *et al.*, 2011) of key lipogenic genes in the adipose tissue of the offspring. These genes include the lipogenic transcription factor, PPARγ, and lipogenic enzymes, lipoprotein lipase (LPL) and glycerol-3-phosphate dehydrogenase (G3PDH). It is the increased activity of these genes that is associated with an increased accumulation of adipose tissue in early postnatal life (Muhlhausler *et al.*, 2006). Furthermore, this increased lipogenic capacity in the adipose tissue persists beyond the immediate post-natal period, such that these offspring have a greater capacity for lipid storage throughout the lifecourse.

Offspring exposed to maternal hyperglycemia or maternal high-fat feeding also exhibit severely impaired glucose tolerance and insulin sensitivity in young adulthood (Catalano & Ehrenberg, 2006). Studies in rodents have demonstrated that this is the result of altered development of key components of the insulin signalling pathway in the offspring; offspring of obese dams exhibited a decreased abundance of insulin-receptor substrate 1 (IRS1) and impaired phosphorylation of Protein Kinase B (PKB), in muscle and liver, consistent with impaired signaling downstream of the insulin receptor (Shelley *et al.*, 2009). The nutritional environment an individual experiences during the perinatal period therefore plays a critical role in determining the structure and function of the adipose tissue, liver and skeletal muscle in postnatal life, and therefore the risk of obesity, glucose intolerance and insulin resistance in the offspring (Poston *et al.*, 2011).

Given this, there is good evidence to suggest that exposure to maternal obesity/overnutrition has substantial impacts on the development of systems regulating energy balance and metabolism, which have lasting effects on the susceptibility of these individuals to obesity and metabolic disease later in life **(Figure 2)**. These studies have highlighted the important

role of maternal nutrition in mediating these effects, and this has led to suggestions that the adverse effects of maternal obesity/maternal overnutrition during critical windows of development could potentially be alleviated or corrected by targeted nutritional interventions.

The Case for Nutritional Interventions

Fetal development is a time during which tissues and organ systems are undergoing rapid and complex development, and exposure to even small amounts of toxins during critical developmental windows can have devastating long-term effects. As a result, the use of drugs either before birth or during early infancy for overcoming the effects of exposure to an increased nutrient supply is unlikely to be a feasible approach. In contrast, nutritional interventions are safe, relatively inexpensive and have the potential to be feasibly implemented on a population level. The efficacy of nutritional interventions during pregnancy/lactation for producing lasting benefits for the offspring has also been demonstrated in cases of micronutrient deficiency. Ensuring adequate Vitamin D intake during pregnancy and lactation in previously deficient individuals resulted in a dramatic decrease in the incidence of rickets in infants and children (Park, 1940) and the wide-spread use of folate supplements in early pregnancy has virtually eliminated neural tube defects (De Wals *et al.*, 2007).

Interventions which reduce even mildly elevated maternal glucose concentrations have also been shown to result in marked improvements in pregnancy outcomes studies (Poston, 2011). In addition to being reported in animal models, the efficacy of nutritional interventions to reduce maternal glucose has been demonstrated in two large-scale clinical studies, including the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and the Maternal-Fetal Medicine Unit (MFMU) Network study. In both cases, aggressive dietary

management of mild gestational diabetes, compared to routine care, resulted in reduced risks of preeclampsia, perinatal morbidity and fetal overgrowth (Crowther *et al.*, 2005; Landon *et al.*, 2009). The search for nutritional interventions that could overcome the effects of overnutrition have focussed on either a whole-diet approach to reduce maternal glucose levels or various single-nutrient approaches. The remaining sections of this review will discuss some nutritional interventions which have shown early promise, including restricting gestational weight gain, maintaining a low glycemic index (GI) diet during pregnancy and targeted maternal nutritional supplements. .

