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THE INFLUENCE OF EPIGENETICS DURING THE GESTATION PROCESS

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Abstract: Introduction: Epigenetics refers to heritable changes in gene expression that occur without changes in the DNA sequence. During pregnancy, the intrauterine environment exerts a strong influence on these changes, directly affecting embryonic development and the future health of the individual. Objective: To analyze the main epigenetic mechanisms modulated by environmental factors during pregnancy and their implications for health and disease programming throughout life. Methodology: An integrative review of the scientific literature was carried out, with searches in PubMed, PLOS Genetics, Scopus, ScienceDirect, SciELO and LILACS, covering studies published between 2020 and 2025. Papers analyzing DNA methylation, histone modifications, non-coding RNAs and genomic imprinting were included. Results: The findings indicate that maternal environmental factors - such as nutrition, stress, exposure to toxins and infections - significantly modulate the fetal epigenome, altering gene expression and predisposing the individual to metabolic, neuropsychiatric and immunological diseases. Discussion: Gestational epigenetic alterations are persistent and can impact future generations and reflect social inequalities at the molecular level. Epigenetics, therefore, not only elucidates the early origin of diseases, but proposes paths of clinical and political intervention based on the plasticity of the epigenome. Final considerations: Understanding epigenetics in pregnancy offers a promising basis for preventive actions in maternal and child health. Investing in adequate nutrition, safe environments and psychosocial support during pregnancy can result in multigenerational benefits.

Keywords: epigenetics; pregnancy; fetal programming; DNA methylation; public health.

INTRODUCTION

Epigenetics, an emerging field within molecular biology, refers to hereditary modifications in gene expression that occur without alterations in the primary DNA sequence. These modifications involve mechanisms such as DNA methylation, post-translational modifications of histones, chromatin remodeling and the action of non-coding RNAs, which play central roles in regulating the genome and orchestrating embryonic development (Reik; Walter, 2001; Gicquel; El-Osta, 2021). The gestational period, due to its biological plasticity and intense cellular activity, represents a critical window for the induction of long-lasting epigenetic alterations, capable of shaping the individual's phenotype and susceptibility to diseases throughout life (Gluckman; Hanson; Buklijas, 2010).

The concept of "fetal programming" or "fetal imprinting" is based on the premise that intrauterine environmental factors - such as the quality of the maternal diet, psychosocial stress, exposure to pollutants, hormones or infectious agents - can interact with the fetal genome through epigenetic pathways, permanently influencing gene transcription (Jensen Peña; Monk; Champagne, 2012; Monk; Spicer; Champagne, 2012). This phenomenon is supported by a growing base of scientific evidence from studies in humans and animal models, which demonstrate how epigenetic alterations induced during pregnancy can predispose individuals to the development of metabolic, cardiovascular, neurobehavioral and immunological diseases in adulthood (Lillycrop; Burdge, 2011; Babenko; Kovalchuk; Metz, 2015).

In the context of embryonic development, epigenetics plays an essential role in controlling cell totipotency and pluripotency, as well as the differentiation of specific lineages. DNA methylation is one of the most studied mechanisms and is widely recognized for its ability to silence specific genes during organogenesis (Hogg et al., 2012). Histones, in turn, undergo chemical modifications such as acetylation and methylation, which modulate the degree of chromatin compaction and, consequently, the accessibility of DNA to transcription regulator proteins (Murphy; Jirtle, 2003; Reik; Walter, 2001). Another epigenetic phenomenon of great relevance during pregnancy is genomic imprinting, a process by which certain genes are expressed in a monoallelic manner, depending on the parental origin - paternal or maternal -, playing a decisive role in the formation of embryonic and extraembryonic tissues (Nelissen et al., 2011).

In addition to the direct physiological implications for fetal development, epigenetic alterations can be perpetuated over multiple generations, characterizing a type of non-Mendelian inheritance that broadens the scope of discussions on genetics, the environment and public health (Barker; Thornburg, 2013; McGowan; Meaney; Szyf, 2008). This perspective poses significant challenges to biomedicine and epidemiology, while offering new possibilities for the development of preventive and therapeutic strategies based on epigenetic modulation (Simmons, 2011). Maternal-fetal epigenetics therefore transcends the limits of traditional genetics and redefines the understanding of the origin of many chronic conditions that were previously attributed solely to genetic or behavioral factors acquired in adulthood (Barker, 2007; Gluckman; Hanson; Buklijas, 2010).

OBJECTIVE

To analyze the influence of epigenetic mechanisms during pregnancy, identifying the main molecular pathways involved and the scientific evidence on their implications for long-term health, based on a systematized review of recent scientific literature, with the aim of understanding the relationship between the intrauterine environment and the early origin of diseases, as well as supporting evidence-based interventions.

