Impact of nutritional interventions on epigenetic influences in the gestational and puerperium period: a systematic review

ABSTRACT

Background: Epigenetic analyzes associated with maternal and child nutrition are the subject of several studies due to their crucial role in fetal development. Significant changes in diet during the gestational period or even in the puerperium can lead to metabolic diseases or even neuropsychiatric disorders.
Aims: The present study sought to carry out a systematic review of such interactions in the pre- and post-pregnancy periods.
Study design: Systematic review
Methodology: Bibliographic research was used as a method and data were obtained from the VHL information portal from 2017 to 2021. Original articles published in the last 6 years, related to nutritional impacts on epigenetic mechanisms, whether in women during the gestational and postpartum period or newborns, were included in this study. in the gestational period and puerperium or newborns.
Results: Nine studies that met the selection criteria and were associated with the topic were selected.
Conclusion: Based on this study, it was possible to understand the relationship between diet and the expression of epigenetic changes in order to promote studies in this area that facilitate the understanding of various diseases of genomic origin.

Keywords: Epigenetics. Genomics. Pregnancy DNA methylation.

1. INTRODUCTION

Epigenetics is characterized by alterations in the genome that are inherited and that do not alter the DNA sequence, which may cause phenotypic modifications due to the change in gene expression. These epigenetic transformations are influenced by environmental modifications that will be transmitted to the offspring [1]. Among these modifications, the nutritional aspect stands out for being the target of several investigations, mainly with regard to epigenetic alterations associated with maternal and child nutrition, having given that it plays a crucial role in fetal development, and may still have repercussions in adulthood [2].

Studies point out that quantitative or qualitative changes in the nutrients provided to the mother during the gestational period can be harmful in the evolution of the fetal organs [3]. In addition, it is also known that in abnormal intrauterine conditions, influences on the development of the fetus may predispose to some chronic diseases, such as obesity and diabetes mellitus [4]. iron deficiency anemia, result in cognitive deficits and increase the risks of neuropsychiatric disorders in the offspring, such as schizophrenia [5]. Another important example is exposure to starvation, which can cause an abnormal development of organs in the newborn [6].

These modifications are due to the ability of the organic and inorganic components present in food to interact with the gene and condition its phenotype [7]. This gene-nutrient relationship occurs due to chromatin remodeling, which, induced by nutrients, through the enzyme DNA methyltransferase, reorganizes the methyl group within the DNA molecule [8]. Nutritional alterations influence this DNA methylation mechanism, since they compromise the absorption of nutrients that induce this process.

Therefore, the present study aims to promote a systematic review on the impact of nutritional interventions on epigenetic influences in the gestational and postpartum period.

2. METODHOLOGY

2.1 Search strategies

For the preparation of this study, the PRISMA protocol was used to produce systematic reviews. This study constituted a systematic review of the literature on the nutritional impacts on epigenetic mechanisms in the gestational and postpartum period. For the elaboration of the present study, a search was carried out in the Pubmed database, using the descriptors: “Epigenetic” and “maternal nutrition” in combination with the boolean operator: AND. For the analysis of the heterogeneity of the studies, the Chi-square test was applied, and the results obtained demonstrated that a meta-analysis would be unnecessary.

2.2 Inclusion criteria

The present study included original articles published in the last 6 years, related to the nutritional impacts on epigenetic mechanisms, whether in women during the gestational and postpartum period or newborns, and which contained information such as: author, year, type of study and conclusions. Some articles published before the mentioned period were also used, to be used as a theoretical reference, but which did not enter the proposed selection strategy.

2.3 Exclusion criteria

The following were not included in this study: literature review articles, studies that aimed to analyze epigenetic interactions in groups other than pregnant women, puerperal women or newborns.

2.4 Selection of studies

Figure 1 shows the results of the successive screening steps and their respective numbers. Of the total, nine articles met the criteria established for eligibility.