Potential Strategies for Nutritional Intervention

Global Calorie Restriction

Independent of maternal weight at the start of pregnancy, the degree of weight gained during pregnancy (gestational weight gain) has been associated with an increased risk of obesity in the child (Dodd *et al.*, 2011a). The suggested guidelines for maternal weight gain during pregnancy are lower for women who are overweight or obese, compared to those in the underweight or healthy weight ranges. However, few overweight and obese women are able to adhere to these weight gain guidelines, and compliance rates are lower than for normal weight women (Dodd *et al.*, 2011a). It has therefore been suggested that limiting weight gain during pregnancy, through diet and life-style interventions, may be an effective strategy for improving the long-term health outcomes of children born to overweight and obese mothers. A recent systematic review focusing on the impact of weight-management programs in pregnant women assessed the results of 88 studies, which were made up of 40 randomised and 48 non-randomised and observational studies, involving a total of 182,139 women (Athukorala *et al.*, 2010). The authors of this review concluded that dietary interventions in pregnancy were the most effective strategy for weight-management. These dietary

interventions to limit gestational weight gain were associated with significant reductions in the incidence of pre-eclampsia, gestational hypertension and preterm birth and also tended to reduce the incidence of gestational diabetes (Athukorala *et al.*, 2010). Importantly, none of these studies identified significant maternal or fetal adverse effects as a result of these interventions.

Despite these encouraging findings, the authors acknowledged that there was considerable heterogeneity in the effect of the dietary interventions in different studies. They suggested that thismay have been due to differences in BMI, age, parity, socioeconomic status and medical conditions in pregnancy between the study populations, as well as differences in genetic background of the populations under study. In addition, there have been no follow up studies in humans which have determined whether these nutritional interventions in the mother have beneficial effects for the later metabolic health of the children. Nevertheless, the evidence to date suggests that limiting gestational weight gain in overweight and obese women may be an effective strategy for improving neonatal outcomes in women who enter pregnancy with a high BMI, and do not appear to carry any significant risks for maternal or fetal health. It is important to exercise caution with this last statement, since it is clear from animal studies that restricting maternal caloric intake before or during pregnancy, independent of maternal BMI, may result in altered development of the HPA axis in the fetus and result in altered functioning of the stress axis in postnatal life (Zhang *et al.*, 2011). The scientific community eagerly awaits the results of large scale randomised controlled trials of limiting weight gain in pregnancy in overweight/obese women, such as the LIMIT study in South Australia (Dodd *et al.*, 2011b), in order to provide more robust evidence for the benefits of diet and lifestyle interventions during pregnancy.

Low GI diets

The glycemic index (GI) describes the effects of different carbohydrate foods on blood glucose levels. Carbohydrates that break down quickly during digestion and release glucose rapidly into the bloodstream have a high GI; whilst carbohydrates that break down more slowly, releasing glucose gradually into the bloodstream, have a low GI (Brand-Miller & Holt, 2004; Brand-Miller, 2004). As a result, a low GI diet is associated with lower fasting and postprandial glucose concentrations than a high GI diets (Brand-Miller, 2004). Low GI diets have received significant attention in adult nutrition in relation to their effects on body weight and insulin action. In support of this, switching overweight and/or type 2 diabetic individuals from typical western (high GI) diets to low GI diets can improve insulin sensitivity and assist with maintenance of weight loss (Jenkins *et al.*, 2008; Larsen *et al.*; Marsh *et al.*).

The GI of the diet is likely to be particularly relevant in pregnancy, given that glucose is transferred directly from the mother to the fetus and is the main energy substrate for intrauterine growth (Fowden, 1995). Based on previous findings in adults, we and others have hypothesised that consuming a low GI diet during pregnancy would be associated with exposure of the fetus to a lower glucose supply compared to a moderate-high GI diet, and thus to a reduced risk of obesity and type 2 diabetes in the offspring. Whilst there have been few studies to date which have investigated the effects of low GI diets during pregnancy on neonatal outcomes, the results from the small number of existing studies have been encouraging. Indeed, a recent systematic review of human studies investigating the effect of maternal intake of low GI diets on pregnancy outcomes reported that four of the eight studies carried out to date showed a protective association between low GI diets and pregnancy-related outcomes, and none showed negative effects (Louie *et al.*, 2010). These studies

