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REVIEW ARTICLE

Maternal Obesity, Maternal Overnutrition and Fetal Programming: Effects of Epigenetic Mechanisms on the Development of Metabolic Disorders

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Abstract: ***Background*:** Maternal obesity and maternal overnutrition, can lead to epigenetic alterations during pregnancy and these alterations can influence fetal and neonatal phenotype which increase the risk of metabolic disorders in later stages of life.

***Objective*:** The effects of maternal obesity on fetal programming and potential mechanisms of maternal epigenetic regulation of gene expression which have persistent effects on fetal health and development were investigated.

***Methods*:** Review of the literature was carried out in order to discuss the effects of maternal obesity and epigenetic mechanisms in fetal programming of metabolic disorders. All abstracts and full-text articles were examined and the most relevant articles were included in this review.

***Results*:** Maternal obesity and maternal overnutrition during fetal period has important overall effects on long-term health. Maternal metabolic alterations during early stages of fetal development can lead to permanent changes in organ structures, cell numbers and metabolism. Epigenetic modifications (DNA methylation, histone modifications, microRNAs) play an important role in disease susceptibility in the later stages of human life. Maternal nutrition alter expression of hypothalamic genes which can increase fetal and neonatal energy intake. Epigenetic modifications may affect the increasing rate of obesity and other metabolic disorders worldwide since the impact of these changes can be passed through generations.

***Conclusion*:** Weight management before and during pregnancy, together with healthy nutritional intakes may improve the maternal metabolic environment, which can reduce the risks of fetal programming of metabolic diseases. Further evidence from long-term follow-up studies are needed in order to determine the role of maternal obesity on epigenetic mechanisms.

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1. INTRODUCTION

Due to the health-related risk factors, obesity has become a major health challenge globally [1]. The prevalence of overweight and obesity among women of childbearing age has been increasing over the past years. Maternal obesity is associated with increased risks of pregnancy outcomes and childhood obesity. In addition, excessive gestational weight gain has a negative influence on outcomes of maternal, fetal and childhood periods [2, 3].

Complex interactions, including a wide range of environmental and genetic factors can lead to obesity. Alterations in metabolic environment during critical periods of organ development can lead to the development of metabolic disorders [4]. During critical periods of fetal development, permanent changes occur in molecular, cellular, metabolic, neuroendocrine and physiological systems as a result of an unfavorable nutritional and/or hormonal environment. For that reason, adverse alterations in the maternal nutritional environment during the fetal period, have important effects on long term health [4, 5].

During fetal development, gene expression can be influenced by epigenetic mechanisms. Differences in fetal gene expression in utero can cause epigenetic modifications [6] that can cause permanent changes in organ structures, number of cells and metabolism. Additionally, epigenetic modifications can contribute to a number of processes; like apoptosis, that affect fetal growth and development. Epigenetic modifications in regulatory genes and growth-related genes play a significant role in developmental programming [7, 8].

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Epigenetic modifications of genes that are involved in deoxyribonucleic acid (DNA) methylation, histone modifications and microRNAs (miRNAs) can contribute to the metabolic diseases later in life. Furthermore, methylation of important genes involved in the hypothalamic-pituitary-adrenal axis and energy metabolism can be affected by fetal epigenetic modification [9, 10].

Molecular mechanisms have highlighted the sensitivity of the offspring epigenome to maternal obesity [4]. Maternal nutrition and maternal environment alter the expression of imprinted genes during pregnancy, and these changes can influence fetal and neonatal phenotype and susceptibility to adult-onset metabolic diseases [9, 10].

This manuscript will review the effects of maternal obesity and maternal excess weight gain on fetal programming and potential mechanisms of maternal epigenetic regulation of gene expression, which has persistent and harmful effects on fetal and neonatal development.

1.1. Search Strategy and Selection of Studies

To identify eligible studies for this review, a computerized search was performed for all publications available up to March 2019 through PubMed, Web of Science and Google Scholar databases using the following keywords: 'maternal obesity', 'maternal nutrition', 'maternal high fat diet', 'epigenetic programming', 'epigenetics', 'epigenetic mechanisms', 'DNA methylation', 'histone modifications', 'microRNAs', 'fetal programming', 'fetal metabolic programming', 'fetal metabolic disorders' 'early life nutrition' and 'develop mental programming'. Reference lists from identified articles and relevant reviews were examined for studies not indexed in the mentioned electronic databases. All abstracts and full-text articles were examined, and the most relevant articles were selected for screening and inclusion in this review. The search was limited to English literature.