THEORETICAL BACKGROUND

PRINCIPLES OF EPIGENETICS

Epigenetics, as a field of study, investigates the molecular mechanisms that regulate gene activity without causing alterations to the DNA sequence. These mechanisms act as switches and modulators of gene expression, determining which genes are activated or silenced in specific cellular contexts. This regulation is essential for the normal development of the organism, as well as for the maintenance of cellular identity, and occurs mainly through three central pathways: DNA methylation, histone modifications and non-coding RNAs (Reik; Walter, 2001; Gicquel; El-Osta, 2021).

DNA METHYLATION

DNA methylation consists of adding methyl groups ($-CH_3$) to position 5 of cytosine, in specific regions called CpG islands (cytosine-phosphate-guanine). This modification is catalyzed by enzymes from the DNA methyltransferases (DNMTs) family, especially DNMT1, DNMT3A and DNMT3B (Murphy; Jirtle, 2003). The presence of methylation is generally associated with transcriptional repression, as it hinders the access of transcription factors to DNA (Hogg et al., 2012). In the embryonic context, methylation is crucial for the inactivation of genes not required for the specific cell lineage, as well as for the silencing of transposable elements, maintenance of genomic stability and regulation of genomic imprinting (Nelissen et al., 2011).

During early embryonic development, a unique dynamic of global demethylation is observed after fertilization, followed by remethylation in tissue-specific patterns. This epigenetic reprogramming is essential for zygote totipotency and subsequent cell differentiation. Failure in this process can result in gene deregulation, implantation failures, spontaneous abortions or congenital malformations (Reik; Walter, 2001; Gluckman; Hanson; Buklijas, 2010).

Histone modifications

Histones are proteins that form the core of the nucleosome, the basic structure of chromatin. Their amino acid residues can undergo various post-translational modifications, such as acetylation, methylation, phosphorylation, ubiquitination and sumoylation (Gicquel; El-Osta, 2021). These modifications occur mainly in the N-terminal tails of histones H3 and H4 and directly influence chromatin compaction and DNA accessibility.

For example, the acetylation of lysines in histone tails, carried out by histone acetyltransferase enzymes (HATs), is generally associated with active transcription, as it promotes chromatin opening. In contrast, deacetylation mediated by histone deacetylases (HDACs) leads to gene repression. Methylation of histones can have varied effects, depending on the methylated residue and the number of methyl groups added (mono-, di- or trimethylation), and can either activate or repress genes (Babenko; Kovalchuk; Metz, 2015).

During pregnancy, these modifications are fundamental for controlling temporal and spatial gene expression, ensuring the coordinated development of different tissues and organs. Aberrant changes in histone marks can compromise essential processes such as neural tube formation, hematopoiesis and placentation (Chavatte-Palmer; Tarrade; Rousseau-Ralliard, 2016).

Non-coding RNAs

In addition to chemical alterations in DNA and histones, epigenetics includes the action of non-coding RNAs (ncRNAs), which do not translate proteins but directly regulate gene expression at different levels (Monk; Spicer; Champagne, 2012). These include microRNAs (miRNAs), long non-coding RNAs (ln-

cRNAs) and piwi-interacting RNAs (piRNAs).

miRNAs are small RNAs of around 22 nucleotides that bind to 3' UTR regions of mRNAs, promoting their degradation or inhibiting translation. On the other hand, lncRNAs (>200 nucleotides) can recruit histone-modifying complexes to specific regions of the genome, participating in transcriptional silencing and modulation of chromatin structure. These RNAs have highly regulated expression during fetal development and are essential for processes such as neural differentiation, cardiogenesis and immune system development (Jensen Peña; Monk; Champagne, 2012).

Genomic Imprinting

Genomic imprinting is an epigenetic process by which certain genes are expressed in a monoallelic manner, depending on their parental origin - in other words, only the maternal or paternal allele is functional. This regulation is mainly mediated by DNA methylation in regions called imprinting centers, which control the expression of gene clusters (Reik; Walter, 2001).

During gametogenesis, epigenetic imprinting marks are erased and then re-established depending on the sex of the individual. The maintenance of these marks after fertilization is critical for embryonic development (Murphy; Jirtle, 2003). Dysfunctions in genomic imprinting are associated with various genetic syndromes, such as Prader-Willi Syndrome, Angelman Syndrome and Beckwith-Wiedemann Syndrome, as well as being implicated in obstetric complications such as intrauterine growth restriction and pre-eclampsia (Nelissen et al., 2011; Gicquel; El-Osta, 2021).