demonstrated that for both normal and diabetic women birth weight, birth weight z-score and ponderal index of offspring were lower in women consuming the low GI diet compared to those consuming a standard Western diet or low-fat diet, and there was a reduced risk of delivering a large for gestational age or macrosomic infant (Louie *et al.*, 2010; Louie *et al.*, 2011). However, while these studies provide important evidence that lowering the GI of the diet consumed in pregnancy may be an effective strategy for improving perinatal outcomes, there are no studies which have evaluated the impact of a low GI diet during pregnancy on the metabolic health of the offspring beyond the immediate postnatal period. It therefore remains to be determined whether this intervention will produce lasting health benefits to the offspring. The added attraction of the low GI diet, in comparison to other diets used for weight-loss and controlling glucose homeostasis, is the fact that they appear to be more acceptable for consumers.

Omega-3 Long Chain Polyunsaturated Fatty Acids (LCPUFA)

The omega-3 long chain polyunsaturated fatty acids (LCPUFA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), play an important role in optimal fetal and neonatal development (Makrides & Gibson, 2002)). Whilst most studies to date have focussed on their role in neurodevelopment, there has been increasing interest in their potential metabolic effects as a result of data from *in vitro* studies which have shown that both DHA and EPA can inhibit the proliferation and differentiation of pre-adipocytes and selectively inhibit the activity of pro-adipogenic factors (Ailhaud *et al.*, 2006; Massiera *et al.*, 2006). In addition, omega-3 LCPUFA also act on mature adipose cells to inhibit the expression of the key lipogenic mediator sterol-regulated binding protein 1 (SREBP-1c), resulting in a reduced expression of downstream lipogenic genes, including Fatty Acid Synthase (FAS) and glycerol 3 phosphate dehydrogenase (G3PDH) and a reduced accumulation of lipid (Masden *et al.*,

2005). Thus, at least in adults, omega-3 LCPUFAs can reduce the accumulation of body fat by limiting both the hyperplastic and hypertrophic expansion of adipose depots (Okuno *et al.*, 1997; Raclot *et al.*, 1997; Ruzickova *et al.*, 2004).

The evidence linking omega-3 LPCUFA with reduced fat deposition, have led us and others to hypothesise that supplementing the diet of the mother with omega-3 LCPUFA during pregnancy and/or lactation may be a potential strategy for reducing fat mass, and thereby improve metabolic outcomes, in their children (Hauner *et al.*, 2009). The studies in this area to date have, however, produced conflicting and disparate results, and there is still a lack of robust evidence that exposure to an increased supply of omega-3 fatty acids during early life has the potential to produce lasting metabolic benefits (Muhlhausler *et al.*, 2010). To date, only 4 published human studies have investigated this have been relatively small with high attrition rates and have, perhaps unsurprisingly given these caveats, produced disparate results (Muhlhausler *et al.*, 2010). Indeed, 2 of these studies reported an increase in fat accumulation in children who had been exposed to omega-3 supplementation during infancy (Lauritzen *et al.*, 2005), which is in complete contrast to the hypothesised effect. Whilst animal studies have more consistently reported a reduction in fat mass in offspring of mothers receiving a diet supplemented with omega-3 LCPUFA during pregnancy and/or lactation (Korotkova *et al.*, 2002; Massiera *et al.*, 2003; Wyrwoll *et al.*, 2006; Ibrahim *et al.*, 2009), all but one of these studies have also weaned the offspring onto a high omega-3 LCPUFA diet. In our laboratory, we found that offspring of dams supplemented with omega-3 fatty acids only during pregnancy and lactation, and then weaned onto a standard rodent feed containing low levels of omega-3 LCPUFA exhibited an increase in relative body fat mass at 6 weeks of age, which was normalised by 3 months (Muhlhausler *et al.*, 2011). There is therefore still considerable work to be done in determining whether omega-3 LCPUFA supplementation of

the maternal diet is an appropriate strategy for curtailing early fat deposition, and if providing these supplements to overweight and obese mothers could help improve the metabolic outcomes in their children.

