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Pregnancy, obesity and insulin resistance: maternal overnutrition and the target windows of fetal development

Abstract: A substantial body of literature has demonstrated that the nutritional environment an individual experiences before birth or in early infancy is a key determinant of their health outcomes across the life course. This concept, the developmental origins of health and disease (DOHaD) hypothesis, was initially focused on the adverse consequences of exposure to a suboptimal nutrient supply and provided evidence that maternal undernutrition, fetal growth restriction, and low birth weight were associated with heightened risk of central adiposity, insulin resistance, and cardiovascular disease. More recently, the epidemic rise in the incidence of maternal obesity has seen the attention of the DOHaD field turn toward identifying the impact on the offspring of exposure to an excess nutrient supply in early life. The association between maternal obesity and increased risk of obesity in the offspring has been documented in human populations worldwide, and animal models have provided critical insights into the biological mechanisms that drive this relationship. This review will discuss the important roles that programming of the adipocyte and programming of the central neural networks which control appetite and reward play in the early life programming of metabolic disease by maternal overnutrition. It will also highlight the important research gaps and challenges that remain to be addressed and provide a personal perspective on where the field should be heading in the coming 5–10 years.

Keywords: adipose tissue; appetite; fatty acids; fetal programming; maternal nutrition.

Abbreviations: PUFA, polyunsaturated fatty acids; ω-3 PUFA, omega-3 polyunsaturated fatty acids; ω-6 PUFA, omega-6 polyunsaturated fatty acids

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Introduction

There is a substantial body of literature, which has demonstrated that the nutritional environment an individual experiences before birth or in early infancy is a key determinant of their health outcomes across the life course [1, 2]. The developmental origins of health and disease (DOHaD) hypothesis was initially focused largely on the adverse consequences of exposure to a suboptimal nutrient supply and provided compelling evidence that maternal undernutrition, fetal growth restriction, and low birth weight were associated with heightened risk of central adiposity, insulin resistance, and cardiovascular disease in later life [3]. More recently, however, the attention of the DOHaD field has increasingly turned toward identifying the impact on offspring of exposure to an excess nutrient supply in early life. This has clear relevance in the context of the obesity epidemic that is currently affecting both developed and developing nations worldwide and the resulting increase in the number of women entering pregnancy overweight or obese coupled with the rise in consumption of palatable (energy-dense, nutrient-poor) foods [4–6].

The association between maternal and childhood obesity has been documented in human populations worldwide and widely replicated in animal models. In addition to supporting the epidemiological and clinical data, the work in animal models has provided insights into the biological mechanisms, which drive this relationship.

The purpose of the current review is to examine the evidence linking maternal overnutrition to the early life origins of obesity and, thereby, define our current understanding of the biological mechanisms through which

exposure to excess nutrients before birth predisposes individuals to obesity in later life. It will also highlight the important research gaps and challenges that remain to be addressed and provide our perspective on where the field should be heading in the coming 5–10 years.

Maternal obesity: a growing obstetric challenge

The worldwide epidemic of obesity has affected children and adults and has led to a corresponding increase in the number of women entering pregnancy with a body mass index (BMI) that places them in the overweight or obese category. In a recent study by Dodd and colleagues, it was reported that over 50% of women in South Australia were overweight or obese when presenting for their first antenatal appointment [4], and similar figures have been reported in the US [6].

Maternal obesity is undesirable for a host of reasons related to maternal health, pregnancy outcomes, and the short- and long-term health of the child. It is well documented that overweight and obese mothers are at an increased risk of a number of pregnancy complications, including gestational diabetes, preeclampsia, fetal overgrowth, and macrosomia. The infants born to these women are also more at risk of neonatal morbidities, including neonatal hypoglycemia, jaundice, shoulder dystosia, and unexplained neonatal death [6].

In addition to these short-term clinical complications, it is now clear that maternal overweight and obesity are also associated with a significant increase in the risk of obesity, diabetes and cardiovascular diseases in the child [1, 7]. The increasing prevalence of overweight and obesity among pregnant women has, therefore, led to the establishment of an intergenerational cycle of obesity and metabolic disease, whereby heavier mothers give birth to heavier infants who go on to be fatter and less metabolically healthy in later life.