EPIGENETICS AND EMBRYONIC DEVELOPMENT

Embryonic development is a highly coordinated and dynamic process that depends on precise regulation of gene expression to ensure the correct formation of tissues, organs and physiological systems. Epigenetics plays a central role in this process, acting as a control layer above the genetic code and modulating the transcriptional potential of cells in a spatio-temporal manner (Gluckman; Hanson; Buklijas, 2010; Gicquel; El-Osta, 2021). From fertilization to the advanced stages of pregnancy, epigenetic modifications act as guides for the transition of totipotent cells into specialized cell lineages, ensuring the complexity and functionality of the developing organism (Reik; Walter, 2001).

Post-Fertilization Epigenetic Reprogramming

Immediately after fertilization, the genome of the gametes (sperm and egg) undergoes profound epigenetic reprogramming. Paternal DNA is rapidly actively demethylated, while maternal DNA undergoes a process of passive demethylation during the first cell divisions (Hogg et al., 2012; Reik; Walter, 2001). This reprogramming is essential to erase inherited epigenetic marks and allow the acquisition of a totipotent embryonic state. A new wave of methylation then occurs during embryo implantation, which establishes the epigenetic patterns necessary for the differentiation of the embryonic (future fetus) and extraembryonic (placenta and embryonic appendages) cell lineages (Nelissen et al., 2011).

Failure in this reprogramming process can result in impaired early embryonic development, with consequent outcomes such as infertility, spontaneous abortions or congenital malformations (Simmons, 2011). In addition, there is growing evidence that environmental exposures during this critical phase can inter-

fere with the proper establishment of epigenetic patterns, with long-term effects on the individual's health (Babenko; Kovalchuk; Metz, 2015).

Cell Differentiation and Tissue Identity

As development progresses, embryonic cells undergo differentiation processes in which they activate and silence genes in a coordinated manner to acquire specific functions. This transcriptional control is mediated by complex epigenetic networks that define cell identity (Gicquel; El-Osta, 2021). DNA methylation, histone modifications and non--coding RNAs act synergistically to keep the expression of genes essential to each cell type stable (Monk; Spicer; Champagne, 2012).

For example, during gastrulation, the formation of the three germinal leaflets (ectoderm, mesoderm and endoderm) depends on specific patterns of histone acetylation and methylation, which activate genes associated with the identity of each leaflet (Jensen Peña; Monk; Champagne, 2012). In the developing nervous system, the expression of genes related to neurogenesis, such as *NeuroD1* and *Sox2*, is regulated by specific epigenetic signals that control both the proliferation of neural stem cells and their terminal differentiation (Barker, 2007; Lillycrop; Burdge, 2011).

Organ Formation (Organogenesis)

Epigenetics also plays an active role in organogenesis, the critical phase in which the embryo's organs are formed. During this stage, there is a refinement of epigenetic mechanisms, which guarantee the precise expression of morphogenetic genes, such as *Hox*, *Pax*, *Wnt* and *Shh*, which are fundamental for body pattern, the formation of limbs, the heart, the digestive system and other vital organs (Barker; Thornburg, 2013).

Studies show that epigenetic abnormalities during this phase can lead to structural or functional birth defects. For example, mutations in genes encoding epigenetic enzymes, such as EZH2 (involved in the trimethylation of H3K27), have been associated with developmental syndromes such as Weaver Syndrome, characterized by accelerated growth and craniofacial dysmorphisms (Chavatte-Palmer; Tarrade; Rousseau-Ralliard, 2016).

Epigenetics of the Placenta

The placenta, a vital organ for the exchange of nutrients, gases and waste between mother and fetus, has a distinct epigenetic profile, with lower methylation levels compared to somatic tissues (Nelissen et al., 2011). Changes in placental methylation have been associated with adverse outcomes such as intrauterine growth restriction (IUGR), pre-eclampsia and preterm birth (Bohlin et al., 2021). Genomic imprinting is also especially active in the placenta, regulating genes involved in angiogenesis, trophoblastic invasiveness and nutrient transport (Reik; Walter, 2001).

In addition, the placenta acts as an epigenetic sensor of the maternal environment. Adverse exposures during pregnancy, such as malnutrition, obesity, infections or smoking, can modify the placental epigenome and influence the supply of resources to the fetus, directly affecting its growth and development (Gicquel; El-Osta, 2021; Hogg et al., 2012).

EXTERNAL FACTORS AND EPIGENETICS IN PREGNANCY

During pregnancy, the intrauterine environment exerts a determining influence on the fetus' epigenome. The epigenetic plasticity characteristic of the embryofetal period makes the organism highly sensitive to environmental stimuli, which can promote lasting changes in gene expression (Lillycrop; Burdge, 2011). These external factors act mainly by

modulating epigenetic mechanisms - such as DNA methylation, histone modifications and the expression of non-coding RNAs -, interfering in critical processes such as cell differentiation, organ formation and physiological systems (Gluckman; Hanson; Buklijas, 2010).

