FETAL PROGRAMMING AND THE DEVELOPMENT OF CARDIOMETABOLIC DISEASES: THE ROLE OF EPIGENETIC CHANGES

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Abstract: Cardiometabolic diseases are among the leading causes of morbidity and mortality worldwide and are influenced not only by genetic and environmental factors during adulthood but also

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by exposures occurring during intrauterine life. In this context, the Developmental Origins of Health and Disease (DOHaD) theory highlights the importance of fetal programming in determining future disease risk. This study aimed to analyze the role of epigenetic alterations in fetal programming and their relationship with the development of cardiometabolic diseases throughout life. An integrative literature review was conducted following the PRISMA 2020 guidelines. Searches were performed in PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Virtual Health Library using descriptors related to fetal programming, epigenetics, and cardiometabolic diseases. Articles published between 2020 and 2026 in English, Portuguese, and Spanish were included, resulting in a final sample of 17 studies after applying the eligibility criteria. The findings demonstrated that gestational factors such as maternal obesity, gestational diabetes, intrauterine growth restriction, and inadequate dietary patterns can induce persistent epigenetic modifications, including DNA methylation, histone alterations, and regulation by non-coding RNAs. These changes influence fetal gene expression and are associated with an increased risk of obesity, insulin resistance, metabolic syndrome, type 2 diabetes mellitus, and cardiovascular diseases in the offspring. Furthermore, the placenta was found to play a significant role in mediating maternal inflammatory and metabolic effects on fetal development. It is concluded that epigenetic mechanisms constitute a fundamental link between adverse gestational exposures and the future development of cardiometabolic diseases, highlighting the importance of preventive strategies focused on maternal health before and during pregnancy, as well as the need for further research to deepen the understanding of fetal programming processes.

Keywords: Fetal programming; Epigenetics; Cardiometabolic diseases; Maternal obesity; DOHaD.

INTRODUCTION

Cardiometabolic diseases represent one of the greatest contemporary challenges for health systems worldwide, constituting an important cause of morbidity and mortality and significantly impacting the quality of life of populations. Conditions such as obesity, type 2 diabetes mellitus,

systemic arterial hypertension and metabolic syndrome have shown significant growth in recent decades, including among children and adolescents, evidencing the need to understand etiological factors that go beyond the habits acquired throughout adult life. In this context, susceptibility to the development of these diseases can be determined during intrauterine life, through biological processes capable of permanently influencing the structure and function of different organs and systems (HARARY; AKINYEMI; CHARRON, 2022; FAA et al., 2024).

From this perspective, the concept of the Developmental Origins of Health and Disease (DOHaD) was consolidated, initially based on Barker's Hypothesis. This theory proposes that stimuli or aggressions occurring during critical periods of fetal development promote physiological adaptations aimed at the immediate survival of the fetus, but that they may result in a greater predisposition to the emergence of chronic diseases in childhood, adolescence and adulthood. Epidemiological evidence accumulated over the last decades has demonstrated an association between low birth weight, inadequate fetal growth, and increased risk of cardiovascular and metabolic diseases in later stages of life, consolidating fetal programming as an important field of biomedical investigation (FAA et al., 2024; TOHI et al., 2022).

The intrauterine environment plays a fundamental role in this process, since maternal factors can significantly modify fetal development. Among the main determinants studied are maternal obesity, gestational diabetes, inadequate nutrition, and inflammatory changes present during pregnancy. These conditions promote modifications in the supply of nutrients, hormones, and inflammatory mediators to the fetus, triggering metabolic adaptations capable of persisting after birth. It is possible that children of pregnant women who are obese or have gestational diabetes have a higher risk of developing obesity, insulin resistance, metabolic syndrome, and cardiovascular diseases throughout their lives, reinforcing the importance of the gestational period as a critical window for determining future health (ALBA-LINARES et al., 2023; SCHEIDL et al., 2023; LOWE JR., 2023).

In addition to immediate metabolic changes, recent research indicates that many of the effects observed in offspring are mediated by epigenetic mechanisms. Epigenetics refers to the set of

modifications capable of regulating gene expression without altering the DNA sequence, including processes such as DNA methylation, histone modifications, and the action of non-coding RNAs. These alterations constitute fundamental mechanisms of fetal adaptation to the intrauterine environment, allowing rapid responses to maternal conditions. However, when persistent, they can promote long-lasting metabolic reprogramming, influencing the expression of genes related to energy metabolism, inflammation, cell growth, and cardiovascular function (CARLBERG, 2023; SAAVEDRA et al., 2024).