Consequences of maternal obesity for the mother

The developing fetus relies exclusively on the mother to supply all the nutritional factors necessary for achieving optimal growth and development [8]. Consequently, any perturbation which impacts negatively on maternal health, is likely to have negative effects on the developing fetus. While some nutrients (e.g., glucose) are able to readily cross the placenta and are transmitted to the fetus down a concentration gradient, the majority of nutrients are transferred via active transport mechanisms or undergo extensive metabolism/conversion before reaching the fetus [8]. This suggests that the effects of overnutrition on the development of the offspring may not be mediated directly by the nutrients, themselves, but by the impact that this diet has on the metabolic/hormonal status of the mother.

Both human and animal data provide clear evidence of substantial alterations to maternal metabolism in response to maternal obesity and/or maternal overnutrition. In humans, maternal overweight and obesity is typically associated with reduced insulin sensitivity and an increased risk of the mother developing gestational diabetes mellitus [6]. Even when overt gestational diabetes does not develop, these women still typically have lower insulin sensitivity and glucose tolerance compared to normal-weight women, which translates into elevated maternal glucose concentrations and exposure of the developing fetus to an increased glucose supply [9, 10]. Plasma triglyceride concentrations are also elevated in obese compared to lean pregnant women, and evidence from nonhuman primates suggests that these triglycerides readily cross the placenta and are deposited in fetal tissues, inducing lipotoxicity [11]. Maternal obesity in humans and high-fat diets in pregnant rodents also result in a heightened inflammatory state in the mothers – and these inflammatory mediators can either be transferred to the fetus or affect the ability of the placenta to transfer other nutrients/oxygen from the maternal to fetal circulation [12, 13]. Clinical studies have reported that obese women (particularly those with BMIs of >35) have an increased risk of placental dysfunction, which may explain the clinical observation that obese women, particular those with morbid obesity, are at an increased risk of stillbirth, fetal growth restriction, and prelabor caesarean delivery [14]. Disturbances to uteroplacental hemodynamics and an increased incidence of stillbirth has also been reported in nonhuman primates maintained on high-fat diets during their pregnancy [15].

The importance of maternal nutrition for the programming of obesity

Given that the nutrients in the maternal circulation provide the sole source of nutrients for the developing fetus, it is not surprising that the maternal diet during pregnancy

plays a major role in determining the short- and long-term developmental outcomes of the offspring.

The impact of maternal overnutrition on the fetus and neonate in humans is, perhaps, most clearly demonstrated by studies of infants of diabetic mothers [16, 17]. As glucose is transferred across the placenta by passive transfer down a concentration gradient, high concentrations of glucose in the maternal circulation result in exposure of the fetus to an increased glucose supply [18]. Metzger was the first to develop the "fuel-mediated teratogenesis" model, in which fetal hyperglycemia results in increased release of insulin by the fetal pancreas, leading to fetal hyperinsulinemia [19]. The increase in fetal insulin concentrations, in turn, results in increased uptake of glucose and amino acids into insulin-sensitive tissues, in particular, the adipose tissue, ultimately leading to the fetal overgrowth and excess accumulation of fat mass that is frequently observed in infants of diabetic mothers at delivery. In addition, these infants were also found to be at an increased risk of obesity in later life [16, 17]. Subsequent studies revealed that, even in the absence of overt maternal diabetes, maternal insulin resistance or even mild impairments to maternal glucose tolerance are also associated with increased fat mass in the neonate and an increased risk of obesity and diabetes in the offspring. Indeed, clinical studies revealed a close association between glucose concentrations in the umbilical cord blood at delivery and neonatal fat mass, implicating glucose as a key driver of excess intrauterine fat deposition [10].

The role of maternal glucose as a driver of fetal programming has been confirmed in animal studies, in which maternal diabetes has been induced by treatment with streptozotocin prior to pregnancy [20] or maternal hyperglycemia induced by maternal overfeeding [21, 22]. In the sheep, direct infusion of glucose to the fetus also results in significant increases in fetal fat deposition in utero [23, 24]. In addition, animal studies have demonstrated that increased maternal nutrient intake, in the form of either an increase in total caloric intake or specific increases in the consumption of saturated fat and/or sugar (semisynthetic or cafeteria diets) is associated with a significant increase in the incidence of obesity and insulin resistance in the offspring after weaning [25]. In addition to supporting clinical and epidemiological findings, these animal studies of developmental programming have enabled researchers to explore the biological mechanisms which underlie the relationship between exposure to an elevated nutrient supply before birth and a predisposition to obesity in later life.

