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# Maternal-placental axis and its impact on fetal outcomes, metabolism, and development

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ABSTRACT

Maternal obesity could impact offspring's health. During "critical period" such as pregnancy insults have a significant role in developing chronic diseases later in life. Literature has shown that diet can play a major role in essential metabolic and development processes on fetal outcomes. Moreover, the placenta, an essential organ developed in pregnancy, seems to have its functions impaired based on pre-gestational and gestational nutritional status. Specifically, a high-fat diet has been shown as a potential nutritional insult that also affects the maternal-placental axis, which is involved in offspring development and outcome. Moreover, some classes of nutrients are associated with pregnancy complications such as reduced intake of micronutrients and diabetes, preeclampsia, and preterm delivery. Thus, we will summarize the current literature on maternal environment factors that impacts the placental development and consequently the fetal an offspring health, or the maternal-placental axis, and this on fetal outcomes, metabolism, and development.

## 1. Introduction

The prevalence of overweight and obesity has increased worldwide. The World Health Organization (WHO) estimates that by 2025, approximately 167 million people will be classified as overweight or obese [1]. Furthermore, the World Obesity Federation predicts that globally, one billion of people will be obese by 2030, including 1 in 5 women. The health risks of obesity include the development of other comorbidities such as cardiovascular diseases, diabetes, and some types of cancer. In women, the nutritional status is an important parameter for both mother's and baby's health [1,2].

The link between maternal nutrition and long-term health of the offspring is well established in the literature. During periods such as pregnancy, weight gain assists for an adequate fetal development and for minimizing risks of possible short- and long-term complications. Overweight or obesity during this phase contributes to higher risks of the fetus developing some diseases and other comorbidities later in life [3]. Furthermore, the nutrient acquisition and baby's development are essential to minimize these risks. Thus, during pregnancy, the placenta is the essential organ that could impact these processes [4].

The placenta is the most relevant organ during gestation. It allows the fetus to get nutrients, hormones, and oxygen, contributing to fetal development throughout pregnancy. Each anatomical region has a distinct way for delivering nutrients to the fetus, with specialized structures responsible for appropriate absorption and supply of nutrients. Thus, obesity during this period can also impact placental efficiency and corroborate to a worse scenario for both maternal and fetal health [3,4].

Therefore, in this review, we summarize recent literature on development, metabolism, and outcome related to the communication between maternal environment factors that impacts on placental development and consequently the fetal and offspring health, or the maternal-placental axis. Moreover, we summarize diseases and comorbidities that has a relevant impact during pregnancy and further, in maternal-fetal health.

### 1.1. The placenta

Pregnancy is a dynamic stage that integrates a series of essential processes for the proper development of the fetus. This phase goes from fertilization to the implantation of the embryo in the uterine wall, the development of unique structures such as the placenta, and finally

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childbirth [5].

Placenta is an organ of high metabolic complexity. It only develops during pregnancy and is formed gradually from the first trimester onward. After this period, placenta grows in parallel with the uterine expansion. In humans, this organ is developed from the outer layer of the blastocyst, known as trophectoderm (later differentiated into a trophoblast), which is formed around five to six days after fertilization. During the first trimester, the human placenta is essentially hemodichorial, presenting two layers of trophoblasts, the syncytiotrophoblast (SYNs) and the cytotrophoblast (CTB) [6]. These layers separate the maternal circulation from fetal circulation (Fig. 1).

As pregnancy progresses, the cytotrophoblast layer thins and disperses. Thus, in the second and third trimester the placenta becomes basically hemomonochorial, with only the SYNs layer. This structure secretes the human chorionic gonadotropin (hCG), estrogen, progesterone, and placental lactogen hormones, while CTB secretes enzymes that disrupt the binding of endometrial cells, allowing SYNs to invade the endometrial wall early in pregnancy [6]. Later, during pregnancy, the invaded endometrium is converted into a specialized tissue known as decidua [7]. The basal decidua derived from the endometrium represents the maternal portion of the placenta, while the SYNs and CTB, alongside the embryonic mesoderm, form the chorion, or the fetal portion of the placenta [6]. In mice, trophoblastic cells differentiate into giant trophoblastic cells, spongiotrophoblasts, and glycogen cells that together form one of the layers of the placenta known as the junctional zone. Similarly, as in humans, placentation in mice has an invasive feature. Thus, with the fixation of the blastocyst in the endometrium, the cells of the uterine stroma begin to differentiate into deciduous cells, giving rise to another layer, the decidua. This region, alongside the junctional zone, produces several gestational hormones [8]. As pregnancy advances, two organizing centers emerge, the maternal interface and the fetal interface. These centers are determined by the depth of the extraembryonic mesenchyma and the vasculature in the trophoblast compartment. The region that encompasses the interaction of the trophoblast and the extraembryonic mesenchyme layer delineates the mouse labyrinthine zone, which represents the highly branched placental layer responsible for the exchange of nutrients and gases (Figs. 1 and 2) [9].

Human and mice gestation share some similarities as seen earlier but show a significant difference in the temporal course of the events and consequently in the time of gestation. Table 1 shows the stages of gestation in both species.