1.2. Developmental Programming of Fetal Metabolic Disorders

Clinical and epidemiological studies showed that genetic and environmental factors can increase the tendency of obesity and obesity-related comorbidities [11-13]. The term 'developmental programming' defines a set of mechanisms that lead to permanent changes in the molecular, cellular, metabolic, neuroendocrine and physiological systems caused by an unfavorable nutritional and/or hormonal environment [4, 5, 14, 15]. Perinatal environments that include; maternal nutrient availability (under/over nutrition), hormonal changes (caused by maternal obesity, excessive gestational weight gain, gestational diabetes), maternal stress and placental dysfunction [15-18], have long-lasting harmful effects on different tissues, organs and overall functions of the human body (like pancreas, adipose tissue, brain, liver and skeletal muscles) [17]. Epigenetic modifications within liver, muscle and adipose tissue in a developing fetus may increase the risk of obesity and associated metabolic disorders [8, 9].

The fetal origins of adult disease (FOAD) or developmental origins of health and disease (DoHAD) have gained more attention after epidemiological outcomes from the 1944-1945 Dutch famine cohort study [19]. Important large cohort studies demonstrated that individuals with low birth weight were at an increased risk of coronary heart disease, glucose intolerance and type 2 diabetes [20-23].

Thrifty phenotype hypothesis suggests that insufficient fetal nutrition leads to permanent metabolic adaptations during the development of vital organs during the fetal period, in order to maximize the chances of survival. Reductions in cell numbers and functional capacities occur in critical organs, such as reduced numbers of nephrons, heart muscle cells and pancreatic cells caused by insufficient maternal nutrition. These short-term adaptations ensure survival in a nutrient-deficient environment during postnatal life. However, when abundant nutrients are involved after birth, long-term detrimental effects occur due to incompatibility between prenatal and postnatal environments [24-26]. Although early studies focused on the effect of maternal undernutrition and low birth weight, it is thought that maternal obesity becomes a high-risk factor for the offspring [27]. Therefore, both low and high birth weights may generate physiological and/or metabolic adaptations in vital organs [28, 29].

Furthermore, epigenetic programming alters gene expression through epigenetic modifications. Epigenetic modifications play a significant role in the developmental programming of obesity and disorders associated with it. Epigenetic modifications during the critical periods of fetal development can be the reason for long term consequences on the offspring as well as on the future generations. It is important to define the link between the epigenetic modifications with clinical and molecular outcomes in the offspring that are related to maternal obesity [11-13]. Epigenetic programming of gene expressions like DNA methylation, histone modifications and microRNAs can contribute to the development of metabolic diseases later in life [9, 10].

1.3. Fetal Metabolic Disorders Associated with Maternal Obesity and Maternal Overnutrition

The prevalence of pre-pregnancy maternal obesity has been increasing worldwide [3]. Maternal obesity has short term and long term adverse outcomes [3, 30-32].

According to the systematic review and meta-analysis of 45 studies, it was found that the pre-pregnancy overweight/obesity increases the risk of higher birth weight, macrosomia and offspring overweight/obesity [33]. A meta-analysis of 12 cohort studies stated that the risk of childhood overweight/obesity is significantly associated with excessive gestational weight gain [34]. A meta-analysis of data from 162,129 mothers and their children from 37 pregnancy and birth cohort studies showed that higher maternal pre-pregnancy body mass index (BMI) and gestational weight gain were associated with the increased risk of childhood overweight/obesity, in addition to the potential effects on later stages of life [35].

Maternal obesity affects fetal metabolism and can cause changes in the amount of nutrients and metabolites, which pass through the placenta [36]. In the case of maternal obesity, metabolic status during pregnancy is characterised by dyslipidaemia, hyperleptinaemia, hyperinsulinaemia and an increasing amount of systemic inflammation [37]. Expo-

sure to an oversupply of energy, fat and sugar during critical windows of fetal development causes maternal obesity and maternal excessive weight gain [38-40]. Thus, alterations in maternal metabolism would expose the fetus to a greater risk of developing metabolic disorders later in life [41].