DNA methylation stands out among the most investigated mechanisms in the context of fetal programming. Recent evidence has shown that maternal obesity and gestational diabetes are capable of modifying epigenetic patterns in genes involved in lipid metabolism, glycemic homeostasis, and cardiovascular development, producing molecular signatures detectable at birth. These modifications may persist during childhood and influence the future risk of cardiometabolic diseases, suggesting that part of the vulnerability observed in individuals exposed to adverse gestational environments is due to epigenetic changes established early during development (ALBA-LINARES et al., 2023; KWEON et al., 2024).

In addition, maternal diets rich in fats and sugars can induce epigenetic changes in metabolic tissues and appetite regulatory centers located in the central nervous system of the offspring. These modifications affect energy control mechanisms, insulin sensitivity, and inflammatory responses, contributing to the development of obesity and cardiometabolic dysfunction. These findings reinforce the notion that the gestational period represents a phase of high biological plasticity, in which environmental exposures can have lasting effects on the individual's health (ELGAZZAZ et al., 2024; KWEON et al., 2024).

In view of this scenario, understanding the epigenetic mechanisms involved in fetal programming becomes essential for the development of preventive strategies aimed at reducing the global burden of chronic non-communicable diseases. The recognition that gestational factors can influence future cardiometabolic risk amplifies the importance of preconception and prenatal care,

highlighting the need for early interventions aimed at maternal health. In addition, the identification of potentially modifiable epigenetic markers can open new perspectives for prevention, early diagnosis, and personalized therapies in the context of cardiometabolic diseases (SAAVEDRA et al., 2024; TOHI et al., 2022).

Thus, the present study aims to analyze the role of epigenetic alterations in fetal programming and their relationship with the development of cardiometabolic diseases, discussing the main gestational factors involved, the molecular mechanisms described in the recent literature, and the clinical and preventive implications resulting from this process.

MATERIAL AND METHODS

The present study consists of an integrative literature review, conducted based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020), with the objective of synthesizing scientific evidence about fetal programming and its relationship with the development of cardiometabolic diseases mediated by epigenetic alterations.

The bibliographic search was carried out in the PubMed/MEDLINE, Scopus, Web of Science, Embase and Virtual Health Library (VHL) databases, as they are widely recognized for their scope and relevance in the indexing of biomedical studies. The search strategy was elaborated from the combination of controlled descriptors and keywords related to the theme, using the Boolean operators AND and OR. Among the main terms used, “Fetal Programming”, “Developmental Origins of Health and Disease”, “Epigenetics”, “DNA Methylation”, “Maternal Obesity”, “Gestational Diabetes”, “Cardiometabolic Diseases”, “Metabolic Syndrome” and “Cardiovascular Disease” stood out.

Studies published between January 2020 and July 2026, in English, Portuguese, and Spanish, available in full and addressing the association between gestational exposures, epigenetic mechanisms, and cardiometabolic outcomes in offspring, were included. Observational studies, experimental trials, systematic reviews, meta-analyses, and narrative reviews that presented relevant

