Clinical Nutrition ESPEN 74 (2026) 103349

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Narrative Review

Placental programming in maternal malnutrition as a crucial determinant of offspring health: A critical-interpretative narrative review

Luisa Annibal Barata [a,1], Matheus Naia Fioretto [a,1], Natália Magosso [a], Flávia Alessandra Maciel [a], Isabelle Tenori Ribeiro [a], Patrick Vieira de Souza [a], Ana Luiza Romano Gabriel [a], Wellerson Rodrigo Scarano [a,b], Luis Antonio Justulin [a,b,*]

[a] Department of Cellular and Molecular Biology, Institute of Biosciences, Sao Paulo State University, Botucatu, SP, Brazil
[b] Brazilian National Institute of Science and Technology in DOHaD

ARTICLE INFO

Article history:
Received 19 September 2025
Accepted 13 May 2026

Keywords:
Maternal malnutrition
DOHaD
Placenta
Development biology

SUMMARY

Maternal malnutrition during pregnancy is a critical environmental factor that can reprogram placental development and, consequently, influence fetal growth and offspring health across the lifespan. According to the Developmental Origins of Health and Disease (DOHaD) theory, adverse intrauterine conditions - such as nutrient deficiencies or excesses - may induce morphological and functional alterations in the placenta, thereby increasing the risk of chronic noncommunicable diseases (NCDs) in adulthood. This critical-interpretative narrative review compiles evidence on how maternal nutritional disorders, including protein restriction, micronutrient deficiencies, and high-fat diets, compromise placental efficiency by altering nutrient transport, hormonal signaling, and epigenetic regulation. We discuss the interplay between placental dysfunction, impaired fetal development, and increased disease susceptibility in offspring from a sex-specific perspective, highlighting the more adaptive placental responses observed in females and the more pronounced adverse effects and underlying potential pathophysiological pathways in males. Drawing on established studies, we synthesize insights and potential molecular and biochemical mechanisms of placental dysregulation, and propose new directions for research that address not only the consequences for offspring and metabolic programming but also the implications for women's health during critical periods, such as pregnancy. From a DOHaD perspective, this review underscores the central role of the placenta as a mediator between the intrauterine environment and health outcomes, pointing toward preventive strategies and future research approaches.

1. Introduction

The Developmental Origins of Health and Disease (DOHaD) concept establishes that adverse conditions during intrauterine and early postnatal life can induce permanent alterations in the structure and function of specific organs in the offspring [1,2], thereby increasing susceptibility to non-communicable chronic diseases (NCDs) later in life [1,2]. In line with this concept, NCDs are increasingly being diagnosed at younger ages worldwide [3]. In addition, the World Health Organization established that malnutrition, encompassing undernutrition, micronutrient deficiencies, overweight, obesity, and related noncommunicable diseases, remains a global health crisis. In 2022, 2.5 billion adults were overweight - 890 million of whom had obesity - while 390 million were underweight. Among children under 5, 149 million were stunted, 45 million wasted, and 37 million were overweight or obese. Nearly half of all deaths in children under 5 are linked to undernutrition, predominantly in low- and middle-income countries. The consequences of malnutrition are profound and enduring, affecting not only individual health but also economic, social, and

* Corresponding author. Sao Paulo State University (UNESP), Institute of Biosciences of Botucatu, SP, 18618-689, Brazil.
E-mail address: l.justulin@unesp.br (L.A. Justulin).
[1] Co-first authors: These authors contribute equally.

https://doi.org/10.1016/j.clnesp.2026.103349

developmental outcomes at both community and national levels [3]. Specifically, improving the nutrition of adolescent girls and women requires stronger governance, access to affordable healthy foods, protection from ultra-processed products, expanded nutrition services and social protection, effective communication and counselling, and gender-transformative food and nutrition policies [4].

As a starting point of this problem, a wide range of environmental factors can affect embryonic and fetal development, including exposure to toxic agents, chronic stress, and, most prominently, nutritional alterations. Among the most widely studied models are dietary interventions, in which both restrictive diets (low-protein, hypocaloric, or deficient in micronutrients) and excessive diets (high-fat or hypercaloric) have been shown to modulate organ and system development in the offspring [5–7]. Epidemiological and experimental evidence have consistently associated maternal undernutrition with an increased risk of cardiovascular disease, hypertension, obesity, and type 2 diabetes in adulthood [1,8]. Likewise, high-fat and hypercaloric diets have been reported to induce an inflammatory intrauterine environment, thereby predisposing offspring to metabolic and hepatic disorders [9].

Within this context, the placenta emerges as a central mediator between maternal nutrition and offspring health outcomes. This transient yet highly specialized organ forms the vital interface between mother and fetus, coordinating the transfer of nutrients and oxygen, the elimination of metabolic waste, and the synthesis of essential hormones [10–14]. Beyond its metabolic and endocrine functions, the placenta also plays a pivotal immunological role by maintaining maternal–fetal tolerance and acting as a protective barrier against potential threats [10,11]. Disruptions in placental development - referred to as abnormal placentation - are closely linked to intrauterine growth restriction (IUGR) and other pregnancy-related complications [12,13]. These associations highlight the placenta's fundamental role in fetal programming and its function as a biological conduit for the non-genomic transmission of risk for NCDs later in life [1,14,15].

Recent evidence suggests that adverse maternal dietary exposures can trigger endocrine and structural dysfunctions in the placenta. High-fat diet (HFD) impairs placental morphology, promotes lipid accumulation, reduces adhesion molecule expression, and compromises trophoblast differentiation. In contrast, a protein-restricted diet alters placental hemodynamics, growth factor expression, and nutrient transport [16,17]. Conversely, interventions such as maternal exercise or nutritional supplementation have shown the potential to attenuate these effects, improving placental function, maternal metabolic status, and the intrauterine environment [18,19]. Another crucial aspect is that male and female fetuses exhibit distinct regulatory and developmental trajectories, largely mediated by sex-specific placental structure and function. The placenta responds in a sex-specific manner to nutritional challenges, influencing nutrient transport, endocrine signaling, and stress responses. These sex-dependent placental adaptations can differentially shape fetal programming and persistently affect postnatal development, thus increasing susceptibility to sex-specific metabolic and physiological dysfunctions [20,21].

In this context, the present critical-interpretative narrative review aims to synthesize current evidence on how different models of maternal malnutrition - particularly low-protein, high-fat, and restrictive diets - affect placental structure and function. Furthermore, we seek to correlate these placental alterations with adverse developmental outcomes in the offspring, highlighting the placenta as a pivotal starting point in the programming of NCDs. Accordingly, we propose, based on already established studies, numerous insights and possible molecular and biochemical mechanisms dysregulated in the placenta, as well as future perspectives for studies not only on the consequences for offspring and metabolic programming, but also for studies that aim to understand maternal health during critical periods such as pregnancy.

2. Review methodology

This critical-interpretative narrative review searched for its literary base on the Pubmed platform (https://pubmed.ncbi.nlm.nih.gov) and applied its search through the following terms used: Maternal Protein Restriction Diet and Placenta (total of 210 manuscripts); Maternal Low Protein Diet and Placenta (total of 125 manuscripts); Maternal High Fat Diet and Placenta (total of 269 manuscripts); Maternal Micronutrient Restriction and Placenta (total of 137 manuscripts) - The manuscript selection years ranged from 2000 to 2025.

Inclusion criteria comprised experimental studies investigating the effects of maternal malnutrition—specifically protein and macronutrient deprivation or restriction, as well as HFD—during the preconception period, pregnancy, or both, on placental structure and function. Eligible studies evaluated outcomes in the placenta itself, in the offspring during fetal or early postnatal stages, and/or in the mothers. In addition, epidemiological and comparative studies establishing associations between maternal malnutrition and IUGR were included, as IUGR is widely recognized as a key indicator of placental dysfunction resulting from inadequate maternal nutrition. Studies assessing potential mitigating strategies, such as maternal exercise or nutritional supplementation, were also considered, given their reported ability to improve placental function, maternal metabolic status, and the intrauterine environment (Fig. 1).

Exclusion criteria included studies employing hypocaloric or hypercaloric diets characterized by excessive carbohydrate intake, as well as those that did not report placenta-specific outcomes. Synthesis studies, including systematic reviews, meta-analyses, and network meta-analyses, were excluded. Furthermore, studies evaluating maternal malnutrition in combination with other adverse exposures were not considered to minimize confounding and allow clearer interpretation of the isolated effects of inadequate nutrition during pregnancy. After considering all these criteria, 80 manuscripts were selected, with 24 related to maternal low-protein diet (LPD), 11 to maternal micronutrient restriction, and 45 to maternal HFD (Fig. 1).

3. Maternal undernutrition

3.1. Maternal protein restriction

LPD is a very interesting model because it mimics aspects of food insecurity and hunger, as well as aspects of malnutrition, emphasizing insufficient protein intake, in contrast to caloric intake that may or may not be sufficient. In C57BL/6J mice exposed to maternal LPD, there was a decreased placental weight, altered fetal biometry, and reduced glycogen content in the junctional zone and glycogen trophoblast markers (*Pcdh12* and *Prl3a1*), indicating impaired energy storage and function [20]. Complementary findings demonstrated that fetal sex modifies this response: male fetuses exhibited IUGR, decreased glycogen in trophoblast and spongiotrophoblast cells, increased *Phlda2* expression, and reduced *Egfr*, while female fetuses remained unaffected at the same stage [21]. Interestingly, these findings may indicate direct impairment not only to the action of glycogen synthase and the anabolic mechanisms associated with

carbohydrates, but also to endocrine impairment of the insulinemic response or even excessive catabolism (e.g., via corticosterone), conditions that are certainly impacting maternal health, but also the essential availability of energy reserves to the fetus.

Additional rodent models confirm growth-related impairments. In pre-implantation models, maternal LPD deficiency altered the biometric aspects of male offspring, including *Igf2* and *H19* levels, as well as placental weight [22]. At the early post-implantation stage, explants from maternal LPD mice showed increased trophoblast giant cell proliferation and spreading, resulting in smaller placentas but larger fetuses at later gestation, leading to higher fetus-to-placenta ratios, without major alterations in mTOR signaling [23]. Wistar rats exposed to maternal LPD showed reduced acetylcholine sensitivity and decreased placental and fetal weights, suggesting that impaired vasodilation may compromise maternal cardiovascular adaptation and limit fetal development [24]. Another study reported an increase in placental weight and placenta-to-fetal weight ratio, reduced fetal weight, with subtle shifts in placental structure, such as an increase in non-labyrinth volume and maternal–fetal surface area [25]. In contrast, *Sprague Dawley* rats fed a 4% protein diet showed no differences in placental or fetal weight until late gestation, when both were significantly reduced. These changes were associated with downregulation of SNAT2 and mTOR in the placenta, likely linked to reduced maternal insulin, leptin, and IGF-I levels [26]. In this context, the placenta displays distinct adaptive responses to varying degrees of protein malnutrition. These adaptations may manifest as structural and angiogenic insufficiency or, conversely, as increased placental weight, potentially reflecting compensatory mechanisms associated with maternal neuroendocrine dysregulation. Across different experimental models and severities of malnutrition, such disturbances are consistently characterized by imbalances in catabolic and anabolic processes, driven by impaired placental handling and systemic circulation of key hormones and growth factors involved in glucose uptake (e.g., insulin), biosynthesis and growth (e.g., IGF), and appetite regulation (e.g., leptin). Collectively, these alterations may program the fetus not only toward delayed somatic development but also toward long-lasting changes in postnatal physiology and behavior.