The placenta regulates fetal growth and maternal physiology. It is the primary respiratory, excretory, metabolic and endocrine organ during pregnancy, which play an essential role to provide an optimal intrauterine environment, and it regulates pregnancy-associated hormones and growth factors. Additionally, overnutrition and undernutrition can lead to changes in placental gene expression that may predict altered transport of important signals to the fetus [42-44].

It was stated that increased nutrient supply to the fetus might cause greater energy intake in the postnatal period because of metabolic programming [38-40]. Especially the consumption of high-fat and high-sugar diets during pregnancy, leads to the rapid weight gain of the fetus [36]. High maternal nutrient intake in pregnancy may result in fetal permanent changes within the central appetite regulatory pathways. Alterations in leptin and insulin induced signals affect the development of eating behaviors by affecting the neural development hypothalamus. According to these neuroendocrine factors, increased fetal appetite, energy intake and adiposity alter the food preferences and body composition after birth [38-40].

Maternal nutrition may permanently affect fetal gene expression by epigenetic mechanisms that lead to metabolic abnormalities. Epigenetic modifications during the critical periods of fetal development can have long-term consequences because of transgenerational inheritance. It is important to define the link between the epigenetic modifications with clinical and molecular outcomes in the offspring that are correlated with maternal obesity [11-13].

1.3.1. Maternal Obesity, High Fat Diet and Inflammation

Maternal obesity is associated with adipose tissue inflammation, systemic insulin resistance and hyperlipidemia. Otherwise, HFD during pregnancy can cause activation of proinflammatory cytokines. Maternal insulin resistance and inflammation lead to increased adipose tissue lipolysis and increased free fatty acid (FFA) uptake [45]. Maternal HFD during pregnancy (35% calories from fat) leads to a significant increase in FFA levels in the fetus. However, both maternal insulin resistance and HFD have adverse effects on adiposity in early life [46].

Maternal BMI is positively correlated with systemic inflammation, including high levels of monocyte chemoattractant protein-1 (MCP-1) and TNF-α. Also, an increase of pro-inflammatory cytokines has been demonstrated in the placenta as a result of HFD. Moreover, in obese models, activation of Toll-like receptor-4 (TRL-4) through FFAs could activate NF-κB and JNK inflammatory signalling pathways [47]. Maternal HFDs cause insulin resistance through inflammatory changes in fetal adipose tissue [48]. As a result of these metabolic alterations, excess fetal lipid exposure may affect fetal growth and development. Increase in inflammation and blood lipids can have detrimental effects on the development of liver, adipose tissue, brain, skeletal muscle and pancreas, which increase the risk for metabolic disorders [45]. All of these maternal metabolic changes may contribute to the childhood obesity epidemic through fetal metabolic programming [36].

1.4. Epigenetic Mechanisms: Fetal Metabolic Disorders Associated with Maternal Obesity

Epigenetic alterations have the ability to modulate gene expression [10, 49]. Changes in gene expression initiate during the early prenatal period, and these changes affect fetal growth and development. Epigenetic changes in regulatory genes and growth-related genes are vital components fetal programming [9, 50].

Maternal nutrition along with environmental exposures, may permanently affect fetal and neonatal gene expression through epigenetic mechanisms which lead to metabolic abnormalities [9, 50]. Dietary factors can affect genome function and gene expression during early life by folate-mediated one-carbon metabolism or transmethylation pathways [51].

Maternal nutrition and its effect on fetal and neonatal growth through the epigenome have increasing evidence in literature [10, 50, 52]. Mechanisms underlying the effects of nutritional and environmental factors, together with maternal obesity, on the epigenetic regulation of genes, are still investigated [6].

Alterations in the expression of imprinted genes during pregnancy can influence fetal and neonatal phenotype [53, 54]. Epigenetic modifications of genes in fetal period that are involved in DNA methylation, histone modifications, microRNAs variations can contribute to the metabolic disorders later in life [10, 45, 52]. Epigenetic modifications, like DNA methylation and histone modification, play key roles in biological activities. Gene expression, chromatin accessibility, and DNA replication are important processes in forming and transferring phenotypes to the next generations [55].