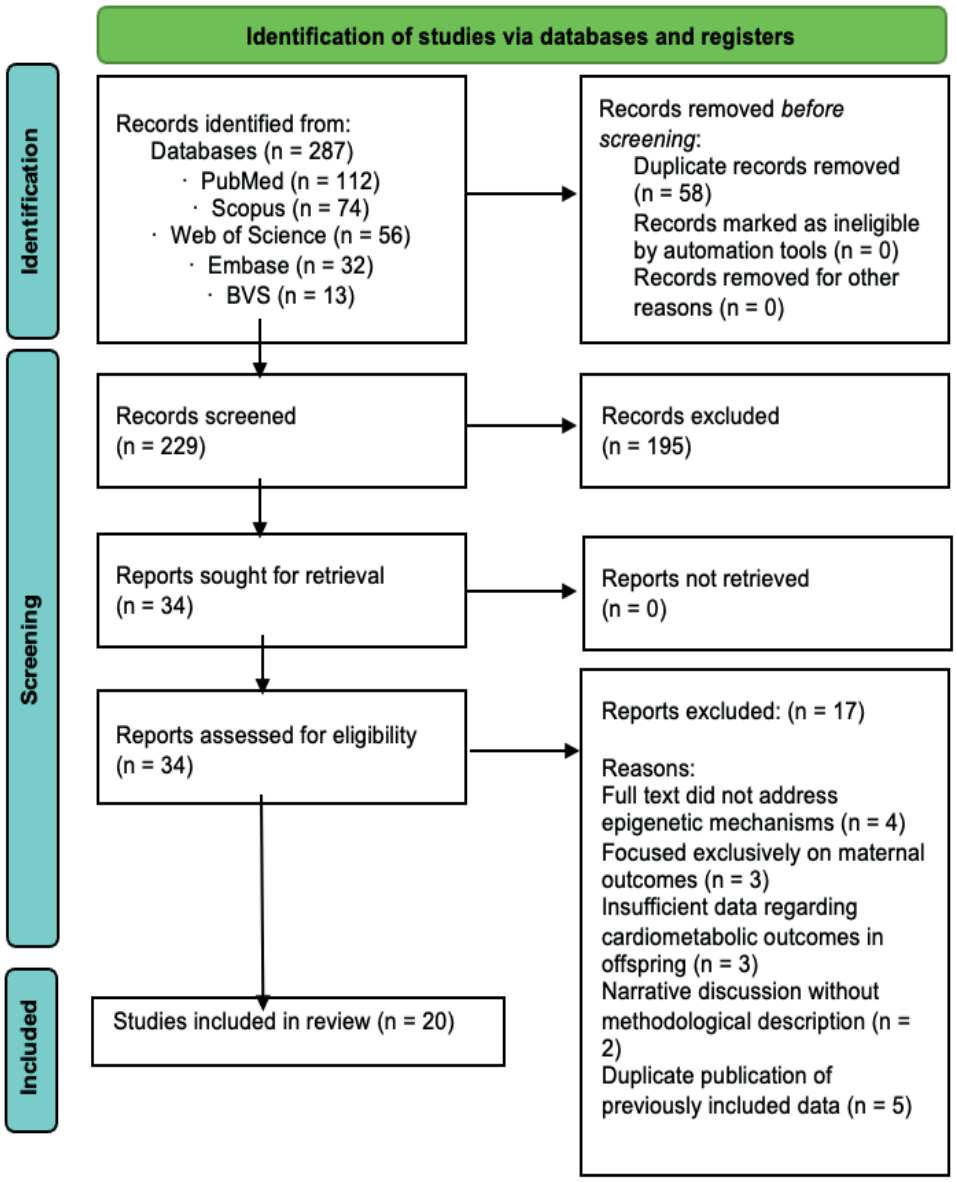
data for understanding the mechanisms involved in fetal programming were considered eligible.

Duplicate articles among the databases consulted, abstracts of scientific events, letters to the editor, editorials, dissertations, theses, book chapters, studies without access to the full text, and publications that did not have a direct relationship with the proposed theme were excluded. Studies whose main focus was not related to epigenetic mechanisms, fetal programming, or cardiometabolic outcomes were also excluded.

The study selection process took place in four stages, as recommended by the PRISMA flowchart. Initially, the articles were identified through search strategies in the selected databases. Then, the duplicates were removed and the titles and abstracts were sorted. Subsequently, potentially eligible studies were submitted to full reading for evaluation of the inclusion and exclusion criteria. At the end of the process, 20 articles that presented greater methodological and scientific relevance were selected to compose the final sample of this review.

After searching the databases, 287 studies were identified. After the removal of 58 duplicates, 229 records were submitted to screening by title and abstract. Of these, 195 were excluded because they did not meet the eligibility criteria. A total of 34 full-text articles were evaluated, of which 17 were excluded after full reading. In the end, 17 studies made up the final sample of this integrative review, as shown in the PRISMA flowchart (FIGURE 1).

Figure 1: PRISMA flowchart of the studies



Source: Authors, 2026

For each included study, information was extracted regarding the authors, year of publication, country of origin, methodological design, population studied, gestational factors assessed, epigenetic mechanisms investigated, and main cardiometabolic outcomes observed. The data were organized in

electronic spreadsheets to facilitate the comparison between the studies and the identification of the main patterns found in the literature.