Maternal Nutritional Supplements

Whilst maternal overnutrition is associated with increased intake of calories, saturated fats and/or sugars, there is data that has suggested that this global overnutrition can occur against a background of deficiency in key micronutrients (Kaidar-Person *et al.*, 2008). Therefore, the potential exists for the negative effects of being exposed to an excess supply of fat and glucose during development to be compounded by those of being exposed to an inadequate supply of key micronutrients. The concentrations of micronutrients in the maternal blood, perhaps with the exception of haemoglobin as an indicator of iron status, are not routinely assessed during pregnancy (Women's and Children's Health Network, (2012), making it difficult to identify the extent of such deficiencies.

Similar to what has been reported for human diets containing excess amounts of junk foods, the cafeteria diet that we have used in our rodent model of maternal overfeeding is also deficient in several key micronutrients, in particular calcium and magnesium *(Gugusheff and Muhlhausler, unpublished observations).* This is potentially significant, since maternal dietary insufficiency of magnesium as well as zinc and iron, even in the absence of maternal overnutrition, has been associated with an increased risk of obesity and its associated metabolic disorders in the offspring. In rodents, maternal magnesium or zinc deficiency are both associated with increased body fat mass, reduced lean mass and reduced insulin secretion in the adult offspring (Venu *et al.*, 2005; Venu *et al.*, 2008). Similarly, offspring of iron deficient mothers exhibit increased visceral adiposity, decreased locomotor activity and

an increased susceptibility to diet-induced obesity (Komolova *et al.*, 2008; Bourque *et al.*, 2012).

Clinically, micronutrient deficiencies have been associated with low birth weights. However, studies in human populations which have investigated the long term metabolic outcomes of children born to women provided with micronutrient supplements during pregnancy are limited. A randomised control trial in Nepalese women and showed that folic acid-iron-zinc supplementation but not folic acid-iron supplementation, reduced the incidence of low birth weight by 15%. Importantly, children of women who received the folic acid-iron-zinc supplement also had reduced peripheral adiposity 6-8 years of age (Stewart *et al.*, 2009). This was supported by a similar study in Peruvian women, which also highlighted the benefits of zinc supplementation in increasing lean body mass in the children in infancy (Iannotti *et al.*, 2008). Whilst it is apparent that further investigations are needed, micronutrient supplementation during pregnancy could act as an important nutritional intervention to improve the metabolic outcomes of children born to mothers consuming an energy dense but nutrient poor western diet. Ideally, these micronutrients would be obtained from the diet, however nutritional supplements are likely to provide a more practical solution. There are an increasing number of nutritional supplements specifically targeted at pregnant and lactating women. However, whether the levels of key micronutrients they contain is sufficient to overcome deficiencies in women consuming diets dominated by processed and convenience foods remains to be investigated.

Summary and Perspective

It is now well-established that the nutritional environment that an individual experiences before birth and in early postnatal life has a critical role in defining the long-term health outcomes of the offspring. Through most of history, insufficient caloric intake and severe micronutrient deficiencies were the major problems for women in pregnancy. Whilst these problems are still, unfortunately, experienced in many parts of the world, in developed countries it has been largely replaced by a new nutritional challenge; maternal obesity and overnutrition. Infants exposed to this obeseogenic environment during early life are at increased risk of obesity and metabolic disease, thereby creating an intergenerational cycle of poor metabolic health.

In this review, we have discussed the mechanisms thought to underlie this association, and some of the potential nutritional strategies through which it may be possible to intervene **(Figure 3)**. Despite the scale of the obesity problem, there remains a paucity of studies which have attempted to test these interventions in either animal models or the clinical setting. It is our view that a greater focus on intervention is essential if we are to break the intergenerational cycle of the obesity and metabolic disease, and that food may indeed be the best medicine to address this. It is also important to note the recent data which has demonstrated that the paternal diet before conception can have independent effects on the metabolic phenotype of the offspring. Two note-worthy studies in this area have demonstrated that paternal high-fat feeding (Ng *et al.*, 2010) and low-protein diets (Carone *et al.*, 2010) are both associated with metabolic programming of the offspring, even when all mothers are maintained on the same diet during pregnancy and lactation. Thus, when developing nutritional interventions to overcome the trans-generational obesity cycle, it may be important to consider the father, as well as the mother, as a potential target.