Furthermore, genes involved in energy metabolism, glucose homeostasis, insulin signaling, adipogenesis, encoding hormones (leptin) and nuclear receptors (adipogenic and lipogenic transcription factors peroxisome proliferator-activated receptor gamma (PPARγ) and proliferator-activated receptor alpha (PPARα) can be affected by fetal epigenetic modifications [11].

Fetal overnutrition resulted in an increment in the expression of the adipogenic factor, PPARγ, and in lipoprotein lipase, adiponectin, and mRNA expression of leptin in an experimental study. Exposure to metabolic and hormonal signals as a result of maternal overnutrition can cause increment in adipogenic, lipogenic and adipokine gene expression in adipose tissue and these changes may lead to obesity in later life [56].

Nutritional, environmental and epigenetic factors interacting with each other and may cause to form obese phenotypes because of epigenetic modifications in utero. These epigenetic alterations pass through subsequent generations, which resulted in long-term consequences [50] (Fig. **1**).

1.4.1. DNA Methylation

DNA methylation is a well known epigenetic mechanism. DNA methylation plays a critical role in long-lasting

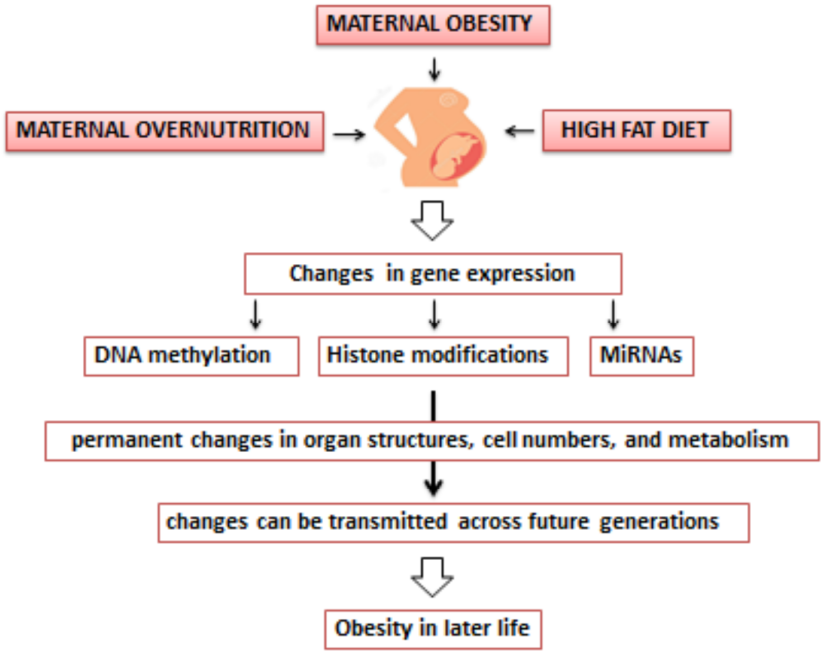

Fig. (1). Basic schematic outlining the consequences of a maternal obesogenic environment on the health and well-being of offspring. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

detrimental effects on the pathogenesis of cancer, metabolic syndrome, cardiovascular and autoimmune diseases [51].

DNA methylation patterns are established during embryogenesis, fetal development and early postnatal life. DNA methylation increases in response to maternal environmental factors during the organogenesis and tissue differentiation [53, 59]. Maternal nutritional factors affect DNA methylation. The impact of nutrition on genomic DNA methylation through one-carbon metabolism is well-documented. Maternal nutrition can influence fetal DNA methylation because of one-carbon reactions. One-carbon metabolism provides the methyl groups for all methylation reactions and is dependent on dietary methyl donors and cofactors [7, 57]. It has been demonstrated that dietary deficiency or excess number of the methyl group donors needed for the cellular methylation reactions can alter epigenetic patterns [51].

Dietary methionine and choline are major sources of dietary methyl donors, while folic acid and vitamin B12 are important cofactors in one-carbon metabolisms, thus, the availability of methyl group donors in the maternal diet is very important [7, 57].

Maternal obesity is associated with altered expression of some epigenetic regulators in the fetal liver and upregulation in the transcript levels of some methyltransferase enzymes [58]. It was suggested that methylation of important genes involved in the energy metabolism is responsible for epigenetic modifications changes in DNA methylation, depending on maternal nutrition, maternal body composition and other endocrine factors [52, 59, 60]. It was found that DNA methylation of human fetal tissue at birth is associated with perinatal DNA methylation and adiposity at 9 years of age [61].