Data analysis was performed in a qualitative and descriptive manner, allowing the synthesis of available evidence on the influence of gestational factors, especially maternal obesity, gestational diabetes, inadequate maternal diet, and intrauterine growth restriction, on epigenetic mechanisms such as DNA methylation, histone modifications, and regulation by non-coding RNAs. From this analysis, we sought to understand how these alterations can contribute to the development of obesity, insulin resistance, metabolic syndrome, arterial hypertension and other cardiometabolic diseases throughout the life of the offspring.

As this is an integrative review based exclusively on secondary data available in the scientific literature, this study did not involve human beings directly and, therefore, did not require consideration by the Research Ethics Committee, in accordance with current regulations.

RESULTS AND DISCUSSION

Characterization of the selected studies

After applying the eligibility criteria and the selection steps proposed by the PRISMA protocol, 17 studies were included to compose the final sample of this review. The analyzed publications were produced between 2022 and 2024, including narrative reviews, systematic reviews, experimental studies, and observational research. The selected studies presented as a common axis the investigation of fetal programming associated with adverse gestational factors and the epigenetic mechanisms involved in the development of cardiometabolic diseases in offspring.

The studies were developed in different geographical contexts, including North America, Europe, Asia, and Oceania, reflecting the global interest in the Developmental Origins of Health and Disease (DOHaD) paradigm. Among the main factors investigated were maternal obesity, gestational diabetes, inadequate dietary patterns during pregnancy, placental inflammatory processes, and

intrauterine growth restriction. Taken together, the evidence indicates that environmental exposures occurring during critical periods of fetal development are capable of inducing persistent biological adaptations that influence susceptibility to metabolic and cardiovascular diseases throughout life.

In order to systematize the evidence identified and facilitate the comparison between the included studies, a summary table was prepared containing the main methodological characteristics and the main findings of the selected publications. Information regarding the authors and year of publication, study title, methodological design, objectives, main results and conclusions were extracted. This organization allowed us to identify convergences and divergences between the studies analyzed, as well as to understand in a more comprehensive way the influence of gestational factors and epigenetic mechanisms on fetal programming and the development of cardiometabolic diseases throughout the life of the offspring. Chart 1 presents the synthesis of the studies included in this review.

Table 1: Summary and data from the included studies

Author/Year	Title (Portuguese)	Method	Objective	Results
BURDEN et al., 2024	Maternal obesity and cardiovascular remodeling of offspring	Systematic review	To assess the impact of maternal obesity on the fetal cardiovascular system	He showed cardiac and vascular structural alterations in the offspring
ELGAZZAZ et al., 2024	Maternal Western diet and cardiometabolic dysfunction of offspring	Experimental study	Investigate epigenetic effects of maternal diet	Observed hypothalamic inflammation and persistent metabolic changes
FAA et al., 2024	The Fetal Programming Theory of Adult Diseases	Narrative review	Review the foundations of Barker's hypothesis	Confirmed association between fetal environment and chronic diseases
KWEON et al., 2024	Maternal obesity and myeloid reprogramming of offspring	Review	Analyze epigenetic mechanisms related to maternal obesity	Identified persistent immunometabolic alterations
PANAGIOTIDOU et al., 2024	Maternal diet, physical activity and epigenome of offspring	Review	To assess the influence of maternal lifestyle	Identified epigenetic modifications associated with healthy and unhealthy habits
SAAVEDRA et al., 2024	Epigenetic programming of obesity and chronic diseases	Narrative review	Discuss epigenetic mechanisms of fetal programming	Demonstrated association between epigenetics and metabolic diseases
SKOWRONSKI; LEIBEL; LEDUC, 2024	Neurodevelopmental programming of adiposity	Review	Assess neural development associated with obesity	Identified alterations in hypothalamic appetite circuits
TEZIKOV et al., 2024	Epigenetic modifications in fetal metabolic programming	Review	Describe epigenetic mechanisms involved in fetal programming	Highlighted DNA methylation, histones, and non-coding RNAs
YANG et al., 2024	Maternal adiposity and perinatal and offspring outcomes	Umbrella Review	Synthesize evidence on maternal adiposity	Consistent association with obesity and metabolic syndrome in offspring
ZHANG; CANDIA; SFERRUZZI-PERRI, 2024	Placental inflammation and maternal obesity	Review	Evaluate placental mechanisms related to obesity	Oxidative stress and placental inflammation
ZURITA-CRUZ, 2024	Fetal programming and cardiometabolic risk	Narrative review	Review evidence on fetal programming	Identified association between gestational exposures and future diseases

