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Developmental Origins of Obesity and the Metabolic Syndrome: The Role of Maternal Obesity

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Abstract

Obesity and its sequelae may prove to be the greatest threat to human lifestyle and health in the developed world this century. The so called obesity epidemic has seen the incidence of obesity and overweight almost double in Western societies and the trend is mirrored in nations that are transitioning to first world economies. There is no doubt that much of the rise in obesity can be attributed to lifestyle factors such as the excess consumption of energy-dense foods and the decline in physical activity. However, the 'fetal origins' hypothesis, first proposed by Barker and colleagues and elaborated by several groups over the past 15 years to be termed the 'Developmental Origins of Adult Health and Disease' (DOHaD), provides an alternative explanation for the rising rates of obesity. The DOHaD hypothesis states that exposure to an unfavourable environment during development (either in utero or in the early postnatal period) programmes changes in fetal or neonatal development such that the individual is then at greater risk of developing adulthood disease. This chapter discusses the effects of maternal obesity on fetal development and birth outcomes as well as the manner in which DOHaD may contribute to the obesity epidemic.

The Obesity Epidemic

Health care systems around the globe are beginning to recognise the risk that obesity poses to human health and many programmes are now being put into place in an effort to reduce the burden of obesity and its related diseases. Current definitions of obesity are based on the ratio of bodyweight (in kg) and height squared (in m^2) and expressed as body mass index (BMI) with a normal BMI defined as 20–24.9, moderate overweight between 25–29.9 and obesity as $\geq$30. In 2000, the World Health

Organisation released the following statement: 'Obesity is a chronic disease, prevalent in both developed and developing countries, and affecting children as well as adults. Indeed it is now so common that it is replacing the more traditional public health concerns, including under-nutrition and infectious disease as one of the most significant contributors to ill health' [1]. At the turn of the millennium and the time of publication of the WHO report, the incidence of obesity in the United States was 30.5% (compared with 22.9% in 1994) and 64.5% of the population were overweight (compared with 55.9% in 1994) [2]. More recent statistics suggest that the incidence of obesity and overweight is rising, not falling, in spite of the apparent efforts of governments and health care agencies. This shift in body mass has occurred over the past one to two generations and as such it is unlikely that genetic drift is the cause of the current obesity epidemic. Rather, a change in lifestyle, compounded by epigenetic or developmental programming of an obese phenotype are the likely causative factors.

Obesity statistics from the United States are most often quoted, perhaps because they give the greatest impact; however, scientific studies conducted in other nations emphasise the fact that obesity is a worldwide problem. A study of cause of death in South Korea illustrates this fact. In 1938, cardiovascular disease accounted for approximately 1% of deaths in South Korea whilst infectious diseases were the cause of approximately 23% of deaths. By 1993, this trend had reversed; approximately 30% of deaths were attributable to cardiovascular disease whereas only 3% of deaths were caused by infection. Certainly such statistics are affected both by the vast improvements in anti-microbial medication and sanitation in that 60-year period; however, the fact remains that obesity-related illness is the next public health hurdle.

Obesity may not, in itself, be a great risk to human health. Indeed, there are some individuals who are overweight or obese but do not show any other signs of disease or ill health. However, for the vast majority, increased body fat is associated with a range of other, more serious conditions. These include increased blood pressure, insulin resistance and diabetes mellitus, atherogenic plasma lipid profiles, and increased levels of vascular inflammatory markers. Collectively, this spectrum of conditions is termed the 'metabolic syndrome' and clinical diagnosis is based on the presence of 3 or more of the above signs. Endothelial dysfunction and leptin resistance are also likely to contribute to the metabolic syndrome [3].