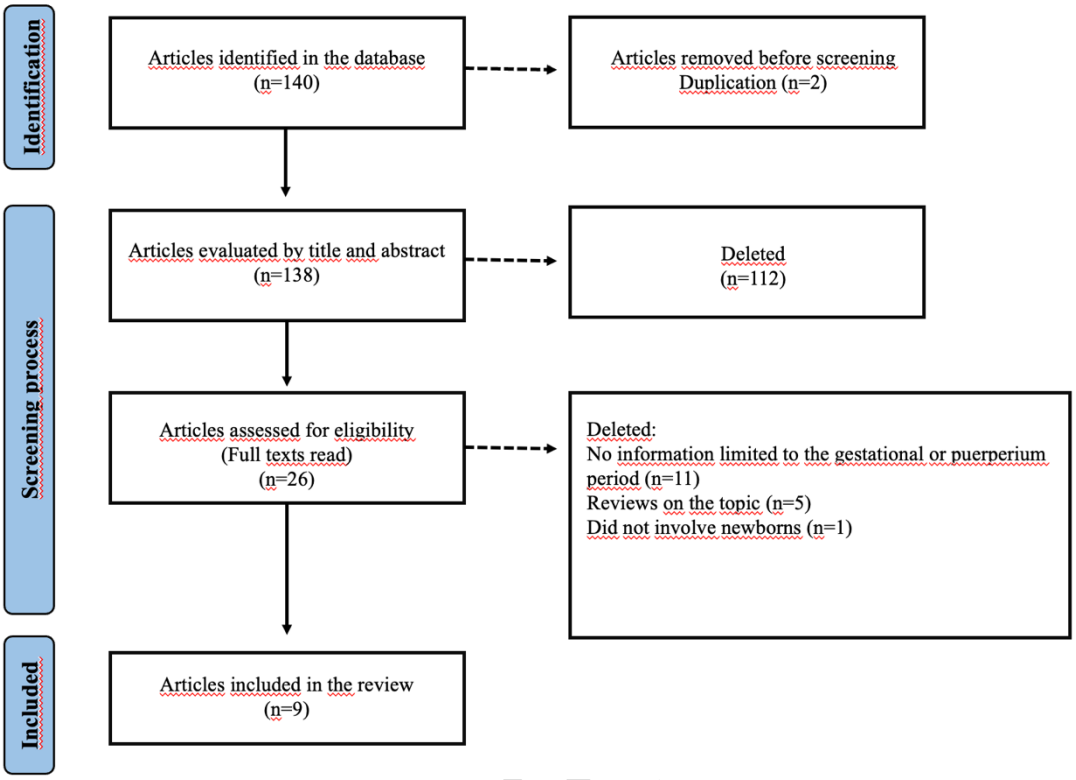

Figure 1. Information flow and stages of the systematic review

3. RESULTS AND DISCUSSION

Based on the established criteria, 09 articles were selected (Table 1) that were related to the nutritional impacts and epigenetic mechanisms during pregnancy and/or in the postpartum period. One of the main interests of the present study was to observe how nutritional deficiencies could impact the gestational period or even the postpartum period. Barks et al. [5] mentioned that iron deficiency anemia causes a deregulation of JARIDs and TETs proteins, which are proteins that act on neuronal development, directly affecting the neuronal development of the embryo., which in the future may result in neuropsychiatric disorders.

Given this, another important approach in the present study was to verify how the supplementation of some essential compounds could affect this epigenetic profile. Still on the study by Barks et al. through the analyses, it had been observed that prenatal supplementation with vitamin B8 (biotin) during the period of high iron demand in the developing hippocampus can mitigate the damage caused by iron deficiency. Another investigation carried out by Anderson et al. [13] pointed out that maternal vitamin D supplementation during pregnancy and lactation alters DNA methylation patterns in both mother and infant. Among infants, genes showing differential methylation mapped more strongly to collagen metabolic processes and the regulation of apoptosis. The study by Caffrey et al. [14] mentioned that continuous supplementation with folic acid (vitamin B9) during the 2nd and 3rd trimesters of pregnancy results in significant changes in DNA methylation in cord blood of genes related to neurodevelopment.