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ALBA-LINARES et al., 2023	Maternal obesity, gestational diabetes, and epigenetic reprogramming	Observational study	Evaluate epigenetic changes in newborns	Detected epigenetic signatures related to metabolism
CARLBERG, 2023	Nutrition and epigenetic programming	Review	Explore the relationship between nutrients and epigenetics	Demonstrated nutritional influence on gene expression
LOWE JR., 2023	Genetics and epigenetics in gestational diabetes	Review	Assess implications of gestational diabetes	Showed persistent metabolic alterations in the offspring
SCHEIDL et al., 2023	Maternal obesity and metabolic syndrome programming	Review	Investigate mechanisms involved in offspring metabolic syndrome	Identified participation of adipocyte progenitors
HARARY; AKINYEMI; CHARRON, 2022	Fetal growth and epigenetic programming of obesity	Review	Discuss fetal growth and cardiometabolic diseases	Showed association between intrauterine growth and metabolic risk
TOHI et al., 2022	DOHaD and adolescence as a critical period	Review	Evaluate strategies to interrupt intergenerational transmission of NCDs	He highlighted adolescence as a strategic phase for intervention

Source: Authors, 2026

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Fetal programming and gestational risk factors

The concept of fetal programming is based on the ability of the developing organism to adapt its structure and function to the environmental conditions present during pregnancy (TOHI et al., 2022; FAA et al., 2024). While these adaptations are critical to immediate fetal survival, they can result in permanent metabolic consequences when the postnatal environment differs from the conditions for which the organism was programmed. This hypothesis has been widely used to explain the increasing incidence of chronic non-communicable diseases in populations exposed to adverse gestational conditions (FAA et al., 2024).

According to the DOHaD model, nutritional, hormonal, and inflammatory stimuli received during intrauterine life influence processes of cell differentiation, tissue growth, and gene expression. In this way, maternal factors such as obesity, gestational diabetes and nutritional alterations are no longer understood only as isolated clinical conditions and are now recognized as biological determinants capable of permanently modifying the health trajectory of the offspring (HARARY; AKINYEMI; CHARRON, 2022; TOHI et al., 2022).

The intrauterine environment acts as an important regulator of fetal gene expression through epigenetic mechanisms. These modifications allow the body to adapt to gestational conditions, but can simultaneously increase the predisposition to obesity, insulin resistance, arterial hypertension and metabolic syndrome in the later stages of life. Thus, fetal programming constitutes a biological link between early exposures and the late onset of cardiometabolic diseases (SAAVEDRA et al., 2024; CARLBERG, 2023).

Maternal obesity as a factor in cardiometabolic programming

Among the gestational factors evaluated in the recent literature, maternal obesity stands out as one of the main determinants of fetal metabolic programming. The global increase in the

prevalence of obesity among women of reproductive age has aroused growing concern due to its effects on intrauterine development and on the future risk of chronic diseases in offspring (SCHEIDL et al., 2023).

Obesity during pregnancy is associated with a metabolic environment characterized by insulin resistance, hyperinsulinemia, dyslipidemia, and chronic low-grade inflammation. These changes promote greater transfer of nutrients to the fetus, especially glucose and fatty acids, stimulating adaptive modifications in fetal tissues. As a consequence, there is a greater predisposition to the accumulation of adipose tissue, changes in energy regulation, and persistent metabolic dysfunctions after birth (SCHEIDL et al., 2023).

In addition to direct metabolic alterations, recent studies have shown that maternal obesity promotes epigenetic modifications in genes involved in energy metabolism and cardiovascular development. Alba-Linares et al. (2023) identified significant changes in DNA methylation patterns in newborns exposed to maternal obesity and gestational diabetes, suggesting that these exposures are capable of inducing epigenetic signatures detectable from birth. Such modifications were observed mainly in pathways related to glucose metabolism, cell growth and tissue differentiation.