Targets of nutritional programming

The relationship between maternal overnutrition during pregnancy and lactation with the programming of increased obesity risk in the offspring has led to a large number of studies focused on the underlying biological mechanisms. These studies have established that exposure of the fetus/neonate to an elevated nutrient supply either in the form of glucose, fat, or global caloric excess during critical developmental windows results in permanent alterations in the structure and function of key systems involved in the regulation of energy balance and metabolic control [25–28] (Figure 1). There is an ever-increasing list of physiological systems whose development is impacted by exposure to increased nutrition; however, this review will focus principally on the role of the adipocyte and the central neural networks which regulate appetite and reward in metabolic programming.

Adipose tissue

The fat cell, or adipocyte, has been implicated as a key target of developmental programming. Indeed, we have

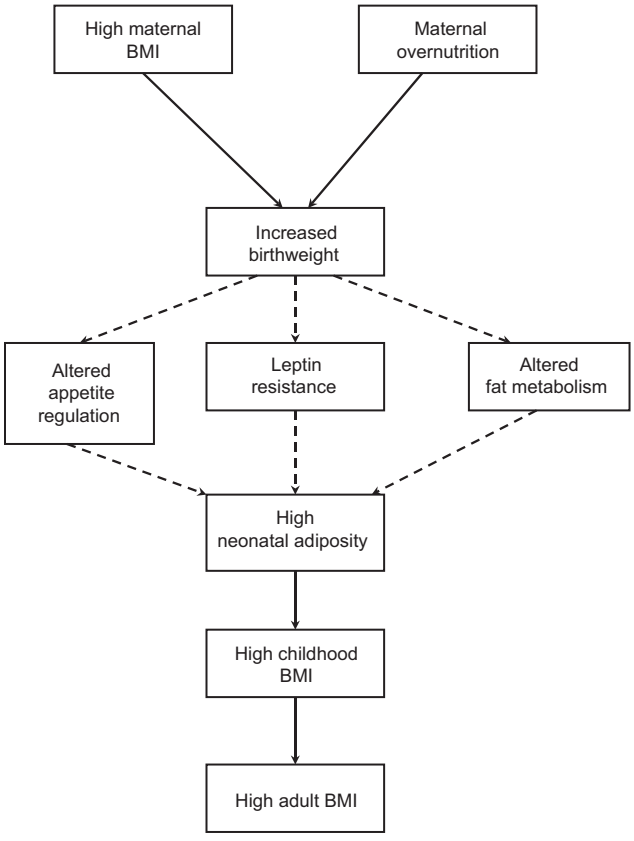

Figure 1 Potential mechanisms proposed to underlie the development of obesity after exposure to maternal overnutrition or maternal obesity before birth.

previously suggested that the increased incidence of type 2 diabetes and cardiovascular disease associated with prenatal exposure to excess nutrition is secondary to the increased accumulation of fat mass, rather than the direct effects of the overnutrition on insulin signaling pathways or the cardiovascular system itself [27]. This hypothesis suggests that the programming of the adipocyte is the primary event that drives the early life programming of obesity in offspring exposed to an increased nutrient supply before birth.

There is certainly evidence from both small and large animal models that exposure to an increased supply of glucose and lipids during critical periods in the development of adipose depots is associated with a precocial upregulation of lipogenic genes within fat depots [29, 30]. Importantly, this is associated with a persistent increase in the capacity of adipocytes for lipid storage, which renders the individual more susceptible to fat storage in postnatal life [22, 28]. Studies in both pigs and sheep, in which fat cell development begins before birth, have demonstrated that maternal hyperglycemia is associated with an increase in the mRNA expression and/or activity of important lipogenic mediators in the adipocyte.

