Chapter 8
Mechanisms Linking Maternal Obesity to Offspring Metabolic Health

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Abstract A wealth of animal and human studies demonstrate that perinatal exposure to maternal obesity results in predisposition of offspring to develop metabolic diseases later in life. This process is a contributing factor to the exponential rise in obesity rates. Metabolic disease in offspring exposed to maternal obesity is associated with disruption of a number of organ systems including the heart, liver, and endocrine pancreas as well as the central nervous system (CNS). These disruptions are mediated through structural and gene regulatory changes, and although the precise molecular mechanisms underpinning these modifications remain uncharacterized, they are likely to involve alterations to offspring epigenetic marks. This chapter summarizes our current knowledge of how maternal obesity programs offspring metabolic health and explores the mechanisms that could mediate these effects.

Keywords Maternal obesity • Developmental programming • Glucose homeostasis • Central nervous system • Cardiovascular system • Aging • Epigenetics • Metabolic hormone

8.1 Introduction

In recent decades, worldwide obesity levels have increased exponentially. Obesity is no longer just a health problem but represents an astronomical financial burden for society. It has been estimated that over the next 20 years, obesity-related costs will account for around 16 % of health spending in developed countries [1], and it was revealed recently that the cost of treating diabetes in England already accounts for 10 % of all prescribing costs [2]. While several genetic polymorphisms linked to obesity have been discovered [3], these are few, only account for small increases in body weight, and explain less than 5 % of the heritability of the condition. In recent

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years, the importance of the early-life environment in shaping later life disease risk—including susceptibility to develop obesity—has been established.

An interaction between the early-life environment and later life metabolic disease risk was first proposed in the seminal papers by Hales and Barker, who reported an association with low birth weight (as a proxy for restricted fetal growth) and cardiometabolic disease in adulthood [4, 5]. Further studies examining individuals who were in utero during the Dutch Hunger Winter, a famine in the Netherlands during the Second World War, confirmed the association between in utero undernutrition and the development of metabolic disease [6]. As well as the detrimental effects of exposure to undernutrition in utero, there is now a wealth of evidence that demonstrates early-life exposure to overnutrition—for instance, in cases of maternal obesity—is also associated with increased metabolic disease. Comparative studies of siblings born before and after the mother underwent gastric bypass surgery have revealed that the children born after the mother had lost weight had great improvements in insulin sensitivity, reduced adiposity, and reduced blood pressure compared to their siblings [7].

8.1.1 Birth Weight and Overnutrition During the First Weeks of Postnatal Life

Since the initial observations by Hales and Barker, it has been confirmed by numerous other studies that individuals born small for gestation age (SGA) show an increased incidence of metabolic disease later in life. Interestingly, recent studies have demonstrated a U-shaped relationship between birth weight and adolescent adiposity [8], showing that being born large for gestational age (LGA) is also associated with metabolic disease. Rapid postnatal catch-up growth after SGA birth appears to exaggerate the effect of suboptimal growth in utero on risk of metabolic and cardiovascular diseases later in life [9]. In addition, there is evidence that accelerated early postnatal growth, independent of growth in utero, is associated with increased obesity [10]. However, these associations are dependent on the socioeconomic environment that the child grows up in [11], and so results from cohorts in different countries must be interpreted independently.

8.1.2 The Use of Animal Models in the Field of Developmental Programming

While it is primarily desirable to examine results from human cohorts in relation to any health issue, for ethical and practical reasons this is often not possible. The early age of sexual maturity and shorter gestation periods of rodents have made mouse and rat models extremely popular within the developmental field.

Furthermore, important and highly translatable research has been conducted in nonhuman primate (NHP) models as well as other large animal models such as sheep. Within the developmental programming field, NHP, ovine, and rodent models of maternal obesity have produced phenotypes in offspring remarkably similar to human observations.

The use of animal models has enabled researchers to address questions that it simply wouldn't be possible to investigate in human subjects. For example, the question of whether maternal diet or maternal adiposity is more important in determining offspring outcomes cannot be conclusively answered in human studies due to the inaccuracy of food intake questionnaires and shared dietary habits within a family household. In contrast, animal models allow researchers to strictly control both maternal and offspring diet, as well as the genotype of the mother and offspring. Furthermore, animal models give the option to examine at a molecular level organs such as the brain that require a terminal end point and for obvious reasons are not possible in humans. Some recent progress has been made in identifying biomarkers in human blood that could be indicative of exposure to an adverse early-life event (see Sect. 8.3.1.4). However, we are a long way from these biomarkers being effectively used in human health care and diagnostics, and therefore extensive research in this field is still required.

Genetically modified rodents are invaluable in elucidating the molecular mechanisms underpinning phenotypes in offspring that have been exposed to an adverse perinatal environment. For example, Vogt et al. have recently utilized genetically modified mice which lack the insulin receptor specifically in pro-opiomelanocortin (POMC) neurons in the hypothalamus, to demonstrate that insulin signaling mediates the disruption in these neuronal projections in offspring exposed to maternal overnutrition [12]. The use of other genetically modified rodent models allowing cell-specific deletion or overexpression of specific proteins will undoubtedly further our understanding of the cellular events mediating the detrimental effects of exposure to maternal obesity.

8.2 Alterations to Organ Structure and Function

8.2.1 Cardiovascular System

Cardiovascular dysfunction and metabolic disease are intrinsically linked. Cardiovascular disease is one of the most serious comorbidities associated with obesity and causes a significant social and financial burden. Evidence from the Helsinki birth cohort has demonstrated significant associations between both gestational weight gain (GWG) and offspring birth weight with enlarged ventricular mass, as well as an association between maternal obesity and offspring cardiovascular disease [13, 14]. Causative associations between maternal nutrition and offspring cardiovascular function have been demonstrated in animal models showing striking

evidence of cardiac structural and functional changes independent of offspring body weight.

8.2.1.1 Cardiac and Renal Structure

In rodent models, maternal obesity is associated with cardiac hypertrophy and increased left ventricular thickness in offspring [15–17]. Furthermore, sheep fetal offspring exposed to maternal obesity and/or overnutrition display increased left ventricular thickness, cardiac hypertrophy, and increased heart weight, all of which are indicative of reduced cardiac function [18–20].

In humans, there is a U-shaped relationship between birth weight and chronic kidney disease [21, 22], suggesting an interaction between the early-life nutritional environment and kidney function. Supporting this theory, recent studies have also demonstrated a positive association between formula feeding of babies and kidney mass in individuals as adults [23, 24]. Similarly, it has been shown in a rodent model of neonatal overnutrition that offspring display morphological changes in the kidney indicative of reduced renal function [25, 26].

8.2.1.2 Hypertension

It has recently been demonstrated that hyperleptinemia is instrumental in mediating the development of obesity-associated hypertension [27]. This is of particular concern as leptin is elevated in mothers in obese pregnancies, and maternal and fetal leptin levels are directly correlated [28, 29]. A shared phenotype in experimental models of both maternal hyperleptinemia and maternal obesity is offspring hypertension [30, 31]. Furthermore, offspring hyperleptinemia during the perinatal period (induced by exogenous administration of leptin) results in the development of hypertension [32, 33]. There is emerging evidence that the development of hypertension in offspring is due to increased sympathetic tone [16, 34, 35]. Recent results from Samuelsson et al. suggest that increased sympathetic tone is due to altered melanocortin signaling in the central nervous system (CNS) of offspring [36]; given the other reports of developmental programming of the hypothalamus (see Sect. 8.2.4.1), this is certainly an important avenue for further investigation.

8.2.2 Liver and Endocrine Pancreas

The liver is essential to maintaining energy homeostasis due to its vital roles in maintaining both glucose and lipid homeostasis. A common offspring phenotype reported in rodent, sheep, and NHP models of maternal obesity is ectopic fat storage in the liver, resulting in nonalcoholic fatty liver disease [37–39]. This negatively

impacts on hepatic function, and therefore glucose homeostasis, resulting in insulin resistance in offspring [40].

Another vital organ in maintaining glucose homeostasis is the endocrine pancreas. Situated within the endocrine pancreas, β-cells are the only cells in the body that can produce insulin. These highly important β-cells can be damaged by chronic hyperglycemia, resulting in less endogenous insulin production and the need for exogenous insulin (as in cases of poorly controlled T2DM). In NHP, both maternal obesity and overnutrition result in impaired vascularization of offspring pancreas and increased markers of pancreatic inflammation and insulin resistance in peripheral tissues [41, 42]. Rodent and sheep models of offspring exposure to maternal obesity have also reported signs of altered pancreatic structure such as altered β-cell number and volume [43, 44]. Recent evidence from a rodent model of maternal obesity showed that impaired pancreatic development and function is stably transmitted to later generations [45].

There is also evidence that in addition to altered structure of the pancreas and liver, exposure to maternal obesity can alter the innervation of these organs by the CNS. In both NHP and rodents, it has been shown that in offspring exposed to maternal overnutrition, there is decreased central innervation of the liver and pancreas, respectively [12, 46].

8.2.3 Adipose Tissue

The amount, type, and distribution of adipose tissue has a substantial impact on metabolic and long-term health independent of body weight [47]. It is now accepted that adipose tissue plays a pivotal role in maintaining whole-body insulin sensitivity by engaging in insulin-dependent glucose uptake and influencing the sensitivity of other tissues to insulin by releasing free fatty acids and adipokines such as leptin and adiponectin.

Fetal sheep exposed to maternal obesity have increased peri-renal brown adipose tissue mass [48]. Adult offspring from the same model display increased adiposity and altered expression of adipose nutrient transporters [49]. Rodent models have consistently reported increased adiposity in the offspring of obese mothers, often due to adipocyte hypertrophy [31]. Exposure to maternal overnutrition during the perinatal period can also alter the distribution of fat between the various peripheral depots. Volpato et al. have reported an increase in epididymal and inguinal fat stores at the expense of subcutaneous adipose depots [50]. This is significant as the distribution of fat depots has an influence on metabolic health independent of total adiposity levels.

8.2.4 CNS

Increased weight gain in offspring exposed to maternal obesity is often preceded by hyperphagia, implicating altered central regulation of energy homeostasis as an underlying cause of metabolic phenotypes. Central control of energy homeostasis can be broadly divided into two areas: homeostatic control of energy homeostasis originating in the hypothalamus and reward-related feeding and behavior orchestrated through the mesolimbic pathways.

8.2.4.1 Homeostatic Feeding Pathways

Over the past two decades, the importance of the hypothalamus within the brain in regulating whole-body energy homeostasis has become increasingly clear. Neurons expressing the orexigenic Neuropeptide Y (NPY) and anorexigenic POMC situated within the arcuate nucleus (ARC) of the hypothalamus are instrumental in sensing changing nutrient status in the rest of the body. These NPY and POMC neurons project to other regions of the hypothalamus including the paraventricular nucleus (PVH) and the brain stem in order to mediate downstream physiological effects to maintain energy homeostasis.

Pioneering work by the Bouret laboratory and others has shown that development of the hypothalamus is plastic and sensitive to metabolic signals in the perinatal period [51]. Evolutionarily, the requirement for metabolic hormones in hypothalamic development enables the hypothalamus to develop in line with the nutritional state of the ex utero environment. However, it also leaves hypothalamic development extremely vulnerable to disruption in instances where metabolic and fetal hormone levels are altered, for example, as a consequence of maternal obesity.

Rodent studies have demonstrated that the offspring of obese mothers display a reduced number of axonal projections between the ARC and PVH [52], as well as a reduction of projections between the ARC and dorso-medial and lateral hypothalamus [12]. This programming of ARC projections occurs even when offspring exposure to maternal obesity is limited to the suckling period, which corresponds with the reported timing of development of these projections. This suggests that the disrupted circuitry reflects a disruption of axonal projections, rather than a cellular defect. These changes are thought to be mediated through altered neuronal insulin and leptin signaling, highlighting the importance of both maternal and fetal metabolic hormone levels during the perinatal period (see Sect. 8.5.1).

8.2.4.2 Reward-Related Feeding

Maternal obesity can also influence offspring feeding behavior and alter dietary preferences. In rodents, maternal obesity has been reported to increase the preference for fatty and sugary food in offspring, leading to obesity [53–55]. This is

particularly relevant when considering the increased availability of highly palatable fat and sugar-rich foods in modern society. The offspring of obese mothers also display increased frequency of feeding episodes and a longer duration of feeding during a given episode [56]. Interestingly, it has also been reported that the offspring of obese mothers display alterations to reward systems in the brain that could explain the frequently reported hyperphagia. Several studies have reported programming of the mesolimbic reward system in offspring, resulting in altered activation in response to diverse stimuli including feeding, and reduced anticipatory responses for food rewards [54, 57, 58].

8.3 Changes to Gene Expression

Changes in the transcriptome and/or proteome of all major organ systems have been reported in the offspring of obese mothers, across a range of species. These include alterations in peripheral organs including heart [59], adipose tissue [60], kidneys [61], and the liver [62]. In the CNS, changes in the expression of genes involved in both energy homeostasis and reward-related feeding have been demonstrated in the hypothalamus and mesolimbic pathways, respectively [63–65].

8.3.1 Epigenetics

The stable nature of phenotypes throughout the lifetime of the exposed offspring, and the recently reported intergenerational transmission of programming effects, suggests permanent changes in gene expression in the exposed individuals. Epigenetic regulation represents a stable but modifiable level of genomic regulation; the term epigenetics literally means “on top of genetics” and refers to a system of processes that induce heritable changes in gene expression without altering the genomic sequence. In utero regulation of epigenetic machinery has recently received a lot of interest as a potential mechanism for causing permanent, heritable changes to gene expression.

There is emerging evidence from human cohorts of the importance of changes to the epigenome. In a recent study of siblings born before and after maternal gastric bypass surgery, significant differences in the methylation of glucoregulatory genes were observed in blood samples [7]. In a different study, maternal glycemic level was shown to contribute to the methylation state of a specific site near the leptin gene, which was in turn associated with cord blood leptin levels [66]. A recent report from the ALSPAC team identified four loci at which offspring methylation state is correlated with maternal GWG [67]; however, this association failed to validate in larger cohorts leading to doubt over the strength of the association [68].

It is worth noting that the (in)heritability of the epigenome can be context dependent (i.e., altered epigenetic markers that are permanent and inheritable) or

germ line dependent (i.e., altered epigenetic markers in offspring gametes that will produce the next generation). Therefore, epigenetic markers must be identified in the F2 and subsequent generations in order to identify truly heritable changes to the epigenome. Additionally, changes to epigenetic marks of functionally relevant genes must be present prior to the development of a phenotype in order to prove causality. This is why animal models of maternal programming are particularly important, as they allow access to vital organs during early life and before the development of metabolic phenotypes.

8.3.1.1 Histone Modifications

The DNA in cells is stored as chromatin. The basic unit of chromatin is a nucleosome, which consists of roughly 147 bp of DNA wrapped around a core histone octamer made up of two copies each of the H2A, H2B, H3, and H4 proteins. This organization leaves the N-terminal tails of histones accessible to modifications including methylation, acetylation, and phosphorylation [69]. Histone acetylation is associated with an active euchromatin state, whereas histone methylation can confer activation or inactivation of associated chromatin, depending on which component of the histone octamer and which particular lysine of that protein is modified [69].

The Histone Acetyl Transferase (HAT) family performs histone acetylation, associated with transcription, whereas the Histone De-acetylase (HDAC) family of proteins performs histone de-acetylation that is inhibitory to transcription. In an NHP model, fetal offspring exposed to maternal overnutrition display reduced HDAC activity, which is associated with hyperacetylation at H3K14 in the liver [70]. Unfortunately, due to the difficulty of analyzing the histone code (which is more technically challenging compared to analyzing for example DNA methylation state), data on histone modifications resulting from exposure to maternal obesity are sparse. However, sheep offspring exposed to IUGR display increased H3K9Ac and decreased H3K27Me3 modifications associated with the POMC promoter. These changes are observed specifically in the hypothalamus, although they are not associated with a corresponding change in *Pomc* mRNA [71]. Although these histone modifications occur in response to offspring exposure to maternal undernutrition—rather than obesity—they demonstrate the dynamic nature of the histone code in relation to the early-life environment.

8.3.1.2 DNA Methylation

DNA methylation is an essential component of normal genomic regulation. Methylation at the 5′ position of a Cytosine base within a CpG dinucleotide is a stable epigenetic mark that can be transferred between generations during mitosis. CpG dinucleotides are randomly distributed throughout the genome, but are particularly frequent near the 5′ promoter regions of genes. Areas with a high frequency of CpG

dinucleotides are termed CpG islands. Whereas CpG dinucleotides are usually methylated, Cytosine residues within CpG dinucleotides in CpG islands are usually un-methylated. A high percentage of CpG methylation is associated with transcriptional silencing of nearby genes, whereas CpG island hypomethylation is associated with transcriptional activation. This is in part due to the fact that the attachment of methyl groups can directly inhibit the interaction between DNA and transcriptional machinery, for example, by attaching to cytosine residues within a transcriptional response element and thus repressing transcription [72, 73]. Furthermore, promoter methylation can also cause recruitment of other proteins (for example, Methyl Binding Domain proteins), which facilitate binding of histone-modifying complexes that subsequently alter chromatin activation state as discussed above [74].

Within normal genomic regulation, DNA methylation is particularly important for the silencing of imprinted genes and the X chromosome during development. The regulation of imprinted genes is also subject to programming by the early-life environment, as demonstrated in a rodent model of hyperglycemia in which reduced expression of the imprinted genes *Igf1* and *H19* in pancreatic islets is attributed to hypermethylation of the promoter regions [75].

DNA methylation patterns are established during the early stages of development, and this time is therefore a critical period during which methylation patterns are vulnerable to change. During the preimplantation stage, the embryonic genome is subjected to widespread demethylation, and then de novo methylation occurs at specific regions to generate a pattern of methylation that is inherited by daughter cells [76]. As the DNA methylation pattern is essentially maintained throughout life, changes to the activity of methyl transferases during these critical periods of development can cause lasting changes to gene regulation.

Tissue-specific expression and relative levels of several hormones—including insulin, leptin, and adiponectin—are regulated by the methylation state of promoter regions, making these genes susceptible to altered expression and abundance. Furthermore, Masuyama et al. have recently demonstrated that the methylation state of the leptin and adiponectin genes can be inherited [77]. Neonatal overnutrition causes hypermethylation of the POMC promoter in the hypothalamus specifically at CpG dinucleotides within a transcription factor binding site, resulting in a lack of *Pomc* mRNA regulation in response to leptin or insulin [78]. Similarly, offspring exposed to maternal obesity in utero display hypermethylation of a region upstream of the POMC gene, which corresponds with decreased *Pomc* expression and increased body weight [79].

8.3.1.3 MicroRNAs

MicroRNAs (miRNAs) are small noncoding RNAs (between 22 and 25 nucleotides in length) that are able to post-transcriptionally modify gene expression. miRNAs bind to the 3′ untranslated region of mRNA transcripts and therein either interact with the DICER complex to target the bound transcript for degradation or inhibit translation of the transcript by physically inhibiting the binding of translational

machinery. Interestingly, miRNA expression can be regulated both dependently and independently of the host gene in which they reside, making their expression highly dynamic.

To date, only a few observations of altered miRNA expression in tissues of offspring exposed to maternal obesity have been published. For example, mir133 is increased in the heart of offspring in a murine model [16], and NHP exposure to maternal obesity results in increased expression of miRNAs associated with cardiovascular disease [80]. Furthermore, in a sheep model of maternal obesity the fetuses displayed altered levels of mir-29b, -103, and -107 in the liver [62]. The only current evidence for miRNA activity mediating maternal obesity-induced changes in gene expression comes from a mouse model in which the levels of mir126 are elevated in the epididymal fat of offspring [81]. As mir126 is a regulator of *Irs1*, this increased mir126 activity could explain the decreased expression of *Irs1* that is also observed in these offspring. Importantly, the effects of maternal obesity on mir126 and *Irs1* expression are cell autonomous and are maintained in vitro when pre-adipocytes are differentiated in culture [81].

8.3.1.4 Epigenetic Markers in Blood for Human Diagnostics

A current challenge for studies of human epigenetic marks is that they are limited to easily accessible biological samples, most commonly blood. Researchers therefore need to identify epigenetic marks that are uniform throughout the whole organism, despite the fact that they may only confer a functional role in specific (inaccessible) tissues. Metastable epialleles are regions of the genome at which DNA methylation is established stochastically in the early embryo and then maintained in differentiated tissues. Focusing on metastable epialleles allows researchers to work around limitations in sample collection from human subjects. Recently, Dominguez-Salas and colleagues have shown persistent changes in DNA methylation in offspring born to mothers either during the rainy season or the dry season in the Gambia [82]. Pregnancies during these two seasons vary greatly in maternal nutrient intake, making this an interesting model of changes to maternal diet. Candidate methylation analysis of blood and hair samples (selected as mesodermal and ectodermal tissues, respectively) from the children of these mothers demonstrated increased methylation of six metastable alleles in individuals who were born in the rainy season.

A recent study by Sharp et al. of the ALSPAC cohort has provided the first evidence that the influence of maternal obesity on offspring metabolic health may be mediated via altered DNA methylation. This study is the first to examine DNA methylation levels at three time points: in neonatal cord blood and later in peripheral blood at 7.5 and 17 years of age. The authors identified several CpG sites that were differentially methylated in blood of offspring exposed to maternal obesity and associated with offspring adiposity. Replication of these results in larger cohorts will identify molecular pathways underpinning maternal programming of

offspring health and potentially lead to the identification of novel epigenetic markers that can be used as a stable indicator of exposure to an early-life insult.

8.4 Aging

As humans undergo the natural aging process, they display increased body weight, a shift in adipose distribution, and deteriorating function of organs such as the heart, kidney, and reproductive system. Many of these natural aging processes recapitulate phenotypes observed in offspring exposed to adverse perinatal nutritional environments. Indeed, a study by Reynolds et al. has shown that the children of obese mothers have a decreased life expectancy due primarily to cardiac dysfunction [83]. This has led researchers to consider whether accelerated aging is one of the primary molecular mechanisms underpinning the changes in health after exposure to an adverse early-life environment. Indeed, macronutrient restriction and undernutrition causes accelerated cellular aging in offspring pancreatic islets, and markers of accelerated aging in the liver [84, 85].

Telomeres are guanine-rich nucleotide sequences present at the ends of chromosomes that prevent chromosomal deterioration. An essential part of the aging process in telomerase-negative somatic cells is telomere shortening that occurs after each cell division. More recently, telomeres have also been shown to shorten in response to oxidative stress [86, 87]. When telomeres become critically short in length, they undergo a conformational change which results in them representing double-stranded breaks, causing the cell to enter growth arrest and senesce or become apoptotic [88]. Differences in telomere length have been implicated in developmental programming in response to maternal nutritional state. Low birth weight offspring of protein-restricted mothers cross-fostered to control dams to enable rapid recuperation during the postnatal period have reduced longevity accompanied by accelerated telomere shortening in several tissues [85, 89, 90]. While there is no evidence yet of accelerated telomere shortening in response to maternal overnutrition, the shared commonality in cellular responses to both ends of the nutritional spectrum predicts that this process is also likely to occur with exposure to maternal obesity.

8.5 Maternal Factors

In order to develop effective intervention strategies and healthcare guidelines, it is necessary to elucidate the mechanisms by which the maternal nutritional and endocrine state is transmitted to and/or sensed by offspring during early life. Put simply, what is the "programming factor" that we need to target in order to prevent the early-life programming of metabolic disease risk? Traditionally, research has focused on maternal hormone and nutrient levels, particularly those that are able to

cross or modulate function of the placenta. However, emerging evidence highlights a role for novel mechanisms by which the maternal environment influences offspring early development. For example, recent research has shown that maternal stress during pregnancy alters the vaginal microbiome, and exposure to this altered microbiome programs development of offspring brain and gut [91].

8.5.1 Metabolic Hormones

A host of metabolic hormones are altered in the obese mother during pregnancy and consequently in the developing fetus. Elevated levels of many of these hormones have been implicated in mediating the effects of the perinatal environment on offspring development (Fig. 8.1).

Maternal leptin levels are elevated in obese pregnancies, and although there is some debate, it is generally accepted that leptin can cross the placenta. As discussed earlier, high leptin levels are implicated in the development of hypertension in both obese individuals and offspring exposed to maternal obesity [27, 34]. Furthermore, the correct regulation of leptin levels in the perinatal period is essential for correct

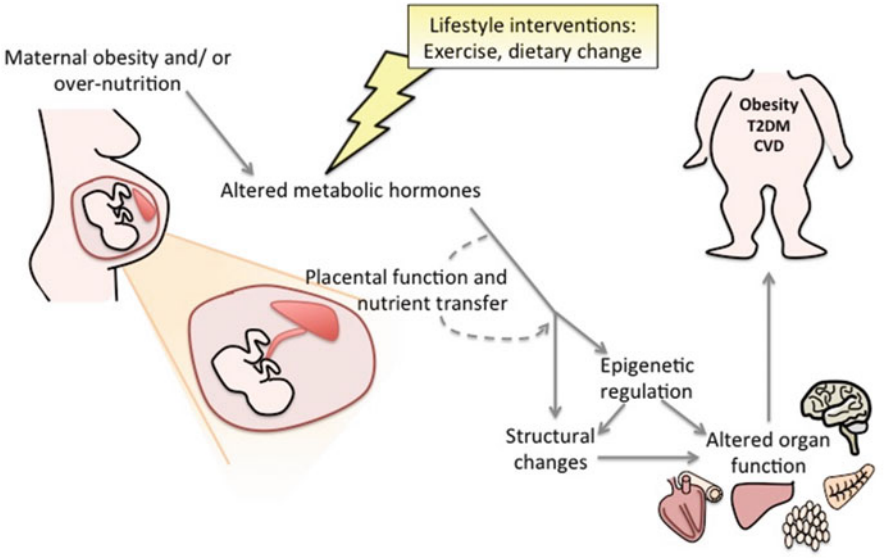

Fig. 8.1 Maternal obesity and/or overnutrition is associated with altered levels of metabolic hormones. These hormones are able to modulate placental function and nutrient transfer, and some can also act on the fetus directly to modulate epigenetic machinery and cause structural changes in organs. These processes ultimately result in a change in organ function and the development of obesity later in life. Lifestyle interventions that increase the mother's metabolic fitness are a promising intervention to inhibit the effects of maternal obesity on offspring metabolic health

development of the hypothalamus, and thus altered leptin levels during this period can have long-term detrimental effects on the ability to maintain energy homeostasis [51]. It is of note, however, that in a rodent model of leptin deficiency, maternal protein restriction is still associated with adverse metabolic outcomes in offspring [92], and therefore leptin cannot be solely responsible for all offspring phenotypes observed in response to an adverse nutritional environment.

Hyperglycemia and insulin resistance, leading also to elevated circulating insulin levels, usually accompany maternal obesity. While insulin can only cross the placenta in limited amounts, maternal hyperinsulinemia is usually accompanied by hyperglycemia, which in turn can induce elevated levels of both fetal insulin and glucose. Increased fetal glucose levels cause increased insulin and IGF signaling and subsequently fetal growth [93, 94]. Furthermore, the activity of members of the DNMT family has been shown to be altered by changing glucose concentrations [95]. As demethylation followed by de novo methylation is an essential process during early embryogenesis, changes to the activity of the epigenetic machinery caused by the in utero nutritional state would cause significant long-term effects on offspring epigenetic regulation. Like leptin, insulin also has a significant role in hypothalamic development [12, 96], and fetal hyperinsulinemia as a response to maternal hyperglycemia will therefore have significant effects on the development of hypothalamic energy homeostasis pathways.

Maternal obesity can alter the macronutrient and hormonal composition of milk, and this is therefore a likely contributing factor to changes in offspring development during the early postnatal period. In particular, elevated leptin content in milk has been reported in both obese human and rodent mothers [38, 97]. Furthermore, cross-fostering of control offspring to a GDM dam during the lactation period has been shown to cause perturbations to the development of hypothalamic energy balance circuitry, suggesting consumption of milk from a diabetic mother can cause long-term changes to body weight and food intake in offspring [98].

8.5.2 The Placenta

An obvious place to look for maternal influence on offspring development is at the maternal–fetal interface, or more specifically at the placenta and at the hormones and nutrients that are able to act on or pass through the placental barrier to the developing fetus. The placenta acts as an important nutrient sensor during pregnancy and can respond to external stimuli to dynamically regulate the transfer of nutrients, including glucose, to the developing fetus [99]. As glucose is the primary fuel source for the developing fetus, the placenta plays an important role in ensuring that fetal circulating glucose levels are maintained within a physiological window to avoid excess or impaired fetal growth.

It is becoming increasingly apparent that nutrient transfer across the placenta can be altered as a consequence of the metabolic state of the mother during pregnancy.

Fetal glucose uptake via the placenta is dependent on the metabolic status of the mother [100]. Numerous murine models of maternal obesity and gestational hyperglycemia have demonstrated increased placental nutrient transfer to the fetus in utero, resulting in increased birth weight [101, 102]. There is also considerable evidence from human studies that maternal hyperglycemia and GDM can alter placental function [103]. NHP models of obesity have shown significant damage to the placenta caused by maternal overnutrition [104]. These changes are independent of maternal obesity but are exacerbated in pregnancies complicated by maternal obesity and insulin resistance. The general clinical accessibility of the placenta as a whole tissue after birth makes it possible to investigate structural and functional changes that occur during obese human pregnancies, and this active area of future research will undoubtedly increase our understanding of the placental origins of developmental programming.

8.6 Interaction Between Genes and the Environment

It is now largely accepted that the polygenic nature of obesity means that susceptibility to develop cardiometabolic diseases is due to a complex interaction between genetic susceptibility and environmental exposures during early life. Perhaps most convincing is a recent study by Rosenquist et al., which demonstrates that the well-studied Fat mass and Obesity-associated (FTO) polymorphism only has a significant association with BMI in individuals born after 1942 [105]. Furthermore, in the Dutch Hunger Winter cohort, there is a significant interaction between a polymorphism in the Peroxisome Proliferator-Activated Receptor γ2 (PPARγ2) gene and famine exposure on glucose and insulin metabolism; the mutant allele is associated with impaired glucose tolerance and T2DM as an adult only if offspring were also exposed to the famine specifically during mid-gestation [106].

The Avon Longitudinal Study of Parents and Children study has also revealed complex gene and environment interactions. The insulin gene variable number of tandem repeats (INS VNTR) is associated with adult obesity and T2DM, and the ALSPAC study revealed that there is an interaction between INS VNTR genotype and postnatal weight gain in relation to adolescent BMI [107]. Other studies have revealed interactions between genetic risk alleles and diet [108, 109] in determining childhood adiposity. However, these studies have focused on offspring diet, rather than maternal diet. Therefore, although there is evidence that the environment and genetic factors interact, this needs to be further explored in both human and animal models where the maternal nutritional state is taken into account.

8.7 Paternal Influences

The predominantly maternal influence that has been noted in most studies of metabolic disease transmission suggests the in utero environment has an effect independent of genetic heritability. However, although the maternal environment undoubtedly exerts a strong influence on fetal development, the paternal environment can in theory exert an independent effect on fetal development through gamete transmission.

There are conflicting reports on the influence of the father's metabolic state during early life and at conception on offspring metabolic disease. Offspring of two overweight parents have an increased risk of childhood obesity compared to offspring with just one obese parent [110, 111]. However, when examining the individual influence of maternal and paternal obesity, the mother–child association is consistently stronger than father–child in relation to offspring BMI [111]. It is therefore important to remember that sex-specific inheritance of X chromosome linked genes and mitochondrial DNA from the mother must also be considered as these confer increased maternal influence in heritability. Interestingly, a recent study in China has suggested that the effects of paternal BMI on fetal growth are sex specific; a positive association between paternal BMI and intrauterine growth was reported in male but not female offspring [112]. A transgenerational link has also been proposed between the paternal grandfathers nutrition during adolescence and incidence of obesity and cardiovascular disease in later generations [113, 114].

Although these few studies suggest that paternal metabolic state around conception may be associated with offspring metabolic disease risk, there is a lack of compelling evidence in humans that this is due to true programming of offspring metabolic regulation, rather than a shared family lifestyle and genetic inheritance. In animal models, however, there is evidence that combined parental obesity has a greater detrimental effect on oocyte implantation and early fetal development than maternal obesity alone [115]. In drosophila, paternal consumption of a high sucrose diet is sufficient to program alterations to fat storage in subsequent generations of offspring [116]. Furthermore, the daughters of obese male mice display disrupted pancreatic function and transcriptional changes in adipose tissue [117, 118]. Given the exponentially increased incidence of obesity in both men and women of reproductive age, it is imperative that the precise influence of paternal metabolic state on offspring metabolic health is defined in order to inform health guidelines.

8.8 Intervention Studies

The use of intervention studies (particularly in animal models) gives us an unrivaled insight into the mechanisms mediating changes in the nutritional environment on offspring health. In the first instance, simple lifestyle or behavioral changes are of primary preference as they are more likely to be adopted by mothers than

pharmaceutical regimes that may have side effects (Fig. 8.1). Also, historic cases such as the devastating effects of thalidomide use during pregnancy have made many people wary of taking medications during pregnancy.

A behavioral intervention model that is being trialed simultaneously in both humans and animal models is the encouragement of maternal exercise during obese pregnancies. Exercise is extremely effective at improving insulin sensitivity and therefore glucose homeostasis, even independently of decreased adiposity [119, 120], and is therefore a viable option for improving the mothers "metabolic fitness" (i.e., glucose and insulin sensitivity) independent of her weight. The UK Pregnancies Better Eating and Activity Trial (UBPEAT) recruited a large cohort of obese pregnant women and encouraged them to partake in a mild exercise regimen alongside weekly meetings with health trainers. The initial results from the UPBEAT trial have shown that although the behavioral intervention was not adequate to reduce the incidence of LGA births, mothers in the intervention group had decreased GWG and skin fold thickness [121]. As both GWG and maternal adiposity have been associated with metabolic parameters in adolescent offspring, close follow-up of this cohort will establish whether the improvement of these maternal parameters is also beneficial to offspring. Indeed, in rodent models both maternal exercise during pregnancy and offspring exercise during the early postnatal period are sufficient to augment the detrimental effects of maternal obesity on offspring metabolic health [122, 123].

Studies conducted in NHPs have suggested that control of maternal diet during pregnancy (even if the mother remains obese) is extremely effective in ameliorating offspring phenotypes. These studies have utilized naturally occurring diet-resistant females who remain lean despite consumption of a HFD to demonstrate that exposure to maternal overnutrition alone (without maternal obesity) causes changes in offspring liver function [37, 63]. Furthermore, switching the diet of NHP obese females immediately prior to pregnancy reverses the alterations observed in offspring hypothalamic feeding pathways—despite the mothers remaining obese—suggesting that this phenotype is mediated by maternal diet alone [63]. These studies therefore suggest that changing the maternal diet to a healthier diet before pregnancy is sufficient to ameliorate the transmission of detrimental phenotypes to offspring. In a human study of dietary intervention, gestational diabetic mothers following a strict calorie-controlled diet have a reduced incidence of LGA births and less birth complications compared to those on a diet of their own choice [124]. Unfortunately, however, it is not clear from this study whether the beneficial effects on offspring are as a result of the mother's dietary change alone, or from the beneficial effect of a healthier maternal diet on diabetes management.

8.9 Conclusions

Extensive evidence from animal models and human studies demonstrates that early-life exposure to maternal obesity increases offspring susceptibility to develop metabolic disease later in life. While the molecular mechanisms remain largely uncharacterized, evidence suggests that altered levels of metabolic hormones in both the mother and fetus cause significant changes to organ development, which may be caused by changes in gene regulation due to altered activity of epigenetic machinery. Disrupted organ development can cause decreased function later in life, resulting in the inability to maintain metabolic homeostasis and the development of obesity. The mother's metabolic health can be improved by lifestyle interventions such as dietary changes and exercise, and therefore represents a tractable target for intervention. Future research using intervention studies conducted in parallel in human and animal models will help elucidate the precise molecular mechanisms mediating the detrimental effects of maternal obesity on offspring metabolic health.

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