Another relevant aspect refers to the participation of the immune system in fetal programming. Kweon et al. (2024) demonstrated that maternal obesity can promote epigenetic reprogramming of fetal myeloid cells, favoring a persistent pro-inflammatory state. This phenomenon contributes to the development of insulin resistance and early metabolic alterations, expanding the understanding of the mechanisms by which gestational obesity influences the future health of offspring.

The placenta also plays a central role in this process. Maternal obesity is associated with increased placental inflammation, oxidative stress, and the production of inflammatory cytokines. These alterations modify the intrauterine environment and directly influence fetal metabolic programming. In addition, they can compromise mechanisms that regulate growth and energy homeostasis, increasing the risk of obesity and metabolic syndrome in childhood and adulthood (ZHANG; CANDIA; SFERRUZZI-PERRI, 2024).

The influence of maternal obesity can exceed a single generation. Epigenetic alterations induced during pregnancy have the potential to persist throughout development and can be transmitted to subsequent generations, contributing to the intergenerational perpetuation of cardiometabolic diseases. This phenomenon reinforces the need for preventive strategies aimed at the preconception and gestational period, with a focus on promoting maternal metabolic health (SAAVEDRA et al., 2024).

Gestational diabetes and fetal metabolic reprogramming

Gestational diabetes is another important factor associated with fetal programming of cardiometabolic diseases. Characterized by glucose intolerance diagnosed during pregnancy, this disorder exposes the fetus to high levels of circulating glucose, triggering metabolic adaptations that can persist throughout life (LOWE JR., 2023).

Maternal hyperglycemia promotes an increase in fetal production of insulin, a hormone that exerts an important anabolic effect during development. Although this response contributes to fetal growth, its prolonged maintenance can permanently alter regulatory mechanisms of energy metabolism. As a result, children of mothers with gestational diabetes have a higher incidence of childhood obesity, insulin resistance, glucose intolerance, and type 2 diabetes mellitus at earlier ages when compared to the general population (LOWE JR., 2023).

Alterations in DNA methylation patterns have been identified in genes related to glucose metabolism, insulin signaling, and pancreatic development of offspring exposed to intrauterine hyperglycemia. These modifications contribute to persistent functional changes that can compromise metabolic homeostasis throughout life (ALBA-LINARES et al., 2023).

In addition to metabolic effects, gestational diabetes also influences inflammatory and cardiovascular processes. Long-term exposure to intrauterine hyperglycemia is associated with increased oxidative stress, endothelial dysfunction, and structural changes in developing cardiovascular

tissues. Such modifications can favor the early onset of hypertension and other cardiovascular diseases, expanding the impact of fetal programming on different organ systems (LOWE JR., 2023).

Intrauterine growth restriction and fetal adaptations

In addition to maternal obesity and gestational diabetes, intrauterine growth restriction (IUGR) is one of the main biological models used to explain the fetal programming of cardiometabolic diseases. According to the sparing phenotype hypothesis, in situations of nutritional limitation or reduction of the placental supply of nutrients, the fetal organism promotes metabolic adaptations aimed at the preservation of vital organs, especially the brain and heart. Although these adaptations favor survival during pregnancy, they can result in permanent changes in energy and cardiovascular homeostasis when the individual is later exposed to environments with nutritional abundance (HARARY; AKINYEMI; CHARRON, 2022).

Individuals born small for gestational age have a higher prevalence of arterial hypertension, insulin resistance, abdominal obesity and metabolic syndrome during adulthood. This phenomenon suggests that adaptations developed during critical periods of development promote structural and functional changes in metabolic organs, including the liver, pancreas, adipose tissue, and cardiovascular system (FAA et al., 2024; ZURITA-CRUZ, 2024). Part of these changes is mediated by epigenetic mechanisms.

Tezikov et al. (2024) highlight that epigenetic modifications established during periods of nutritional deprivation can permanently alter the expression of genes related to energy metabolism, cell growth, and vascular function. Thus, intrauterine growth restriction represents an important example of how early environmental stimuli can influence cardiometabolic risk throughout life.

Epigenetic mechanisms involved in fetal programming

Epigenetics is currently the main biological mechanism capable of explaining the persistence of the effects of fetal programming after birth. Unlike genetic mutations, epigenetic alterations do not modify the DNA sequence, but regulate gene expression in response to environmental stimuli. Among the most studied mechanisms are DNA methylation, histone modifications, and the action of non-coding RNAs (CARLBERG, 2023; TEZIKOV et al., 2024).