## 2. Placental function

The placenta performs important functions such as connecting the circulatory systems, the mother and the child, supplying nutrients and oxygen, forming the placental barrier, another internal barrier composed by maternal and fetal tissue, that protects the embryo development, secreting numerous proteins and hormones, and eliminating fetal metabolites [5]. Here, two very important functions will be highlighted: nutrient transport and endocrine function.

### 2.1. Nutrient transport

#### 2.1.1. Lipids

The absorption of lipids from the maternal circulation is facilitated by different carrier proteins and lipases. Triglycerides packaged in circulating lipoproteins are hydrolyzed into non-esterified fatty acids and glycerol by lipoprotein lipase (LPL) and endothelial lipase (EL) before entering the syncytiotrophoblast. Long-chain fatty acids cross the microvillous plasma membrane (MVM) with the support of fatty acid carrier proteins (FATPs) and fatty acid translocase/differentiation cluster 36 (FAT/CD36). After internalization, free fatty acids are esterified with coenzyme A (CoA) producing acyl-CoAs. The acyl-CoAs are then transported by the fatty acid-bound cytosolic proteins for placental mitochondrial respiration, fat droplets incorporation to placental storage, or transfer to the fetus through the basement membrane [11].

#### 2.1.2. Amino acids

Amino acids are essential for normal fetal growth since they are used in protein synthesis, energy production, and signaling pathways. Placental system amino acid transporters (SNATs) are responsible for the uptake of essential and non-essential amino acids and are predominantly found in the maternal membrane of the syncytiotrophoblast. Approximately 20 different SNATs have been identified in the human