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FIGURE LEGENDS

Figure 1. Proposed pathways through which maternal obesity results in increased fetal growth. Maternal obesity and/or overnutrition results in increased nutrient delivery to the developing fetus. This increases fetal glucose concentrations and stimulates the fetal pancreas to release insulin. The resulting fetal hyperglycemia and hyperinsulinemia promotes tissue growth and fat deposition, resulting in a heavy infant who is also at risk of obesity and type 2 diabetes (TDM) later in life.

Figure 2. Summary of the biological mechanisms implicated in the early life origins of obesity. Exposure of the developing fetus/neonate to an increased nutrient supply results in altered development of the systems which regulate appetite, motivation and reward, fat deposition and insulin signalling which results in persistent changes to how these systems operate in postnatal life and thus prediposes the individual to obesity and metabolic disease. These effects may be exacerbated by deficiencies of key micronutrients during the development of these systems.

Figure 3. Proposed nutritional interventions for overcoming the programming of obesity by maternal obesity/overnutrition. These strategies focus on either global dietary approaches to improve maternal glycemic control and thereby reduce glucose delivery to the developing fetus (diet lifestyle interventions, low GI diets) or targetting specific developmental pathways using single nutrients (omega-3 LCPUFA, micronutrient supplementation).

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Figure 1.

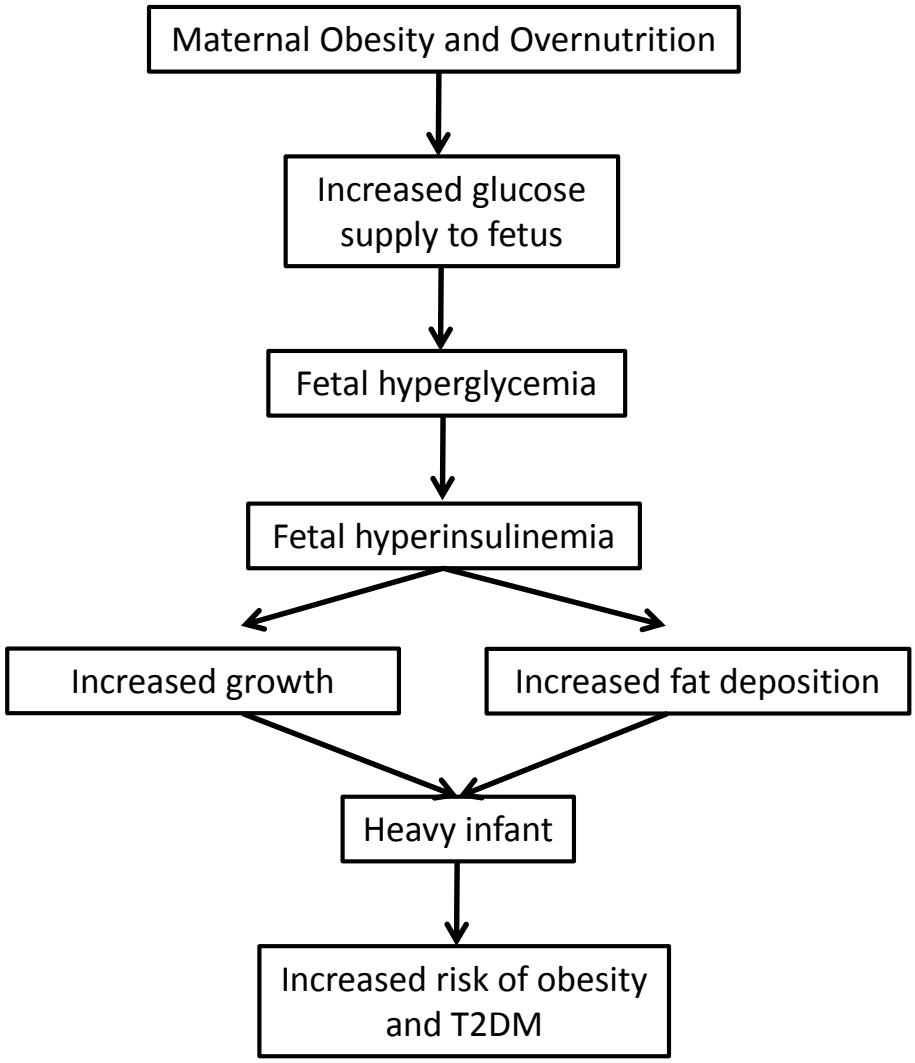

Maternal Obesity and Overnutrition
Increased glucose supply to fetus
Fetal hyperglycemia
Fetal hyperinsulinemia
Increased growth
Increased fat deposition
Heavy infant
Increased risk of obesity and T2DM

Figure 2.

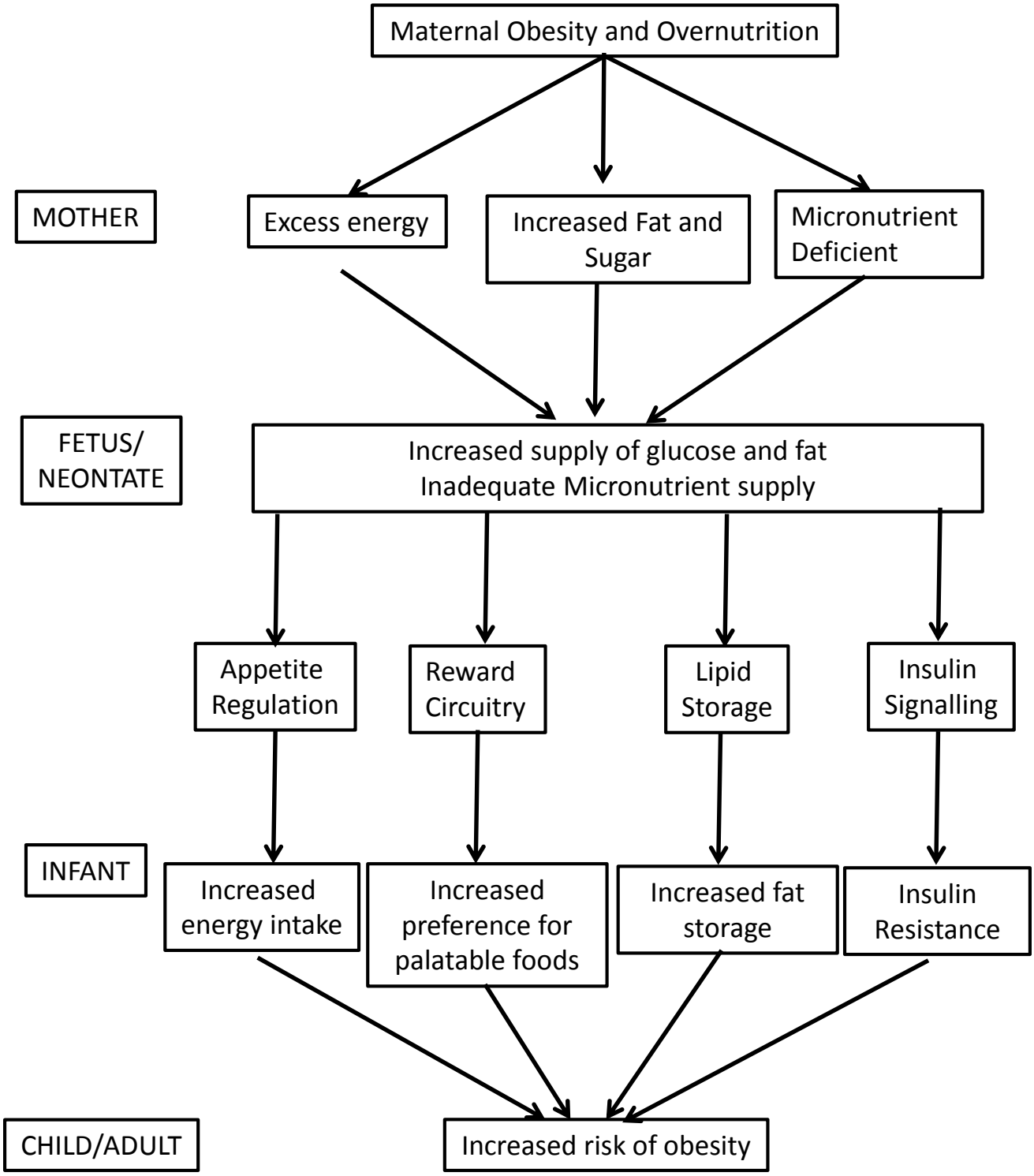
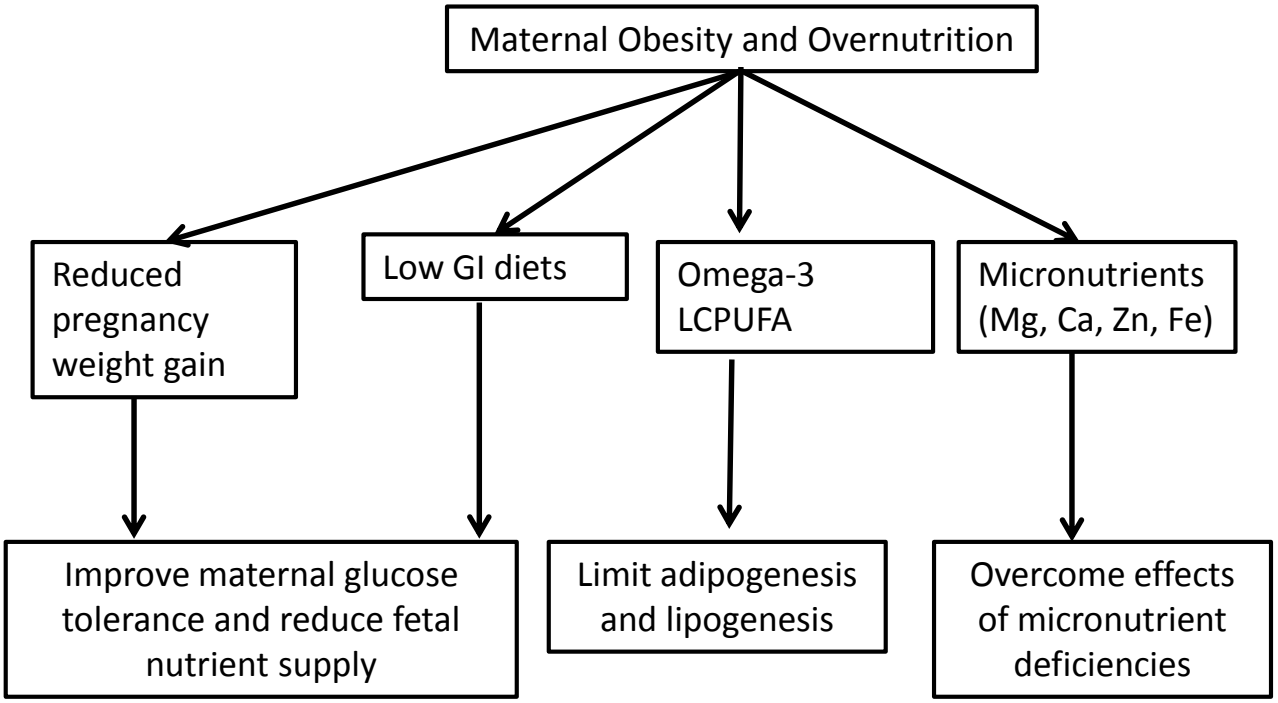

Maternal Obesity and Overnutrition
MOTHER
Excess energy
Increased Fat and Sugar
Micronutrient Deficient
FETUS/ NEONTATE
Increased supply of glucose and fat
Inadequate Micronutrient supply
Appetite Regulation
Reward Circuitry
Lipid Storage
Insulin Signalling
INFANT
Increased energy intake
Increased preference for palatable foods
Increased fat storage
Insulin Resistance
CHILD/ADULT
Increased risk of obesity

Figure 3.


Maternal Obesity and Overnutrition
Reduced pregnancy weight gain
Low GI diets
Omega-3 LCPUFA
Micronutrients (Mg, Ca, Zn, Fe)
Improve maternal glucose tolerance and reduce fetal nutrient supply
Limit adipogenesis and lipogenesis
Overcome effects of micronutrient deficiencies