Maternal LPD led to IUGR, decreased *Wnt2* and increased *Dlk1* placenta expression, with hypomethylation at CpG sites in the *Wnt2* promoter, suggesting an epigenetic basis for programming development [27]. In TIE2-GFP transgenic mice, LPD reduced placental and fetal weights, shortened labyrinthine vessels, and disrupted vascular cadherin and β-catenin organization [28]. Ultrastructural analyses in Wistar rats revealed cytoplasmic disorganization, vacuolization, and mitochondrial alterations in placental cells from both sexes [29]. Maternal LPD also reduced pup weight while maintaining placental weight but triggered transcriptional reprogramming with activation of apoptotic and *p53* pathways and downregulation of genes involved in nucleotide metabolism and epigenetic regulation, suggesting compensatory but maladaptive adaptations [30]. Together, these studies underscore that maternal LPD alters placental growth, morphology, and metabolism through both structural, epigenetic, and molecular mechanisms.

Specifically, maternal LPD led to growth alterations that persisted into adulthood as obesity and insulin resistance. These effects coincided with upregulation of angiogenic factors such as FGF2, VEGFR2, and IGF2, likely reflecting compensatory angiogenesis. Moreover, maternal LPD increased pro-angiogenic M2 macrophages and TNF-α-producing macrophages while reducing anti-angiogenic iNKT cells, highlighting inflammatory modulation of placental angiogenesis [31]. Primate models provide further evidence of impaired vascular function. Severe maternal LPD impaired placental oxygenation and perfusion, reduced vascular caliber and density, and increased pregnancy loss [16,32]. Additional studies reported reduced taurine uptake, increased PLGF

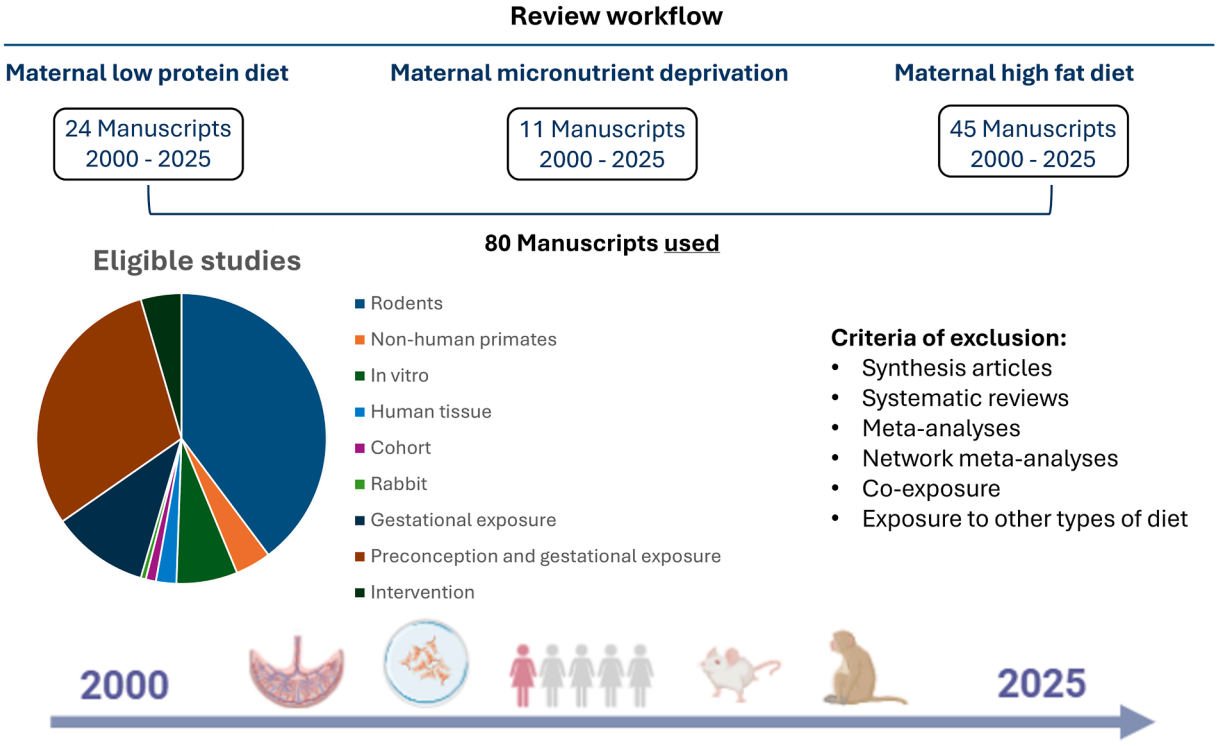

Fig. 1. The workflow of the manuscript illustrates the methodological approach used for the selection and exclusion, analysis, and integration of studies addressing the effects of maternal malnutrition on placental development and function. The Figure was composed using some illustrations from biorender.com (https://app.biorender.com/).

expression, and accelerated villous maturation under restriction, with preserved fetal growth in moderate deficiency, but fetal growth restriction and hypoxia in severe restriction [17,33]. In female golden Syrian hamsters, maternal LPD from preconception through lactation causes intrauterine inflammation, increased amniotic fluid hsCRP, neutrophil recruitment at the fetal–placental interface, and upregulation of pro-inflammatory mediators. Placental chorioamnionitis was associated with elevated NF-κB, IL-8, COX-2, and TGFβ expression in the chorioamniotic membrane. These placental changes occurred alongside maternal metabolic alterations such as reduced pre-gestational body weight and placental and fetal weights, lower serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and increased platelets, lymphocytes, insulin, and high-density lipoprotein (HDL) levels [34]. Collectively, these findings emphasize that the severity of protein restriction determines whether adaptive metabolic, vascular, inflammatory, and growth responses succeed or fail. Given this, it is quite plausible to consider that there are systemic, neuroendocrine, and organ-specific adjustments and adaptations to the dietary challenge of malnutrition, to sustain maternal, placental, and fetal brain metabolism, which will certainly lead to negative and perhaps irreversible consequences in other organs such as the pancreas, liver, and muscles.

Maternal LPD also activates adaptive and maladaptive signaling pathways in the placenta. In *Sprague Dawley* rats, maternal LPD increased expression of *Atf3*, *Asns*, and *Snat2*, alongside elevated *Atf4* and phosphorylated *Eif2α*, indicating activation of the amino acid response pathway as a fetal survival mechanism under nutrient restriction [35]. Similarly, glucocorticoid regulation is altered: maternal LPD decreased placental *Hsd11b2* expression, increasing fetal glucocorticoid exposure and contributing to long-term programming of hypertension in both male and female offspring [36]. From a steroidogenic and hormonal perspective, placentas from maternal LPD-exposed rats showed deregulation of *Cyp11a1*, *Hsd3b1*, and *Cyp17a1* driven mainly by gestational age rather than diet, whereas *Hsd17b2* displayed zone- and sex-specific regulation, suggesting a role in testosterone modulation. Additionally, reduced *Ace2* expression in the labyrinth zone under protein restriction implicates altered uteroplacental renin–angiotensin system activity and potential programming of hypertension [37,38]. These results strongly suggest a systemic imbalance that may be associated with the adrenals and gonads, as well as the basal placental capacity for steroidogenesis and fetal protection, which may directly expose maternal catabolic disorders to fetal development, leading to metabolic programming and fetal growth restriction, mechanisms that determine the risk of developing metabolic diseases in postnatal life.

Finally, mitochondrial adaptations have been identified. In rats exposed to maternal LPD, placental weight, *Slc38a2*, and *Igf2* expression decreased, whereas placental ATP content increased. Complementary experiments in BeWo trophoblast cells showed that amino acid deprivation induced mitochondrial hyperfusion, suggesting a stress-induced response to enhance energy efficiency [39]. This study highlights that nutrient stress drives a spectrum of adaptive placental signaling mechanisms, specifically on mitochondrial function.

Given the adverse outcomes of maternal LPD, interventions have been explored. In an experimental model, supplementation with citrulline or arginine improved fetal growth despite protein restriction by increasing fetal arginine availability and enhancing expression of placental amino acid transporters such as SNAT4, LAT1, and LAT2. Notably, while low-protein diets alone decreased SNAT4 and increased LAT2 and SNAT1, supplementation reversed these effects [40]. Similarly, curcumin supplementation attenuated maternal LPD-induced reductions in placental and fetal weights, restored placental efficiency, improved antioxidant defenses, and reduced apoptosis, suggesting a protective role against placental dysfunction and fetal growth restriction [19].

Overall, studies linking the effects of maternal LPD on the placenta elucidate numerous characteristics of impairment and adaptations in placental structure and the maternal–fetal interface, providing important mechanistic and molecular changes in biomarkers associated with placental circulation, growth factors, hormonal response, cell cycle control, and inflammation. This provides a solid foundation for future studies that comprehensively investigate changes at the transcriptomic, proteomic, and even epigenomic levels - tracing the possible developmental origins of the disease and metabolic programming in offspring, as well as highlighting placental and maternal health and extraplacental consequences. This will inform translational and clinical studies, as well as public policy initiatives to mitigate food insecurity and hunger. The general insights about maternal LPD and placental consequences are compiled in Table 1 and Fig. 2.

3.2. Maternal micronutrient deprivation

In addition to macromolecular malnutrition, there may also be a deprivation of micronutrients essential for biochemical processes, enzymatic action, and, consequently, placental function. This context encompasses both an aspect of malnutrition and low food/dietary quality [10–12]. In rats, iron-restricted diets starting from weaning until mating led to marked reductions in maternal and fetal hemoglobin and iron levels, alongside reduced fetal and liver weights, but increased placental weight [41]. These compensatory effects were accompanied by upregulation of placental transferrin receptor and *Dmt1* + IRE mRNA expression, optimizing iron uptake and release to sustain fetal demands [41]. Maternal iron deficiency reduced maternal and fetal hemoglobin levels, decreased fetal and liver weights, and increased placental weight through junctional zone expansion. *In vitro*, iron chelation promoted trophoblast differentiation toward junctional zone subtypes, while transcriptomic analysis identified 464 placental genes altered in pathways related to oxygen transport, lipoprotein metabolism, and iron homeostasis [42]. In addition, iron restriction impaired placental vascularization, reduced capillary area and length densities, while endothelial cell volume increased. Interestingly, two weeks of iron restriction specifically increased labyrinthine volume and maternal–fetal interface surface area, indicating time-dependent placental remodeling that likely contributes to fetal growth restriction [43]. Therefore, maternal iron deficiency appears to directly disrupt placental vascular homeostasis. This factor will certainly impair the supply of fetal oxygen and nutrients, as well as the elimination of metabolic waste.

In primary human trophoblast cells, folate deprivation for up to 90 h preserved cell viability but markedly inhibited mTORC1 signaling, reducing S6K1 phosphorylation by ~75%. System A and L amino acid transporter activity was also diminished, indicating direct impairment of placental nutrient transport [44]. Pregnant mice carrying a functional deficiency in the MTHFD1 enzyme and fed a low-folate diet showed a twofold increase in developmental delays and embryonic defects. Placental dysmorphisms included abnormal maternal sinus formation and defective labyrinth and spongiotrophoblast layers [45]. In contrast, mice exposed to lipopolysaccharide (LPS), high-dose folic acid administration prevented preterm delivery and fetal death. Mechanistically, folate inhibited NF-κB activation in placenta and trophoblast cells, reduced COX-2 expression, and decreased IL-6 and KC levels in amniotic fluid, highlighting its anti-inflammatory role in pregnancy protection [46]. These data are quite interesting, as folic acid (vitamin B9) acts as a coenzyme (5-methyltetrahydrofolate) by

Table 1
General and specific results, exposure, animal model, and studies about maternal LPD and placenta.