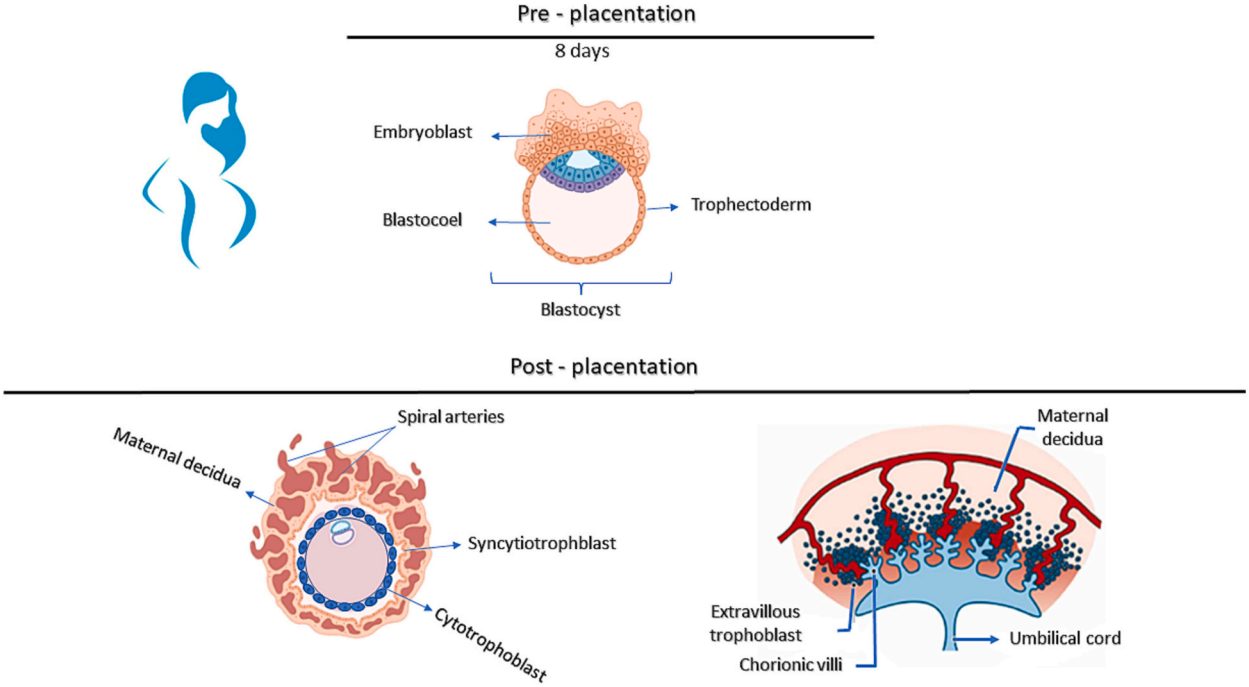


**Fig. 1.** Schematic representation of human placentation.

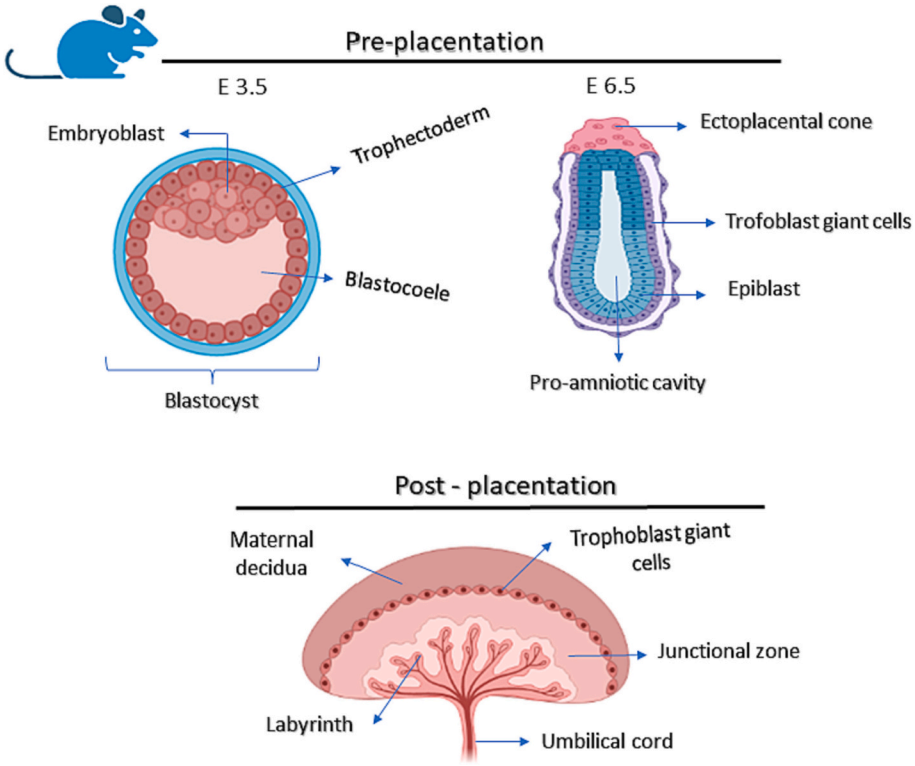


**Fig. 2.** Schematic representation of mice placentation.

**Table 1**
Comparison of the temporal course of gestational events in mice and humans. Adapted from Blum et al., 2017 [10].

| Phenomena | Mouse (gestational days) | Human (gestational days) |
|---|---|---|
| First trimester | | |
| Fertilization | 0 | 0 |
| Cleavage | 1–2.5 | 2–3 |
| Blastocyst | 2–4 | 2–4 |
| Implantation | 4.5–5 | 6–12 |
| Placentation | 6–14 | 28–91 |
| Complete organogenesis | 14 | 84–98 |
| Second trimester | | |
| Placental and fetal growth | 14–17 | 99–196 |
| Third trimester | | |
| Accelerated growth | 17 | 197 |
| Birth | 19–21 | ~ 294 |

placenta, though the main placental SNATs are SLC38A1 (SNAT1), SLC38A2 (SNAT2), and SLC38A4 (SNAT4) [12]. These three isoforms catalyze the liquid, sodium-dependent absorption of neutral amino acids in the cell [13]. Their expressions and activities increase with the progression of pregnancy while contributing to fetal growth and development. Reduced expression of these proteins has been associated with reduced fetal growth in baboons [14].

### 2.1.3. Glucose

Glucose is the main energy substrate during embryogenesis and is largely transported by the placenta. The transfer of glucose from maternal to fetal circulation occurs through facilitated diffusion using around seven glucose-transporting proteins, known as GLUTs. However, the most studied are GLUT 1 and GLUT3 [15]. The GLUT1 has two isoforms, GLUT1-45kda and GLUT1–55kda. The first one is expressed only on the maternal side and is responsible for transporting glucose within the placental tissue, at the placental metabolism place [16]. Meanwhile, GLUT1–55 is located on both maternal-fetal sides, participating in the transfer of glucose to the fetus. The GLUT3, in turn, is mainly located in the MVM of the syncytiotrophoblast but also expressed in the cytotrophoblast and endothelium. Its expression is higher in the first semester, suggesting a possible role in glucose capture in early pregnancy; in the second and third trimesters, its expression seems to be diminished compared with the first one [17].

### 2.1.4. Hormones

The placenta is a very dynamic endocrine organ in pregnancy that secretes a wide variety of hormones for proper fetal development. Placental hormones include members of the prolactin (PRL) and growth hormone (GH) family and steroid hormones. The PRL-GH family is one of the main families of hormones secreted by the placenta during pregnancy. The PRL and placental lactogen (LP) induce the expansion of pancreatic beta cells, both by increasing their proliferation and decreasing islet apoptosis. Thus, these hormones increase insulin secretion during pregnancy, particularly in response to glucose. The growth hormone, however, seems to be responsible for the physiological insulin resistance, a common pregnancy adaptation [18].

The placenta is also the primary source of steroid hormones during pregnancy. Two hormones, estrogen, and progesterone, seems to develop similar roles in the pancreas. Both have been shown to induce islet hypertrophy and/or increase pancreatic insulin levels and glucose-stimulated secretion. These hormones may also play an important role in uterine contractability and labor [18,19]. A study carried out by Lindheim et al. [20] showed that healthy postmenopausal women supplemented with moderate doses of estrogen had an improvement in insulin sensitivity, however, on the other hand, high doses seem to worsen this effect. They also observed that progesterone decreased sensitivity to insulin in this population. Moreover, in animals, a study showed the effects of 17-β-oestradiol (E2) and progesterone (P) in insulin sensitivity, concluding the important role of E2 in the maintenance of normal insulin sensitivity [21]. Another one, have shown that E2 suppresses

hepatic gluconeogenesis through activation of estrogen receptor (ER)α–phosphoinositide 3-kinase–Akt–Foxo1 signaling, revealing an important mechanism for E2 in the regulation of glucose homeostasis. Altogether, these may help explain why premenopausal women have lower incidence of T2D than age-matched men and suggest that targeting ERα can be a potential approach to modulate glucose metabolism and prevent diabetes [22].