Maternal HFD contributes to the rapid early weight gain, increased adiposity and hyperleptinemia in offspring at the weaning period. It was determined that during prenatal and postnatal periods, HFDs were determined to cause hyperphagia, an increase in fat mass, and insulin resistance in offspring. According to an experimental study, it was found that maternal HFD programs long-term epigenetic alterations in the offspring's hypothalamic proopiomelanocortin (POMC) gene, which plays a key role in the control of energy balance, by causing changes in DNA methylation [62]. It was found that maternal HFD is associated with changes in hypothalamic regulation of body weight and energy homeostasis by altering the expression of leptin receptor, POMC and neuropeptide Y in offspring [63, 64].

Neuropeptides play a key role in the regulation of eating behavior, food intake and body weight. POMC is an anorexigenic and neuropeptide Y (NPY) is an orexigenic neuropeptide. Furthermore, leptin and insulin hormones stimulate the expression of the POMC while inhibiting the NPY. Early excessive energy intake, together with maternal obesity, lead to altered DNA methylation within promoter regions of hypothalamic genes. As a result of epigenetic changes in these hypothalamic circuits, involved genes such as insulin, leptin and neuropeptides, permanently increased total energy intake [64].

Similarly, methylation changes can occur in other specific regulatory genes such as peroxisome proliferator-activated receptor *(PPAR)* that is the main regulator of adipogenesis [65]. HFD has been associated with epigenetic changes in animal models [49]. Maternal HFDs alter methylation and gene expression of dopamine and opioid-related genes (including the dopamine reuptake transporter, the opioid receptor (MOR) and preproenkephalin) which cause changes in feeding behavior [51, 52].

The mechanisms affected by nutritional challenges may alter permanent dysregulation of these hypothalamic circuits,

including functional resistance to insulin and leptin, which may be the underlying cause of permanently increased food intake and overweight status [64].

In animal models, maternal HFD can lead to increased body fat, elevated leptin levels and impaired glucose tolerance in offspring [11, 66]. It was found that maternal obesity causes increased leptin gene expression in animal models through epigenetic modifications [67, 68]. In relation to this, it was determined that maternal obesity and HFD during pregnancy are associated with rapid weight gain and fetal fat mass increment in the early stages [46].

Methylation and gene expression of genes that are involved in cellular differentiation, such as paxillin, integrin and ILK pathways were altered as a result of HFD [69]. Mmp9 is a gene that shows upregulation in obesity and it is found in the ILK pathway exposure to a maternal HFD resulted in hepatic hypermethylation, a significant increase in gene expression of Mmp9 gene and trigger development of metabolic syndrome in animal models [69, 70].

1.4.2. Histone Modifications

It was suggested that histone modifications and DNA methylation patterns work together [71]. Both of these epigenetic modifications can induce genes by modifying chromatin structures through DNA methylation and modifications of histone tails [72, 73]. Posttranslational histone modifications (including acetylation, methylation, phosphorylation, ubiquitylation and sumoylation) cause a stable change in chromatin structure (chromatin remodeling). Histone modifications have an influence on chromatin remodeling enzymes [74].

Histone modifying enzymes either add or remove epigenetic marks on histone tails. These enzymes are histone methyltransferases (HMTs) or demethylases (HDMs) and histone acetyl transferases (HATs) or deacetylases (HDACs) [75]. Transcription factors bind to the genes, promoting the increase of their expression, which is mediated by the histone acetyltransferase (HAT) enzyme. Additionally, histone deacetylase (HDAC) enzyme mediates the deacetylation process [72]. The altered expression and/or activity of several histone-modifying enzymes have been linked to disease development [76].

Nutritional factors can modulate the histone acetylation process in animal models. These changes can impact the eating behavior and maintenance of body weight [77]. In animal models, maternal consumption of HFD can induce changes on histone H4 acetylation status in hippocampus of the offspring, which may modulate the expression of specific genes [78]. It was stated that maternal HFD affects neonatal hepatic metabolism with epigenetic modification of histones, which leads to metabolic complications on the developing offspring [79]. Maternal overnutrition alters fetal chromatin structure by covalent modifications of histones, thus leading to epigenetic programming of obesity [80]. Furthermore, maternal obesity is another factor that effects the acetylation process and can negatively affect fetal development [58].