Main result	Time and type of exposure	Animal model	Sex	Reference
Changes in the placental microvasculature	13% protein during the pre-gestational period (at least 3 months prior to timed-mated breeding)	Rhesus Monkeys	N/A	[16]
Increased PLGF expression and accelerated villous maturation.	13% and 17% protein during gestation	Rhesus Monkeys	N/A	[17]
Maternal curcumin supplementation attenuates the negative effects of placental function and fetal growth.	8% protein plus curcumin supplementation during gestation	Mice	N/A	[19]
Alterations in the placental glycogen, *Pcdh12,* and *Prl3a1* expression.	6% protein 10.5, 17.5, and 18.5 days of gestation	C57BL/6J mice	N/A	[20]
Sexual dimorphism and specific cellular changes in the junctional zone (e.g., greater efficiency in females and a transient increase in transporters in males).	6% protein for two weeks before mating	C57BL/6 mice	Male and Female	[21]
Alterations in the *H19* and *Igf2* expression in males.	9% protein for the preimplantation period and gestation	Wistar rats	Male	[22]
Changes in post-implantation trophoblast phenotype and their consequences for the placenta and fetal profile	9% protein for the preimplantation period and gestation	Mice and *in vitro* studies	N/A	[23]
Vasodilatory responses and inadequate cardiovascular adaptation to pregnancy	9% protein during gestation	Wistar rats	N/A	[24]
Changes in placental composition and surface area	8% protein during pregnancy	Wistar rats	N/A	[25]
Downregulation of placental system A transport in response to maternal LPD	4% protein starting at GD 2 and continuing throughout pregnancy	*Sprague Dawley* rats	N/A	[26]
Differential gene expression of *Wnt2* and *Dlk1* between IUGR and control placentas.	9% protein during gestation	Wistar Han rats	N/A	[27]
Alterations in the vascular integrity of the placenta	9% protein during gestation	Tie2-GFP transgenic mice	N/A	[28]
Alterations in placental morphology and mitochondrial function	6% protein during gestation	Wistar rats	Male and Female	[29]
Upregulation of apoptosis and downregulation of cell proliferation and growth	Diet with 50% less protein between postcoital days 10.5 and 17.5.	FVB/NJ mice	N/A	[30]
Alterations in angiogenic and pro-inflammatory factors in the placenta.	8% protein for 3 weeks prior to breeding and throughout pregnancy	*Sprague Dawley* rats	N/A	[31]
Impact on placental hemodynamics in severe LPD	13% and 17% protein for preimplantation period and gestation	Rhesus Monkeys	N/A	[32]
Placental dysfunction and fetal hypoxia	13% protein for preimplantation period and gestation	Rhesus Monkeys	N/A	[33]
Placental inflammation or chorioamnionitis by hsCRP, NF-κB, IL-8, COX-2, and TGF-β.	10% protein for preconception until lactation	Golden Syrian hamsters	N/A	[34]
Alterations in placental genes associated with the amino acid pathway.	9% protein during gestation	Sprague Dawley rats	N/A	[35]
Alteration of glucocorticoid expression in placental and fetal tissues	9% protein during gestation	Wistar rats	Male and Female	[36]
Reduction in the expression of angiotensin I-converting enzyme 2 and temporally differential expression of *Ace2* and ACE in males and females.	6% protein from day 1 of pregnancy to days 14 and 18	*Sprague Dawley* rats	Male and Female	[37]
Changes in *Cyp11a1* and *Cyp17a1* (higher in females), *Hsd3b1* and *Hsd17b2* (reduced in males) expression.	6% protein from day 1 of pregnancy to days 14, 18, or 21	*Sprague Dawley* rats	Male and Female	[38]
Alterations in the expression of *Slc38a2* and *Igf2*, as well as changes in placental content and ATP levels	8% protein from two weeks prior to mating to the end of pregnancy.	C57BL/6 mice and human trophoblast cells (BeWos)	N/A	[39]
Increase the gene expression of several amino acid transporters in the placenta	4% protein, either alone or supplemented with 2 g/kg/d of L-citrulline or isonitrogenous arginine	*Sprague Dawley* rats	N/A	[40]

participating in metabolic reactions of carbon unit transfer, being essential for the synthesis of DNA, purines and thymidine, and for the metabolism of amino acids such as homocysteine and serine, that is, anabolic aspects, and its depletion appears to have an evidently negative role on placental structure and development.

Considering other nutrient deprivation, vitamin D-deficient rats developed gestational hypertension, with reduced vascular diameter in the labyrinth zone on embryonic day (E) 14, indicating impaired perfusion. Fetuses initially showed increased weight, but exhibited late-onset growth restriction by postpartum day 14. Periconceptional vitamin D supplementation attenuated these effects, suggesting partial reversibility [47]. Additionally, maternal vitamin D_3 supplementation protected against inflammation-induced placental dysfunction. In pregnant mice exposed to LPS, pretreatment with vitamin D_3 suppressed NF-κB activation in labyrinth trophoblasts, reduced inflammatory responses, and prevented IUGR. This protective mechanism was mediated by enhanced vitamin D receptor signaling and direct interaction between the vitamin D receptor (VDR) and NF-κB p65 subunit [48].

Maternal selenium deficiency increased maternal thyroid hormones (T3 and T4) while reducing fetal glucose levels and body weight. Placental adaptations included elevated glycogen content,

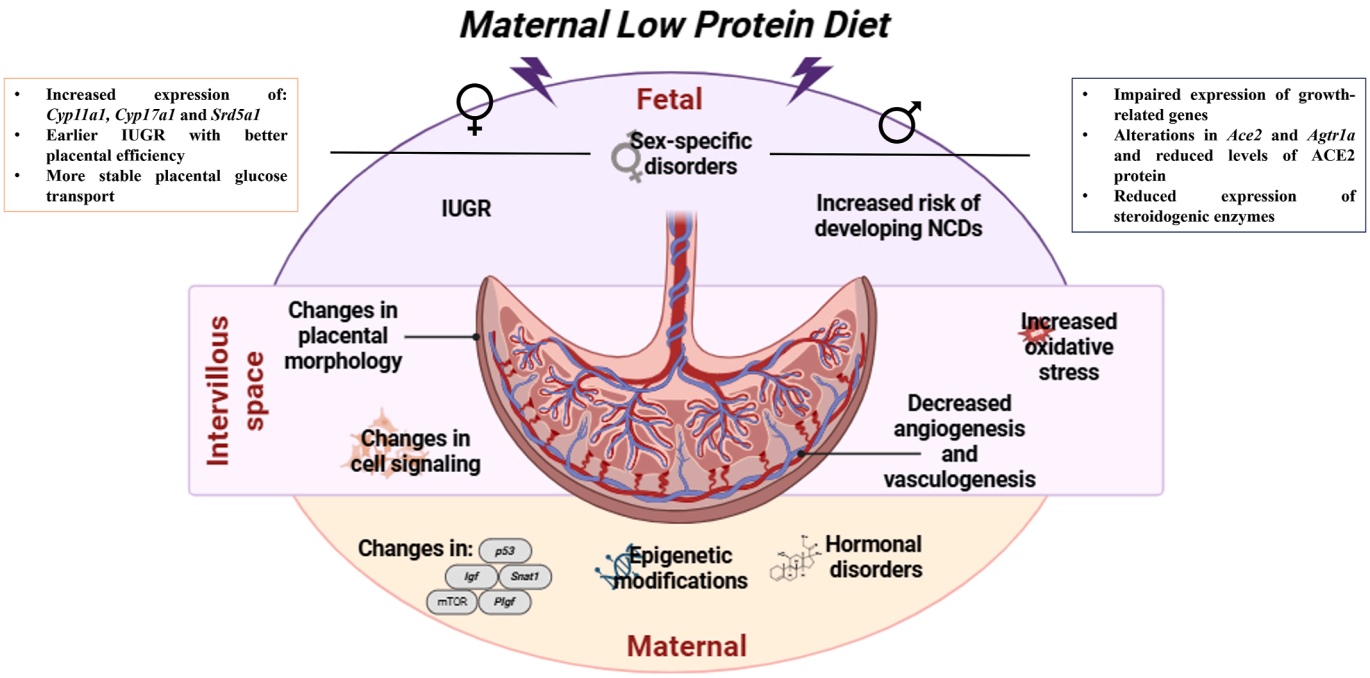

Fig. 2. Placental alterations resulting from preconceptional and gestational maternal LPD and their impact on fetal development, as demonstrated by experimental and epidemiological studies. The Figure was composed using illustrations from biorender.com (https://app.biorender.com/).

increased *Slc2a3* expression, and downregulation of selenium-dependent deiodinases (DIO2 and DIO3), indicating disrupted nutrient allocation and endocrine signaling. These effects were sex-specific: female placentas showed greater sensitivity, with pronounced alterations in glucose and amino acid transporters and reduced DIO2 expression, whereas male placentas exhibited stronger activation of antioxidant defenses, including increased SOD1 expression [49].

Micronutrient restriction involving vitamin E, zinc, and copper in Swiss albino mice caused reduced offspring body size and programmed long-term metabolic dysfunctions, including glucose intolerance, hyperinsulinemia, hyperlipidemia, and elevated systolic blood pressure. Placental mechanisms involved decreased *Hsd11b2* expression, limiting the inactivation of maternal cortisol and exposing the male fetus to glucocorticoid overexposure [50]. In humans, a large cohort study with over 3000 pregnant women in China showed that maternal zinc deficiency was associated with low birth weight and small-for-gestational-age (SGA) births. Placental analyses revealed excessive NF-κB p65 activation in trophoblasts, accompanied by elevated maternal inflammatory proteins (CRP, TNF-α, IL-8). Interestingly, cord blood zinc levels were not reduced, suggesting that placental inflammation, rather than fetal zinc deficiency per se, underlies the observed growth restriction [51]. These results are also relevant, especially considering the epidemiological basis - specifically, zinc acts as a cofactor in many biochemical pathways, participating in processes such as antioxidant defense, immune function, cell division, the Krebs cycle, and the metabolism of amino acids and proteins - that is, its depletion can lead to severe biochemical impacts on placental function and the maternal–fetal interface.

In general, studies linking the effects of deprivation of specific nutrients (water-soluble and fat-soluble vitamins and minerals) on the placenta elucidate numerous potential consequences for important biochemical pathways associated with carbohydrate and protein metabolism, paving the way for studies investigating these consequences for lipid metabolism. This provides a solid foundation for future studies investigating the combined depletion of various types of micronutrients - tracing the possible origins of disease development and metabolic programming in offspring - particularly regarding the association of these molecules as coenzymes and cofactors of placental enzyme action. The general insights about maternal micronutrient deprivation and placental consequences are compiled in Table 2 and Fig. 3.

4. Maternal overnutrition - maternal high-fat diet

The context of the maternal HFD is also of great relevance, given the Western consumption pattern established after the industrial revolution, which encompasses not only ultra-processed foods with low nutritional value, but also foods with exorbitant amounts of saturated fats, which contextualizes a situation of malnutrition resulting, mainly, from a pattern of excessive consumption. Experimental models elucidated that maternal HFD upregulates placental mRNA expression of *Ptgs2*, *Limk1*, *Pla2g2a*, *Itga1*, and *Serpine1* in *Sprague Dawley* rats [52]. Wang et al. (2021) reported that maternal HFD altered placental structure, maternal gut microbiome, and the metabolism-related transcriptome, while reducing the expression of G-protein-coupled receptor 43 (GPR43). These changes were associated with fetal hepatic steatosis, characterized by oxidative stress and increased expression of lipogenic markers such as acetyl-CoA carboxylase 1 (ACC1) and lipoprotein lipase (LPL), in *Sprague Dawley* rats [53]. Together, these data highlight the potential of HFD to impact placental lipid metabolism, possibly potentiating arachidonic acid pathways and post-transcriptional disturbances, which impact the maternal–fetal interface and expose the fetus to excessive diet, impairing liver health.

Maternal HFD reduced pup and placental (labyrinthine zone) weights in both sexes in a *Sprague Dawley* model, altering the placental transcriptome (*Ren*, *Atp6ap2*, *Ace*, and *Agtr1a* through the ACE/Ang II/AT1R axis expression). This finding suggests that disturbances in the fetoplacental renin–angiotensin systems may

Table 2
General and specific results, exposure, animal model, and studies about maternal micronutrient deprivation and placenta.

Main result	Time and type of exposure	Animal model	Sex	Reference
Alterations in *Dmt1* + IRE, transferrin receptor (*Tfr*), and iron transport	Low iron (7.5 mg/kg) diet from weaning and for 4 weeks prior to mating	Wistar rats	N/A	[41]
IUGR, expanded junctional zone size, and altered gene expression within the placenta	Iron-restricted diet group (3 mg/kg), two weeks before mating	*Sprague Dawley* rats	N/A	[42]
Iron deficiency in the litter alters placental vascularization, contributing to IUGR	Low iron diets (iron 3 mg/kg), 1 or 2 weeks before mating, and reinforced with these diets throughout gestation.	Wistar rats	N/A	[43]
Folate deficiency reduces mTOR pathway activation in trophoblasts.	Folate-deficient media	Term placental tissue from healthy pregnant women; primary PHT cells	N/A	[44]
A combination of a low folate diet and maternal MTHFD1 synthetase deficiency increases the incidence of defects and developmental delays	Folic acid–deficient diet for 4–8 weeks before mating and throughout pregnancy	BALB/cAnN MTHFD1S mice	N/A	[45]
Folic acid may mitigate inflammation-related gestational complications.	Oral administration of folic acid at doses of 0.6, 3, or 15 mg/kg prior to LPS injection (high dose: 300 μg/kg/low dose: 75 μg/kg) in pregnant mice	ICR mice and Human trophoblast-like cell line JEG-3	N/A	[46]
VitD deficiency predisposes to placental dysfunction and gestational hypertension	Vitamin D-sufficient or -deficient diets from weeks 4 of age until mating	BL6 mice	N/A	[47]
$VitD_3$ suppressed placental inflammation and protected against IUGR	LPS (100 μg/kg) from GD15 to GD17 and VitD3 supplementation (25 μg/kg) daily from GD14 to GD17.	ICR mice and Human JEG-3 cells, a placental trophoblast-derived cell line	N/A	[48]
Low selenium intake disrupts placental transport and metabolic regulation, increasing sensitivity in females and SOD1 activation in males.	Low selenium (<50 μg kg-1) diets 4 weeks prior to mating and throughout gestation.	C57BL/6 mice	Male and Female	[49]
Maternal micronutrient deficiency may program placental expression of *Hsd11b2*	Diet restricted to 50% of vitamin E, Zn, or Cu, and mated	Swiss albino mice	Male	[50]
Zinc deficiency is responsible for inflaming the placenta, altering the levels of CRP, TNF-α, and IL-8	For serum zinc level: Sufficient (≥56 μg/dL) and 247 deficient (<56 μg/dL).	Cohort that recruited 3187 pregnant women (mothers and singleton offspring)	N/A	[51]

cause poor placental vascularization and placental dysfunction, in turn compromising fetal growth [54]. Another study with maternal HFD in C57BL/6 mice observed a reduction in the volume of the placental labyrinth zone and an imbalance in the proteomic placental profile (downregulation of cell adhesion proteins, impaired syncytial fusion, increased linoleic acid), a condition that promotes lipid accumulation and reduces adherent junction stability through beta-catenin regulation [18]. In HFD-fed Swiss mice, obesity-prone dams developed placental insufficiency and IUGR, whereas obesity-resistant dams maintained glucose homeostasis and upregulated PGF, protecting placental function [55]. Complementary evidence from in vivo (C57BL/6 mice) and in vitro models demonstrated that maternal HFD increases circulating chemerin levels while reducing placental GPR1 expression and downstream targets, including GLUT3 and FABP4, via the AKT signaling pathway. These alterations resemble those observed in placentas from patients with gestational diabetes mellitus (GDM). GPR1 knockdown in BeWo cells recapitulated these effects, supporting a direct role for GPR1 signaling in regulating placental glucose and lipid metabolism. Collectively, these findings identify GPR1 as a key mediator of metabolic adaptations at the maternal–fetal interface and suggest its potential as a biomarker and therapeutic target in GDM [56]. In C57BL/6J mice, maternal HFD increased adiposity, lowered adiponectin, and caused fetal overgrowth, accompanied by enhanced placental transport of glucose and neutral amino acids through selective upregulation of GLUT1 and SNAT2 in microvillous membranes [57]. Maternal HFD also altered the metabolome, particularly lipid pathways, with reduced myo- and chiro-inositol in C57BL/6J mice. In parallel, transcriptomic changes in placental precursors affected angiogenesis and vascular development, leading to reduced placental vascular density and impaired fetal development, being more pronounced in males than females [58]. There was increased expression of *Slc38a2*, *Igf2*, and *Igf2r* in male placentas, *Slc38a4* in females, and *Nr3c1* in both sexes, suggesting that enhanced glucocorticoid signaling may stimulate amino acid transporter expression in maternal HFD C57BL/6J mice model [59]. These studies provide important insights into a model-specific and omics view of how maternal HFD impacts placental structure, metabolic response, and growth factors, certainly compromising the capacity of the maternal–fetal interface.

Another experimental study in *Sprague Dawley* rats showed that maternal HFD exacerbated gestational hyperlipidemia and the effects of diabetes, placental lipid accumulation, and decreased expression of fatty acid transporters (*Cd36*, *Fabp3*, *Pparg*, *Plin2*, *Adrp*, and *Irs1*) [60]. In a vascular endothelial injury model in C57BL/6J mice, maternal HFD induced glucose intolerance, increased fetal resorption rates, reduced the placental sinusoidal area ratio, and decreased CD31 expression, indicating impaired placental angiogenesis and adverse pregnancy outcomes. Notably, modulation of KLF4 was suggested as a potential strategy to preserve placental vascular integrity [61]. In female C57BL/6J mice exposed to a high-fat/high-sugar (HF/HS) diet, increased maternal adiposity and glucose intolerance were observed. Placentas from obese dams exhibited elevated protein expression of nutrient transporters, including GLUT1 and GLUT3 (glucose transport), SNAT2 (System A), and LAT1 (System L), along with increased transporter activity. Protein expression analysis revealed placental activation of the mTOR, insulin/IGF-I, and leptin signaling pathways, as evidenced by increased phosphorylation of S6 (S235/236), 4E-BP1 (T37/46), IRS-1 (Y608), AKT (T308), and STAT3 (Y705) [62,63]. Combined exposure to HFD and high-sugar diets further impaired maternal insulin sensitivity during late gestation, increased adiposity, and disrupted glucose homeostasis, while also compromising fetoplacental glucose metabolism and growth. Additionally, this dietary condition reduced placental expression

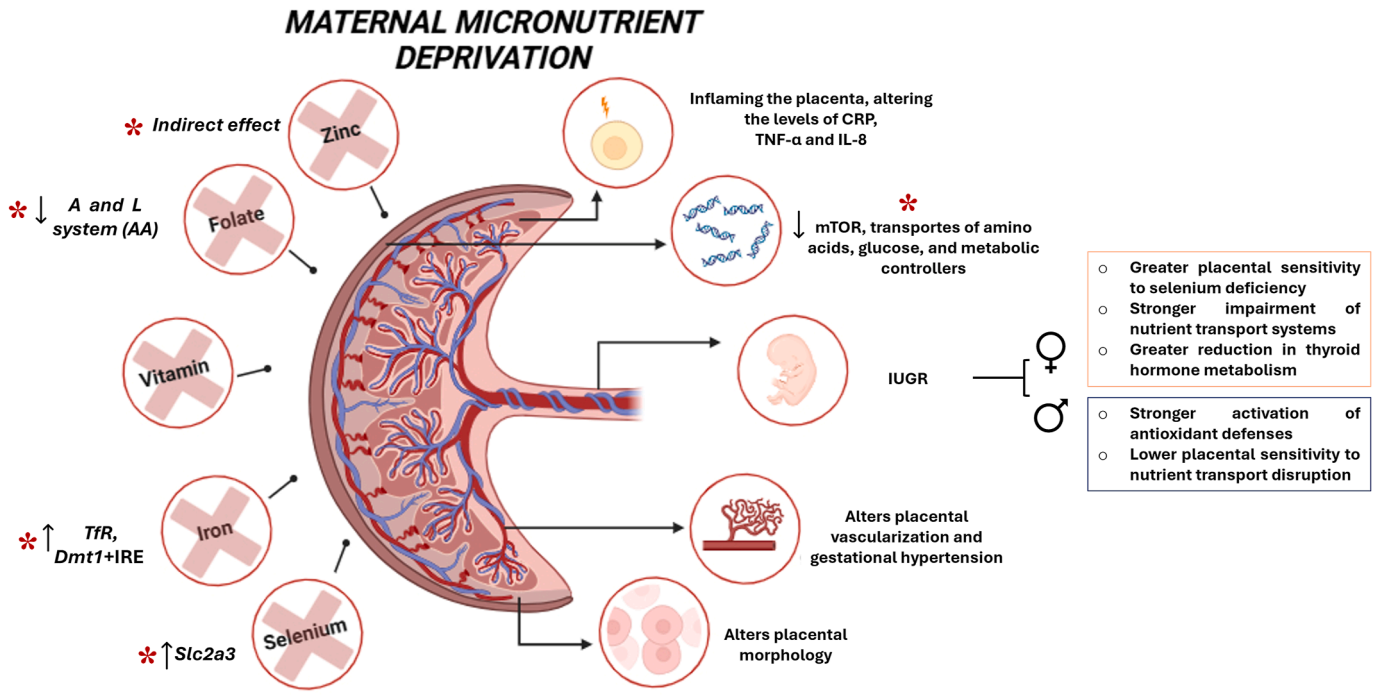

Fig. 3. Placental alterations resulting from a maternal micronutrient-deprivation diet during preconception and gestation and their impact on fetal development, as demonstrated by experimental and epidemiological studies. The Figure was composed using illustrations from biorender.com (https://app.biorender.com/).

of prolactin-related genes (*Prl/Pl family*) [64]. Collectively, these findings highlight the importance of experimental models that incorporate combined dietary exposures, as they better reflect human metabolic conditions and provide valuable insights for translational and clinical research.

In C57BL/6J mice, maternal HFD intake before and during gestation disrupted gut microbiota and intestinal barrier integrity, elevating circulating LPS and contributing to placental dysfunction marked by vascular immaturity, hypoxia, altered carnitine metabolism, and changes in inflammatory, autophagy, and ER stress markers in both sexes, highlighting its multifactorial impact on maternal metabolism and placental development [65]. In nonhuman primates (Japanese macaques), maternal HFD reduced uterine blood flow and increased the expression of inflammatory cytokines and TLR4 in the placenta, accompanied by a higher frequency of placental infarctions, inadequate vascular remodeling, and thickening of the trophoblast membrane [66]. Mayor et al. (2015) also showed that mice exposed to HFD demonstrated a significant increase in *Nlrp3* and *Il1b* mRNA and the number of resorbed sacs in the placenta, while Hayes et al. (2012) found doubled CD31-positive area, altered vascular maturity, and increased carbonic anhydrase levels in C57BL/6 mice and *Sprague Dawley* rats [67,68]. These studies link maternal HFD to placental pathology, stress, and inflammation, which increase fetal mortality and reduce neonatal survival, suggesting that inadequate vascular remodeling and hypoxia are central mechanisms underlying the adverse outcomes of maternal obesity.

In FVB/N mice, maternal HFD before conception and throughout gestation reduced placental expression of angiogenic and oxidative stress–related genes (*Hif1a, Angpt1, Pgf, Hmox1, Sod1, Tfap2,* and *Nfe2l2*), whereas *Gpx1* expression was increased. These changes were accompanied by morphological alterations in glycogen trophoblasts and uterine NK cells, indicating hypovascularity and impaired placental efficiency [69]. In another similar model with CD-1 mice, there were increased placental weight, expanded blood sinusoidal areas, and a greater number of Ki-67-positive cells in the labyrinthine layer of the placenta, as well as elevated expression of the placental transporters FATP1, FATP4, and SNAT2. Additionally, maternal serum and amniotic fluid showed elevated levels of inflammatory markers (CRP and TNF-α) [70]. In DBA/2 male and C57BL/6J female mice, maternal HFD during gestation revealed that neither the sex of the offspring nor the maternal diet triggered gross morphological changes in the structure and size of the placental layers; however, there were alterations in the sex chromosomes (*Kdm5c* and *Kdm5d*) and components of the epigenetic machinery (*Dnmt3l*), suggesting that placental programming is sex specific [71].

From a lipid metabolism perspective, pregnant Wistar rats exposed to HFD showed a high proportion of linoleic acid, resulting in a significant increase in the expression of genes such as *ApoA2*, *ApoC2*, *Cubn*, *Mttp*, and *Ttr*, suggesting a greater cholesterol transport capacity across the placenta [72]. In a non-human primate model (Japanese macaques - *Macaca fuscata*), maternal Western diet induced placental metabolic and hemodynamic alterations, including elevated triglyceride levels, reduced uteroplacental blood flow, delayed spiral artery transit, and increased expression of inflammatory markers such as TNF-α, IL-12, and IL-1β [73]. Similarly, in C57BL/6 mice, maternal HFD also led to a significant increase in lipoprotein lipase (LPL) activity and protein levels in the placenta, an increase in mRNA levels of genes involved in lipid transport (*Cd36, Vldlr, Fabp3, Fabppm,* and *Gpat2*), and reduced SIRT1 expression. *In vitro* analyses further demonstrated that the SIRT1–PPARγ axis regulates LPL expression in trophoblasts [74]. Consistent with these data, maternal obesogenic diets also increased placental FATP6 and FABP3 protein expression in C57BL/6 mice [75]. Collectively, these studies indicate that maternal HFD enhances placental lipid transport and metabolism, favoring fatty acid transfer to the fetus and contributing to hepatic lipid programming. Such alterations may also affect triglyceride and

cholesterol handling, promote inflammatory responses, and ultimately impact fetal development.

Borengasser et al. (2014) demonstrated that maternal HFD reduced placental mRNA expression of key regulators of mitochondrial biogenesis (*Esrra, Nrf1,* and *Ppargc1b*), along with genes involved in mitochondrial dynamics (*Mfn2, Fis1,* and *Parl*), ultimately impairing placental efficiency in *Sprague Dawley* rats [76]. In C57Bl/6J OlaHsd mice, maternal HFD altered the expression of epigenetic genes, particularly in the placental labyrinth and fetal liver, including increased levels of *Kat2a*, *Kat3b*, and *Kat13b*. In addition, *Bdnf* and *Lpl* showed higher expression in females. These results indicate that maternal obesity reprograms development through epigenetic alterations, and preconception weight loss may mitigate these effects [77].

In a C57BL/6N mouse model, Appel et al. (2019) reported that maternal HFD induced IUGR and reduced placental protein levels of INSR-β, IGF-1Rβ, GLUT1, and IGF-2R, accompanied by decreased glycogen content, impaired canonical WNT/GSK3β signaling, and reduced placental transfer zone across gestation [78]. Under beneficial conditions, such as voluntary maternal exercise, HFD-induced metabolic disturbances were partially reversed, including improvements in maternal adiposity and circulating leptin and insulin levels. These effects were associated with modulation of amino acid transport, particularly SNAT2 expression, as well as activation of mTORC1/4E-BP1 and LepRb/STAT3 signaling pathways, which regulate placental nutrient transport. Notably, exercise normalized SNAT2 expression under HFD conditions [79]. Conversely, maternal physical activity modifies hypothalamic gene expression in the fetuses, which may impact the long-term health of the offspring in *Sprague Dawley* rats [79]. In a maternal HFD model, placentas from C57BL/6J mice showed lipid accumulation, hypoxia, and impaired angiogenesis and nutrient transport, whereas moderate exercise restored maternal insulin sensitivity, reduced placental lipid and HIF-1α, normalized angiogenesis and transporter gene expression, and prevented insulin resistance in male offspring [80]. Son et al. (2019), using a C57BL/6J mouse model, also revealed that physical exercise in dams exposed to HFD improved the placental junctional zone, labyrinth zone, the levels of inflammatory cytokines (TNF-α and IL-1β), APLN, VEGF, VEGFR1, and HIF-1α in male and female fetuses [81]. Collectively, these studies demonstrate that maternal exercise mitigates HFD-induced placental dysfunction and metabolic programming, highlighting its potential as a non-pharmacological strategy to improve maternal–fetal health outcomes.

Lin et al. (2019) confirmed the placental structural disruptions of maternal HFD, in addition to disorders in the placental transcriptome, altering the renin-angiotensin system (RAS), increasing the mRNA expression of *Ren*, *Atp6ap2*, *Ace*, and *Agtr1a* through the ACE/Ang II/AT1R axis. Maternal HFD during preconception and gestation induced obesity, glucose intolerance, and insulin resistance in dams in *Sprague Dawley* rats [54]. These effects were accompanied by alterations in the RAS, including increased expression of the AT1R receptor in the placenta and uterus, elevated expression of angiotensin-converting enzyme (ACE) in the uterus, and reduced expression of MAS1 in the placenta of C57BL/6 mice, which impacts the central role in regulating blood pressure, inflammation, energy metabolism, and tissue growth [82]. These studies reflect important effects of excess dietary fat on the risk of placental and maternal hypertension, impacting not only vascular aspects but also potentially leading to risk to maternal–fetal life.

Obese mice exhibited a significant increase in placental Cell-Free DNA (cfDNA) release, suggesting a direct effect of maternal obesity on the placenta. Furthermore, fetuses of obese mothers exhibited altered growth and body weight, reducing the impact on fetal development. These results suggest that maternal obesity alters cfDNA release in placental explants from C57BL6/J mice, possibly reflecting placental stress or mitochondrial dysfunction, and reinforce the role of the placenta as a mediator between maternal health and developmental profile [83]. Translational studies in hGH/CS transgenic (TG) and CD-1 non-TG mice fed an HFD, as well as in healthy lean and obese pregnant women, showed the reduced expression of *C/EBPβ* and hGH-V genes, along with reduced association of RNA polymerase II with their promoters. Experiments using siRNA against *C/EBPβ* in human placental cells confirmed that reduction of this transcription factor directly decreases the expression of hGH-V and hCS [84]. Placentas from obese women (BMI>30) and fetal livers from non-human primates exposed to an HFD demonstrated a reduction in microsomal CYP1A1 activity [85].

In Albino Wistar rats, maternal HFD elevated maternal and fetal triglycerides, leptin, and insulin, and increased maternal, fetal, and placental weights. Placental signaling analyses indicated activation of mTORC1, as evidenced by increased phosphorylation of 4E-BP1 (Thr37/46 and Ser65) and RPS6 (Ser235/236), accompanied by reduced p-AMPK and p-eIF2α levels, suggesting enhanced protein synthesis as a driver of placental and fetal overgrowth [86]. Maternal HFD also increases the levels of saturated fatty acids (myristic and stearic) in the placenta of Wistar rats and reduces the concentrations of essential polyunsaturated fatty acids (linoleic and docosahexaenoic acids), suggesting that maternal diet significantly alters the placental lipid profile, potentially compromising the availability of essential fatty acids for fetal development [87].

In vitro, BeWo (CCL-98) cells, which were treated with the saturated fatty acid palmitate and monounsaturated fatty acid oleate (the most abundant circulating NEFAs during pregnancy), demonstrated increased mitochondrial respiratory function in villous trophoblast cells, with mitochondrial dysfunction, potentially leading to oxidative stress and mitochondrial damage [88]. Mitochondrial deregulation, inflammation, and oxidative stress can be associated with adverse conditions. In an experimental study using a Wistar rat model, maternal HFD significantly lower serum TG levels, placental apoptosis and inflammation (p–NF–κB and the macrophage marker protein), leading to cellular stress and restoring autophagic flux - superoxide dismutase 1 (SOD1), NAD(P)H quinone dehydrogenase 1 (NQO1), and heme oxygenase 1 (HO-1) [89]. The HFD for 8 weeks before conception induced morphological changes in the placenta (reduction in labyrinth thickness and an increase in decidua thickness), decreased cell proliferation (pH3 immunostaining), and increased inflammation (*Cd11b* and elevated placental *Il6*, *Il1b*, *Tnf*, and *Il10* expression). Additionally, some cytokines were more abundant in the fetal circulation in HFD pregnancies. These changes were more pronounced in placentas of male fetuses, indicating that the effects of maternal obesity on placental morphology, proliferation, and inflammation are fetal sex-dependent and may influence the development and future health of the offspring in C57BL/6 mice [90]. Consistently, Napso et al. (2022) reported that maternal HFD induced marked placental alterations in male fetuses, including reduced trophoblast size, impaired oxygen diffusion, and increased barrier thickness in C57BL/6J mice [91]. Although overall mitochondrial respiration was not significantly altered, clear sex-specific differences were observed. In males, mitochondrial adaptations included increased abundance of respiratory chain components (complex II and ATP synthase), elevated DRP1 levels, reduced p-AMPK, decreased lipid synthesis, and increased oxidative stress. In females, increased mitochondrial biogenesis and

lipid synthesis were observed, whereas uncoupling protein 2 (UCP2) was reduced in both sexes. These studies highlight the potential disorders of HFD on mitochondrial function and the sex-specific differences in consequences.

In a white rabbit model exposed to HFD, there was intrauterine growth retardation and dyslipidemia, with a greater impact on male fetuses than on females. In the placenta, lipid droplet accumulation was observed in the trophoblast, with increased concentrations of cholesterol esters, triacylglycerols, and stored fatty acids. Notably, accumulated fatty acids were higher in female placentas, while triacylglycerol increased specifically in male placentas. Lipid accumulation was also detected as early as the blastocyst stage, indicating that maternal diet has early effects. At the molecular aspects, the authors found sex-specific deregulations in the LXRα, ABCG1, CD36, placental membrane PUFA, expression of glucose (*Slc2a*) and amino acid (*Slc38a*) transporters, with males being more affected than females [92]. In embryo transfers from donor C57BL/6J female mice to recipient CF1 female mice fed an HFD, there were alterations in the expression of imprinted genes, vasculogenesis, and lipid metabolism (*Cyp17a1*, *Maoa*, *Dio3*, and *Cts6*). However, only gestational exposure resulted in persistent metabolic effects in the offspring, manifested as obesity and glucose intolerance in adulthood. These findings indicate that, even in a normal gestational environment, pregestational maternal obesity impairs fetal and placental growth, extending the window of vulnerability to the adverse effects of an HFD to include the oocyte and its preconception environment. In addition, subtle differences were observed between the sexes, such as transient changes in females and higher postnatal mortality in males [93]. C57BL/6J mice fed a HFD before and during pregnancy presented reduced fecal production of short-chain fatty acids and increased intestinal pro-inflammatory activity, while the placenta exhibited hypoxia, increased angiogenesis, and elevated transcript levels of glucose and amino acid transporters, in addition to disorders in the fatty acid receptors (FFAR2, FFAR3, and HCAR2) [94]. Interestingly, a lower energy density C57BL/6J HFD mice model also developed GDM, exhibiting weight gain, insulin resistance, and similar alterations, including inflammation, oxidative stress, hypoxia, and abnormal vascular development, which were associated with increased levels of HIF-1α, VEGF-A, and MDA levels [95].

Overall, studies linking the effects of a diet high in different lipid classes on the placenta elucidate numerous consequences for lipid metabolism and problems in placental metabolic and hormonal responses. This provides a solid foundation for future studies investigating how to mitigate these effects and inhibit the likelihood of developing maternal metabolic diseases and fetal metabolic programming, thereby fostering multidisciplinary and multiprofessional interventions on nutritional quality, maternal–fetal health, and mitigating the risks of NCDs, in the context of the global obesity epidemic. The main findings related to maternal HFD and placental alterations are compiled in Table 3 and Fig. 4.

5. Main mechanisms and future perspectives

Based on the evidence discussed, it is clear that both malnutrition and overnutrition exert deleterious effects on placental biology, with consequences that extend beyond gestation to impact maternal health, fetal development, and postnatal outcomes. However, a critical avenue for future research lies in identifying strategies capable of mitigating or reversing these adverse effects. Emerging evidence highlights the potential of targeted interventions, such as physical exercise and nutritional supplementation (e.g., curcumin, arginine, and citrulline), applied at key windows, including the preconception period and early gestation.

Collectively, experimental studies indicate that such interventions can confer beneficial effects, promoting the restoration of placental epigenetic regulation, improving placental function, enhancing fetal nutrient supply, and supporting optimal fetal growth. Therefore, while this body of work underscores the significant risks associated with inadequate maternal nutrition, it is equally important to emphasize its non-deterministic nature. In this context, a critical and translational perspective is essential, highlighting that effective intervention strategies may counteract, at least in part, the biological programming induced by maternal dietary adversity.

5.1. Maternal protein restriction

This review compiles potential placental biomarkers of the consequences of maternal LPD and their possible correlation with disturbances in maternal and fetal health, metabolic programming, and the developmental origins of the disease. Of note are the impacts on glycogen storage capacity (*Pcdh12* and *Prl3a1*) and growth factors and growth signaling pathways (EGFR, SNAT2, mTOR, WNT2, DLK1, p53, FGF2, VEGFR2, TGFβ, and IGF2) - which certainly demonstrates direct impacts on the placental hormonal response and subsequent cell signaling factors. These factors demonstrate the need for a deeper understanding of these specific pathways and others involved in growth regulation. The literature also lists that there are maternal systemic disorders, such as reduced levels of AST, ALT, insulin, leptin and IGF-I, which clarifies a notable impairment in anabolism and the capacity for divergent pathways, which can be justified by a maternal adaptive mechanism of catabolism/steroidogenesis (*Cyp11a1*, *Hsd3b1*, *Cyp17a1*, *Hsd17b2*, *Hsd11b2*) that can impair maternal reserves, placental structure and fetal development - as the neuroendocrine core of intrauterine growth restriction. Furthermore, the data demonstrate placental vascular and inflammatory mechanisms (TNF-α, iNKT, M2 macrophages, PLGF, NF-κB, IL-8, COX-2), direct effects on mitochondrial capacity (*Atf3*, *Asns*, *Snat2*, *Slc38a2*, ATF4, p-eIF2α, Ace2, SNAT4, LAT2, and SNAT1), and epigenetic aspects (hypomethylation in CpG sites in the *Wnt2* promoter) - promoting interesting cellular, organelle-specific, and epigenetic changes as a basis for future omics, functional, and even studies that investigate such correlations at the translational and clinical level.

5.2. Maternal micronutrient deprivation

In general, another relevant point is vitamin or micronutrient depletion or insufficiency. In this review, we elucidate that folate deprivation affects growth signaling (mTORC1, S6K1 phosphorylation) and amino acid transport (System A and L amino acid transporters), while iron deficiency impacts important hemoglobin transport receptors (*Dmt1*+IRE). In these two contexts, the impacts on cellular mechanisms of passive or active transport will certainly affect the maternal–fetal interface, subsequently affect fetal development, and lead to fetal programming. On the other hand, vitamin D deficiency appears to lead to pro-inflammatory conditions, as does folate depletion (COX-2, IL-6, and KC), while iron deficiency affects glycogen (*Slc2a3*) and basal metabolism (DIO2 and DIO3). Finally, regarding co-exposure depletion, general micronutrient restriction impairs placental protection (*Hsd11b2*)

Table 3
General and specific results, exposure, animal model and studies about maternal HFD and placenta.

Main result	Time and type of exposure	Animal model	Sex	Reference
Impaired trophoblast differentiation, basement membrane disruption, and placental dysfunction	Fat (60%) after weaning (between 12 and 16 weeks of age) and until the E15.5	C57BL/6 mice	N/A	[18]
Changes in placental growth patterns, blood supply, and the expression of genes involved in arachidonic acid.	Fat component (pork lard and rapeseed oil) for 3 weeks before conception and during gestation	*Sprague Dawley* rats	N/A	[52]
Obesity shapes the composition of the maternal gut microbiota and remodels the placenta	Fat (58%; hydrogenated coconut oil) for 11 weeks before conception and during gestation	*Sprague Dawley* rats	N/A	[53]
Alterations in placental morphology, transcriptome, and RAS associated with IUGR	Fat (58%) for 10 weeks before conception and during gestation	*Sprague Dawley* rats	Male and Female	[54]
Maternal-fetal constraint, placental inefficiency, and IUGR	Fat (45%) during the 4 weeks before conception	Swiss mice	N/A	[55]
GPR1 regulates placental metabolism, affecting glucose and lipid transport, and its dysfunction contributes to complications associated with GDM.	Fat (45%) during gestation	C57BL/6 mice pretransfected with small interfering RNA for GPR1 and BeWo cells	N/A	[56]
Upregulation of specific isoforms of placental nutrient transporters	Fat (32%) for 8 weeks before mating and throughout gestation	C57/BL6 mice and isolated trophoblastic MVMs	N/A	[57]
Changes in placental formation – more pronounced effects in males (e.g., *Bdh1* and *F2r* expression).	Fat (60,3%) for 12 weeks prior to, and during, pregnancy (E4,5; 6,5; 12,5 and 18,5)	C57BL/6J mice	Male and Female	[58]
Transient and sex-specific placental changes in genes linked to nutrient transport and fetal growth – increased *Slc38a2*, *Igf2*, and *Igf2r* expression (males); and increased *Slc38a4* in females.	58% fat from 5 weeks to E14,5 and E18,5	C57BL/6 mice	Male and Female	[59]
Placental lipid droplet accumulation, perinatal mortality, and aberrant FA profiles	40% fat at least 28 days prior to breeding until E21	*Sprague Dawley* rats	N/A	[60]
Impairments in placental angiogenesis and KLF4 as a possible therapeutic intervention	60% fat during pregnancy	C57BL/6J mice and porcine vascular endothelial cells (PVECs)	N/A	[61]
Downregulation of placental amino acid transporters and IUGR in late pregnancy.	41% HF/HS pelleted diet supplemented by ad libitum access to sucrose solution (20%) - 4 to 6 weeks preconception and through gestation	C57BL/6J mice	N/A	[62]
HF/HS in mice activates placental insulin/mTOR and STAT3 signaling.	41% HF/HS pelleted diet supplemented by ad libitum access to sucrose solution (20%) from 4 to 6 weeks preconception through gestation	C57BL/6J mice	N/A	[63]
Changes in placental *Prl/Pl* expression impact metabolic responsiveness.	30% fat and 36% sugar during gestation	C57Bl/6J mice	N/A	[64]
Blood vessel immaturity and placental hypoxia; NF-κB pathway activation increased only in the large intestine of female fetuses	60% fat for 6 weeks before mating	C57BL/6J mice	Male and Female	[65]
Increased levels of inflammatory cytokines, placental infarcts, and inadequate vascular remodeling	32% of calories from fat for at least 4 years until G130	Japanese macaques	N/A	[66]
Placental inflammation, placental insufficiency, and IUGR	42% fat from 3 to 5 months before mating to late gestation	C57/Bl6 mice	N/A	[67]
Increased expression of placental hypoxia markers and endothelial vessel density, accompanied by impaired vascular maturity.	45% kcal fat for 16 weeks before being mated	Sprague Dawley rats	Male and Female	[68]
Genetic dysregulation of factors important for placental vascular development is associated with decreased placental efficiency.	60% fat during pregnancy (HFD-P) or HFD initiated 4 weeks before conception and throughout pregnancy (HFD-PreCP).	FVB/N mice	N/A	[69]
HFD exerts opposite effects on fetal development depending on the timing of exposure	37% fat, 12 weeks before mating and during pregnancy.	CD-1 mice	N/A	[70]
Placental gene expression and epigenetic alterations are sex-specific: Females show changes in immune signaling and amino acid metabolism, while males exhibit alterations in vascular function and glucose/lipid metabolism.	60% fat during gestation	DBA/2 male and C57BL/6J female mice	Male and Female	[71]
Changes in genes related to cholesterol transport/ packaging in the placenta	36% fat and linoleic acids from 4 weeks before mating to the end of gestation	Wistar rats and a human sample	N/A	[72]
HFD increases the expression of inflammatory markers in the placenta; however, reversing the diet before pregnancy reverses these changes.	36% fat maintained for 4–7 years and then switched to a control diet (14%) 3 months before breeding's	Japanese macaques - *Macaca fuscata*	N/A	[73]
Reduction in SIRT1 expression, leading to increased PPARγ activity and greater LPL expression, facilitating lipid accumulation in the fetus	60% fat from gestation to E15,5, E17,5 e E18,5	C57BL/6 mice and Human BeWo and JEG-3 trophoblast cells	N/A	[74]
Gestational obesity increases the availability of lipids to the fetus via the placenta - accumulation of lipids in the fetal liver	40% high in fat and sugar before mating (after 4–6 weeks on the obesogenic diet) and throughout pregnancy.	C57/BL6J mice	N/A	[75]

(*continued on next page*)

Table 3 (*continued*)

Main result	Time and type of exposure	Animal model	Sex	Reference
Alterations in mitochondrial health regulators PGC-1α, PGC-1β, ERRα, and maternal–fetal mitofusins	40% fat for 3 weeks before mating	*Sprague Dawley* rats	N/A	[76]
Alterations in the epigenetic machinery of obese mothers, restored with dietary intervention – Higher expression of *Bdnf* and *Lpl* in females.	59,9% HFD during 4 months before conception and throughout gestation.	C57Bl/6J OlaHsd mice	Male and Female	[77]
Alterations in the levels of INSR-β, IGF-1Rβ, and IGF-2R, as well as WNT-GSK3β, are associated with an altered pattern of placental and fetal development.	60% fat, after weaning until mating and throughout pregnancy	C57BL/6N mice	N/A	[78]
Gestational exercise prevents the effect of HFD on placental SNAT2 expression	60% fat during pregnancy plus prenatal exercise (GD3 until GD20)	*Sprague Dawley* rats	N/A	[79]
Physical exercise as an effective strategy to mitigate placental hypoxia and preserve placental function	Obesogenic diet (approx. 10% simple sugars, 20% animal lard, 28% polysaccharide, 23% protein) supplemented with sweetened condensed milk, during preconception, pregnancy, and lactation	C57BL/6 J mice	Male and Female	[80]
Dysregulation in TNF-α and IL-1β, as well as APLN levels, all improved by physical exercise	60% fat for 8 weeks to induce obesity. One week preconception, the diets were switched to 45% fat	C57BL/6 J mice	Male and Female	[81]
Changes in the expression of AT1R, MAS1, and ACE in the uterus and placenta suggest dysregulation of RAS expression.	HFD 60% for 2 months preconception and during gestation	C57BL/6 mice	N/A	[82]
Decreased cfDNA release from the obese placenta	60% HFD for 14 weeks before and throughout gestation.	C57BL6/J mice placentas for explants	N/A	[83]
Alterations in the expression of the transcription factor *C/EBPβ* and human placental growth hormone genes	60% total fat for 4 weeks pre-conception until the end of pregnancy	hGH/CS-TG mice and non-TG CD-1 mice; and studies with healthy, lean, and obese pregnant participants	N/A	[84]
Maternal lifestyle impacts CYP1A1 activity, implying a potential role for this enzyme in fetoplacental growth	Non-obese (BMI <30) and obese (BMI >30) women and 35,2% fat - non-human primate fetal for a minimum of 3 years	Human placental tissue and non-human primate fetal	N/A	[85]
Increased mTORC1 activity and decreased p-eIF2α may upregulate protein synthesis and contribute to placental and fetal overgrowth.	High-saturated-fat diet for 7 weeks before mating and during pregnancy.	Albino Wistar rats	N/A	[86]
Compromised maternal metabolic status during gestation due to changes in fatty acid profiles	40% fat during the first (HF1), second (HF2), or third (HF3) week of gestation, or for all three (HFG)	Wistar rats	N/A	[87]
Dietary fats independently modulate villous trophoblast mitochondrial function.	Treated with saturated FA palmitate (PA) and monounsaturated FA oleate (OA)	BeWo cells (CCL-98)	N/A	[88]
Feeding only during a metabolically active phase (dark phase in rodents) mitigates the adverse effects of maternal obesity on placental health and fetal growth	60% kcal HFD for 20 weeks prior to mating until gestation, and another group fed the same % and period, but only for 9 h/day	Wistar rats	N/A	[89]
Sex-specific alterations in the placenta related to *Cd11b*, *Il6*, *Il1b*, *Tnf,* and *Il10*.	45% fat for 8 weeks preconception	C57BL/6 mice	Male and Female	[90]
Sex-dependent alterations in both placental morphology and mitochondrial function - male fetuses showed greater placental dysfunction, whereas females exhibited a more adaptive mitochondrial and metabolic profile.	HFD and sugar for 6 weeks prior to, and during pregnancy	C57BL6/J mice	Male and Female	[91]
Trophoblastic adaptive strategies in response to maternal hyperlipidemia at early stages of development - males being more affected than females.	Diet enriched with 6% soybean oil and 0.2% cholesterol	White rabbit	Male and Female	[92]
HFD prior to pregnancy may reprogram imprints during oocyte and early embryo development - transient changes in females and higher postnatal mortality in males.	60,3% fat from 12 weeks before mating to pregnancy	C57BL/6J and CF-1 mice	Male and Female	[93]
Maternal intestinal dysfunction during pregnancy is associated with structural and functional alterations in the placenta.	60% kcal from fat before (6 weeks) and during pregnancy	C57BL/6J mice	N/A	[94]
Induction of GDM and alterations in TNF-α, IL-6, and levels as a factor in placental hypoxia	40% energy from fat for 14 weeks before mating and throughout gestation	C57BL/6J mice	N/A	[95]

and also leads to placental inflammatory responses (NF-κB p65, CRP, TNF-α, IL-8). Certainly, many more studies are needed to highlight the neuroendocrine, molecular, and biochemical roles of different micronutrient depletion on the placenta, to understand which enzymatic or receptor cascades are directly affected by maternal micronutrient deprivation.

5.3. Maternal high-fat diet

Notably, given the global context of the obesity and metabolic disease pandemic, models that correlate HFD with placental adversities are the most studied in the dietary context. Interestingly, here we provide a series of biological mechanisms and possible

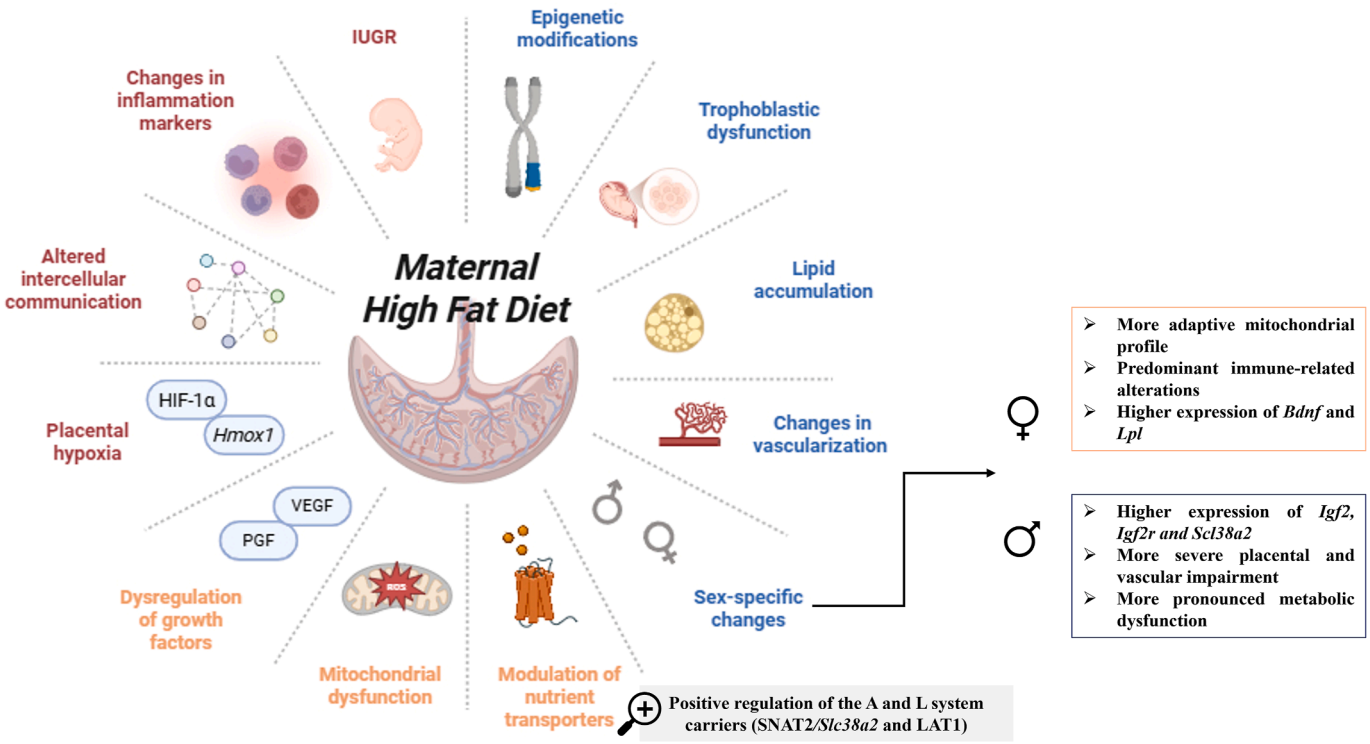

Fig. 4. Placental changes resulting from maternal HFD during preconception and gestation and their impact on fetal development, as demonstrated by experimental and epidemiological studies. The Figure was composed using illustrations from biorender.com (https://app.biorender.com/).

biomarkers of maternal–fetal disorders and metabolic programming in the face of HFD, among them: Problems in the early and late placental structure, with disturbances in genes and proteins determining the structure, growth and maintenance of the placenta (*Itga1*, *Serpine1*, GPR43, *ApoA2*, *Apoc2*, *Cubn*, *Mttp*, *Ttr*, PRKDC, p-AMPK; mTORC1/4E-BP1 and LepRb/STAT3 pathways, mTOR, 4EBP1 (Thr37/46 and Ser65); RPSS6 (Ser235/236), p-eIF2α, hypoxia (*Hif1a*, *Angpt1*, *Pgf*, *Hmox1*, *Sod1*, *Tfap2* and *Nfe2l2*), as well as its response to growth factors and hormones (AKT signaling pathway, GLUT3, P57Kip2, adiponectin, INSRβ, IGF-1Rβ, GLUT1, SLC38A2, *Igf2* and *Igf2r*, IGF and GR/NR3C1) and placental transporters (FATP1, FATP4, SNAT2, GLUT1 and GLUT3, ACC1, FFAR2, FFAR3, HCAR2, SLC2A, SLC38A, LAT1, *Prl/Pl family*). These contexts provide a strong basis for future studies that investigate, in depth, the neuroendocrine causes or metabolic disorders behind these dysregulated mechanisms, as well as the specific role of lipid excess on such placental mechanisms (e.g., liver and muscle function, anabolism, and catabolism). It was also possible to observe impairments in the vascular response and associated blood pressure, which can certainly bring a risk to hypertension and pre-eclampsia (APLN, VEGF, VEGFR1, and HIF-1α, RAS, *Ren*, *Atp6ap2*, *Ace*, *Agtr1a*, ACE/Ang II/AT1R axis, PGF, AT1R, MAS1, ECA). Given all these contexts, maternal HFD apparently leads to a highly concerning level of oxidative stress (GPX1, SOD1, NQO1, and HO-1) and inflammation (CRP, NK cells, TNF-α, IL-12, IL-1β, TLR4, CD11B, IL-6, p–NF–κB and IL-10) – including in aspects attached to the placenta, as well as directly in the fetus – in a sex-specific manner – in the uterus and in the amniotic fluid – aspects that certainly have direct consequences on mitochondrial function or are consequences of disorders in it. Thus, effectively, from an organelle-specific point of view, maternal HFD appears to directly impact mitochondrial function (complex II, ATP synthase, UCP2, ERRα and NRF1, PGC1β, MFN2, FIS1 and PARL, KAT2A, KAT3B and KAT13B). Regarding lipid metabolism (myristic and stearic saturated fatty acids and linoleic and docosahexaenoic essential polyunsaturated fatty acids) and aspects of fat accumulation, it is clear how maternal HFD impacts these placental mechanisms (FABP4, GPR1, *Cd36*, *Fabp3*, *Pparg*, *Plin2*, ADRP, *Irs1*, *Cyp17a1*, *Maoa*, *Dio3*, *Cts6*, LXRα, ABCG1, CD36, CYP1A1, PTGS2, COX2, *Limk1*, *Pla2g2a*); in addition to lipid metabolism and the capacity of trophoblast cells for glycogen storage. Alterations in chromosomes (*Kdm5c* and *Kdm5d*) and in components of the epigenetic machinery (*Dnmt3l*, C/EBPβ, hGH-V, RNA polymerase II, and its promoters) were also observed, but studies with the complete characterization of the epigenome can still be considered a gap in this topic.

5.4. Sex-specific placental responses

Although relatively few studies have explicitly addressed sex-specific placental responses to nutritional challenges, available evidence indicates clear sexual dimorphism. In models of maternal LPD, females exhibit alterations in steroidogenesis but show comparatively better glucose transport and placental efficiency, whereas males are more strongly affected in pathways related to fetal growth and antioxidant defense. Under micronutrient deprivation, females again appear to mount a more adaptive response, although with disturbances in placental transport systems, while males show prominent activation of antioxidant pathways. Similarly, in maternal HFD models, females display a more favorable mitochondrial adaptive response, whereas males exhibit greater impairments in growth, vascular development, and metabolic regulation. Collectively, these findings indicate that restrictive or excessive maternal diets exert sex-dependent effects on placental function, with male fetuses generally appearing more susceptible to maternal adversities. This sexual dimorphism raises important questions regarding long-term postnatal outcomes,

including whether females maintain greater resilience to fetal programming -potentially mediated by estrogenic signaling - or whether this advantage diminishes or reverses later in life.

Consistent with these observations, recent multi-omics studies of the human placenta highlight fetal sex as an important determinant of placental molecular regulation. Transcriptomic analyses reveal sex-biased gene expression patterns, particularly in pathways related to immune regulation, trophoblast differentiation, and cellular signaling [96], while genomic studies have identified sex-dependent methylation quantitative trait loci (mQTLs) in placental tissues [97]. However, the interaction between maternal nutritional exposures and these sex-specific molecular mechanisms remains incompletely understood.

In this context, the present review aimed to synthesize the available evidence regarding maternal and placental malnutrition, considering the different biological mechanisms associated with developmental programming. The major novelty is highlighting biological mechanisms arising from different dietary adversities; however, sex-specific mechanisms remain a gap in the literature, which should certainly be addressed in future studies.

Finally, these observations highlight the urgent need for studies that explicitly stratify analyses by fetal sex and placental compartment, as most investigations still assess the placenta as a single unit. Advances in omics-based approaches offer powerful tools to address these gaps and to strengthen the translational relevance of sex-specific placental programming.

5.5. Translational and clinical perspectives

Collectively, the evidence discussed in this narrative review provides a robust biological foundation demonstrating that nutritional adversities induce significant structural and functional alterations in the placenta, as shown in animal models and human cell-based studies. Despite these advances, there remains a critical need to translate these findings into the clinical setting, particularly to identify reliable placental and fetal biomarkers of nutritional stress and to develop preventive or therapeutic strategies capable of mitigating or reversing diet-induced damage. However, translating mechanistic findings from experimental models into clinical practice remains challenging. Species-specific differences in placental structure, gestational physiology, and metabolic regulation limit the direct extrapolation of experimental results to humans, and accurately characterizing maternal dietary exposures in human populations represents an additional methodological challenge.

Nevertheless, epidemiological and cohort studies provide complementary evidence supporting the developmental programming effects of adverse intrauterine nutritional environments. For instance, long-term follow-up of individuals exposed to prenatal undernutrition during the Dutch Hunger Winter [98,99] and the Chinese Great Famine [100], a historical event distinct from the classical famine model frequently cited in DOHaD research, has demonstrated increased risks of cardiometabolic disorders, metabolic dysregulation, and altered epigenetic profiles in adulthood. Large prospective birth cohorts, including the Avon Longitudinal Study of Parents and Children [101], further support the relevance of maternal nutritional status during pregnancy for offspring growth trajectories, metabolic risk, and long-term health outcomes. Beyond clinical interventions, such knowledge is essential to inform public health policies that reinforce the importance of adequate maternal nutrition during critical developmental windows. An important translational challenge is determining whether the molecular pathways and gene or protein alterations identified in experimental models are conserved in humans and can be detected through clinically accessible biomarkers. Addressing this gap would strengthen obstetric practice by improving risk stratification, prognostic assessment, and early intervention in pregnancies exposed to nutritional adversity.

Within the DOHaD framework, such advances have the potential not only to improve pregnancy outcomes but also to reduce the medium- and long-term burden of fetal programming–related diseases, ultimately alleviating pressure on healthcare systems. Although epidemiological evidence remains limited within the specific scope of placental mechanisms reviewed here, the integrative synthesis and critical interpretation presented in this article contribute to advancing the fields of DOHaD, placental biology, and fetal programming and provide a conceptual foundation to guide future translational and clinical research. Table 4 summarizes the main potential clinical relevance investigated in our results.

5.6. Limitations

This narrative review focused primarily on placenta-specific aspects associated with maternal exposure to protein or micronutrient restriction, as well as lipid exacerbation, establishing two distinct panoramas and critically interpreting and addressing the findings to date. Given its established focus (critical-interpretative narrative), there are gaps that other studies already in the literature could fill, particularly regarding neuroendocrine aspects and physiological responses, as well as omics mechanisms and a more global view of these consequences. The scarcity of studies examining direct effects in humans highlights the need to expand scientific research on this topic. Furthermore, this review focuses exclusively on placental aspects, without comprehensively addressing neuroendocrine or extraplacental organ effects. This review certainly may encourage others who focus on these other models of dietary restriction or exacerbation. Another limitation was focusing on the placenta and failing to understand how such diets influenced maternal health during lactation; furthermore, we believe that including these data would detract from the central focus of fetal programming and health during pregnancy.

Another limitation is the absence of studies addressing caloric restriction or hypercaloric diets. Although these conditions are highly relevant within the DOHaD framework and placental health, their inclusion would substantially broaden the scope of this review by encompassing numerous additional dietary models. To maintain focus, we prioritized contrasting nutritional conditions that are both antagonistic and socially relevant. Nevertheless, this approach highlights important perspectives from the current literature while also encouraging future studies to provide a broader synthesis of hypo- and hypercaloric dietary models within the DOHaD context.

5.7. Future perspectives

From a physiological/biochemical perspective, these maternal conditions demonstrate direct impacts on nutrient signaling and amino acid transport through various mechanisms—be it problems with placental transporters, placental enzymatic capacity, or even substrate insufficiency. Notably, vascular immaturity, hypoxia, and altered glucose and lipid metabolism (mainly in HFD) are observed, mediated by aspects of oxidative stress, inflammation, and autophagic disorders that are likely associated with organelle-specific disorders, such as those affecting the endoplasmic reticulum and mitochondria. Future studies should further unravel these placental physiological mechanisms (e.g., association with other organs - liver, pancreas, hypothalamus, pituitary, microbiome - neuroendocrine integration - balance between anabolic,

Table 4
Human evidence linking maternal nutritional status and placental function.

Reference	Study type	Human model	Nutritional/metabolic factor	Placental biomarkers or pathways	Main findings
[44]	Cell culture study (trophoblast cells)	Human trophoblast cell model	Folate availability	mTOR signaling pathway (folate sensing); trophoblast cell function	Folate regulates trophoblast function through mTOR signaling, linking micronutrient availability to placental nutrient sensing and cellular metabolism.
[46]	Experimental study (*in vivo* + *in vitro*)	Human trophoblast cell line JEG-3	Folic acid under inflammatory stimulus (LPS)	NF-κB signaling pathway; inflammatory cytokines (TNF-α, IL-6); placental inflammatory pathways	Folic acid suppressed the activation of NF-κB and decreased the expression of pro-inflammatory cytokines.
[48]	Experimental study (*in vivo* + *in vitro*)	Human trophoblast cell line (HTR-8/SVneo)	Vitamin D3 under inflammatory stimulus (LPS)	VDR; NF-κB signaling pathway; inflammatory cytokines (TNF-α, IL-6)	Vitamin D3 increased the interaction between the vitamin D receptor and the NF-κB p65 transcription factor, reducing NF-κB activation and decreasing the expression of pro-inflammatory cytokines.
[51]	Population cohort	Pregnant women	Maternal zinc deficiency	Maternal nutritional biomarkers	Maternal zinc deficiency during pregnancy was associated with an increased risk of IUGR
[56]	In vitro cell experiments + analysis of human placental samples	Human placental tissue and BeWo cells	Maternal HFD –related lipid metabolic signaling	GPR1 signaling; AMPK pathway; placental lipid metabolism	In trophoblast cells, altered AMPK signaling and lipid metabolism; analysis of human placental samples showed altered GPR1 expression
[72]	Molecular study	Human placenta	Maternal obesity	Cholesterol transport and metabolism genes	Maternal obesity alters the expression of genes involved in placental cholesterol metabolism.
[74]	*In vitro* cell study	Human trophoblast cell line (BeWo cells) and primary trophoblast cells	Lipid-related metabolic signaling; modulation of SIRT1	SIRT1 signaling; LPL expression and activity; lipid metabolism pathways	Reduced SIRT1 expression increased LPL expression and enzymatic activity
[84]	Molecular study	Human placenta	Maternal obesity	Placental growth hormone regulatory pathways (*C/EBPβ*)	Maternal obesity may dysregulate genes involved in placental growth hormone signaling.
[85]	Molecular study	Human placenta	Maternal obesity	Placental metabolic enzymes (cytochrome P450)	Alterations in placental metabolic activity were associated with maternal obesity
[88]	Experimental study	Human trophoblast cell line (BeWo)	Exposure to saturated fatty acids (palmitate)	Mitochondrial metabolism and cellular respiration	Prolonged palmitate exposure impairs trophoblast metabolic function.

catabolic, orexigenic, anorexigenic hormones), biochemical mechanisms (e.g., specificities of carbohydrate metabolism - pentose phosphate pathway, action of glycogen synthase and phosphorylase on trophoblast cells, investigation of allosterism within the Krebs cycle and the formation of NADH and FADH2, as well as the functional capacity of the electron transport chain - lipid - b-oxidation, carnitine transport system - and amino acid - balance between transport and interaction capacity between essential/non-essential and glucogenic/ketogenic amino acids), as well as organelle-specific, molecular and epigenetic mechanisms (long non-coding RNAs, Piwi RNAs, microRNAs), and single-cell RNAs. In this context, advancing our understanding of how dietary deprivation or excess shapes placental function through specialized approaches will enable the identification of biomarkers of fetal metabolic programming and maternal health risks across multiple biological levels. Such knowledge will support future translational and clinical studies, driving public policies to address food insecurity, malnutrition, and diet-related excesses. Ultimately, these efforts will foster global health, help mitigate NCDs and transgenerational effects, and promote women's health during critical developmental windows.

6. Conclusion

This critical-interpretative narrative review compiles the multiple placental mechanisms affected by maternal malnutrition or exacerbation of micronutrients, proteins, or lipids, elucidating impacts on nutrient transport, hormonal signaling, vascular homeostasis, oxidative, glucose, and lipid metabolism, and epigenetic regulation. Evidence suggests that such conditions affect placental remodeling, leading to inflammatory and oxidative stress aspects, which certainly affect fetal growth and lead to fetal metabolic programming and disease risks in offspring throughout developmental biology. Furthermore, we highlight the importance of addressing maternal health, as negative consequences for the placenta not only program offspring for postnatal risks but can also provide important clues to maternal metabolic disorders that can harm their short-term health. Future research should investigate the combined effects of multiple nutritional deficiencies or exacerbations, their integrated impact on essential biochemical pathways, and their relationship with metabolic programming and the risk of chronic diseases in offspring. Furthermore, preventive and therapeutic strategies involving good nutrition before and during pregnancy may offer opportunities to mitigate adverse placental effects and support long-term fetal health, inciting translational and clinical outcomes.

Authors' contributions

Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Funding acquisition, Writing – original draft, Writing – review & editing: **LAB & MNF**. Writing – original draft, Writing – review & editing: **NM, FAM, ITR, PVS, ALRG, WRS**. Conceptualization, Data curation, Formal analysis,

Investigation, Methodology, Supervision, Funding acquisition, Writing – original draft, Writing – review & editing: **LAJ**.

Declaration of Generative AI and AI-assisted technologies in the writing process

All the text of the manuscript was initially written without Generative AI. Generative AI (ChatGPT) was partially used to correct some English formulations or to improve the formulation of a few sentences.

Funding statement

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES 88887.112689/2025-00 MNF) – Finance Code 001; The São Paulo Research Foundation (FAPESP) (2024/00809-9 to LAB; 2024/22188-6 to MNF; 2022/03990-0 and 2025/21512-7 to LAJ); Conselho Nacional de Desenvolvimento Científico e Tecnológico (310663/2018-0 LAJ); CNPq/INCT DOHaD (Proc #409165/2024-7).

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