Mainly, the placenta has an essential association with fetal health. Its impacts on nutrient acquisition and development have a major role in the fetal outcome. Furthermore, the maternal nutrition also affects these processes, based primarily on macronutrients and micronutrients consumption.

## 3. Environmental insults and fetal outcome: nutrition

### 3.1. Macronutrients

Maternal nutrition plays an important role for both pregnant woman's and baby's health. For a healthy gestation, observing the quality of diet is fundamental, especially to prevent common complications associated to unhealthy habits during this period. For this, the balance between macronutrients it is important. This class of nutrients is composed by carbohydrates, protein, and lipids. Another class is composed by micronutrients, which corresponds to vitamins and minerals needed in very small amounts. Both macro and micronutrients are important for functions in our bodies and health. Considering that, processes such as nutritional transition and the change in dietary pattern establish another perspective about the importance of diet for pregnant women [23].

The literature has shown that the increasing consumption of food mostly composed of sugar and saturated fatty acids, or the ultra-processed and processed food, increases the risk of developing obesity and other associated comorbidities [24,25]. Furthermore, the literature has also shown that the nutritional quality of maternal diet, especially higher consumption of saturated fatty acids, has an impact on maternal and fetal health and are associated with the risk of developing chronic diseases in adult life [24,26].

Experimental research already shown the impact of maternal obesity in the offspring, , induced by a high fat diet (HFD) in cardiovascular [27], neuroendocrine [28], and gastrointestinal systems [29], showing an systemic effect in essential organs. Besides, another interesting modification from consuming an HFD occurs in the placenta, a transient organ that establishes the communication between mother and fetus. Some studies have reported a morphology alteration, which impacted the placental function and gene expression [30], the fetal nutrient acquisition, and could lead to different offspring outcomes [31]. These placental effects are related to a transgenerational response, improving offspring risk for developing chronic diseases later in life, such as obesity.

In humans, some cohorts have already established a similar relation between maternal obesity and offspring health. Recently, the consumption of ultra-processed foods was reported as a risk for offspring overweight or obesity, based in three prospective cohorts [32]. They found a 26 % higher risk for the group of mothers with the highest consumption of ultra-processed food, highlighting the importance and necessity for developing programs and strategies to improve women's reproductive health. Regarding the child outcomes, they found that 12.4 % developed overweight or obesity after. This highlights the importance of improving nutrition for both women and child, aiming to refine the dietary recommendations and remove financial and social barriers [32].

Another study have also reported the consumption of artificially sweetened beverages during pregnancy as significantly associated with infant body mass index (BMI) at 1 year of age and the development of childhood obesity [33]. Similarly, Pinto et al. [34] found a relation between intake of sugary drinks and maternal obesity, leading to an increased risk of early and higher exposure to added sugar before the child's second year of age [34]. Taken together, these findings are relevant, mostly since this age comprehends a period called the first 1000 days of life, which is also known as a window of opportunities, based on the Development Origins of Health and Disease (DOHaD) hypothesis [35,36]. According to this hypothesis, the environment is an important factor to the development of diseases later in life. Here, the intrauterine environment is fundamental and can generate different metabolic responses, affecting fetal outcome [36].

Therefore, the nutritional status is a relevant factor that impacts child health. Although overnutrition has a major role in unhealthy outcomes, the first studies in this area came from the opposite spectrum. Maternal undernutrition has been documented as a factor for similarly outcomes since the 1910's [37,38]. One of the most important cohorts is the Hertfordshire cohort study, based in the United Kingdom, which evaluated the relationship between intrauterine environment and postnatal development, during adult life, specifically. To this end, they used parameters such as diet, lifestyle, and genetics to assess the etiology of cardiometabolic diseases, such as obesity and cardiovascular diseases [39].

Briefly, Dr. David Barker, an epidemiologist, observed the impact of maternal nutrition during the Second World War. Besides other nutritional factors, he evaluates the maternal undernutrition due to lower availability of protein. The women who were pregnant at this period and exposed to a food shortage environment had children with low weight at birth, particularly those exposed to adverse conditions in the first gestational trimester. Furthermore, when adults, these children presented higher obesity prevalence, as well as high blood pressure and a greater propensity to develop type 2 diabetes. These observations were then called Barker's hypothesis [37].

Together, these aspects show the importance of nutritional environment for maternal-child health, considering the abundance and lack of nutrients. Significantly, the similarity between a high-fat diet (HFD) and a typical Western diet has resulted in an increased focus on conducting numerous experimental studies to examine their effects, particularly during crucial developmental stages such as pregnancy. Besides, during this period, the placenta plays a relevant role for fetal nutrient, oxygen, and hormones supply, impacting on development and outcomes [38] (Fig. 3).

