Impact of Maternal Obesity on Offspring Adipose Tissue: Lessons for the Clinic

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Abstract/Summary

Maternal obesity is a major risk factor for the subsequent development of obesity and type 2 diabetes in the child. This relationship appears to be driven largely by the exposure of the fetus to an increased nutrient supply during critical periods of development, which results in persistent changes in the structure and function of key systems involved in the regulation of energy balance, appetite and fat deposition. One of the key targets is the fat cell, or adipocyte, in which prenatal overnutrition programs a heightened capacity for fat storage. The increasing prevalence of maternal obesity has led to an urgent need for strategies to break the resulting intergenerational cycle of obesity and metabolic disease. This review will discuss the relationship between maternal obesity and poor metabolic health of the offspring, with a particular focus on the involvement of adipose tissue, recent clinical studies examining potential strategies for intervention and priority areas for further research.

Keywords:
obesity, pregnancy, maternal nutrition, adipose tissue, fetal programming, lipogenesis
Introduction

The world-wide increase in the prevalence of overweight and obesity has led to a corresponding increase in the number of women who are classified as overweight or obese when they enter pregnancy. Recent statistics from Australia and the US suggests that over 50% of women have a body mass index (BMI) >25kg/m² at the time of their first antenatal appointment, and there are predictions that this figure is likely to increase [1,2].

Maternal obesity has both short- and long-term adverse consequences for the mother and her infant. Obese women have a significantly increased risk of a number of pregnancy complications, including gestational diabetes (GDM) and pre-eclampsia, and their infants have a higher incidence of neonatal morbidity and mortality [3,4]. Infants born to overweight/obese women are more likely to be born large for gestational age (LGA) or macrosomic (>4000g), require resuscitation at birth and to suffer from jaundice and neonatal hypoglycaemia [4,5].

Most recently, attention has turned to the impact of maternal obesity on the longer term outcomes of the infants. Clinical studies from across the developed and developing world have provided compelling evidence that infants of overweight and obese mothers, in addition to being heavier at birth, have a significantly increased risk of obesity and associated metabolic disorders later in life [4,6]. This association between maternal obesity and the risk of obesity in the child has created an intergenerational cycle of obesity and metabolic disease, which threatens to continue to impact on the metabolic health of future generations.

This review will focus on current understanding of the mechanisms which underlie the increased risk of obesity in infants of overweight/obese mothers, with a specific focus on the effects on adipose tissue development. It will summarise the current state of the field in this
area of research, and provide insights into the key challenges and opportunities over the
coming 5 year period.

Maternal Obesity: A New Obstetric Challenge

The number of women entering pregnancy overweight or obese has risen dramatically in
recent years, in line with the rising prevalence of obesity in the general population. Data from
the US in the early to mid-2000s indicated that just over 30% of pregnant women were
classified as overweight or obese [2], however more recent studies suggest that this figure is
now likely to be closer to 50% [3]. This substantial rise in the number of overweight and
obese pregnant women represents a major challenge to clinicians, since this sector of
pregnant population is well-known to be at increased risk of a host of pregnancy
complications [3]. Furthermore, this risk increases with increasing maternal BMI and the
presence of other co-morbidities, including pre-pregnancy diabetes or hypertension. Women
who enter pregnancy overweight or obese are at higher risk of developing gestational
diabetes (GDM), pregnancy hypertension and pre-eclampsia. There is also a much greater
risk of infants being large for gestational age or macrosomic (a birth weight >4000g), which
creates difficulties during the delivery process, in particular shoulder dystosia, and the
majority of these infants are delivered by caesarean section [4,7]. Pregnancies complicated by
maternal obesity are also more likely to end in still birth or significant neonatal distress. The
infants born to overweight and obese women are also at higher risk of neonatal complications
than infants born to lean women, in particular post-natal hypoglycaemia, jaundice and
admission to neonatal intensive care [3].

While it is not unexpected that heavier mothers give birth to heavy infants, there is now
compelling evidence that the adverse effects of maternal obesity extend beyond the
immediate postnatal period, and predispose the infant to an increased risk of obesity and its
associated metabolic complications throughout child and adult life.