In pigs, Kasser and colleagues reported that induction of gestational diabetes in the pregnant sow increased adipose tissue thickness in fetuses at 112 days gestation via an upregulation of lipogeneic activity in fetal fat depots [28]. Similarly, in studies of an obesity-prone breed of pig by Hausman and colleagues, pre-obese fetuses exhibited increased fat mass, increased adipocyte size, and increased lipogenic activity in their fat depots prior to the onset of obesity in postnatal life [31]. In the sheep, feeding ewes ~55% above their maintenance energy requirements during the final 35 days of gestation was associated with significant increases in maternal and fetal glucose concentrations [21]. Importantly, fetuses of overfed ewes exhibited an increased expression of the key lipogenic transcription factor peroxisome proliferator activated receptor gamma (PPARγ) in the perirenal fat depot in late gestation [29], and the lambs exposed to this intrauterine environment exhibited an increased fat mass by the end of the first month of life [22]. An interesting observation in these sheep studies was that the increases in PPARγ expression in the fetus were present in the perirenal adipose tissue, the only dissectible fat depot in the fetal sheep before birth, whereas it was subcutaneous fat mass that was increased to the greatest extent in the lambs of well-fed ewes at 1 month of age [22]. This implies, therefore, that the prenatal nutritional environment can act to program preadipocytes within the subcutaneous depot and/or that signals from the perirenal depot influence the development of other fat depots in early life. The concept of cross-talk is well explored in other organ systems, but the notion of one fat depot directing the development of another has yet to be empirically demonstrated.

Taken together, studies in large animal models provide clear evidence of the acute sensitivity of the developing adipocyte to the early nutritional environment. The studies in large animal models are more readily translatable to the human context than studies in rodents, as there is limited development of adipose tissue before birth in rats and mice. Nevertheless, rodent studies provide a large body of support for the programming of the adipocyte by the nutritional environment experienced by the offspring during suckling, the major period of fat cell development [32, 33].

Appetite regulation

There is an extensive literature that has described the relationship between maternal/infant overnutrition and increased food intake in the offspring, which is driven by altered development of the neuronal pathways, which regulate appetite [22, 34, 35] (Figure 2).

The concept that adult appetite could be influenced by manipulating nutritional intake in early life

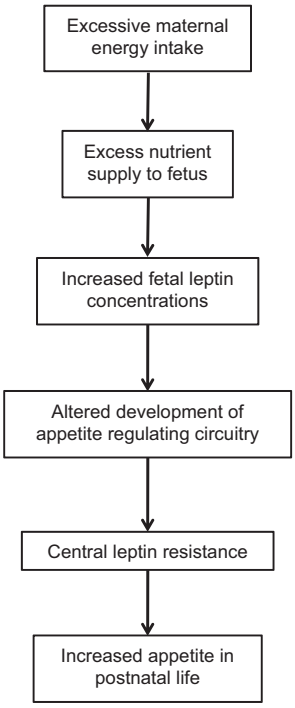

Figure 2 Summary of the proposed pathways through which maternal overnutrition results in dysregulation of appetite control in the offspring.

was established as early the late 1970s by Oscai and colleagues, who showed that the amount of food that rats consumed as adults was directly related to the amount of food they consumed in the early postweaning period [36]. It was not until almost 30 years later, however, that the work of Plagemann and colleagues provided insights into the underlying biological mechanisms. These studies provided the first evidence for the programming of the central neural network for appetite regulation, by demonstrating that early postnatal overnutrition induced by rearing animals in small litters was associated with alterations in the architecture of the key hypothalamic nuclei within the appetite-regulating network [34, 37, 38] and altered expression of the key neuropeptides implicated in appetite regulation [34, 39]. These structural and functional changes persisted throughout the life of these animals, and as a consequence, these animals exhibited persistent hyperphagia leading to weight gain and increased fat mass. Postnatal hyperphagia is also seen in offspring of rats fed a high-fat diet during pregnancy and lactation; these offspring consume more energy postweaning and have a higher body weight compared to the control offspring when weaned onto either a standard rat chow [35] or high-fat diet [40].

Studies in large animal models, in which the major period of development of the appetite-signaling pathways occurs before birth, as in the human, provide additional support for the programming of appetitive structures. Exposure to maternal overnutrition in late gestation was shown to be associated with an increased appetite in the lambs during the first 3 weeks after birth [22]. Importantly, lambs of well-fed ewes exhibited a reduced capacity to upregulate the expression of the appetite-inhibiting neuropeptide, cocaine- and amphetamine-regulated transcript (CART), in response to increases in their fat mass [22], indicative of a dysregulation of appetite control. This suggests, therefore, that lambs exposed to an increased nutrient supply before birth do not appropriately switch off their appetite when satiated thus rendering them more prone to overeating and weight gain.

While the mechanisms that lead to the early programming of the appetite-regulating pathway are still unclear, two key hormones, insulin and leptin, which are known to be critical for the regulation of energy balance in adults, appear to play an important role. Plagemann's group showed in rodent studies that the effects of postnatal overnutrition could be replicated by prenatal hyperinsulinemia, which led to the conclusion that insulin was the key factor responsible for mediating the structural and functional changes which were observed in postnatally overnourished offspring [41]. In addition to increases in circulating insulin, periods of overnutrition are also associated with increased concentrations of the adipocyte-derived hormone leptin, and perinatal exposure to either insufficient or excessive leptin concentrations can also alter the development of the neural circuitry in the appetite-regulating network [42]. In 2004, Sebastian Bouret and Richard Simerly performed an elegant series of studies using the anterograde tracer DiI, showing that leptin-deficient ob/ob mice had a reduced density of neuronal connections linking the arcuate nucleus to other hypothalamic nuclei involved in the regulation of appetite, suggesting that leptin is required for the normal development of connections of the hypothalamic appetite-regulating circuits. This mechanism was further supported when this phenotype was subsequently rescued by the administration of exogenous leptin in the immediate postnatal period, when the appetitive structures were still developing, but the same treatment was not effective when applied in adulthood [43, 44]. The importance of leptin in the development of appetitive connections within the hypothalamus was further confirmed by the addition of leptin to hypothalamic explants, which was shown to promote neurite outgrowth [43]. Therefore, the levels of insulin and leptin in the circulation during the development of neural circuits have the potential to permanently alter the structure, and therefore function, of these networks.

Reward pathways

In addition to the programming of food intake overall, there is a growing body of evidence that early nutritional exposures also have the capacity for programming food preferences. Work from our group and others has shown that exposure to maternal diets dominated by palatable foods before birth and in early infancy shifts food preferences in the offspring toward an increased "liking" for high-fat and high-sugar foods [40, 45]. In our studies, we demonstrated a specific preference for high-fat foods in offspring of rat dams fed a cafeteria junk food diet during pregnancy and lactation, which persists from weaning until at least 3 months of age in both males and females [45]. The precise mechanisms through which this programming of food preferences occurs remain poorly understood; however, the results of recent studies have implicated the programming of the central neural network, which regulates motivation and reward as playing a central role [40, 46] (Figure 3).

Palatable foods, i.e., those with high levels of saturated fat and simple sugars, have been described as

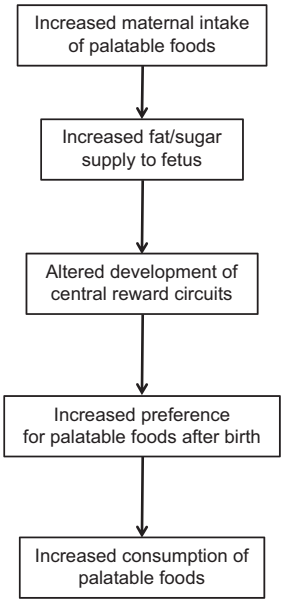

Figure 3 Summary of the mechanisms through which excessive maternal intake of palatable diets program food preferences in the offspring via programming of the central reward pathway.

natural rewards on the basis of their ability to activate the same central reward circuits as those recruited by illicit drugs and alcohol [47]. Thus, the consumption of high-fat and/or high-sugar diets in rats stimulates the release of dopamine and opioids within the central reward circuitry, which are responsible for eliciting the pleasurable sensation characteristic of rewarding substances [48]. There is also evidence suggesting that prolonged intake of a palatable diet, or sucrose or fat alone, produces similar alterations in gene expression in the reward pathway as seen in rats addicted to cocaine, alcohol, or nicotine [49, 50]. This altered pattern of gene expression reduces the sensitivity of the reward pathway and drives the animal to obtain increasing quantity of the drug (or food) to maintain the same intensity of the resulting "high" [51].

It is well documented that mothers who consume illicit substances during their pregnancy give birth to infants who are addicted to this same substance at birth and who are more susceptible to other forms of addiction in later life [52]. Both human and animal studies have also shown that prenatal exposure to ethanol predisposes individuals not only to later ethanol dependence but also to other types of addiction [53, 54], and mice exposed to cocaine before birth exhibit an increased susceptibility to ethanol and cocaine addiction [55].