The placental structure could also be compromised in regions responsible for transporting nutrients to the fetus when considering a maternal HFD. Considering that, there are important experimental studies describing the effects of a HFD stimuli in the placenta regions. A classic study from Challier et al. [40] showed the stimulus for macrophage accumulation and inflammation in the placenta of women with obesity. Briefly, obesity during pregnancy can result in an inflammatory response, since pro-inflammatory mediators accumulate. They reported an increased expression of the pro-inflammatory cytokines such as Interleukin-1 family (IL-1), Tumor necrosis factor alpha (TNF- alpha), Interleukin 6 (IL-6), leading to a chronic villitis signature. Also, inflammatory changes, including plasma concentrations of C-reactive protein and IL-6, were higher in obese compared to lean women. In conclusion, when this occurs during pre-pregnancy, the chronic inflammation initiates a cascade of events, affecting the in-utero environment and influencing the fetus's health [40].

Recently, Sanches et al. [41] showed a relationship between a maternal obese phenotype and placental disfunction. Using Swiss mice, they observed changes in the placental layer thickness, in the transportation of fatty acids, and in the expression of growth factors such as epidermal growth factor receptor (EGFR) in the obesity-prone group. Furthermore, in the obesity-resistant group, the maintenance of maternal glucose homeostasis and overexpression of placental growth factor (PGF) seems to protect the placenta and fetuses from morphological and functional damage. Combined, these changes lead to a placental insufficiency, and impaired fetal outcome, restricting fetal growth [41].

Another study reported the impact of HFD on placental metabolism

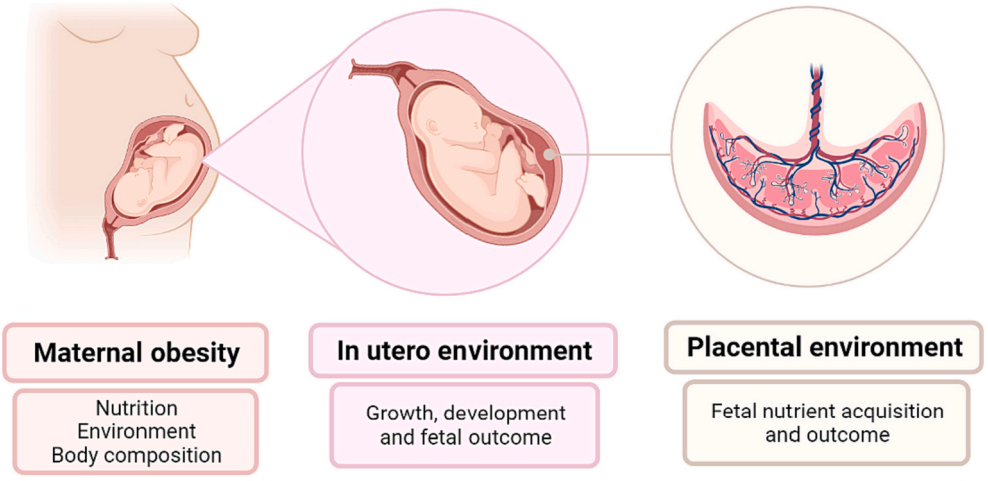


**Fig. 3.** Association between maternal and in utero environment in placental response to fetal outcomes.

in women with obesity, also evaluating the sex dimorphism response. They found a decrease in protein expression for regulators responsible for energy and lipid metabolism such as Pparg coactivator 1 alpha (PGC1α), NAD- dependent deacetylase sirtuin-3 (SIRT3), Estrogen-related receptor alpha (ERRα), Carnitinepalmitoyltransferase 1 alpha (CPT1α), and Carnitine palmitoyltransferase II (CPT2), with sex-dependent difference, as well as in acylcarnitine's levels C16:0, C18:2, and C20:4, indicating a decrease in β-oxidation process. Regarding metabolic parameters, they found an increased cord blood insulin and insulin resistance in babies born to OB women. These shows that newly-born offspring of obese mothers begin their lives dyslipidemic and insulin resistant, which could be explained by an abnormal placental metabolism, that leads to potential long-term consequences. In conclusion, they established that placental adaptation to maternal obesity had a fetal-sex dependent response [42].

The same response was reported when evaluating the placental pro- and anti-inflammatory status [43] as well as oxidative stress and fetal growth and sex response [44]. These cellular processes are related to impaired placental morphology and to pregnancy complications [45]. Overall, the literature associates HFD with this response, affecting placental parameters such as weight and surface area as well as essential areas for fetus nutrition. Recently, an in invo study demonstrated the impact of HFD in fetal-placental growth, placental morphology, mitochondrial and lipid metabolism, and oxidative stress function. Furthermore, the authors found a sex-specific response [44].

Recent experimental studies also showed offspring alterations and a sex-specific response after HFD consumption in cardiac [46] and hypothalamic tissues, adipocytes, as well as in glucose and lipid metabolism [47–49]. Thus, the effects of macronutrients in maternal diet must be considered as an important way to evaluate mother's and fetus' health. Moreover, considering the contribution and importance of maternal nutrition to pregnancy development, placental function, and fetal outcomes, guaranteeing healthcare assistance and information during this period is essential. Additionally, termed micronutrients are also involved in cellular and metabolic processes. They are essential for preventing pregnant complications and assuring mother's and fetus' health.