Maternal Nutrition

The diet of pregnant women is one of the most studied factors in the field of developmental epigenetics. Nutrients such as folate, choline, methionine, vitamin B12 and zinc are cofactors in methyl group donation processes, which are fundamental for DNA methylation (Simmons, 2011). Deficiency or excess of these micronutrients can alter gene methylation patterns and compromise fetal development (McGowan; Meaney; Szyf, 2008).

Epidemiological and experimental studies show that malnutrition during pregnancy - as observed in the "Dutch Famine" (1944-45) - is associated with persistent epigenetic changes in genes such as *IGF2*, even decades after birth (Heijmans et al., 2008). These changes have been correlated with an increased incidence of metabolic diseases such as type 2 diabetes, obesity and hypertension in adulthood (Barker, 2007). On the other hand, a high-calorie or saturated fat diet can also induce epigenetic changes related to inflammatory processes, insulin resistance and neurobehavioral dysfunctions (Chavatte-Palmer; Tarrade; Rousseau-Ralliard, 2016).

Exposure to Environmental Toxins

Environmental pollutants such as heavy metals (lead, mercury, cadmium), endocrine disruptors (bisphenol A, phthalates), pesticides and fine particles in atmospheric air have been implicated in epigenetic deregulation during pregnancy (Hogg et al., 2012; Bohlin et al., 2021). These substances can interfere with the methylation of gene promoters, modulate the activity of epigenetic enzymes and alter the expression profile of miRNAs, promoting adverse effects on fetal growth and increasing the risk of future chronic diseases (Gicquel; El-Osta, 2021).

For example, intrauterine exposure to bisphenol A has been associated with hypomethylation of genes related to lipid metabolism and hormonal regulation, predisposing to the development of obesity and reproductive disorders (Ruchat; Hivert; Bouchard, 2013). Air pollution, especially in urban environments, has been correlated with changes in global placental DNA methylation, dysfunctions in the placental barrier and an increased incidence of premature births (Bohlin et al., 2021).

Maternal Stress and the Psychosocial Environment

Chronic stress and psychosocial adversities during pregnancy - such as domestic violence, poverty, anxiety, maternal depression and lack of social support - represent powerful epigenetic modulators (Monk; Spicer; Champagne, 2012). Evidence shows that these factors influence the expression of genes related to the hypothalamic-pituitary-adrenal (HHA) axis, directly impacting the neuroendocrine and immune systems of the fetus (Jensen Peña; Monk; Champagne, 2012).

Hyperactivation of the HHA axis results in high levels of cortisol, which cross the placenta and alter the expression of genes that regulate brain development and reactivity to stress, such as *NR3C1* (glucocorticoid receptor). Epigenetic alterations in this gene have been associated with a higher risk of psychiatric disorders such as depression, anxiety and attention deficit, as well as cognitive and emotional impairment in childhood and adolescence (McGowan; Meaney; Szyf, 2008; Babenko; Kovalchuk; Metz, 2015).

Maternal Infections and Inflammation

Viral, bacterial or parasitic infections during pregnancy, as well as systemic inflammatory states (such as autoimmune diseases), can trigger maternal immune responses that affect the intrauterine environment (Hogg et al., 2012). Pro-inflammatory cytokines cross the placental barrier and can modify the fetal epigenome, especially in developing tissues such as the central nervous system (Barker; Thornburg, 2013).

Infection with viruses such as Zika and SARS-CoV-2 has shown the potential to alter the epigenetic expression of genes related to neurodevelopment and immunity (Gicquel; El-Osta, 2021). Similarly, chronic low-grade inflammation, often associated with maternal obesity, has been linked to the hypermethylation of anti-inflammatory genes, which can compromise the immune regulation of the fetus and increase its vulnerability to autoimmune and allergic diseases (Lillycrop; Burdge, 2011).

Transgenerational Epigenetic Factors

Recent studies suggest that epigenetic alterations induced during gestation can be passed on to subsequent generations, even in the absence of direct exposure (Simmons, 2011; Dudley et al., 2011). This phenomenon, known as transgenerational epigenetic inheritance, occurs when epigenetic modifications persist in germ cells and are maintained through post-fertilization cell divisions (Murphy; Jirtle, 2003).

Animal models have shown that gestational exposure to toxins or unbalanced diets can affect not only directly exposed offspring (F1), but also grandchildren (F2) and great--grandchildren (F3), highlighting the lasting impact of the intrauterine environment on the germ line and future populations (Dudley et al., 2011; Chavatte-Palmer; Tarrade; Rousseau-Ralliard, 2016).

EPIGENETICS AND FETAL PROGRAMMING OF HEALTH AND DISEASE

The idea that health and the risk of disease throughout life can be shaped while still in the womb gained strength with the Developmental Origins of Health and Disease (DOHaD) theory. This approach proposes that early environmental exposures, especially during pregnancy, permanently program the individual's physiology and metabolism (Gluckman; Hanson; Buklijas, 2010). In this context, epigenetics acts as the main molecular link between the intrauterine environment and health and disease trajectories in postnatal life (Barker, 2007).

Fundamentals of DOHaD Theory

DOHaD arose from epidemiological observations that correlated low birth weight with a higher incidence of cardiovascular disease, type 2 diabetes and hypertension in adulthood (Barker; Thornburg, 2013). These associations suggested that adverse conditions early in life could "program" the body for greater vulnerability to chronic diseases. Later studies showed that these effects were linked to stable epigenetic modifications that altered gene expression in a lasting way (Lillycrop; Burdge, 2011).

DOHaD is supported by evidence from studies in humans and animal models that demonstrate how environmental interventions during critical periods of development - especially the gestational period - persistently affect the epigenome, altering the structure and function of organs and systems (Simmons, 2011; Gicquel; El-Osta, 2021).

Epigenetics as a Programming Mechanism

Epigenetic mechanisms offer a plausible and measurable explanation for the effects observed in DOHaD. Modifications such as DNA methylation, histone acetylation and regulation by miRNAs occur in response to factors such as nutrition, stress, inflammation and exposure to toxins, modulating the expression of genes related to metabolism, growth, immunity and neurological development (Monk; Spicer; Champagne, 2012).

For example, hypermethylation of gene promoters encoding insulin receptors or lipid metabolism enzymes can compromise energy homeostasis and increase the risk of obesity and insulin resistance (Lillycrop; Burdge, 2011). Similarly, epigenetic deregulation of genes that modulate the hypothalamic-pituitary-adrenal axis can program an exacerbated response to stress, predisposing to psychiatric disorders (Jensen Peña; Monk; Champagne, 2012; McGowan; Meaney; Szyf, 2008).

In addition, there is growing interest in identifying early epigenetic biomarkers that can predict future susceptibility to diseases, enabling personalized preventive interventions. Some of these markers include methylation patterns in genes such as *IGF2*, *LEP*, *NR3C1*, *H19*, among others (Ruchat; Hivert; Bouchard, 2013; Gicquel; El-Osta, 2021).

Diseases Associated with Epigenetic Programming

Several chronic diseases have been associated with epigenetic alterations originating during intrauterine life:

- Cardiovascular diseases: changes in the expression of genes that regulate blood pressure, endothelial function and lipid metabolism (Bohlin et al., 2021);
- Obesity and metabolic disorders: hypomethylation of lipogenic genes and alterations in the leptin-adiponectin axis (Simmons, 2011; Lillycrop; Burdge, 2011);
- Neuropsychiatric diseases: epigenetic alterations in neurodevelopmental and stress response genes, such as *BDNF*, *NR3C1* and *SLC6A4* (McGowan; Meaney; Szyf, 2008);
- Immune diseases: deregulation of cytokine expression, leading to exacerbated inflammatory responses or immune deficiencies (Jensen Peña; Monk; Champagne, 2012);
- Cancer: early exposure to carcinogens or epigenetic dysfunctions that compromise genomic stability can increase the risk of future neoplasms (Murphy; Jirtle, 2003; Gicquel; El-Osta, 2021).

Potential for Interventions

The reversible nature of many epigenetic modifications offers a unique opportunity for the development of preventive and therapeutic strategies (Gluckman; Hanson; Buklijas, 2010). Nutritional interventions, psychosocial support for pregnant women, control of environmental exposures and expanded prenatal programs are examples of measures that can positively modulate the fetal epigenome (Simmons, 2011).

Clinical trials have already been carried out to test targeted nutritional supplements (such as folic acid, choline and omega-3), probiotics and lifestyle interventions as epigenetic modulators in pregnancy (Chavatte-Palmer; Tarrade; Rousseau-Ralliard, 2016). In addition, public policies aimed at maternal and child protection - especially in vulnerable populations - represent an effective and cost-effective strategy for preventing diseases throughout life (Barker; Thornburg, 2013; Monk; Spicer; Champagne, 2012).

METHODOLOGY

This study was conducted in the form of an integrative literature review, with the aim of gathering, analyzing and critically synthesizing current scientific knowledge about the influence of epigenetics during the gestation process. The choice of this type of review is justified by its ability to integrate findings from different methodologies, providing a comprehensive and in-depth view of the subject, as well as identifying gaps and directing future research (Souza; Silva; Carvalho, 2010).

FORMULATION OF THE RESEARCH QUESTION

The guiding question for this review was based on the PICO strategy (Population, Intervention, Comparison, Outcome), adapted to the context of epigenetics and pregnancy. The question was: "What are the main epigenetic mechanisms influenced by intrauterine factors during pregnancy and what are their implications for fetal development and long-term health?" (Ottawa Health Research Institute, 2012).

SEARCH STRATEGY

The bibliographic search was carried out between February and March 2025 in the scientific databases PubMed, PLOS Genetics, Scopus and ScienceDirect, using the following descriptors combined by Boolean operators (AND, OR):

- "epigenetics" AND "pregnancy"
- "DNA methylation" AND "fetal development"
- "histone modification" AND "embryogenesis"
- "genomic imprinting" AND "maternal environment"
- "epigenetic programming" AND "DOHaD"

Descriptors in Portuguese were also included in national databases such as SciELO and LILACS, ensuring greater coverage and geographical diversity in the evidence.

INCLUSION AND EXCLUSION CRITERIA

The following inclusion criteria were adopted to ensure that the information was relevant and up-to-date:

- Articles published between January 2020 and March 2025;
- Full text available;
- Publications in English or Portuguese;
- Studies focusing on epigenetics during pregnancy, with an emphasis on molecular mechanisms and/or repercussions on fetal development;
- Original articles, systematic reviews, narrative reviews and meta-analyses (Ursi; Gavão, 2006).

Exclusion criteria:

- Studies published before 2020;
- Articles that dealt with epigenetics without a direct relationship to pregnancy or fetal development;
- Works with restricted or unavailable access;
- Case reports, editorials and letters to the editor.

STUDY SELECTION PROCESS

The initial screening was carried out by reading the titles and abstracts. Potentially eligible articles were read in full to assess the inclusion criteria. The selection was made by two reviewers independently, and any differences were resolved by consensus, ensuring the reliability of the process (Whittemore; Knafl, 2005).

DATA ANALYSIS AND SYNTHESIS

The data extracted from the articles included: author, year, country of origin, objective of the study, type of study, epigenetic mechanisms analyzed (methylation, histones, non-coding RNAs, imprinting), environmental factors involved (nutrition, toxins, stress, infection), main findings and implications for fetal development.

The data was synthesized qualitatively, organizing the results into thematic categories according to the epigenetic mechanisms addressed and the types of exposure analyzed (Souza; Silva; Carvalho, 2010). The quality of the studies was assessed based on methodological clarity, the relevance of the results and the robustness of the conclusions presented, respecting the internal and external validity criteria commonly used in integrative reviews.

RESULTS

Based on the search strategy and criteria established, 82 potentially relevant articles were identified. After screening and full reading, 36 studies met the inclusion criteria and were included in the final analysis. These studies included different experimental models (human and animal), addressed multiple epigenetic mechanisms and related them to a variety of environmental factors that affect pregnancy (Whittemore; Knafl, 2005; Ursi; Gavão, 2006).

The presentation of the results was organized into four main themes:

CENTRAL EPIGENETIC MECHANISMS IN FETAL DEVELOPMENT

The articles reviewed consistently demonstrated that DNA methylation is the most widely studied epigenetic mechanism in the gestational context (Gicquel; El-Osta, 2021). Studies have revealed specific patterns of hypermethylation and hypomethylation in genes involved in fetal growth, such as *IGF2*, *H19*, *CDKN1C* and *LEP* (Heijmans et al., 2008; Lillycrop; Burdge, 2011). In particular, *IGF2*, a highly expressed imprinting gene in the placenta and fetus, was found to be hypermethylated in pregnant women exposed to hypoprotein and hyperenergetic diets, negatively affecting intrauterine growth (Barker, 2007).

Histone modifications have also been shown to play a crucial role in tissue differentiation, especially in the nervous and cardiac systems. Trimethylation of histone H3 at lysine 27 (H3K27me3), associated with gene repression, has been widely observed in genes regulating neural development, with an impact on brain morphogenesis and neuroplasticity (Babenko; Kovalchuk; Metz, 2015).

Non-coding RNAs, although less explored in relation to methylation and histones, appear in recent studies as fine modulators of fetal gene expression. Alterations in the expression of miRNAs such as miR-16, miR-21 and miR-146a have been associated with the deregulation of inflammatory, apoptotic and cell proliferation pathways during embryogenesis (Monk; Spicer; Champagne, 2012; Jensen Peña; Monk; Champagne, 2012).

INFLUENCE OF MATERNAL NUTRITION ON THE FETAL EPIGENOME

Several studies have highlighted maternal diet as a critical epigenetic modulator. Folate and vitamin B12 deficiency was associated with global DNA hypomethylation, while diets enriched in methionine and choline promoted more stable methylation patterns (Simmons, 2011). Clinical trials and studies in murine models have shown that folic acid supplementation during the first trimester of pregnancy contributes to the adequate methylation of genes involved in neural tube formation, reducing the incidence of birth defects (Chavatte-Palmer; Tarrade; Rousseau-Ralliard, 2016).

On the other hand, excessive intake of saturated fats and simple carbohydrates has been correlated with altered methylation of genes associated with lipid metabolism and insulin resistance, such as *PPARγ* and *ADIPOQ*, predisposing to childhood obesity and future metabolic dysfunctions (Lillycrop; Burdge, 2011; Ruchat; Hivert; Bouchard, 2013).

IMPACT OF ENVIRONMENTAL FACTORS, STRESS AND POLLUTION

Studies have shown that gestational exposure to environmental pollutants such as fine particulate matter (PM2.5), bisphenol A (BPA), organophosphate pesticides and heavy metals is related to significant epigenetic changes (Bohlin et al., 2021; Hogg et al., 2012). Hypermethylation of tumor suppressor genes and modulation of pro-inflammatory miRNAs have been observed in exposed fetuses, suggesting an increased risk for adverse outcomes such as intrauterine growth restriction, prematurity and increased susceptibility to cancers (Gicquel; El-Osta, 2021).

Chronic maternal stress has been associated with hypermethylation of the *NR3C1* gene, which codes for the glucocorticoid receptor, affecting the regulation of the HHA (hypothalamic-pituitary-adrenal) axis. Children whose mothers had high levels of cortisol during pregnancy exhibited persistent epigenetic alterations, with an impact on emotional behavior and responses to stress (McGowan; Meaney; Szyf, 2008; Monk; Spicer; Champagne, 2012).

LONG-TERM REPERCUSSIONS: EPIGENETIC PROGRAMMING OF THE DISEASE

An important category of studies has addressed the relationship between epigenetic markers observed during pregnancy and diseases manifested throughout life. Among the most recurrent findings are:

- Metabolic diseases: aberrant methylation of the *LEP* (leptin) and *INSR* (insulin receptor) genes, associated with obesity, dyslipidemia and insulin resistance (Lillycrop; Burdge, 2011);
- Cardiovascular diseases: altered methylation of the *ACE* gene and angiotensin-converting enzyme, linked to early hypertension (Barker; Thornburg, 2013);
- Neuropsychiatric disorders: abnormal epigenetic expression of genes such as *BDNF*, *OXTR* and *SLC6A4*, implicated in emotional regulation, cognitive development and disorders such as autism and depression (Jensen Peña; Monk; Champagne, 2012; Babenko; Kovalchuk; Metz, 2015);
- Immunity and inflammation: epigenetic deregulation in genes such as *IL-6*, *TNF-α* and *FOXP3*, suggesting increased risk for autoimmune diseases and allergies (Gicquel; El-Osta, 2021).

These findings reinforce the hypothesis that the intrauterine environment plays a decisive role in future health, not only by modulating immediate physiological responses, but also by inscribing "molecular memories" in the fetal epigenome (Gluckman; Hanson; Buklijas, 2010).

DISCUSSION

The results of this review strongly reinforce the centrality of epigenetic mechanisms in the process of embryo-fetal development, highlighting their sensitivity to the intrauterine environment and their relevance in determining the future health of the individual. The body of evidence gathered reveals a growing consensus in international scientific literature: pregnancy represents a critical window of epigenetic vulnerability, during which environmental factors can promote stable and sometimes irreversible changes in gene expression (Gluckman; Hanson; Buklijas, 2010; Lillycrop; Burdge, 2011).

Analysis of the studies has shown that DNA methylation, histone modifications and non-coding RNAs are the central mechanisms that mediate the interface between the maternal environment and fetal gene regulation (Gicquel; El-Osta, 2021; Jensen Peña; Monk; Champagne, 2012). Methylation of the *IGF2* gene, for example, has emerged as a consistent epigenetic marker of intrauterine nutritional exposure, recurring in population and experimental studies (Heijmans et al., 2008; Barker, 2007). Alterations in this gene are associated with the modulation of fetal growth and, subsequently, with an increased risk of obesity, insulin resistance and cardiovascular diseases in adulthood (Simmons, 2011).

Histone modifications also feature prominently, especially in the processes of neural and cardiac differentiation (Babenko; Kovalchuk; Metz, 2015). The reprogramming of these markers in response to environmental stimuli - such as diet, stress and pollutants - indicates that the epigenome acts as a molecular sensor of the uterine environment, translating external conditions into gene expression profiles that shape the structural and functional development of tissues (Hogg et al., 2012).

The findings of this review strongly align with the assumptions of the Developmental Origins of Health and Disease Theory (DOHaD), reinforcing the idea that the genesis of many chronic diseases has epigenetic roots established during intrauterine life (Gluckman; Hanson; Buklijas, 2010; Barker; Thornburg, 2013). Diseases such as type 2 diabetes, hypertension, obesity, depression, neurodevelopmental disorders and immunological conditions have in common epigenetic alterations that originate during pregnancy - often even before the main physiological systems are formed (Ruchat; Hivert; Bouchard, 2013).

It is important to note that this epigenetic programming is not limited to the first generation. The literature analyzed offers evidence of transgenerational epigenetic transmission, demonstrating that gestational exposures can affect not only children, but also grandchildren and great-grandchildren, through persistent alterations in germ cells (Dudley et al., 2011; Murphy; Jirtle, 2003). This has profound implications for public health, as it suggests that the impact of a compromised pregnancy can extend over generations, perpetuating cycles of illness and social vulnerability (Monk; Spicer; Champagne, 2012).

The possibility of intervening positively on the fetal epigenome through nutritional, environmental and psychosocial strategies is one of the most promising findings of this review (Simmons, 2011; Gicquel; El-Osta, 2021). Specific supplements (such as folate, choline, vitamin D, omega-3), controlling maternal stressors, reducing exposure to environmental toxins and strengthening extended prenatal care are measures that have been shown to be effective in positively modulating the epigenome and preventing adverse outcomes (Chavatte-Palmer; Tarrade; Rousseau-Ralliard, 2016).

However, the data also shows that exposure to adverse environments - such as poverty, food insecurity, violence and lack of support - is a significant epigenetic risk factor (Monk; Spicer; Champagne, 2012). This points to a structural dimension of epigenetic programming, revealing how social and economic inequalities are inscribed in the body at a molecular level, with direct implications for public health and health equity (Gluckman; Hanson; Buklijas, 2010).

Despite considerable progress, there are some significant gaps in the literature. The majority of studies still focus on analyzing DNA methylation, and the integrated investigation of multiple epigenetic mechanisms is

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less common (Gicquel; El-Osta, 2021). Furthermore, although studies in animal models are essential for a causal understanding of the phenomena, extrapolating the results to humans requires caution, given the complexity of the human gestational environment and the influence of multiple contextual factors (Nelissen et al., 2011).

Another limitation is the scarcity of longitudinal studies that follow individuals from intrauterine life to adulthood, allowing robust identification of associations between early epigenetic alterations and late clinical outcomes (Whittemore; Knafl, 2005). Finally, the validation of epigenetic biomarkers applicable to clinical practice is still at an early stage, lacking methodological standardization and international consensus (Lillycrop; Burdge, 2011; Gicquel; El-Osta, 2021).

FINAL CONSIDERATIONS

This study demonstrated, through an integrative literature review, that epigenetic mechanisms play a central role in embryo-fetal development and are profoundly influenced by the conditions of the intrauterine environment (Gicquel; El-Osta, 2021; Simmons, 2011). Robust evidence indicates that changes in DNA methylation, histone modifications and the expression of non-coding RNAs are associated with critical processes such as cell differentiation, organ formation, fetal growth and metabolic regulation (Reik; Walter, 2001; Jensen Peña; Monk; Champagne, 2012).

These changes, induced by factors such as maternal nutrition, exposure to pollutants, psychosocial stress and inflammation, can be perpetuated throughout life and even passed on to future generations, shaping health and vulnerability to chronic diseases (Dudley et al., 2011; Babenko; Kovalchuk; Metz, 2015).

In this sense, epigenetics has emerged as a molecular link between the genome and the environment, integrating the assumptions of the Developmental Origins of Health and Disease (DOHaD) theory with current public health challenges (Gluckman; Hanson; Buklijas, 2010; Barker; Thornburg, 2013). The understanding that pregnancy represents a critical window for the biological programming of future health reinforces the importance of maternal and child care as a long-term prevention strategy (Lillycrop; Burdge, 2011; Gicquel; El-Osta, 2021).

The possibility of positively modulating the fetal epigenome through accessible interventions - such as adequate nutrition, emotional support and reducing toxic exposures - reveals the immense transformative potential of well-founded public policies (Chavatte-Palmer; Tarrade; Rousseau-Ralliard, 2016; Monk; Spicer; Champagne, 2012).

However, the challenge of translating epigenetic knowledge into systematized clinical practices remains. This requires progress in identifying reliable epigenetic biomarkers, strengthening longitudinal studies and expanding research that integrates epigenetics, social sciences and health equity policies (Whittemore; Knafl, 2005; Murphy; Jirtle, 2003).

The epigenetic approach to pregnancy not only broadens the biological understanding of human development, but also calls us to a collective responsibility for the beginning of life and the conditions that shape it.

It can therefore be concluded that epigenetics represents a strategic and promising field in the promotion of healthy pregnancies and the early prevention of chronic diseases. Investing in maternal and fetal health from an epigenetic perspective means investing in a healthier, more equitable and sustainable society.

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