Table 1. Distribution of studies

Author/Year	Title	outcome
Barks et al., 2021[5]	Iron-deficiency anemia in early life programs the epigenetic landscape of the hippocampus	Iron-deficiency anemia (ID) during the prenatal and postnatal periods has an effect on neurodevelopment resulting in long-term effects such as cognitive impairment, increased risk, and neuropsychiatric disorders. ID in early life causes stable changes in gene regulation throughout life.
Hartwig et al., 2020[10]	Association between breastfeeding and DNA methylation across the lifespan: results from the Avon Parent-Child Longitudinal Study (ALSPAC)	The findings indicate that DNA methylation in childhood and adolescence can be predicted by breastfeeding.
Verlinder et al., 2020[11]	Time course of altered DNA methylation evoked by critical illness and early administration of parenteral nutrition in the Pediatric ICU (PICU)	Changes in DNA methylation were observed in leukocytes of children at PICU discharge, impairing their long-term development. In this study, the time course of altered DNA methylation in the PICU and the impact of early nutritional management were documented. Most abnormalities remained at least partially or worsened with longer PICU stay.
Jiang et al., 2020[6]	Prenatal starvation exposure and estimated glomerular filtration rate in consecutive generations: association and epigenetic mediation in a population-based cohort study in Suihua China	Prenatal malnutrition can promote kidney dysfunction in adulthood, but it is unclear whether the harmful effect can be passed on to the next generation. Overall, prenatal starvation exposure may have long-term effects on eGFR decline in consecutive generations, which may be partially mediated by methylation changes in AGTR1 and PRKCA.
Phang et al., 2020[12]	Epigenetic aging in newborns: role of maternal diet	The study provides evidence of maternal traits that are associated with epigenetic aging in offspring. Epigenetic acceleration of age was not associated with heart rate variability in preterm infants, but was associated with feeding.
Anderson et al., 2018[13]	Effects of maternal vitamin D supplementation on maternal and infant epigenome	Maternal vitamin D supplementation during pregnancy and lactation alters DNA methylation in breastfed mothers and infants.
Caffrey et al., 2018[14]	Gene-specific DNA methylation in neonates in response to folic acid (FA) supplementation during the second and third trimesters of pregnancy: epigenetic analysis of a randomized controlled trial	Continued supplementation with FA during the 2nd and 3rd trimesters of pregnancy results in significant changes in DNA methylation in cord blood of genes related to brain development. The findings offer a potential biological mechanism linking maternal folate status to offspring neurodevelopment.

McGee et al., 2018[15]	A crucial role for dietary methyl donor intake in epigenetic programming and fetal growth outcomes	Dietary intake of different amounts of methyl donors and cofactors during pregnancy may alter fetal growth and development.	
Pauwels et al., 2017[16]	Dietary and supplemental intake of maternal methyl group donors and cord blood DNA methylation	Long-term folic acid use before and during pregnancy was associated with greater cord blood methylation LEP and RXRA, respectively. The results suggest significant epigenetic modifications when taking a folic acid supplement beyond current advice.	

The appearance of future diseases also proved to be the target of several investigations, in order to observe what role changes in the epigenome could trigger in the offspring. The study by Pauwels et al. [16] described that the ingestion of methyl group donors, by the mother, before and during pregnancy, favors the occurrence of epigenetic modifications in genes related to metabolism. In addition, the article mentioned that the period of use, both before fertilization and after fertilization, will be directly related to the concentration of methyl group donors found in the baby's umbilical cord. Phang et al. [12] brought evidence that stated that modifiable dietary characteristics, that is, nutritional discipline in the prevention and treatment of diseases in health promotion, are associated with the epigenetic age of the newborn. Jiang et al. [6] pointed out a cohort study carried out in Shihua (China) which concluded that prenatal malnutrition may be associated with a high risk of Type 2 Diabetes Mellitus, obesity, metabolic syndrome, cognitive impairment, schizophrenia and promote renal dysfunction in adulthood. The previously mentioned renal dysfunction can perpetuate for two consecutive generations and this decline could be partially mediated by methylation alterations in AGTR1 (angiotensin II receptor 1) and PRKCA (protein kinase C alpha).

The breastfeeding period also brings very interesting results regarding the impacts of epigenetic modifications on the offspring. Hartwig et. al. [10] mentioned that being breastfed has been associated with a lower risk of being overweight or being obese as well as with a lower risk for the development of type 2 diabetes mellitus, in addition to having a positive effect on cognitive development and reducing the risk of infections in childhood. It should be mentioned that the difference in the breastfeeding period also interferes with the consequences. Jiang et al. [6] documented that malnutrition at the beginning of life can increase the abnormal development of several organs. Verlinder et. al. [11] mentioned a study which was carried out with children undergoing treatment in the pediatric intensive care unit (PICU) and pointed out that providing complete nutritional intake early with the use of parenteral nutrition (PN) to supplement insufficient enteral nutrition (early PN) proved to be clinically inferior to accepting the initial macronutrient deficit by delaying any PN beyond the first week in the PICU (late-NP). Early NP not only caused more infections and delayed recovery from illness, it also prevented the normal development of executive functions and/or caused behavioral problems, as assessed 2 and 4 years later.

Consumption of methyl donors may also be associated with fetal consequences. Exposed fact that is evidenced by Pauwels et al. [16] where the study had proven that the nutritional intake of methyl donors, such as folate, vitamin B12, choline and betaine, during pregnancy can modify DNA methylation patterns in the fetal epigenome affecting not only the growth of the neonate but also contributing to potentiate several diseases in adulthood. Furthermore, the same study had shown that mothers who were supplemented with high levels of one-carbon nutrients (methionine, choline, folic acid, vitamin B, and zinc) during pregnancy had significantly higher mid- and late-pregnancy fetal weights.

The intake of some specific substances is associated with epigenetic age in newborns. According to Phang et al. [12] the main modifiable exposures associated with greater acceleration of epigenetic age included higher maternal dietary intake of SFAs and MUFAs during pregnancy - in particular, palmitoleic acid, oleic acid (18:1 MUFA) and palmitic acid (16:0 SFA). In contrast, higher maternal carbohydrate intake was associated with less acceleration of epigenetic age in newborns. There was also some evidence that the proportion of maternal dietary fat as n-3 PUFAs, in particular α-linolenic acid, may also be associated with less acceleration of epigenetic age in the newborn. Still on the study by Phang et al. [12] newborns with positive age acceleration were more likely to be female and have greater body fatness. Therefore, epigenetic age acceleration begins before birth, and prenatal exposures, including modifiable maternal dietary characteristics, are associated with newborn epigenetic age.

Not far from the reality presented by the articles presented in this selection, other more recent studies also highlight the nutritional impacts that affect the newborn. The study by Koemel and Skilton [16] demonstrated that diets higher in glycemic load, fat, saturated fat, and ω-6 fatty acids demonstrate a positive association with epigenetic aging. Maternal and early life nutrition directly and indirectly influences epigenetic aging via changes in one-carbon metabolism, cardiometabolic health, and the microbiome. Costanzo et al. [17] goes even further and points out that these changes do not only affect the first years of life, but can affect the adult period, where these individuals can develop changes in the immune system, becoming more susceptible to infections or even the development of allergies.

4. CONCLUSION

From the selected and verified studies, it was possible to observe that the ingested nutrients act in a direct and crucial way in the fetal and infant development, together with the epigenetic mechanisms, in which their main actions are in the prenatal period and in the puerperium. Therefore, there were nutritional influences affecting the neuronal development of the embryo, the onset of diseases such as diabetes mellitus and obesity, even during the prenatal period. As for the postpartum period, in breastfeeding it was noted that breastfed children have a lower risk of developing chronic diseases, infections and have better cognitive development. Given the above, it is concluded that understanding the mechanisms involved in the gene-nutrient process will guarantee new means of prevention, diagnosis and treatment for potential diseases and problems of embryo-fetal and child development. Thus, further studies are needed to further investigate this relationship between diet and epigenetics.

COMPETING INTERESTS

Authors have declared that no competing interests exist

AUTHORS' CONTRIBUTIONS

All authors read and approved the final manuscript.

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REFERENCES

1. Pray LA. Epigenetics: Genome, meet your environment: as the evidence for epigenetics, researchers reacquire a taste for Lamarckism. The scientist. 2004;18(13):14-20.

2. Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. Annual Review of Nutrition. 2007; 27:363-388.

3. Miranda VRM, Slim BDLPF. Relationship between intestinal microbiota, epigenetics and exposure in maternal and child health. Revista Cubana de Pediatría. 2019; 91(2):1-13.

4. Costa CC, MilanI DG, Barbara HMB, et al. Maternal and child nutritional care in the puerperium. Ciência ET Praxis. 2019;11(22):23-30.

5. Barks AK, Liu SX, Georgieff MK, et al. Early-Life Iron Deficiency Anemia Programs the Hippocampal Epigenomic Landscape. Nutrients.2021;13(11):3857 – 3868.

6. Jiang W, Han T, Duan W, et al. Prenatal famine exposure and estimated glomerular filtration rate across consecutive generations: association and epigenetic mediation in a population-based cohort study in Suihua China. Aging. 2020;12(12):12206 – 12221.

7. Medeiros IGA, Ferreira IAA. Nutritional epigenetics: food that shapes us. Journal of Academic Works-Universo Recife. 2018;5(1): 167-194.

8. Sneider TW, Teague WM, Rogachevsky LM. S-Adenosylmethionine: DNA-cytosine 5-methyltransferase from a Novikoff rat hepatoma cell. Nucleic Acids Research. 1995;2(10)1685-1700.

9. Hartwig FP, Davey Smith G, Simpkin AJ, et al. Association between Breastfeeding and DNA Methylation over the Life Course: Findings from the Avon Longitudinal Study of Parents and Children (ALSPAC). Nutrients. 2020;12(11):3309 – 3326.

10. Verlinder I, Guide F, Derese I, et al. Time course of altered DNA methylation evoked by critical illness and by early administration of parenteral nutrition in the pediatric ICU. Clinical epigenetics. 2020; 12:1-10.

11. Phang M, Ross J, Raythatha JH, et al. Epigenetic aging in newborns: role of maternal diet. The American Journal of Clinical Nutrition.2020;111(3):555-561.

12. Anderson CM, Gillespie SJ, Thiele DK, et al. Effects of Maternal Vitamin D Supplementation on the Maternal and Infant Epigenome. Breastfeeding Medicine. 2018;12(5):371-380.

13. Caffrey A, Irwin, RE, Mcnulty H, et al. Gene-specific DNA methylation in newborns in response to folic acid supplementation during the second and third trimesters of pregnancy: epigenetic analysis from a randomized controlled trial. The American Journal of Clinical Nutrition. 2018;107(4):566-575.

14. Mcgee M, Bainbridge S, Fontaine-Bisson B. A crucial role for maternal dietary methyl donor intake in epigenetic programming and fetal growth outcomes. Nutrition Reviews. 2018;76(6):469-478.

15. Pauwels S, Ghosh M, Duca RC, et al. Dietary and supplemental maternal methyl-group donor intake and cord blood DNA methylation. Epigenetics. 2017; 12:1-10.

16. Koemel NA, Skilton MR. Epigenetic Aging in Early Life: Role of Maternal and Early Childhood Nutrition. Current Nutrition Reports. 2022;11(2):318-328.

17. Di Costanzo M, De Paulis N, Capra ME, Biasucci G. Nutrition during Pregnancy and Lactation: Epigenetic Effects on Infants' Immune System in Food Allergy. Nutrients. 2022;14(9):1766-1780.