### 3.2. Micronutrients

Regarding micronutrients, they are known to be extremely important for the metabolism and functioning of cellular processes, acting as co-enzymes and precursors. However, dietary intake of some micronutrients is usually below recommendation, which may contribute to adverse effects [50]. In pregnant women, this reduction has been associated with gestational diabetes, preeclampsia, preterm birth, low birth weight (LBW), small for gestational age, large for gestational age, reduced offspring survival, and increased risk of chronic diseases later in life [51]. Although several micronutrients are indispensable to reduce the risk of pregnancy complications, iron, zinc, and selenium are the most studied and show the most promising data.

During pregnancy, iron demand is increased by fetal growth and maternal physiological changes. Recent data shows a high prevalence of pre-existing anemia in women of reproductive age. Therefore, the World Health Organization recommends iron and folic acid supplementation for all pregnant women to prevent anemia and adverse fetal outcomes. Notably, iron deficiency affects approximately one third of pregnant women globally [52]. Women who do not use iron supplementation during pregnancy have children with low body weight at birth, which is even more expressive in mothers with iron deficiency anemia [53], as well as the increased risk of preterm birth. Birth weight is an indicator of fetal growth, nutritional status, and newborn's health. When the child has low weight or macrosomia at birth morbidity and mortality risks are increased throughout life [54].

Evidence in how maternal iron deficiency affects fetal growth is still scarce, but some studies support the placenta as a mediator organ [55,56], and DNA methylation as a potential underlying mechanism associated with ferritin status (reflects iron stores in the body) during pregnancy and offspring health, as it was observed in Taeubert, M et al. [57] in an epigenome-wide meta-analysis, using robust linear regression analyses, that serum ferritin concentrations in early pregnancy were associated with differential DNA methylation in the umbilical cord that persisted in older children. Research on animals has shown that a low-iron diet two to three weeks before mating and maintained during pregnancy reduces maternal and fetal hemoglobin, liver and fetal weight and increases the weight of the placenta and as well as the area of the junctional zone, leading to anatomical deformities and a high rate of fetal reabsorption (40 to 100%). Gene expression analyses show that an iron-deficient diet during pregnancy modulates substantial numbers of genes in the placenta related to different placental biological pathways and processes, such as oxygen transport and lipoprotein metabolism [54].

As a precautionary factor, obesity should be prevented and treated before pregnancy, since maternal obesity reduces iron absorption at the end of pregnancy, restricting the transfer of iron to the fetus even in mothers under iron supplementation. This leads to an iron stock reduction in the baby's body, corroborating for inadequate outcomes in the fetus, newborn, and during childhood [58]. In addition to outcomes at birth, reduced levels of maternal ferritin serum seems to be linked to symptoms of inattention in boys aged 4–5 years. However, higher levels

show a protective association to symptoms of attention-deficit/hyperactivity disorder (ADHD) [59]. By age 7 to 8, children whose mothers had higher levels of serum ferritin during pregnancy present better neuropsychological outcomes, such as working memory and executive function, with better academic performance compared with children of mothers with low ferritin levels [60].

Increased supplemental iron intake during pregnancy has also been associated with reduced risk of autism spectrum disorder (ASD) in children [61]. Maternal iron deficiency during pregnancy increases risk susceptibility for schizophrenia spectrum disorders (SSDs) in their children in adulthood [62]. Therefore, maternal iron intake and levels during pregnancy are associated with the neuropsychological function of their children throughout life. On the other hand, excess iron levels during pregnancy seems to contribute to the occurrence of congenital heart defect in offspring [63].

Concerning zinc, it plays a critical role in the growth and development of the fetus, thus its mild to moderate deficiency during pregnancy may already contribute to unfavorable outcomes [64]. Recent studies with humans show that regarding birth weight, newborns with adequate weight have higher concentration of zinc in the umbilical cord [65] and the amount of blood in the cord is significantly related to maternal zinc status [66]. In babies born with low birth weight, postnatal zinc supplementation also seems to contribute to increased growth in the first months of life [67].

Regarding the placenta, the absence of supplemental zinc during pregnancy positively regulates the expression of zinc uptake proteins in the placental tissue, possibly to meet fetal demands in the face of low maternal supply [68]. The literature indicates that selenium helps prevent gestational complications such as gestational diabetes, preeclampsia, miscarriages and protects against neural tube defects and low weight in the fetus, both for its antioxidant function and for the functions related to modulating the metabolic endocrine system and the energy balance. These nutrients corroborate to the regulation of the cell cycle and structuring of tissues, including the placenta [69]. In humans, the low plasma concentration of maternal selenium during pregnancy contributes to low birth weight, possibly by reducing the antioxidant defense of the placenta, directly affecting fetal growth [70], and suggest being related to premature birth [71].

Research on animals has been demonstrating that selenium deficiency for 4 weeks before mating and during pregnancy increases the concentrations of triiodothyronine and tetraiodothyronine in the mother. Meanwhile, in the fetus, it reduces blood glucose and induces growth restriction [72]. Moreover, selenium supplementation 3 weeks before mating, during pregnancy, and 3 weeks during lactation in rats with metabolic syndrome, (show signs of improving) seems to improve the metabolic parameters of their descendants [73].