The rise of obesity is certainly due to the increased availability of food, and the preponderance of energy dense (high fat and simple carbohydrate) foods that are regularly consumed in developing and developed societies. Moreover, the industrial era has produced all manner of labour saving devices that has ultimately seen a reduction in the physical activity quotient over time [4]. However, despite the obvious importance of food intake and energy expenditure during adulthood, there is now evidence that adult lifestyle may not be the only factor at play in determining obesity [5]. The environment encountered during the in utero and early postnatal periods may also act to 'programme' an individual to have a greater risk of developing obesity and the metabolic syndrome.

The Developmental Origins of Adult Health and Disease

The developing fetus and neonate orchestrates its growth and development to best meet the environmental conditions encountered at any given period. Where environmental challenges or stimuli span a period of organogensis or developmental plasticity, the adaptations made may be permanent.

Epidemiological data from Norway provide the first of many reports that that environment encountered in early life may affect later health outcomes with regard to cardiovascular disease [6]. The concept of 'programming' was introduced by Lucas [7] and provides a conceptual framework for the observations made by Barker and Osmond [8] with regard to an individual's birth weight and the later risk of disease in United Kingdom cohort studies. These early Barker studies focused on the relationship between the weight at birth, and subsequently fetal nutrition, with death from coronary heart disease [9, 10].

The direct relationship between maternal nutrition and later offspring obesity was revealed in a study of conditions encountered by a discrete population during the Dutch Hunger Winter of 1944–1945. During the World War II military operations by Allied forces to liberate The Netherlands, the occupying Nazi forces blockaded areas of Holland over the winter of 1944–1945 and official rations were cut to 300–500 kcal per day. Later study of adults (at 50 years of age) who were in utero during this defined period of famine indicate that exposure to famine during the first half of pregnancy predisposed individuals to the development of obesity [11] and coronary heart disease [12] and that famine exposure later in gestation resulted in glucose intolerance and insulin resistance [13]. This direct evidence for the role of maternal nutrition in the programming of adulthood obesity and disease in the offspring was followed by studies from UK cohorts with several studies showing an inverse association between birth weight and BMI in adulthood [14] as well as insulin resistance. BMI is used as an indicator of obesity because of the simplicity by which it can be measured in large trials or retrieved retrospectively from records. However, use of the BMI parameter as an indicator of obesity has been challenged, and there are suggestions that it is a measure of heaviness rather than obesity per se. Consistent with this, studies of monozygotic twin pairs [15] found that lower birth weight was associated with increased waist–hip ratio, skin fold thickness and reduced muscle mass, but not necessarily BMI. Nonetheless, body fat measurement by dual energy X-ray absorptiometry in adult men born of low birth weight shows these individuals to have a 5% increase in fat mass compared with subjects born of normal birth weight [16].

These studies formed the basis for various experimental animal models of maternal undernutrition in which to study the Developmental Origins of Adult Health and Disease (DOHaD) hypothesis and these models support the hypothesis that fetal or neonatal undernutrition results in aberrant development of the endocrine pancreas, liver, kidney and cardiovascular systems, such that the offspring born from protein or

calorie deprived dams demonstrate many facets of the metabolic syndrome in adulthood [reviewed by 3, 17].

In the face of an obesity epidemic, it may be more useful to examine the maternal factors that result in the developmental programming of obesity [18]. Although maternal undernutrition is not manifest in many of the societies currently experiencing the increase in obesity rates, one factor that may result in offspring programming is maternal diabetes. Indeed, insulin resistance and alterations in the structure and function of the endocrine pancreas is seen in offspring born to calorie or protein-deprived mothers [reviewed by 3]. This is observed in humans, as evidenced by the finding of insulin resistance in those that were exposed to the effects of the Dutch Hunger Winter in the second half of gestation [13], as well as in experiential animal models. Provision of a low protein diet (50% reduction in protein content but isocaloric) to rats during pregnancy resulted in a reduction in pancreatic insulin content, reduced islet size and vascularisation and a reduction in cell proliferation in term rat fetuses [19]. These animals develop frank insulin resistance later in life [19]. Uteroplacental deficiency, induced by ligation of the uterine artery, produced a similar phenotype of insulin resistance in adult offspring [20].