DNA methylation is considered the most widely investigated epigenetic mechanism in the context of DOHaD. Recent evidence shows that factors such as maternal obesity, gestational diabetes, and inadequate diet during pregnancy can alter methylation patterns in genes involved in insulin signaling, lipid metabolism, and cardiovascular development. These changes are detectable at birth and may persist during childhood, contributing to an increased risk of future cardiometabolic diseases (ALBA-LINARES et al., 2023; TEZIKOV et al., 2024).

Histone modifications also play a relevant role in fetal programming. These processes regulate the degree of chromatin compaction and directly influence the transcriptional activity of different genes. According to Saavedra et al. (2024), changes in histones associated with adverse nutritional exposures can modify metabolic pathways related to energy storage, inflammation, and cell differentiation, favoring the development of obesity and metabolic syndrome.

Another important mechanism involves non-coding RNAs, especially microRNAs. These molecules regulate gene expression in a post-transcriptional way and participate in fundamental processes for fetal development. Changes in the expression of these RNAs can influence the formation of metabolic tissues, insulin sensitivity, and cardiovascular function, increasing the complexity of the mechanisms involved in fetal programming (TEZIKOV et al., 2024; SAAVEDRA et al., 2024).

Maternal nutrition, fetal epigenome, and metabolic development

Maternal feeding during pregnancy represents one of the most important environmental factors for fetal epigenetic modulation. Specific nutrients act as methyl group donors or influence enzymes responsible for epigenetic regulation, exerting direct effects on the gene expression of the conceptus (CARLBERG, 2023).

Panagiotidou et al. (2024) demonstrated that healthy dietary patterns during pregnancy are associated with epigenetic profiles that are more favorable to the metabolic development of offspring. On the other hand, diets high in saturated fats, simple sugars, and ultra-processed foods can promote epigenetic changes related to increased risk of obesity, insulin resistance, and future cardiovascular diseases.

Corroborating these findings, Elgazzaz et al. (2024) observed that fetal exposure to Western diets promotes epigenetic changes in hypothalamic regions responsible for controlling appetite and energy expenditure. These modifications result in persistent metabolic alterations, reinforcing the importance of maternal nutritional quality as a determinant of the future health of the offspring.

Development of cardiometabolic diseases in offspring

The fetal programming mechanisms discussed above converge to increase susceptibility to different cardiometabolic diseases. Among the outcomes most frequently described in the literature are childhood obesity, insulin resistance, type 2 diabetes mellitus, systemic arterial hypertension, and metabolic syndrome (ZURITA-CRUZ, 2024).

Obesity represents one of the earliest manifestations of metabolic programming. Skowronski, Leibel, and LeDuc (2024) demonstrated that adverse intrauterine exposures can modify the development of hypothalamic neural circuits involved in the control of hunger, satiety, and energy balance. These changes favor higher food intake and predisposition to excessive weight gain during

childhood and adolescence.

In the cardiovascular sphere, evidence indicates that exposure to unfavorable gestational environments can promote structural and functional remodeling of the fetal cardiovascular system. Burden et al. (2024) observed that children of pregnant women with obesity have early changes in cardiac and vascular structure, potentially associated with increased risk of hypertension and future cardiovascular diseases.

In addition, the multi-review analysis performed by Yang et al. (2024) demonstrated a consistent association between maternal adiposity and adverse metabolic outcomes in offspring, including obesity, insulin resistance, and metabolic syndrome. These findings reinforce the existence of a causal relationship between gestational conditions and the development of chronic non-communicable diseases throughout life.

Clinical implications and preventive strategies

The prevention of cardiometabolic diseases should be started even before birth. The recognition of the gestational period as a critical window for future health planning amplifies the importance of preconception, prenatal, and neonatal care strategies (TOHI et al., 2022).

In this context, measures aimed at maternal weight control, prevention of gestational diabetes, promotion of healthy eating habits, and adequate monitoring of pregnancy can significantly reduce fetal exposure to metabolic risk factors. In addition, the identification of epigenetic biomarkers may in the future contribute to the development of early screening strategies and personalized interventions aimed at individuals with greater cardiometabolic vulnerability (PANAGIOTIDOU et al., 2024; YANG et al., 2024).

FINAL CONSIDERATIONS

It was possible to verify that the intrauterine environment exerts a determining influence on the future health of the offspring, acting as an important modulator of physiological processes capable of reverberating from childhood to adulthood.

The results found reinforce the foundations of the concept of Developmental Origins of Health and Disease (DOHaD), demonstrating that exposures occurring during critical periods of fetal development can promote permanent biological adaptations. Although these adaptations are initially compensatory and contribute to the survival of the fetus in the face of adverse conditions, they can result in structural and functional changes that increase susceptibility to the development of chronic non-communicable diseases in later stages of life.

Among the gestational factors most frequently associated with fetal programming were maternal obesity, gestational diabetes, nutritional inadequacy during pregnancy, and intrauterine growth restriction. Evidence has shown that these conditions alter the metabolic, hormonal, and inflammatory environment to which the fetus is exposed, triggering adaptive responses capable of influencing the development of organs and systems involved in energy, metabolic, and cardiovascular regulation. Thus, pregnancy should be understood not only as a period of fetal development, but also as a critical phase for determining the future risk of illness.

Epigenetic mechanisms constitute the main biological link between gestational exposures and cardiometabolic outcomes observed in offspring. Modifications such as DNA methylation, histone alterations, and regulation mediated by non-coding RNAs have been widely associated with modulation of gene expression in tissues that are fundamental for energy metabolism and cardiovascular function. These alterations have the ability to persist after birth, influencing the activity of genes related to insulin sensitivity, lipid metabolism, appetite control, inflammatory response, and vascular homeostasis.

Another relevant aspect identified in this review refers to the multifactorial and complex

nature of fetal programming. There is no single mechanism responsible for the development of cardiometabolic diseases, but rather a dynamic interaction between genetic, environmental, nutritional, and epigenetic factors. This interaction occurs continuously throughout development and can be influenced by maternal characteristics, placental conditions, environmental exposures, and lifestyle habits. This finding reinforces the need for integrated approaches to understand the processes involved in the genesis of these diseases.

Among the main outcomes associated with fetal programming were childhood obesity, insulin resistance, metabolic syndrome, type 2 diabetes mellitus, systemic arterial hypertension and other cardiovascular alterations. The evidence analyzed suggests that many of these diseases originate in biological processes initiated during intrauterine life, which significantly expands the traditional understanding of their etiology. Thus, cardiometabolic risk should not be interpreted exclusively as a consequence of behavioral factors acquired in adult life, but also as a result of early exposures capable of permanently modifying the individual's health trajectory.

From a clinical and public health perspective, the findings of this review have important implications. The recognition of pregnancy as a critical window for the prevention of future diseases reinforces the importance of preconception and prenatal care, especially with regard to maternal weight control, prevention and adequate management of gestational diabetes, promotion of healthy eating habits, and strict monitoring of fetal growth. Interventions performed during these periods have the potential to significantly reduce fetal exposure to risk factors and, consequently, decrease the burden of cardiometabolic diseases in future generations.

In addition, the advancement of research in epigenetics opens up promising prospects for the development of biomarkers capable of early identification of individuals with greater susceptibility to the development of these diseases. The identification of epigenetic signatures associated with fetal programming may in the future contribute to screening, monitoring, and individualized intervention strategies, allowing for more effective and targeted preventive approaches.

However, despite the advances observed in recent years, there are still important gaps in

scientific knowledge. Many of the epigenetic mechanisms involved in fetal programming remain partially understood, especially as it relates to their persistence throughout life and the potential for intergenerational transmission. In addition, the methodological heterogeneity among the available studies highlights the need for long-term longitudinal investigations to allow a more comprehensive understanding of the relationship between gestational exposures, epigenetic alterations and the development of cardiometabolic diseases.

It is concluded, therefore, that epigenetic alterations play a central role in fetal programming and constitute one of the main mechanisms responsible for the association between adverse gestational factors and the development of future cardiometabolic diseases. The evidence analyzed demonstrates that the intrauterine environment has the capacity to permanently influence gene expression and the function of different organ systems, contributing to the determination of health throughout the life cycle. Thus, the understanding of these mechanisms strengthens the importance of preventive strategies aimed at maternal and fetal health, highlighting the need for investments in research, qualified prenatal care, and public policies capable of promoting better health conditions from the early stages of life.

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