Studies also evaluate the influence of some bioactives on gestational outcomes, especially omega-3 s. Docosahexaenoic acid (DHA) supplementation in the last half of pregnancy seems to reduce the risk of preterm birth, prolonging pregnancy, and increasing the newborn's birth weight, length, and head circumference [74]. In mothers with gestational diabetes, DHA seems to reduce insulin resistance [75], and by simply increasing the intake of polyunsaturated fatty acids food sources the glycemic and lipid profile of pregnant women improves [76]. Another example is the combination between different substances, such as concomitant supplementation of magnesium, zinc, calcium, and vitamin D for 6 weeks for women with gestational diabetes mellitus (GDM), reducing biomarkers of oxidative stress and inflammation, providing benefits to maternal health and full-term delivery [77].

It should be mentioned that excessive or indiscriminate supplementation of micronutrients during pregnancy can also cause adverse effects, from changes in health to teratogenic effects on the offspring [78], therefore, a nutritionally balanced maternal diet, reaching dietary needs for macro and micronutrients and adequate weight gain during pregnancy contributes significantly to reduce adverse outcomes related to both mother and child [79]. Therefore, policies to encourage healthy eating habits in this period and access to essential supplements and nutritional knowledge should be guaranteed for this population.

## 4. Environment insults and fetal outcome: environment and diseases

### 4.1. Physical activity

During pregnancy, women experience a unique period in their lives characterized by various hormonal, physiological, and biomechanical changes. These transformations include an increase in blood volume and heart rate, as well as weight gain and a shift in the center of mass, which are generally normal physiological phenomena [80].

Research on physical activity during pregnancy addresses several topics, encompassing continuous exercise throughout pregnancy or specific periods, as well as different levels of intensity, given the large number of available modalities such as walking, running, cycling, and swimming. This fact highlights the complexity of reaching definitive conclusions about the effects of physical activity on fetal growth, as different modes and intensities can result in different implications [81].

Some studies indicate an association between maternal physical activity and a reduction in neonatal adiposity. These studies demonstrate that this relationship may be inversely proportional, suggesting fetal body fat mass may be reduced as the mother's physical activity level increases. This effect was observed in pregnant women who practiced moderate-intensity exercises during the middle of pregnancy [82]. Another study found that women who frequently practiced moderate-intensity exercises at the beginning of pregnancy had a lower prevalence of infants with high fat mass [83]. A study revealed that offspring born to obese mice who engaged in exercise exhibited lower levels of triglycerides and leptin compared to those born to sedentary obese mothers, thereby indicating the beneficial impact of exercise in mitigating early-onset obesity [84].

Harrod et al. (2014) [85], showed a negative correlation between increasing levels of maternal physical activity, especially in late pregnancy. The impact of exercise on fetal development is not fully understood but is a crucial aspect, since the practice of physical activity during pregnancy has been positively associated with several health benefits for the mother and the newborn [82].

Wiebe et al. [86] demonstrated that pregnant women who engaged in structured exercise had a 31 % reduction in the likelihood of delivering a large or macrosomic baby. Several studies suggest that the effect of exercise on fetal development is due to placental modifications. Regular aerobic exercise, such as running and stair climbing, led to an increase in placental size in mid-pregnancy that persisted until delivery. Regular moderate-intensity physical exercise, initiated early (within the first 20 weeks of gestation), may increase placental blood flow and functional capacity [87].

It is believed that exercise-induced maternal stress is one of the most important mechanisms for improving vascular function, which contributes to maintaining vascular tone and is also important for blood supply to the placental circulation. All these factors contribute to proper placentation and fetal growth and development [88]. A study conducted by Jackson with humans demonstrated that women who engaged in regular exercise during the first 20 weeks of pregnancy showed vascular and villous growth of the placenta, along with an increase in parenchymal tissue [89].

Collings et al. [82] demonstrated that higher levels of physical activity in mid-pregnancy were associated with lower triceps and subscapular skinfold thickness. Abdominal and arm circumference and umbilical cord leptin concentration were also influenced by physical exercise, since physically active women had fetuses with a reduction in these parameters compared with inactive women.

Physical activity may impact fetal outcomes differently depending on the timing of exercise during pregnancy, since maternal-fetal physiology undergoes constant changes throughout gestation.

### 4.2. Diabetes

Gestational diabetes mellitus (GDM) is a condition that can lead to various complications for both the mother and the fetus. Complications include fetal macrosomia, hypoglycemia, and traumatic delivery situations. Studies indicate that children born to mothers with GDM may experience accelerated growth, which is related to maternal hyperglycemia even before diagnosis [90]. Therefore, early diagnosis and nutritional, medical, or pharmacological intervention can improve fetal growth and development, as well as maternal health [91].

In the placenta of obese women, GDM specifically increased the density of the intervillous spaces, and selected morphological features such as the density of stem villi were significantly affected by an interaction between obesity and GDM [92]. Placentas in pregnancies with Gestational Diabetes Mellitus (GDM) are larger and heavier compared to placentas in normal pregnancies [93]. Additionally, the central region of the placenta is thicker, and the number of cotyledons is also higher in cases of GDM compared to normal pregnancies [94]. This is because hyperglycemia is a factor that leads to vascular resistance in the cotyledon arteries [95]. The growth of the placenta can be an adaptive response during its development, ensuring adequate nutrient transport to the fetus [96].