Consistent with the developmental programming hypothesis, maternal diabetes appears to programme a similar offspring phenotype of insulin resistance and type 2 diabetes mellitus. This is observed in both human populations and in experimental animal studies. One of the earliest, but most striking, studies of programming effects of maternal diabetes was carried out in Pima Indian women. After accounting for confounds such as paternal diabetes, age of diabetes onset in the parents and offspring BMI, Pettitt et al. [21] observed that in this discrete population 45% of offspring born to diabetic mothers went on to develop type 2 diabetes mellitus themselves by the age of 24. Only 1.4% of those born to non-diabetic mothers showed signs of type 2 diabetes mellitus themselves at the same age. The authors conclude that those findings suggested that the intrauterine milieu was an important determinant in the development of diabetes in the offspring, and that the effects were additive with any genetic factors [21]. Macrosomia is often observed in offspring of diabetic mothers, and there is supportive evidence for a 'U-shaped' relationship between birth weight and the development of adult obesity [22]. Thus high birth weight may prove to be just as deleterious to later health and well-being as low birth weight. Data from a Swedish birth cohort suggest that within the past decade there has been a 25% increase in the incidence of large for gestational age babies and regression analysis suggests that this increase is attributable to a 25–36% increase in maternal BMI [23]. The association between maternal obesity and offspring macrosomia may be partially influenced by genetic factors; however, a recent study of 150,000 women suggests that weight gain between successive pregnancies is associated with macrosomia in the second pregnancy [24]. Given the same maternal genetic transmission, this study suggests that, at least in part, large for gestational age birth weight is attributable to maternal obesity. Given the link between maternal obesity and maternal diabetes, a range of animal models of diabetes in pregnancy have been developed.

Experimental animal models of diabetes induced by streptozotocin (STZ, which results in pancreatic β-cell death) have been used to dissect the contribution of intrauterine environment from genetic factors. Aerts et al. [25] studied offspring of STZ diabetic rats and found increased insulin secretion, plasma insulin concentration and decreased renal insulin uptake in these rats when compared with controls [25]. A subsequent study by Holemans et al. [26] utilised euglycaemic hyperinsulinaemic clamp in the adult offspring of STZ diabetic rat dams to assess the developmental programming of insulin resistance. This insulin resistance was characterised by a reduction in insulin sensitivity in peripheral tissue and a reduction in hepatic insulin sensitivity and responsivity [26]. Offspring of rats made mildly diabetic by injection of STZ are born macrosomic, and develop insulin resistance and diabetes later in life [27]. Moreover when those first-generation females (that are diabetic as a result of maternal diabetes) are mated, they produce offspring that are also diabetic [27].

Thus evidence from human and experimental animal models supports the hypothesis that fetal undernutrition may result in programming of adulthood obesity and metabolic syndrome. Fetal undernutrition is, in general, not manifest given the current dietary status of many women of child-bearing age in westernised societies. In an era where many women become pregnant whilst obese or overweight, consideration of the effects of maternal obesity on pregnancy outcome and developmental programming of offspring health are of great relevance and maternal diabetes may prove to be a condition of great importance when considering the manner in which the developmental programming of obesity may occur.

Pregnancy Outcomes Associated with Maternal Obesity and Gestational Diabetes

Given the overall rates of obesity within the general population of many societies, it is not surprising that rates of maternal obesity are rising. A retrospective analysis of 287,213 pregnancies in the United Kingdom reports that 27.5% of pregnant women in the cohort were moderately obese (BMI 25–29.5) and a further 10.9% were very obese (BMI $\geq$30) [28]. This trend is also seen in the US population, where recent studies estimate that between 18 and 35% of pregnant women are obese [29].

Maternal obesity is associated with a range of adverse effects that directly affect maternal health and pregnancy outcome. These include, pre-eclampsia, post-partum haemorrhage, hypertensive disorders and complications of delivery [30]. The financial cost of obesity is also an important consideration. As health systems have finite, and often, constrained budgets with which to provide care, any increase in the burden of cost will further limit the abilities of health care systems to cope with the obesity epidemic. In the year 2000, a French study estimated that complications arising from obesity in pregnancy (pre-gravid BMI >30) resulted in a 5.4- to 16.2-fold increase in

the financial cost of prenatal care as well as a 4.4-day increase in the postnatal care period than that required for women with a BMI of 18–25 [30].

In the context of developmental programming of adult disease, gestational diabetes mellitus (GDM) may prove to be of long-lasting detriment to the fetus. GDM manifests in approximately 8.8% of pregnancies in the developed world and the risk of GDM is directly proportional to maternal BMI. This risk of developing GDM is reported to be 2.9-fold (95% CI 2.2–3.9) for women with a BMI $\geq$30 compared with women with a BMI $\leq$20 [31], but may be as high as 20-fold [30]. In addition to the risk of obese individuals developing GDM, it is also established that being overweight predisposes the development of type 2 diabetes, characterised by whole body insulin resistance and higher plasma insulin concentrations. A study of New Zealand women, by Cundy et al. [32] observed the rate of fetal or neonatal death in offspring of women with type 2 diabetes or GDM to be greater than that seen in non-diabetic controls. This was mainly due to late fetal death. The authors highlight a strong relationship, observed in their study as well as others, between the perinatal mortality rate and maternal obesity in pregnancy women with type 2 diabetes [32]. This relationship between obesity and complications of labour is also observed in a recent study of Jewish and Beduin populations in Southern Israel [33]. Major complications in obese women (pre-gravid BMI $\geq$30, compared with controls pre-gravid BMI $\leq$30) were labour induction (OR 2.3, 95% CI 2.1–2.6), failure to progress to 1st stage of labour (OR 4.0, 95% CI 3.2–4.9), meconium-stained amniotic fluid (OR 1.9, 95% CI 1.2–1.6) and malpresentation (breech or shoulder dystocia) of the fetus (OR 1.6, 95% CI 1.3–1.9). The overall odds ratio for caesarean delivery in that population was 3.2 (95% CI 2.9–3.5) [33].

In addition to the acute complications of delivery, maternal obesity and diabetes mellitus (either GDM or existing type 2 diabetes) are associated with long-term risks to fetal and neonatal health. A Spanish study by Garcia-Patterson et al. [34], of 2,060 infants born to mothers with GDM assessed the incidence of serious (life-limiting: requiring surgery, or resulting in significant functional impairment) congenital abnormalities involving the heart, renal/urinary or skeletal systems. By multiple logistic regression analysis, these authors observed that pre-gravid obesity and the severity of GDM (also related to BMI) predicted the increase in congenital malformations observed in the offspring [34]. Neural tube defects are also more common in offspring of obese mothers (OR 1.9, 95% CI 1.1–3.4 for a maternal BMI $>$29) [35]. Notwithstanding the devastating impact of such congenital abnormalities, these are present in only 4% of births [34]. The programming of obesity and metabolic syndrome in the offspring of such pregnancies has the potential to exact an even greater burden on future generations.

Programming Vectors – Factors That May Result in DOHaD

The factors present in the maternal or fetoplacental milieu that may instigate alterations in organogenesis or induce morphometric changes in the fetus and thus result

in developmental programming of obesity or other diseases may be termed 'programming vectors'. Despite the strong association between maternal obesity, GDM and subsequent offspring developmental programming of obesity and its related sequellae, there is an incomplete understanding as to which vectors present in the maternal milieu may be most deleterious to fetal growth and development.

A comprehensive assessment of the maternal milieu in a small cohort of otherwise healthy obese (n = 23, median BMI = 31) and lean (n = 24, median BMI = 22.1) pregnant women in the UK found that maternal obesity was associated with statistically significant elevation of plasma concentrations of triglycerides, very-low density lipoprotein cholesterols, insulin, leptin and inflammatory markers (interleukin-6, C-reactive protein) as well as decreased plasma high-density lipoprotein cholesterols. Additionally, the obese group demonstrated a statistically significant elevation in systolic blood pressure and a reduction in endothelium-dependent and -independent vasodilatation in the microvasculature [36]. This milieu, consistent with that of the metabolic syndrome, is also observed in experimental animal models of maternal obesity. Holemans et al. [37] fed rats a highly palatable cafeteria-style diet for 4 weeks to induce obesity and then mated these obese rats, maintaining the same cafeteria-style diet regimen. These rats, when pregnant, were insulin resistant (measured by euglycaemic, hyperinsulinaemic clamp), and demonstrated elevated plasma leptin concentrations compared with control-fed pregnant rats [37]. Taylor and Poston [38] fed rats a lard-rich diet for 10 days prior to mating and during pregnancy. Interestingly, consumption of the lard-rich diet did not change plasma leptin or lipid concentrations in these animals; however, this may reflect the relatively short period of time that the rats were obese. Despite the short period of fat feeding, when compared with control-fed rats, fat-fed rats demonstrated significant increases in plasma insulin and corticosterone concentrations, and blunted endothelium-dependent vasodilatation in mesenteric but not uterine arteries [38].

Thus, the developing embryo and fetus are exposed to an altered maternal environment in the presence of maternal obesity. These alterations are marked, and despite the capacity that the placenta has to buffer these changes, it is quite likely that the intra-uterine environment is altered. Interestingly, thus far unidentified culture conditions used for embryo transfer and cloning also seem to programme the development of obesity in the offspring, further highlighting the importance of understanding what factors are most important for ideal fetal or embryonic development [reviewed in 39].

The mechanisms by which these programming vectors may drive changes in fetal development are not established unequivocally; however, an emerging hypothesis of alteration of DNA methylation status appears promising. The promoter regions of many genes contain long repeat sequences of cytosine and guanidine residues and these regions are prone to methylation. Simplistically stated, high levels of methylation in the promoter region decrease transcription of a gene [40]. Maternal diet and the early post-weaning diet have both been shown to alter the methylation status of

several genes in the fetus and neonate, including the insulin-like growth factor [41]. Although the hypothesis is in its infancy, and there are no reports of aberrant gene methylation status in offspring of obese women, this remains an attractive candidate mechanism.

The Role of Maternal Obesity and Fat Intake in DOHaD

The previous sections of this chapter have focussed on the effect of maternal obesity and offspring exposure to obesity in the in utero period, and the following chapter considers in detail the determinants of childhood obesity. Nonetheless, when considering the developmental origins of obesity, it is important to consider both in utero and early neonatal environments as the hypothalamic appetite centres ultimately responsible for the maintenance and determination of body weight set-points mature in early life [5, 42]. This section will consider the role of maternal obesity and fat intake in both the in utero and postnatal suckling periods on the developmental programming of obesity.

The current dietary intakes in many Western populations are high in saturated fatty acids, and clearly the intake of energy-dense and potentially pro-inflammatory fats (those that are prone to becoming oxidised low-density lipoprotein cholesterols) impacts on adult obesity. However, fat intake and obesity may also be of great importance in the developmental programming of disease. Despite the obvious reflection on the food intake in Western societies, there is still a paucity of experimental animal studies considering the role of maternal overnutrition in the developmental programming of adult disease.

Early studies in baboons showed that overnutrition in the suckling period resulted in permanent increases in plasma cholesterol concentrations [43] and adipocyte size [44]. Rats exposed to a lard-rich diet during gestation and suckling (via maternal diet), then weaned onto a control diet, are obese, hypertensive, insulin resistant, dyslipidaemic, and demonstrate blunted endothelium-dependent vasodilatation [45–47]. Interestingly, the type of fatty acid predominating in the maternal diet impacts on the programming of offspring disease. High-fat diets that are also rich in ω–3 polyunsaturated fatty acids have been shown to result in a largely normal offspring phenotype despite the increased total fat and caloric load of the diet [48, 49]. Moreover, neonatal rat pups suckled by dams fed fat-rich diets supplemented with ω–3 and ω–6 essential fatty acids show reduced adipose tissue weight and reduced plasma leptin concentrations [50]. Therefore, it appears that exposure to maternal diets that are rich in saturated fatty acids is deleterious to later offspring health, whereas even relatively high essential ω–3 and ω–6 fatty acid intake in the diet results in a normal offspring phenotype. There is also emerging evidence in humans that lowering total fat intake whilst increasing the proportion of ω–3 and ω–6 essential fatty acid may have beneficial effects on offspring and maternal health [51].

Experiments utilising cross-fostering of pups between control and fat-fed dams suggest that exposure to the maternal fat-rich diet during either the in utero or suckling periods results in a metabolic syndrome-like phenotype [52]. Combined with other studies of postnatal overfeeding [53] there is clear evidence that the first 21 days of rodent life is a developmental critical period. Moreover, overfeeding during this period can override genetic predisposition; obesity-resistant rats cross-fostered to obese mothers during the suckling period develop diet-induced obesity later in life [54].

As previously discussed, maternal diabetes often accompanies obesity. Pups suckled by dams that are obese or diabetic demonstrate permanent alterations in the manner by which hypothalamic appetite circuits respond to the peripheral signals that normally instigate hunger and satiety. This is a bourgeoning area of research and warrants review in its own right [see reviews 5, 55]. However, briefly summarising a complex neural circuitry model, it appears that exposure to the obese or diabetic milieu during suckling programmes a selective neural leptin resistance at the level of the hypothalamic arcuate nucleus [56]. The mechanism for such resistance is seen in a reduction in synaptic integrity of neurons that normally inhibit appetite but not those that stimulate appetite [56]. The net result of such synaptic plasticity is that normal satiety signals are not attended and animals develop hyperphagia that persists through life.

Thus, exposure to a saturated fat, diabetic or energy-rich environment in early life may programme alterations in the hypothalamic neural circuitry that is ultimately responsible for the establishment of growth trajectory and energy balance in young humans and animals. It is most likely that alterations in the plasma concentrations of peripheral appetite signals such as insulin, leptin and ghrelin are altered in the fetus or neonate carried or suckled by obese or diabetic mothers. The developing neural networks in the hypothalamus are then affected and because these changes occur during a critical period of development, the changes to appetite and energy expenditure circuits become permanent, thereby setting the scene for the subsequent development of obesity in the next generation.

Conclusions

There are a myriad of socioeconomic, lifestyle and dietary behavioural factors that have contributed and continue to add to the worldwide obesity epidemic. Complications of maternal obesity or type 2 diabetes are summarised in table 1. The developmental programming of adult disease appears to be one more factor that warrants serious consideration and one that should be tackled by public health initiatives. Because of the alarming rate of obesity in young children across many societies, obesity-related disease will not be eradicated in the near future; however, it is vital that not only is the population informed of the risks and consequences of obesity to maternal health, but also of the potential risks to the health of future generations.

Table 1. Complications of maternal obesity or gestational diabetes

Pre-eclampsia
Post-partum haemorrhage
Hypertensive disorders
Complications of delivery
Labour induction
Failure to progress to 1st stage of labour
Meconium-stained amniotic fluid
Malpresentation
Financial cost
Fetal or neonatal death
Congenital malformations
Heart
Renal/urinary system
Skeletal systems
Neural tube defects
Developmental programming of adult health and disease of the fetus
Obesity
Type 2 diabetes
Hypertension
Atherosclerosis
Altered hypothalamic appetite circuitry

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