As a result of HFD during gestation (35% calories from fat); hyperacetylation of histone H3K14, H3K9 and H3K18, increase in DNMT1 expression, decrease in HDAC1 expression, and increase in hepatic triglycerides, were observed in fetal offspring liver [80]. Recent data have shown that maternal HFD leads to metabolic programming through increased acetylation of histone H3K14 and decrease in SIRT1 expression in fetal liver and heart [81, 82]. Further examples include global hyper-acetylation of histone H3 in the offspring and alteration of methylation and expression of genes related to the mesocorticolimbic reward circuitry (dopamine and opioids) by maternal HFD [83, 84].

1.4.3. MicroRNA's

In addition to DNA methylation and histone modifications, microRNAs are the potential third epigenetic mechanism that can be affected by maternal obesity and nutrition. MiRNAs are small non-coding RNA molecules which function in post-transcriptional regulation of gene expression [85]. MiRNAs are involved in the regulation of biological processes, including differentiation, cell proliferation and energy metabolism [86]. They appear to regulate events throughout the life cycle, including embryonic and post-embryonic stages [87].

Dietary factors have been shown to modify miRNA expression profiling, notably in maternal nutrition-induced epigenetic modifications in offspring with lipid metabolism, insulin resistance and inflammation [88]. Maternal high fat feeding during gestation and lactation in animal models resulted in impaired metabolic health in offspring. The maternal high-fat feeding modulated hepatic miRNA expression (miR-615-5p, miR-3079-5p, miR-124b, and miR-101b were down-regulated, whereas miR-143 was up-regulated in offspring livers) and increased body weight and impaired glucose metabolism at weaning. It was found that maternal consumption of an HFD affects the early lipid metabolism [89, 90] of offspring by modulating the expression of hepatic β-oxidation-related genes and expression of miRNAs [89]. It was determined in a pregnancy-cohort study that the expression of miRNAs (number of 27 different miRNAs expression level) was positively associated with the pre-pregnancy body mass index. It was also emphasized that most of these differentially expressed miRNAs were related to adipogenesis [91].

According to the pre-pregnancy BMI, newborns of women within normal weight range and obese women were compared. There were significant differences in the expression of three different miRNAs (expression of miR-155, miR-181a and miR-221) between newborns of obese women and women within the normal weight range. Depending on these changes, it was thought that alterations in miRNA expression could participate in the epigenetic programming of metabolic disorders in children born to obese women [92].

CONCLUSION

Prevalance of obesity in women at childbearing age is increasing in the world. Newborns of these obese mothers are predisposed to being overweight or obese in their adult lives. Therefore, mechanisms associated with fetal programming on the susceptibility of adult-onset metabolic diseases are still being investigated. Permanent changes occur in metabolic and epigenetic mechanisms due to the unfavorable maternal nutritional and/or hormonal

environment. There is an increasing body of evidence, suggesting that maternal obesity and maternal HFD can have detrimental effects on fetal health.

During fetal development, alterations in fetal gene expression can cause epigenetic modifications. Maternal nutrition alters the expression of hypothalamic genes during pregnancy and these changes can influence fetal and neonatal food and energy intake. Epigenetic modifications of genes in utero that are involved in DNA methylation, histone modifications and miRNAs could be one of the factors that affect the increasing rates of obesity and other metabolic disorders worldwide, as the impact of these changes can be transmitted across future generations. Therefore, weight reduction before pregnancy and starting pregnancy within the normal weight range should be the principal goal in reducing the risks of obesity and metabolic disorders. Dietary interventions are the most effective type of intervention during pregnancy to improve the maternal metabolic environment.

Limitations: This is a narrative review on the role of maternal obesity on epigenetic mechanisms. Maternal obesity, maternal overnutrition and excessive fat intake affect epigenetic modifications. We have concluded that weight management before and during pregnancy, together with healthy nutritional intakes, may improve the maternal metabolic environment. In this review, the relationship between epigenetic mechanisms and nutrition was investigated and other associated factors were not included.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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