Fetal macrosomia, characterized by excessive fetal growth, affects up to 45 % of pregnancies in women with GDM. These babies have a higher risk of developing overweight, childhood obesity, and type 2 diabetes in adulthood. Excessive weight gain can lead to complications during childbirth, such as clavicle fractures, shoulder dystocia, and brachial plexus injuries. High maternal glucose levels can also lead to fetal hyperinsulinemia, resulting in neonatal hypoglycemia at birth. This occurs due to the interruption of the supply of maternal glucose, after the umbilical cord is cut, while the fetal pancreas continues to secrete high levels of insulin [97].

The 20th week of gestation is considered a sensitive phase, during which fetal growth becomes proportional to the mother's glycemic state. In a randomized and longitudinal study, GDM diagnosed in the 28th week was positively associated with fetal macrosomia, which persisted until delivery even with medical treatment. This data was corroborated by other studies that showed that fetuses of mothers with GDM grew larger, both in size and amount of adipose tissue, compared with those from mothers with normal glucose tolerance [98].

Furthermore, mothers with medium or low risk of GDM who received standard treatment between the 24th and 28th week can optimize fetal growth, leading to newborns with normal birth weight [90]. Women at high risk of GDM who receive diagnosis and treatment between the 16th and 18th week can normalize fetal growth until delivery more efficiently than those diagnosed later in pregnancy. This possibly occurs due to the prevention of fetal hyperinsulinemia induced by maternal glucose intolerance [99]. Other studies have concluded that mothers with GDM and who had obesity before pregnancy, with altered fasting glycemia, presented higher estimated fetal weight and waist circumference at the 20th week of gestation [91].

On the other hand, early treatment for GDM, with blood glucose control, before the 20th week – can reduce fetal macrosomia but may increase the likelihood of small-for-gestational-age babies compared with late treatment (24th to 28th week) [100]. In this sense, early treatment may be necessary to reduce perinatal morbidity and mortality, since the combined effects of maternal hyperglycemia, the macroenvironment, and the intrauterine hormones cannot be completely reversed if treatment is delayed until the end of pregnancy [90].

Regarding pharmacological interventions, insulin, and oral hypoglycemic agents, such as insulin-sensitizing metformin or sulfonylurea glibenclamide, are often used. However, these oral hypoglycemic agents are not recommended as a first-line treatment since, unlike insulin, they can cross the placental barrier and generate adverse effects on the fetus, as highlighted by the American Diabetes Association (2021) [101]. The results of the study comparing the effects of insulin, metformin, and glibenclamide on neonatal biometrics demonstrated that, despite similar glycemic control at the end of pregnancy, variation in failure rates with glibenclamide were of 0–21 % and with metformin, 14–46 %, suggesting that insulin treatment was frequently necessary for glycemic normalization of mothers receiving oral hypoglycemic agents. When comparing birth weight, neonates of mothers treated with glibenclamide were heavier than those treated with metformin. Furthermore, compared with insulin, neonates exposed to metformin had lower birth weight and lower lean mass [102].

### 4.3. Preeclampsia

Preeclampsia is a medical condition that can occur during pregnancy, characterized by arterial hypertension and proteinuria. Although it can affect women of all ages, this condition is more common in younger women, primiparous women, and those undergoing cesarean section, when compared with women without a history of childbirth complications. The condition can lead to serious complications for both the mother and the fetus, including lower placental weight and smaller babies at birth [103].

In severe cases of preeclampsia, macroscopic pathological changes are more frequent and usually occur before term. The characteristic placental changes of preeclampsia are associated with placental ischemia. Consequently, the preeclamptic and preterm placenta is small and has several infarctions. The macroscopic changes of severe pre-eclampsia are very similar to those of fetal growth restriction [104].

In women with early-onset pre-eclampsia, it is believed that normal trophoblastic invasion "closes off" the maternal spiral arteries until vascular remodeling slows down the blood flow in the intervillous space, invasion is stronger in the center of the placenta and weaker in the periphery. Villi in peripheral regions with reduced invasion and obstruction are damaged. This can occur due to mechanical effects or excessive oxidative stress, resulting from increased oxygenation caused by decreased trophoblast invasion and obstruction of maternal vessels in the periphery [105].

In pre-eclampsia, there is a limitation of placental invasion into the adjacent decidual layer, resulting in a lack of dilation of spiral arteries and their responsiveness to vasomotor influences. This leads to a high-resistance corioplacental circulation [106]. Consequently, the average diameter of blood vessels decreases, placental ischemia accelerates villous branching, and there is an increase in total villous volume. Additionally, the formation of numerous syncytial knots, clusters of apoptotic cells, occurs, which are associated with villous diffusion and inflammation [107].

The treatment of preeclampsia consists of managing arterial hypertension and monitoring mother's and fetus' health. For early-onset pre-eclampsia, a cautious approach is necessary, involving the use of antihypertensive medications, bed rest, and in-hospital monitoring of the mother and fetus. These patients often have reduced blood volume and are more susceptible to sudden drops in blood pressure caused by medications [108].

In severe cases of preeclampsia, performing a premature delivery may be necessary to prevent serious complications such as eclampsia, premature placental detachment, liver failure, renal failure, seizures, as well as maternal and fetal death. Thus, note that preeclampsia is a serious clinical condition that requires regular medical follow-up and adequate obstetric care, aiming to ensure the well-being of the mother and fetus [109].

## 5. