Review Article

Gestational Nutrition as a Predisposing Factor to Obesity Onset in Offspring: Role for Involvement of Epigenetic Mechanism

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Summary: Maternal lifestyle has been implicated as a predisposing factor in the development of metabolic disorders in adulthood. This lifestyle includes the immediate environment, physical activity and nutrition. Maternal nutrition has a direct influence on developmental programming through biochemical alterations in maternal metabolism and can lead to modifications in the fetal genome through epigenetic mechanisms. Imbalance in basic micro or macro nutrients due to famine or food deficiency during critical gestational periods can lead to onset of metabolic syndrome including obesity. A major example is the Dutch famine which led to a serious metabolic disorder in adulthood of affected infants. Notably due to gene variants, individualized responses to nutritional deficiencies are unconventional, therefore intensifying the need to study nutritional genomics during fetal programming. Epigenetic mechanisms can cause hereditary changes without changing the DNA sequence. The major mechanisms include small non-coding RNAs, histone modifications and most stable of all is DNA methylation. The significance association between obesity and DNA methylation is through regulation of genes implicated in lipid and glucose metabolism either directly or indirectly by hypomethylation or hypermethylation. Examples include CPT1A, APOA2, ADRB3 and POMC. Any maternal exposure to malnutrition or overnutrition that can affect genes regulating major metabolic pathways in the fetus, will eventually cause underlying changes that can predispose or cause the onset of metabolic disorder in adulthood. In this review, we examined the interaction between nutrition during gestation and epigenetic programming of obesity.

Keywords: *Epigenetic, Fetal programming, Gestation, Nutrition, DNA Methylation*

INTRODUCTION

Diets eaten by women before, after, and most especially during pregnancy have been known over time to influence the body system of their offspring such as metabolism and even reproductive abilities (Taylor *et al*., 2014). Extensive epigenetic programming and reprogramming take place during embryogenesis (Muktabhant *et al*., 2012) with maternal nutrition playing a key role (Malgorzata *et al*., 2010) (Figure1).

Epigenetics is the study that explains the modification of gene expressions without changes in DNA sequence (Marsal 2002). These expressions can be brought about by different modifying reactions within the genome that is largely attributed to the diet of an individual although can be caused by other factors (Gallou-Kabani and Junien 2005; Dolinoy *et al*, 2007; Liyanage *et al*. 2014). Epigenetic changes include short-term histone methylation, acetylation, phosphorylation, ubiquitination and longer-term DNA silencing as a result of DNA methylation (Palou *et al*., 2010; Martinez *et al*., 2014). These epigenetic changes are known to be transferable, and in response to in-utero conditions can induce permanent changes to the metabolic systems and functions (Palou *et al*., 2010; Devlin and Bouxsein 2012),

consequently leading to increased susceptibility to corresponding non-communicable diseases (Warner *et al*., 2010; Innis 2011).

Developmental programming and changes that occur during the process in its entirety is a major and important scientific interest which has been able to give some explanations to the early adult onset of non-communicable diseases (Figure 1). This has especially helped prenatal nutritional prescriptions and regulations for a healthy community. This review aims to summarize contemporary studies of the epigenetic changes brought about by gestational nutrition that can predispose to metabolic abnormalities such as obesity in offspring..

Nutritional Status and Developmental Programming

It was believed that fetal growth and development were driven by inherited traits from its parent's genome (Marsal 2002; Myatt 2006), our current understanding of epigenetics mechanisms has shown the need for better understanding of the science of fetal programming. For example, maternal malnutrition, or increased maternal nutritional demand can lead to fetal undernourishment (Marsal 2002; Myatt 2006).
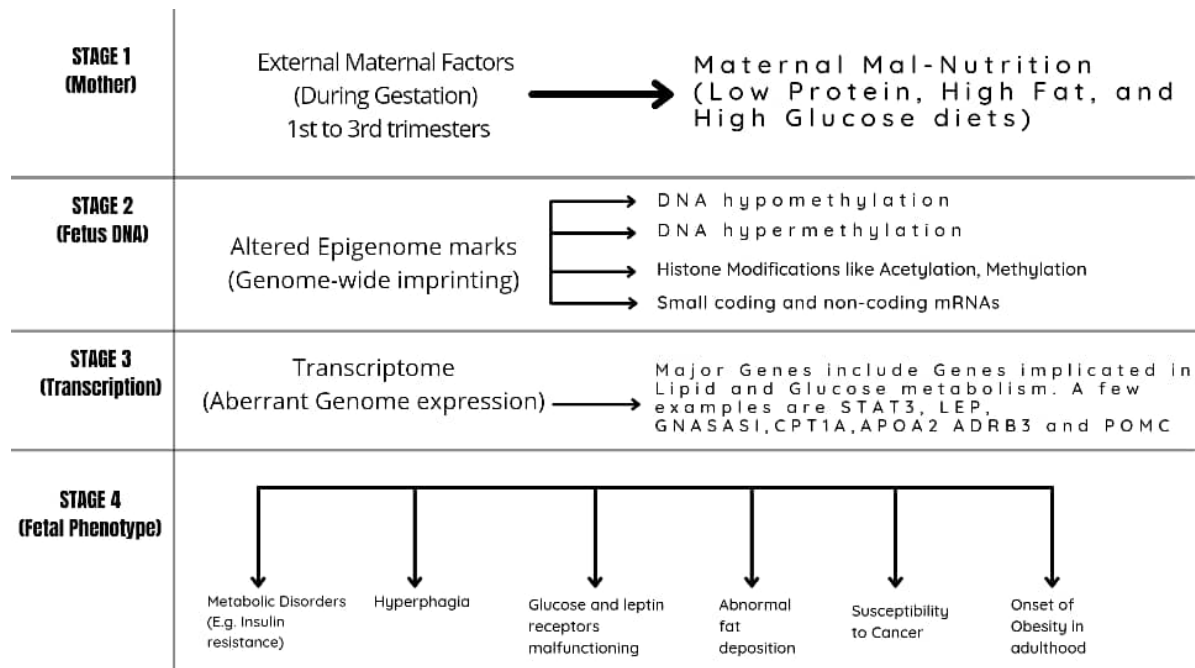
Figure 1:
Schematic presentation of interaction between maternal environment and epigenetic programming of non-communicable diseases

Excessive supply of nutrients to the fetus is also detrimental. Fetal overgrowth (macrosomia) can occur due to excessive placental transport of glucose and other nutrients from the mother (Freinkel 1980). During the critical periods of fetal development especially the first and second trimester of gestation as shown by studies from the Dutch famine (Selassie and Sinha 2011), any stimulus such as undernutrition or overnutrition may cause fetal response and adaptation, leading to long-term or permanent changes in the structure or function of the offspring's body. These changes in later life of the offspring often predispose such offspring to adult onset Non-Communicable Diseases (NCDs) such as obesity (Lukas 1991; Ozanne *et al*., 2004). These changes do not distort the normal DNA sequence but they alter the epigenetic state of the fetal genome (Gallou-Kabani *et al*., 2005).

**Maternal Malnutrition and Adult-Onset of Obesity in offspring**
Maternal malnutrition which includes undernutriiton and overnutrition can epigenetically and evidently make significant changes in the physiology of the offspring's metabolism. Although this is still controversial in the scientific space, research has shown that factors such as low-protein diet or high-fat diet during gestation can cause adult onset obesity in the offspring (Zhao *et al*., 2012). A meta-analysis of fifteen epidemiological and clinical studies involving a total of ~22,000 individuals found that higher, but not lower, birth weight which is usually as a result of the mother's gestational overnutrition is associated with an increased risk of being overweight or obese (Zhao *et al*., 2012). Considering that nutritional deficiency has varying effects on adult body weight, depending on its timing within gestation (Hytten & Chamberlain 1980; Gernand *et al*., 2016). Discrepancies in the epidemiological literature may be associated with differences in onset, duration and type of nutrient-deprivation.

Effect of Low Protein Diet or Protein Deficiency
During pregnancy, it is important to consume the required amount of protein, which is the basic building block of maternal and fetal tissues. The required amount of protein needed during gestation is about 0.8-1.5 g/kg per day. As discussed above, human growth restriction early in gestation increases the probability of developing obesity in later life, particularly if combined with rapid compensatory growth after birth (Tian *et al*., 2006; Dolan *et al*., 2007; Chen *et al*., 2012). Studies in experimental animals such as rodents and sheep reproduce these findings (Jimenez-Chillaron *et al*., 2006; Desai *et al*., 2007). If protein deficiency is prolonged, the fetus changes its metabolic rate and alter the production of hormones and the sensitivity of tissues to them (Figure 2).

Gestational High-Fat Diet
Weight gain and adiposity as a result of fetal exposure to a maternal obesogenic diet can be attributed to hyperphagia and change in food preference (Wardle *et al*., 2001). The child might tend to eat more and enjoy more of such diet because Children from obese/overweight families also have a higher preference for fatty foods (Wardle *et al*., 2001). As stated above, offspring's resistance to hormones such as leptin which is responsible for metabolic regulations might predispose offspring to obesity through hyperphagia. It has been reported that altered maternal nutrition can programmed leptin resistance in the offspring (Vickers and Sloboda, 2012). In contrast to nutrient deficiency, global nutrient excess and obesity is emerging as one of the greatest health problems in the industrialized world (Selassie & Sinha 2011). More than half of all pregnant women in the US are considered obese, with 8% considered extremely obese (Stüber *et al*., 2015).
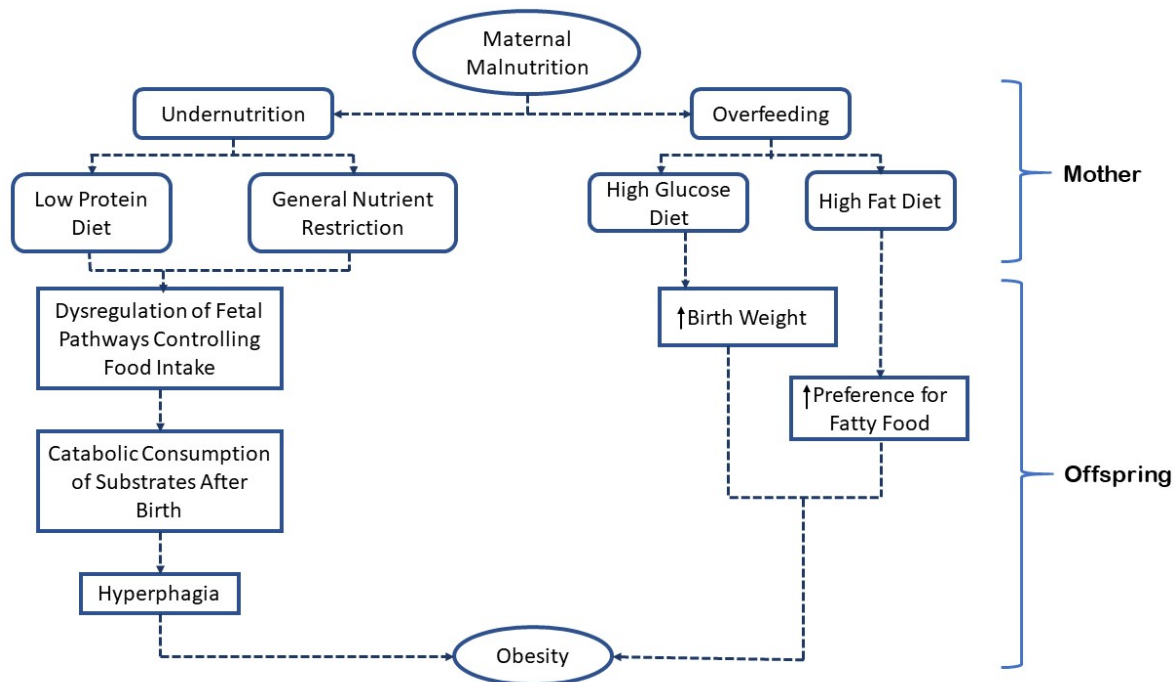
Figure 2:
Schematic presentation of interaction between maternal Nutrition and obesity in the offspring.

INHERITANCE OF METABOLIC COMPLICATIONS LEADING TO OBESITY

Hyperphagia: This is an abnormal desire or appetite for food that often leads to overeating. When the fetus is exposed to nutrient restriction during gestation, this might lead to abnormal hunger sensation and desire for food later after birth (Parlee *et al.*, 2013). This can be caused through the dysregulation of central pathways controlling food intake (Yura *et al.*, 2005; Desai *et al.*, 2007; Ikenasio-Thorpe *et al.*, 2007). The system basically programs the baby for an environment with limited nutrients and requires the need to always store enough when available. This is obviously not done by the formation of bigger gastrointestinal tract or bigger storage organs from birth but an alteration in the workings of cells responsible for the control of metabolic pathways (Desai *et al.*, 2007). For example, there may be resistance to anorexigenic hormones when the child is later born into an environment with enough and regular food source. The child could have lesser feeding habit control because of a possible epigenetic modification during programming. Hyperphagia will usually later lead to obesity (Parlee *et al.*, 2013). A particular research shows that at birth, pups exposed to maternal global nutrient-deficiency have reduced hypothalamic phosphorylation of STAT3 in response to leptin (Desai *et al.*, 2007). Following compensatory growth to three weeks of age, phosphorylation of STAT3 and reduction in food intake in response to leptin are both impaired (Desai *et al.*, 2007). During postnatal development, a surge in circulating leptin is associated with hypothalamic growth. Leptin resistance increases density of the hypothalamic neurotransmitter's neuropeptide Y, and cocaine and amphetamine regulated transcript, and causes hyperphagia (Yura *et al.*, 2005; Ikenasio-Thorpe *et al.*, 2007).

Epigenetic mechanisms: The main epigenetic mechanisms are DNA methylation, histone modifications and small non-coding RNAs. These types of modifications play an important role in gene expression regulation across vast biological processes at the level of chromatin structure and organization (Liyanage *et al.*, 2014). Epigenetic changes can give rise to transgenerational inheritance, which can be carried through both male and female germline.

DNA methylation is the most studied mechanism due to its stable epigenetic system. It occurs by addition of a methyl group at the 5- position of cytosine residues, mainly within CpGs, 60–80% of which are methylated within the promoter regions of genes. In most instances, hypermethylated DNA regions act to reduce gene expression and vice versa (Dolinoy *et al.*, 2007). Most DNA methylation states are stably maintained and inherited during cell division by the maintenance methyltransferases (DNMT1). These marks are critical for maintaining the physiological differentiated states of tissues and organs. Furthermore, DNMT3A, DNMT3B and co-factor DNMT3L are de novo DNA methyltransferases (DNMTs) which methylate DNA during embryogenesis and in differentiated cells. Other mechanisms able to affect DNA methylation exist. In fact, the methyl group on the fifth carbon of the cytosine residue within the CpG can be oxidized by the ten-eleven translocation (TET) dioxygenase family, creating the 'sixth base' defined as 5-hydroxymethylcytosine (5hmC) (Dolinoy *et al.*, 2007; Liyanage *et al.*, 2014) which are essential in regulatory functions (Auclair & Weber 2012).

Histone modifications is a dynamic and unstable process, it can be easily induced and removed by many enzymes (Kouzarides, 2007). These changes can determine the DNA exposure to transcription factors due to winding and unwinding ability of the histones. This plays a major role in the gene expression regulation (Lawrence *et al.*, 2016).

Lastly, microRNAs (miRNAs) are endogenous small non-coding RNAs, playing an important role that affects gene expression in many biological processes like development, differentiation and cell cycle (Esguerra *et al*., 2014) and immune system homeostasis (Wilczynska & Bushell 2015). This mechanism has been implicated in insulin secretion regulation, beta-cell differentiation (Kaspi *et al*., 2014) and a new biomarker of several diseases (Ibarra *et al*., 2018; Guarino *et al*., 2018).

Some of these epigenetic modulations occur in vital non-imprinted genes that are involved in energy metabolism (Weinstein *et al*., 2010). Genes that regulate adipogenesis, glucose homeostasis, inflammation, and/or insulin signaling are regulated by epigenetic mechanisms (Yang *et al*., 2011), including genes encoding hormones (e.g., leptin) (Milagro *et al*., 2009), nuclear receptors (adipogenic and lipogenic transcription factors PPARγ and PPARα, respectively (Fujiki *et al*., 2009) gluconeogenic enzymes (e.g., phosphoenolpyruvate carboxykinase, PEPCK) and transmembrane proteins (e.g., uncoupling protein 1) (Stepanow *et al*., 2011).

Maternal Nutrition and Offspring's Epigenomics
There are critical periods during development such as periods of pre-conception, oocyte insemination, gestation and first few infant years, during which tissues are overly sensitive to environmental exposures and lifestyle. Exposure to such environmental alterations impart on the tissues susceptibility to disease in the future (Blackmore & Ozanne 2013; Heindel *et al*., 2015). Several studies have shown how epigenetic changes induce lifetime effects on offspring exposed to different aberrant maternal nutrition and lifestyle (Gagné-Ouellet *et al*., 2017). This has made analysis of epigenetic modifications occurring during pregnancy an important topic in the study of environmental influence on fetal metabolic programming (Nolan *et al*., 2011).

Epigenetics and Programmed Obesity
The effects of perinatal malnutrition on babies were studied through the Dutch famine in 1994/95. Mothers exposed to the famine during the first two trimesters of pregnancy had offspring with lower birth weights. These low-birth weight infants rapidly grew in the first several years of life and had higher risk of adult obesity and metabolic syndrome (Monteiro & Victora 2005). The fact that maternal overnutrition induced fetal programming is beginning to gain momentum, specifically the association of maternal pre-pregnancy obesity and increased weight gain with higher birth weight in newborns (Oken *et al*., 2008). This has been reported to leads to an increased risk of diabetes and obesity in the later life (Armitage *et al*., 2008). Low birth weight in animal models can be induced using varieties of methods such as maternal nutrient restriction, placental uterine ligation or glucocorticoid exposure, leading to an increased risk of offspring adiposity (McMillen & Robinson 2005). Also, recent animal models of maternal over nutrition, including maternal obesity and high fat diets, similarly replicate human experience in the offspring and predispose to adult obesity (Howie *et al*., 2009). Programmed changes occur during developmental period of growing fetuses and neonates, making them vulnerable to perturbations of the maternal nutritional and non-nutritional milieu. These programmed changes affect organ structure, cellular responses and gene expression that impact metabolism and physiology of the offspring (Desai *et al*., 2015).

As the association was specific for periconceptional exposure it was concluded that the periconceptual period is crucial for establishing and maintaining epigenetic marks (Heijmans *et al*., 2008). Several genes including *INSIGF2, GNASAS1, MEG3, IL-10*, and *LEP*, some of which have a known role in metabolic disorders, were identified to exhibit an altered DNA methylation in blood cells of the offspring of mothers exposed to famine (Tobi *et al*., 2009). However, nowadays most populations are confronted with an obesogenic environment and prenatal and neonatal overfeeding programs disposition to obesity.

DNA Methylation Markers in Obesity
Numerous cross-sectional studies have reported a significant association between adiposity status and DNA methylation. For example, the offspring of obese mothers presented several CpG sites differentially methylated in cord blood in comparison with offspring from normal weight mothers (Sharp *et al*., 2015). Other regions studied, were mainly hypomethylated in obese children located in the gene body region, and revealed a unique cluster of obese individuals that was differentiated from the normal weight children (Rhee *et al*., 2017). In addition, some of these genes are implicated in lipid metabolism, glucose metabolism, differential body size and body composition in children (Rzehak *et al*., 2017).

Another analysis in adult population found methylation changes in carnitine palmitoyl-transferase 1A (CPT1A) gene, associated with obesity and T2D (Aslibekyan *et al*., 2015). CPT1A is also implicated in the control of fasting triglycerides (TG) and very low-density lipoprotein (VLDL) levels (Irvin *et al*., 2014). These studies suggest an important role for this gene in obesity and metabolic complications. A study in three populations of diverse ancestries found that the methylation levels of the apolipoprotein A2 (APOA2) regulatory region was associated with the consumption of saturated fatty acids (Pauwels *et al*., 2017), a nutritional factor that has been associated with an increase in the risk of obesity in previous studies. Not only is the methylation profile of blood cells associated with obesity, but also the methylation of other tissues and body fluids.

An Epigenome Wide Association Study (EWAS) identified predominantly DNA hypermethylation in White Adipose Tissue (WAT) from obese subjects, which was related to gene expression of proinflammatory pathways. These findings suggest that DNA methylation may link dysfunctional adipocytes to WAT inflammation and Insulin Resistance (IR) in obesity (Petrus *et al*., 2017). Hypermethylation of the beta-3 adrenoceptor (ADRB3) gene was also reported in WAT of obese subjects, which was linked with an increased susceptibility to visceral obesity and altered body fat distribution (Guay *et al*., 2014). Similar results were previously described in blood cells (Guay *et al*., 2014), revealing that the methylation changes of ADRB3 gene in blood may reflect obesity-related DNA methylation changes of this gene in WAT.

In addition, a case-control study demonstrated an association between hypomethylation of leptin (LEP) gene

in obese individuals, measured in saliva, and obesity-related parameters (Dunstan *et al*., 2017). Likewise, an EWAS performed in 92 children's saliva samples described 17 CpGs associated with maternal BMI (Oelsner *et al*., 2017). The saliva sample analysis in 50 girls with and without obesity found two interesting genes, neuron navigator 3 (NAV3) and melanocortin 2 receptor (MC2R), whose methylation levels were associated with BMI (Rounge *et al*., 2016). These studies evidenced that saliva may be a viable probe for epigenetic testing in obesity. However, further studies would have to include both, saliva and blood samples, to demonstrate that saliva is consistent with whole blood findings. Prospective studies during the early life stage described DNA methylation of several weight linked loci in newborns that continued to show a longitudinal association with adiposity, fat mass, body size and other obesity parameters in childhood (Van Dijk *et al*., 2018; Lin *et al*., 2017; Perng *et al*., 2013). Interestingly, several prospective studies including adult life stage evidenced that these DNA methylation pattern changes were associated with the later risk of developing metabolic and other diseases (Dayeh *et al*., 2016; Dayeh *et al*., 2018). These examples described an association between early cues (environmental stimulation in utero, and in early infancy) and the later development of disease. Actually, this is the basis of the 'epigenotype model' of Developmental Origin of Health and Diseases (DOHaD) , in which the environment can modulate the epigenetic signature during human life (Samblas *et al*., 2019).

Pomc Gene

Epigenetic alterations in the *Pomc* gene, known for its important role in the regulation of food intake, were first observed in rats and later confirmed in human. Neonatal overfeeding of rats led to rapid early weight gain and the metabolic syndrome, which was associated with a hypermethylation of the *Pomc* promoter and the inability of a *Pomc* upregulation in response to elevated leptin and insulin concentrations (Plagemann *et al*., 2009). Accordingly, in postmortem human melanocyte-stimulating hormone (MSH)-positive neurons' alterations in DNA methylation of the *POMC* gene were strongly associated with individual body mass index (BMI). Epigenetic alterations of *POMC* appeared to be established in the early embryo and offspring methylation correlated with the paternal somatic methylation pattern (Kuhnen *et al*., 2016).

CONCLUSION

In conclusion, understanding the concept of developmental programming and the epigenetic basis of metabolic syndrome (such as obesity) could provide an exciting window of opportunity to prevent its development at origin or treat postnatally to reduce and control the progression of the disease. According to reports from the various studies, maternal nutrition during gestation could epigenetically modify the DNA and as a result alter nutrient metabolism in the offspring.

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