There is now increasing evidence from animal studies that prenatal exposure to high-fat, high-sugar diets is associated with comparable alterations in the development of the central reward circuits. Naef and colleagues investigated the effect of feeding rat dams a high-saturated fat diet during the last week of gestation and throughout lactation on dopamine function in the key nuclei of the reward system and found that offspring of high fat-fed dams exhibited increased dopamine content in the nucleus accumbens and reduced sensitivity to stimulation by amphetamines, suggesting a permanent alteration to the function of the reward system [56]. Similarly, Vucetic and colleagues found that offspring of mice fed a high-fat diet during pregnancy had an increased preference for sucrose and fat, which was accompanied by higher levels of endogenous opioids and increased expression of the μ-opioid receptor [57]. As the opioid system is known to have an important role in promoting the intake of palatable foods in adults, this could explain the increased preference for sucrose and fat displayed by these offspring. The involvement of the opioid system in the programming of food intake and preference is supported by recent studies in our laboratory, in which we found that the expression of the μ-opioid receptor in a key region of the central reward system, the ventral tegmental area, was lower at weaning in offspring exposed to a maternal palatable diet before birth and during the suckling period [58]. Importantly, we also demonstrated that this had functional consequences for the regulation of opioid signaling in these offspring, since those offspring exposed to the palatable diet in early life were less sensitive to the effect of the μ-opioid receptor antagonist, naloxone, in suppressing palatable food intake in the immediate postweaning period [58].

In addition to the opioid system, there is also evidence implicating the dopamine system in the early life programming of food preferences. In their study, Vucetic and colleagues showed that the expression of the dopamine active transporter, which is responsible for the reuptake of dopamine from the synapse into the presynaptic neuron, was significantly increased, and dopamine receptors, D1 and D2, were significantly downregulated in the offspring of mice fed a high-fat diet during pregnancy [57]. This is similar to results from our laboratory, in which we demonstrated that offspring of dams fed a cafeteria diet during pregnancy and lactation exhibited an increased expression of the dopamine active transporter in the central reward system at 3 months of age [45]. These alterations within the dopamine-signaling pathway are consistent with hyposensitivity within the dopamine system that could drive further drug (i.e., food)-seeking behavior. This reduced sensitivity of the dopamine system has also been observed in mice that were exposed to a short period of high-fat feeding early in life, which also exhibited a strong preference toward high-fat foods in adult life [59].

Can programming be reversed? New insights into the critical windows

As illustrated in the preceding paragraphs, a compelling series of experimental animal studies have demonstrated that maternal overnutrition impacts on the development of the adipocyte and neural pathways, and these changes serve to predispose the offspring to obesity and metabolic disease through the life course. The evidence for the programming of obesity and metabolic disease by early life nutrition has increasingly led to the question of the extent to which these effects can be reversed by interventions, which are applied in postnatal life.

A number of studies in rodents have suggested that programming of the neural network for appetite regulation and food preferences persist even when offspring are fed on nutritionally balanced diets from weaning to adulthood [35, 60]. However, other studies have suggested that there may be the potential to overcome at least some of the adverse effects of perinatal overnutrition through nutritional interventions applied in postnatal life. In one study, Velkovka and colleagues examined the effect of early postnatal overnutrition, induced by small-litter weaning, on blood pressure, hypothalamic expression of the appetite-stimulating neuropeptide NPY, and adiposity markers. Their key finding was that the negative metabolic effects associated with early postnatal overnutrition could be largely overridden by providing a nutritionally balanced diet after weaning [61].

In a recent study, we set out to determine whether providing rodent offspring that had been exposed to a maternal palatable diet before birth and during the suckling period with a standard rodent feed after weaning could mitigate the impact of the palatable diet on food preferences and gene expression in the reward system of the offspring. The key finding of this study was that providing offspring with a nutritionally balanced chow for 3 months after weaning was sufficient to overcome the effects of the perinatal diet on food preferences and the reward system in male, but not female, offspring [62]. However, while providing offspring with a nutritionally balanced diet for 3 weeks after weaning (the equivalent of consuming such a diet from weaning to adolescence) initially normalized fat mass and food intake, both male and female offspring exhibited a higher energy consumption and gained more weight than the control offspring when their access to a palatable diet was reinstated, suggesting that the increased preference for the palatable diet was retained [62]. This adds to the growing body of evidence suggesting that the programming effects of perinatal overnutrition cannot be readily overcome by interventions applied later in life, and that while the phenotype can be controlled, an underlying susceptibility to metabolic challenges remains. Consequently, the key to breaking the intergenerational cycle of obesity is likely to rely more so on prevention through improved nutrition in the mother and infant, rather than trying to correct these changes once they have occurred.

Maternal nutrition to optimize offspring outcomes: a major research challenge

If we accept that optimizing the maternal nutritional environment offers the greatest potential for improving the long-term metabolic health of the offspring, then, it stands to reason that identifying the dietary factors which are the key drivers of developmental programming is of paramount importance in designing effective interventions. However, despite this realization, it remains unclear which components of the maternal diet are the most significant drivers of developmental programming. The majority of animal models of maternal obesity involved providing pregnant and lactating rats with diets that contain high amounts of dietary fat (up to 60% energy). While these studies have consistently demonstrated that these high-fat diets are associated with a myriad of adverse effects on the mother and her offspring, including obesity, insulin resistance, endothelial dysfunction, and hyperphagia to name a few [63, 64], it is difficult to relate these findings to human diets, where fat intake even in obese individuals is significantly lower [65]. In addition, most “high-fat” diets are also high in calories, which make it impossible to separate the effects of consuming high amounts of fat from those of consuming excess energy overall.

Moreover, even in those studies that have attempted to isolate the contribution of fat and calories, there are conflicting findings. In both rodents and sheep, increasing the total energy intake in the absence of increased fat intake has been associated with increased fat mass and insulin resistance in the offspring [22]. One interpretation of these findings is that excessive calorie intake in pregnancy is associated with an increased predisposition to obesity and poor metabolic outcomes in the offspring, independent of the level of fat. However, other studies have suggested that dietary composition, in particular the fat content of the diet, is the most

important factor in developmental programming [64]. Thus, the role of macronutrient balance (particularly the ratio of fat to other dietary components) compared to total energy intake in metabolic programming remains uncertain.

In addition to the total amount of fat in the diet, there is increasing human and animal evidence that the relative proportion of saturated, monounsaturated, and polyunsaturated fat (PUFA) in the diet has important implications for the programming of metabolic disease [66, 67]. The majority of "high-fat" rodent diets have contained high levels of saturated fat, in line with the prevailing view that the saturates are the "bad guys" in relation to metabolic health [63]. These studies have certainly provided evidence that very high levels of saturated fat intake (often in excess of 30% energy) have negative effects on metabolic outcomes in the offspring, including increased body fat mass, increased appetite, insulin resistance, and dyslipidemia [63, 64]. However, the role of saturated fat as the key driver of the intergenerational cycle of obesity in humans is difficult to reconcile with data from human populations in which obesity is increasing, but the intake of saturated fat has actually declined in recent decades [65]. Importantly, animal and human studies have demonstrated that increasing maternal PUFA intake, in the absence of high intake of saturates, also results in an increased fat mass in the offspring [68].

To complicate things further, the two classes of PUFA, the ω-6 and the ω-3, are not equipotent in promoting adipose tissue deposition and have different effects on the metabolic outcomes of the offspring [66, 67]. In mice, chronic exposure over four generations to a diet with a high ω-6 PUFA content (comparable to that in the typical Western diet) was sufficient to trigger a gradual transgenerational enhancement of fat mass [69]. In another study, offspring of mice fed on high-ω-6 PUFA diets were 40% heavier from 1 week after weaning than those fed on a high-fat diet containing a mixture of ω-6 and ω-3 PUFA, despite no difference in the total fat or calorie intake of the dams [66]. There are also human data supporting a relationship between maternal ω-6 PUFA intake and offspring fat mass, including a recent study of 293 women in the UK, which reported that maternal plasma ω-6 PUFA concentrations positively predicted offspring fat mass at 4 and 6 years of age [70]. Collectively, these findings have led to suggestions that the increase in the ω-6 PUFA content of the typical Western diet and, therefore in the diets of pregnant and lactating women, in recent decades, may be contributing to the increased prevalence of obesity and metabolic disease [71, 72]. Conversely, some animal and human studies have shown that increasing maternal ω-3 PUFA intake during pregnancy and lactation can actually reduce body fat mass in the offspring [73]. However, a systematic review of this research area indicates that the data is conflicting and provides a limited basis for drawing robust conclusions [68, 74]. Indeed, we have recently shown in our laboratory that maternal ω-3 PUFA supplementation (without any change in maternal energy intake) in rats was associated with a higher relative body fat mass in the offspring at 6 weeks of age [68].

Taken together, these data provide evidence of the complexity of the relationship that exists between the maternal diet and offspring health and highlight the need for studies that focus specifically on defining the separate and synergistic contributions of different dietary components to the programming of metabolic health and disease.

Expert opinion and outlook

The DOHaD is a relatively new field of research, and studies into the impact of maternal obesity/maternal overnutrition on the offspring have only appeared to any significant extent in the last 10–15 years.

After initial resistance from clinicians, the concept that the nutritional environment in early life has critical relevance for the life-long health of the individual has now gained much wider acceptance, evidenced by a reference to the DOHaD hypothesis in the 2013 Australian Dietary Guidelines recently released by the National Health and Medical Research Council of Australia (NHMRC). In relation to the early origins of obesity, it is particularly notable that the World Health Organization has suggested that early life is likely to provide the optimal window of opportunity for effective strategies for obesity prevention. However, despite the growing recognition of the importance of early life nutrition, the translation of these findings into public policy and clinical practice remains problematic. Part of the reason for this is the complexity of the issue – it is relatively simple to implement a zero-tolerance policy on cigarettes or alcohol during pregnancy, whereas doing the same in nutrition becomes much more complex. The issues around food safety during pregnancy (e.g., avoidance of listeria) have generally been well publicized, but the importance of other factors in the diet and the potential long-term risks associated with inappropriate nutritional choices during pregnancy and lactation has perhaps been less effectively communicated. Therefore, over the next 5–10 years, we hope that clearer and

more consistent nutritional messages are being effectively communicated to the population by clinicians and policy makers.

A large part of the problem is the confusion within the field itself regarding the key drivers of programming. The majority of studies in animal models of maternal obesity have focused on the effects of diets containing high levels of saturated fats (much higher than those that are typically found in human diets), and the mechanisms induced by such exposure may not be relevant to human diets. In addition, it is becoming increasingly apparent that different types of dietary fats (saturates, monounsaturates, and PUFA) have different effects on the developing fetus/infant and that recommendations to simply limit fat intake may not be sufficient (or indeed correct). Human diets consist of a mixture of macro and micronutrients, and there is a need to determine which components of the diet are most important in determining programming effects. As alluded to above, the effects may not be mediated by the nutrients themselves, but be secondary to the effects of these nutrients or patterns of dietary intake on maternal physiology. There have been increasing calls for studies that attempt to study the independent and synergistic effects of different macro/micronutrients in this area. We would, therefore, speculate that the next 5–10 years will see more defined studies which dissect out the role of different dietary components on offspring outcomes and an increased understanding of which dietary components play the predominant role in metabolic programming. This is clearly important for developing clear and consistent dietary guidelines for pregnant and lactating women.

In terms of underlying mechanisms, there is increasing interest in the role of epigenetics in a number of programming phenomena, including the programming of obesity. As the cost of technologies for assessing epigenetic changes decreases further, we anticipate that this will expand further into human studies.

As our understanding of the underlying biological mechanisms improves, it will be important to use this information to design and test potential strategies for mitigating or ameliorating these effects. An increasing number of clinical studies have begun to test the effect of specific interventions, including limiting gestational weight gain, low GI diets, and omega-3 supplementation, on metabolic outcomes in the offspring [75–77]. In the next 5-10 years, as the results of these studies emerge, we anticipate and hope that the translation of studies of developmental programming to clinical practice and guidelines for pregnant and lactating women will increase and that the practical applications of our knowledge of the importance of the early nutritional environment for the long-term health of individuals will be realized.

Highlights

- Maternal obesity is associated with an increased risk of obesity and metabolic disease in the offspring.
- The mechanisms involved are still the subject of intense investigation, but appear to relate to the effects of exposure to an excess nutrient supply before birth on the development of key metabolic systems.
- Perinatal overnutrition has been associated with the programming of increased lipogenic capacity in fat cells of the offspring, which may be the primary event underlying the early life origins of obesity.
- Perinatal overnutrition also results in programming of the central neural network for the regulation of appetite and reward, which is associated with hyperphagia and increased preference for palatable foods.
- The current data suggests that it may be possible to limit the impact of these programming effects by following a nutritionally balanced diet in postnatal life.
- Importantly, however, individuals exposed to perinatal overnutrition retain an increased susceptibility to the overconsumption of palatable foods, weight gain, and obesity and exhibit an exaggerated response to metabolic challenges (e.g., Western-style diets) during the postnatal period.
- The composition of the maternal diet, in particular, the fatty acid composition, may have important implications for the developmental outcomes of the offspring; however, which dietary components are the key drivers remains unclear.

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