**Maternal Obesity and Nutrient Supply to the Developing Fetus**

The short and long term consequences of maternal overweight/obesity on the developing
infant are thought to result from the exposure of the fetus to an excess nutritional supply
during critical periods in its development [8-10]. This increased nutrient supply appears to be
due to the combined effects of the tendency of overweight/obese women to consume diets
which are poorer in quality than lean women [11] and the fact that these women also tend to
be more insulin resistant than their lean counterparts [2] (**Figure 1**). While a reduction in
insulin sensitivity in the mother is a normal adaptation to pregnancy, designed to maximise
transfer of nutrients from mother to fetus rather than them being utilised by maternal tissues,
a large proportion of women in the overweight/obese population already have compromised
insulin sensitivity (or indeed are already borderline diabetic) when they fall pregnant. In these
cases, the normal adaptation to pregnancy can often progress to GDM, which is characterised
by maternal hyperglycemia during both post-prandial and fasting periods.

In addition to hyperglycemia in the mother, GDM is associated with elevated glucose
concentrations in the developing fetus. This fetal hyperglycemia stimulates the fetal pancreas
to secrete more insulin, resulting in fetal hyperinsulinemia which stimulates anabolic
processes in the fetus and results in increased fetal growth and fat deposition [12]. This ‘fuel
mediated teratogenesis’ was first described by Freinkel in the 1980s, is associated with the
increased birth weight and risk of fetal macrosomia which are characteristic of infants of
diabetic mothers. In addition to being heavier and fatter at birth, there is also compelling
evidence from both clinical and epidemiological studies that infants born to diabetic mothers
are at higher risk of obesity and its associated metabolic disorders throughout childhood and adulthood [13,14] (Figure 1).

The Underlying Mechanisms: The Role of Adipose Tissue
There have been a large number of studies in both small and large experimental animals which have begun to shed light on the biological mechanisms which underlie the increased risk of obesity in infants born to overweight/obese mothers. In small animal studies, maternal obesity has most commonly been modelled by feeding rat/mouse dams on cafeteria or semi-synthetic high-fat diets prior to pregnancy and during pregnancy and lactation [15,16]. We and others have consistently demonstrated that offspring born to dams fed on these types of diets have a significantly elevated body fat mass at weaning and remain heavier and fatter through the life course than offspring of dams fed on control diets [17-19]. Importantly, maternal high-fat and/or high-sugar diets have been associated with altered gene expression within both the adipose tissue and hypothalamic appetite-regulating networks of the offspring, which result in higher fat deposition and increased appetite drive (hyperphagia) in the offspring into adult life [18-20].

Studies in large mammals, such as sheep and pigs, have the advantage over studies in smaller animals that the ontogeny of fat development is much more similar to that in the human; i.e. fat cell development begins before birth and extends into early postnatal life. This differs from altical rodent species, in which fat development is virtually absent in utero and appreciable fat deposits only start to appear during the suckling period. Some years ago, we developed a model of maternal overnutrition in the sheep in which pregnant ewes were fed ~55% above their maintenance energy requirements (as specified by the Ministry of Agriculture, Fisheries and Food, UK [21]) in the later third of pregnancy, in order to mimic exposure of the fetus to a moderate increase in nutrient supply during the major period of
intrauterine fat development [22]. This maternal overnutrition was associated with significant increases in maternal glucose concentrations, and fetal glucose and insulin concentrations were also significantly increased in fetuses of over-fed ewes compared to fetuses of ewes fed at maintenance energy requirements [22].

Using this model, we studied the effect of fetal hyperglycemia/hyperinsulinemia on fetal fat cells, and fat deposition in the lamb in the early postnatal period. We demonstrated that maternal overnutrition was associated with a significant increase in the expression of the key adipogeneic/lipogenic transcription factor, Peroxisome Proliferator Activated Receptor gamma (PPARγ), in the fetal perirenal adipose depot (the main fat depot in fetal life), in conjunction with an increase in the mRNA expression of key lipogeneic genes, lipoprotein lipase (LPL) and glycerol-3-phosphosphate dehydrogenase (G3PDH) [23]. Importantly, this upregulation of lipogeneic genes was associated with an increased accumulation of fat in the early postnatal period, and lambs of over-fed ewes had a significantly higher mass of subcutaneous fat relative to body weight by the end of the first month of life [24,25]. These results suggested, therefore, that prenatal hyperglycemia led to a precoical upregulation of lipogenic genes in adipose tissue, which resulted in increased fat deposition after birth. The importance of the increased availability of nutrients in driving these effects is highlighted by the presence of a direct relationship between fetal glucose concentrations and the level of PPARγ mRNA expression in the perirenal adipose tissue in late gestation – consistent with clinical evidence that intrauterine glucose concentrations provide a sensitive marker of fetal adiposity [26]. In other studies, we and others have also reported that infusing glucose directly into the fetal sheep in late gestation is associated with a significant increase in the size of the lipid droplets in fetal fat depots, fetal fat mass and in leptin mRNA expression in
fetal fat depots [27,28], providing further evidence of the central role of glucose supply in driving fat deposition in utero.

In addition to effects of maternal overnutrition on the adipose tissue and fat mass, there were also significant effects on the regulation of appetite and feeding behaviour. Thus, lambs of over-fed ewes had a significantly higher milk intake over the first month of postnatal life, and did not appropriately upregulate the expression of the appetite-inhibiting neuropeptide, Cocaine and Amphetamine Regulated Transcript (CART) in response to a positive energy balance [25]. This appeared to be a result of a downregulation of the expression of the leptin receptor in the central appetite regulating centre of these lambs as their fat mass increased, consistent with the development of central resistance to the actions of leptin’s appetite-suppressing actions [25]. These findings, summarised in Figure 2, led us to hypothesise that the primary event in the pathway linking an increased nutrient supply in utero to increased propensity to obesity in postnatal life was the programming of an increased capacity for lipogenesis in fetal fat depots [9].

These sheep studies are supported by the finding from studies in pigs, largely conducted by Hausman and colleagues, which examined the effect of maternal diabetes and obesity on the structural and functional development of fetal adipose tissue in late gestation. In these studies, diabetes in the sow was associated with increased adipose tissue mass in fetuses at 112 days of gestation, without a change in body weight [29]. Importantly, the activity of key lipogenic genes, in particular lipoprotein lipase (LPL), was significantly upregulated in the fat depots of fetuses of diabetic sows, and the number and size of the lipid droplets within the fetal fat depots were significantly increased [29,30]. These observations supported the concept that fetal adipose de novo fatty acid synthesis was stimulated in diabetic pregnancies,
and is likely to represent the primary mechanism by which increased lipid accumulates in the
offspring. In a separate series of studies, Hausman and colleagues studied the development of
fat depots in fetal pigs from sows who were genetically obese, compared to lean controls. As
in the fetuses of diabetic sows, the adipocytes of fetuses of obese sows were large, more
abundant and had higher LPL activity in late gestation, and these changes preceded the onset
of obesity in this genetically obese breed [31,32].

Taken together, the results of large animal studies suggest that fetal overnutrition, induced as a
result of either maternal obesity and/or maternal hyperglycemia, is associated with a
precocial upregulation of lipogeneic genes in fetal adipose depots which persists after birth
and is associated with an increased capacity for lipid storage in postnatal life, and consequent
propensity to obesity.

Maternal Obesity before Conception: Another Important Window

While the majority of studies to date have focussed on the consequences of maternal obesity
and/or overnutrition during pregnancy, there is mounting evidence that poor metabolic health
in the mother prior to and immediately after conception may also have negative effects on the
long-term metabolic health of the offspring. Both clinical and experimental studies have
shown that maternal obesity/overnutrition in the periconceptional period, independent of the
nutritional environment later in development, can result in altered development of the adipose
tissue and increased propensity to obesity in the offspring later in life. In humans, it is clearly
very difficult to separate the effects of these two periods in the vast majority of pregnancies,
however it has been reported that maternal obesity is associated with poorer developmental
competence and poorer quality oocytes – which has negative effects on subsequent embryo
development [33,34].
The negative impact of maternal obesity prior to conception on long-term offspring development has also been demonstrated in experimental animal models. McMillen and colleagues conducted an elegant study in the sheep in which embryos were transferred from a donor ewe who had been fed either on a control diet or on a high plane of nutrition (to induce maternal weight gain) for the 4 months before conception to a lean recipient ewe at 6 d post-conception, such that embryos of the ‘over-fed’ ewes were only exposed to the obesogenic environment during the periconceptional period [35]. The lambs from the ‘obese’ and ‘lean’ donor ewes were subsequently studied at 4 months of age. The study showed that female offspring exposed to maternal obesity in the periconceptional period had a higher fat mass as a percentage of body weight at 4 months of age compared to control lambs [35]. The study also determined whether these effects could be reversed by restricting the energy intake of the ‘obese’ dams to induce weight loss in the period immediately prior to conception. While maternal weight loss in the ‘obese’ donors prevented the subsequent increase in fat mass in the lambs [35], periconceptional weight loss also resulted in heightened stress responsiveness, suggesting that maternal energy restriction diets before or in the early part of pregnancy may not be desirable [36,37].

Implications for the Clinic

In humans, as in sheep and pigs, the major period of fat development begins in late gestation and extends into the first year of life. The rising incidence of maternal overweight and obesity, coupled with the increased consumption of energy-dense, nutrient poor ‘junk’ foods, by pregnant and lactating women has led to growing concerns about the long-term consequences of this obesogenic environment on future generations. As a result, more recent
studies, in both humans and experimental animal models, have become increasingly focussed on identifying potential strategies for intervention. This is particularly important in light of the evidence from animal studies suggesting that the structural and functional changes induced in adipose (and other) tissues as a result of prenatal exposure to an increased nutrient supply in utero are very difficult, if not impossible, to reverse through nutritional interventions applied later in development [15,38,39]. In humans, three key windows of opportunity have been identified in relation to introducing nutritional interventions to improve long-term health outcomes in the offspring, namely prior to pregnancy, during pregnancy and in early infancy.

**Interventions Prior to Pregnancy**

As discussed above, the evidence showing that exposure to maternal obesity/overnutrition during the periconceptional period alone can result in an increased propensity for fat accumulation in the offspring suggests that, ideally, women who are overweight/obese should consider undertaking diet/lifestyle interventions to normalise body weight and improve metabolic health prior to conceiving. In addition, the fact that significant weight loss immediately before conception or in the early stages of pregnancy has the potential to negatively impact on the stress axis of the offspring [36], implies that any weight reduction program should be undertaken some time before the woman plans to conceive. To date, there have been no clinical trials in this area, and there remains an urgent need for research to enable evidence-based guidelines for the nutritional management of overweight/obese women in the lead up to pregnancy to be developed.
Interventions During Pregnancy

While weight reduction/improved nutrition prior to pregnancy may be ideal, this is not always possible or practical, and pregnancies are not always planned and many clinicians do not see women until they are well into their pregnancy. As a result, the majority of clinical studies which have focussed on diet/lifestyle interventions introduced during pregnancy and/or lactation. A summary of some of the potential nutritional interventions which have been suggested/tested to date is presented in Figure 4, and the proposed interventions discussed in more detail in the following paragraphs.

Early studies in this area focussed on the potential for interventions aimed at improving maternal glucose control to improve pregnancy/neonatal outcomes. The findings from two large-scale clinical studies, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and the Maternal-Fetal Medicine Unit (MFMU) Network study, provided encouraging data which suggested that aggressive treatment of mild gestational diabetes, compared to routine care, resulted in reduced risks of pre-eclampsia, perinatal morbidity and fetal overgrowth (large for gestational age deliveries and fetal macrosomia) [40,41]. While the long-term consequences of these interventions on the fat mass/metabolic health of the children is not known, these studies nevertheless suggest that improving maternal glucose control, and thereby reducing maternal and fetal glycaemia, has the potential to improve the long term metabolic health outcomes of the child.

The absorption of digested carbohydrate from foods in the form of glucose is the major dietary factor affecting postprandial blood glucose concentrations and insulin secretion, and as a result the quality and quantity of carbohydrates in the diet are key determinants of postprandial glucose concentrations[42]. 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 whereas carbohydrates that break down more slowly, releasing glucose more gradually into the bloodstream, have a low GI. Thus, consumption of a low GI diet is associated with lower fasting and postprandial glucose concentrations than consumption of high GI diets [42]. Low GI diets have received significant attention in adult nutrition in relation to their effects on body weight and insulin action, and switching overweight and/or type 2 diabetic individuals from typical western diets to low GI diets can improve insulin sensitivity and assist with maintenance of weight loss [43-46].

The role of low GI diets in improving glucose control have led to suggestions that reducing the GI of diets consumed by women during pregnancy may have the potential to improve the metabolic health outcomes of the child by reducing maternal and fetal glucose concentrations. There is some evidence that adopting a low GI diet during pregnancy may offer benefits for maternal/child health, with a systematic review of human studies reporting 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 [47]. In both normal and diabetic women in these studies 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 [47,48]. Again, however, there are limited data on the potential for this intervention to improve the metabolic health of the offspring in the longer term. An exception is a recent study by Danielsen and colleagues, which reported a direct relationship between the GI of the maternal diet at gestational week 30 and markers of the metabolic syndrome, including fasting insulin, insulin sensitivity (assessed by HOMA-IR) and leptin, in the children at 20 years of age [49]. While interesting, it is important to note that this was an observational study, rather than a controlled trial, so it is not possible to
exclude the possibility of bias/confounding. Further follow-up of existing randomised trials will help to determine whether low GI diets may offer true potential to improve the metabolic health outcomes in offspring of diabetic mothers. Nevertheless, the available evidence suggests that low GI diets can be followed safely during pregnancy, and are associated with favourable effects in the mother, including reduced pregnancy weight gain, improved glucose tolerance and lower fasting glucose/insulin concentrations [47].

More recently, two large-scale randomised controlled trials have specifically focussed on nutritional/lifestyle interventions in overweight/obese pregnant women for improving pregnancy/neonatal outcomes. The LIMIT study, led by Dodd and colleagues at the University of Adelaide, included over 2200 overweight and obese women who were randomised to receive either standard antenatal care or a comprehensive diet and lifestyle interventions in the second half of pregnancy [50]. As the name suggests, one of the principal aims of this study was to limit gestational weight gain in this population of pregnant women, since previous studies had suggested that a high percentage of overweight/obese pregnant women exceed the recommended weight gains for pregnancy, and that this is associated with poor pregnancy/neonatal outcomes [51]. The first results of the LIMIT trial, published in the British Medical Journal in early 2014, suggested that the nutritional and lifestyle intervention was associated with significant improvements in the nutritional quality of the maternal diet, but no differences in gestational weight gain in comparison with standard care [50]. Despite this however, there was a significant reduction in the number of babies born >4000g in the intervention arm, suggesting that the diet and lifestyle intervention had the potential to reduce the incidence of fetal overgrowth [50]. Importantly, these results also imply that it may be possible to achieve beneficial outcomes in the absence of reductions in gestational weight gain. The UPBEAT trial, led by Poston in the UK and colleagues, is another large-scale RCT which aims to test the ability of a complex diet and lifestyle intervention during pregnancy to
reduce the incidence of GDM and LGA deliveries (defined as a birth weight >4000g) [52].

Again, this study is specifically targeted towards overweight and obese women, and researchers aim to recruit in excess of 1500 pregnancies in order to achieve appropriate statistical power to test their primary hypotheses [52]. The results of these large scale RCTs, and further follow-ups of the children in these trials in order to examine the longer term metabolic outcomes will be important to guide policy and practice decisions in relation to the management of overweight and obese pregnancies.

In addition to whole diet approaches to improving the metabolic health outcomes of children, interventions with specific nutrients, or combinations of nutrients, have also received some attention, particularly in relation to the level of omega-6 and omega-3 polyunsaturated fatty acids (n-6 and n-3 PUFA) in the maternal diet during pregnancy and lactation. This interest has stemmed largely from data derived from in vitro and adult rodent studies suggesting that these two classes of fatty acids have contrasting roles in relation to fat cell differentiation and lipid storage. These studies indicate that the n-3 PUFA, in particular the marine-derived long chain n-3 PUFA (n-3 LCPUFA) docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), inhibit the proliferation and differentiation of pre-adipocytes [53,54] and inhibit the expression of the key lipogenic genes in adult adipose tissue, resulting in a reduced accumulation of lipid [55-58]. In contrast, the n-6 PUFA, LA and AA, have pro-adipogenic actions and promote the hyperplastic and hypertrophic expansion of adipose depots [53,59].

These data have led to the suggestion that increasing the ratio of n-3 to n-6 PUFA in the maternal diet during pregnancy and/or lactation may be a potential strategy for reducing fat mass in the offspring [60]. To date there is little evidence from either animal or human studies to support this hypothesis [61,62]. However, there have been no attempts to date to determine whether specific sub-groups, for example women who consume poor quality diets
or are obese/overweight, could potentially benefit. The field awaits the outcomes of larger, adequately powered clinical studies to resolve this question.

Management of Infants of Obese Mothers

In human infants, fat development is not complete at birth, but continues throughout the first year of postnatal life [54]. Consequently, infant nutrition also plays an important role in defining an individual’s future risk of obesity. Importantly, data from animal studies provides evidence of an interaction between the prenatal and early postnatal nutritional environment in defining an individual’s risk of obesity and insulin resistance in the longer term. Thus, fat deposition and metabolic/cardiovascular deficits in offspring of rat dams fed on high-fat/cafeteria diets during pregnancy and lactation are exacerbated when these offspring are also fed on high-fat diets after weaning [18].

As discussed above, infants born to obese mothers are likely to be more susceptible to weight gain and fat disposition after birth compared to infants from lean women. Thus, close monitoring of the growth and nutritional intakes of these infants in the early postnatal period has the potential to provide a means of limiting the negative impacts of the intrauterine obesogenic environment. Research in this area is still in its infancy, and there are currently no specific guidelines for the management of infants of obese mothers, and this remains a fertile area for research. There have been some suggestions that encouraging ‘catch down’ growth, that is limiting the rate of infant weight gain, of infants who are born heavy at birth may be beneficial for reducing the subsequent risk of obesity, but studies in this area are lacking. It is also important to note that weight gain in and of itself does not always provide an appropriate measure of growth quality (i.e. lean vs fat mass), and assessment of body composition, and
the distribution of fat between subcutaneous and visceral fat compartments, is necessary to
gain an overall picture of the growth profile of these infants.

Perhaps the most important issue in relation to infant nutrition is the impact of breastfeeding
vs formula feeding on long-term health outcomes. A number of systematic reviews have
supported the suggestion that breastfeeding, particularly an extended duration of breast
feeding, reduces the risk of obesity by ~20% in comparison with formula feeding [63]. It is
important to note, however, that the biological effects are difficult to separate from social
factors and that many of these studies were conducted at a time when the range of infant
formulas available was much more restricted, such that the true effect size is difficult to
assess. In addition, no studies of breast vs formula feeding in relation to obesity risk have
specifically focussed on infants of obese mothers. It is also evident that the composition of
the breast milk, in particular the fat content, varies markedly between women and closely
related to the fatty acid composition of the maternal diet [64,65]. There is strong evidence
that the n-3 and n-6 PUFA content in human breast milk are directly related to the content of
these fatty acids in the maternal diet [54,66]. In addition, studies in rodents, including recent
work in our laboratory, indicate that higher maternal intakes of saturated and trans fatty acids
is directly related to increased content of these in the milk supply [67] (Vithayathil, Gibson &
Muhlhausler, unpublished observations). This implies that the composition of the maternal
diet during lactation, as well as during pregnancy, is likely to be important in determining the
long term metabolic health outcomes of the child.

If the mother is unable to or chooses not to breastfeed, then the selection of an appropriate
formula becomes important. Recent studies have implicated the higher protein content of
infant formulas in comparison to human breast milk in the higher infant growth rates and
heightened obesity risk in formula fed infants [68], and one randomised controlled trial has suggested that feeding infants a formula with a lower protein content reduced their BMI and obesity risk at 6 years of age [69]. There has also been a recent randomised trial specifically focussed on infants of obese mothers, which reported that providing these infants with a lower protein formula was associated with a lower rate of weight gain between 3 and 6 months of age [70]. Long-term follow up of the infants in this study to evaluate their long-term outcomes in relation to fat deposition and metabolic health will provide critical insights into the potential utility of low protein formulas in the management of infants born to overweight/obese mothers.

**Expert Commentary**

The rising incidence of maternal obesity has led to an urgent need to identify appropriate and effective interventions to control the resulting intergenerational cycle of obesity and poor metabolic health. From early studies of development programming, largely focused on the metabolic consequences of exposure to sub-optimal nutrition intake [71], the attention of the developmental programming field has turned to the long-term consequences of periantal exposure to maternal obesity. It is clear from these studies that infants born to obese women are at increased risk of obesity and its related comorbidities as both children and adults, and this has created an intergenerational cycle of poor metabolic health which is fuelling the propagation of the obesity epidemic.

While the underlying mechanisms are still being explored, the data to date suggests that it is exposure of the fetus/infant to an increased nutrient supply (in particular glucose and potentially fat) during critical periods of development which plays a central role in the early programming of obesity and metabolic disease. The work from our group and others suggests that the developing fat cell is a particularly important target of this metabolic programming,
and that exposure to an increased nutrient supply in utero results in persistent alterations in the structure/function of adipose cells which increases their capacity to store lipid in postnatal life. While not the topic of this review, there is also evidence that other key organs/regulatory systems, including the liver, skeletal muscle and central systems regulating appetite, reward processing and glucose control, are also impacted by prenatal nutritional excess (Figure 3). As a consequence of these programmed alterations in the structure and function of these systems, individuals exposed to an obesogenic environment in utero have an increased propensity to accumulate fat deposits after birth, and are therefore at increased risk of obesity.

From this increased understanding of the biological mechanisms underpinning the relationship between maternal and infant/child obesity has come the recognition that the manifestations of prenatal overnutrition are largely permanent, and unlikely to be reversed by interventions applied later in life. Thus, while it may be possible to prevent excess weight gain by closely monitoring diet and physical activity, the heightened susceptibility to weight gain and obesity remains. As a result, it is clear that interventions to improve the metabolic health of infants of obese mothers need to be applied as early as possible in order to be effective in improving long term outcomes.

More recently, research has turned toward potential interventions before and during pregnancy, and after birth, which could potentially improve the long-term metabolic health of the increasing number of infants whose mothers enter pregnancy overweight and obese. As highlighted above, while improving metabolic health well before conception is likely to be ideal, this is not always practical, and encouraging weight loss immediately prior to conception or in the early stages of pregnancy also appears to carry short and long-term risks.
For this reason, the majority of intervention studies have focussed on diet and lifestyle interventions applied during pregnancy.

There is evidence from animal studies that maternal exercise may offer some benefits for offspring of mothers consuming high-fat/high-sugar junk food diets during pregnancy, however human studies suggest that increasing the physical activity in pregnant women is extremely challenging [50]. There is emerging evidence from large randomised controlled trials that improving the quality of the maternal diet during pregnancy independent of the level of physical activity and maternal weight gain, may reduce the incidence of LGA deliveries [50]. Further well-powered and robustly designed clinical studies are needed to determine whether specific nutritional interventions, for example increasing the supply of n-3 LCPUFA, limiting n-6 PUFA intake or reducing the GI of the diet in overweight/obese women has the potential to reduce the subsequent risk of obesity/poor metabolic health in their offspring. In addition, there is growing interest in identifying potential approaches for management of infants of obese mothers to improve their long-term metabolic health; research in this area is currently extremely limited research, and more studies are urgently needed.

Five-Year View

As animal studies have provided new insights into the mechanisms which underlie developmental programming of obesity by nutritional exposures during the perinatal period, it has become increasingly clear that intervening early, preferably well before birth, to improve the nutritional environmental experienced during development is critical for improving long term metabolic health outcomes.
While there has been a move, both in experimental animal models and in clinical studies, towards research focussed on potential strategies for optimising the metabolic outcomes of infants from pregnancies complicated by maternal obesity, more such studies are desperately needed. Over the coming 5 years, the results of current large-scale RCTs in this area and of follow-up of the infants from these studies will start to emerge and will begin to develop a basis for clear evidence-based guidelines regarding the nutritional management of overweight/obese pregnant women.

In addition, the ability to more accurately measure body composition and body fat distribution in infants will provide more insights into how different nutritional practices influence growth quality (as well as quantity), and whether specific nutritional modifications, such as increasing n-3 LCPUFA or reducing protein supply, in infants of obese mothers may help to improve their long-term metabolic health. The ability to conduct genetic and epigenetic studies in minute amounts of starting material, offers the potential to explore the mechanistic pathways underlying the early origins of human obesity in more detail than ever before, and the coming 5 years promises to see an explosion in the number of studies in this area.

However, while technological advances will provide further insights into the underlying biology, it will be critical to ensure that the design of clinical trials to test nutritional interventions in pregnancy remains focussed on the core elements of the CONSORT statement; a defined nutritional intervention, appropriate controls, a defined primary outcome, adequate statistical power to address the primary question and, in the case of follow-up studies, low rates of attrition to preserve the integrity of the randomisation [72]. While
epidemiological and cohort studies are important for identifying potential links, it is only through RCTs that we can confirm cause and effect relationships and establish definitely whether specific interventions are (a) safe and (b) effective in improving the long-term metabolic health outcomes in infants of overweight/obese mothers. Consequently, such studies will be important in the effective translation of this research into clinical practice over the coming 5 year time-frame.

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Key issues

1. Maternal obesity is a major risk factor for obesity and associated metabolic disorders in the child

2. The association between maternal obesity and obesity in the child is a result of an increased nutrient supply to the fetus during critical periods of development

3. The fat cell is a key target of this developmental programming, and exposure to an increased nutrient supply before birth prematurely ‘switches on’ key genes in adipose tissue which are responsible for lipid storage and this results in an increased propensity for fat accumulation after birth

4. The increase in fat storage places the individual at increased risk of obesity and associated co-morbidities.

5. These effects are not easily reversible – therefore early intervention is essential.
6. In humans, the major period of fat cell development before birth to first year of life

7. Exposure to an increased nutrient supply during this period is an important determinant of fat cell size and number and the capacity for individuals for storing fat throughout the life course

8. Current research is focussed on potential nutritional interventions to improve outcomes in infants born to overweight/obese mothers, but few results have been published to date

9. There is an urgent need to accelerate this research, and to also focus on mechanistic studies in humans

10. The next 5 years is likely to see a move to the development of specific guidelines for the nutritional management of overweight/obese mothers and their infants.
References


Discusses in detail the role of the adipocyte in developmental programming of obesity by prenatal overnutrition.


A study of 301 overweight or obese pregnant women in South Australia which reported that dietary quality in this population was typically low, and that dietary quality actually decreased across pregnancy and lactation.


22. Muhlhausler BS, Roberts CT, McFarlane JR, Kauter KG, McMillen IC. Fetal leptin is a signal of fat mass independent of maternal nutrition in ewes fed at or above maintenance energy requirements. *Biol Reprod*, 67(2), 493-499 (2002).

23. **Muhlhausler BS, Duffield JA, McMillen IC. Increased maternal nutrition stimulates peroxisome proliferator activated receptor-γ (PPARγ), adiponectin and leptin mRNA expression in adipose tissue before birth. *Endocrinology*, 148, 878-885 (2007).**


Following on from the study above, we demonstrated in this study that exposure to maternal overnutrition before birth resulted in higher fat mass and increased food (milk) intake in the lambs in the first month of life - indicating that the pre- and postnatal upregulation of PPARγ in fetal fat resulted in increased fat accumulation in early postnatal life.


An elegant study which provided direct evidence that being exposed to maternal obesity during the periconceptional period, independent of the nutritional environment experienced for the remainder of development, was associated with increased fatness in female lambs in young adult life.


Provides a more in-depth discussion of nutritional interventions in pregnancy, with a focus on strategies to break the current intergenerational cycle of obesity and poor metabolic health
Ong ZY, Muhlhausler BS. Consuming a low-fat diet from weaning to adulthood reverses the programming of food preferences in male, but not in female, offspring of 'junk food'-fed rat dams. *Acta physiologica*, 210(1), 127-141 (2014).

Provided evidence that the increased susceptibility to diet-induced obesity in offspring exposed to a maternal junk food diet persists even when they are fed on a control (nutritionally balanced) rodent diet after weaning.


50. **Dodd JM, Turnbull D, McPhee AJ et al. Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. *Brit Med J*, 348, g1285 (2014). The first large-scale RCT to test the effect of delivering a comprehensive diet and lifestyle intervention to women who enter pregnancy overweight or obese on pregnancy and neonatal outcomes, and showed that improving the nutritional quality of the maternal diet reduced the incidence of large-for-gestational age deliveries in the intervention arm in the absence of any differences in maternal gestational weight gain.


52. **Briley AL, Barr S, Badger S et al. A complex intervention to improve pregnancy outcome in obese women; the UPBEAT randomised controlled trial. *BMC Preg Child Birth*, 14, 74 (2014). This large scale RCT focuses specifically on improving glucose control in overweight/obese pregnant women through a highly structure diet and lifestyle intervention. Once completed, this trial will make a major contribution to the development of guidelines for the management of pregnancies complicated by maternal overweight/obese to improve pregnancy/infant outcomes.


Refs 61 and 62 provide a systematic review of the current studies (in both humans and animal models) which have examined the association between increased maternal n-3 LCPUFA intake during pregnancy and/or lactation and body composition of the offspring.


**Figure 1.** Schematic representation of the association between maternal obesity/overnutrition, increased fetal growth and increased risk of obesity in later life.

**Figure 2.** Schematic of the proposed role of adipose tissue in the development of obesity and metabolic dysfunction after prenatal exposure to an excess energy supply. (1) Prenatal overnutrition results in increased expression PPARγ mRNA in visceral adipocytes before birth (2) After birth, signals from visceral adipocytes promote growth of the subcutaneous fat depot, leading to an increase in subcutaneous fat mass (3) Increased mass and leptin secretion from subcutaneous fat is associated with increased plasma leptin concentrations and development of central leptin resistance which leads to increased weight gain, obesity and ultimately metabolic dysfunction (from [9]).

**Figure 3.** Summary of potential mechanisms implicated with the association between exposure to maternal obesity before birth and increased risk of obesity in later life (adapted from

**Figure 4.** Nutritional interventions which may have potential to improve metabolic health of infants of obese mothers. Improving the overall quality of the maternal diet, increasing physical activity or reducing dietary GI during pregnancy could act either indirectly, through reducing pregnancy weight gain, or directly to improve maternal glucose tolerance and reduce fetal nutrient supply. Similarly, increased n-3 LPCUFA or decreasing n-6 PUFA intake may increase fetal n-3 LCPUFA supply and thereby reduce fetal fat deposition.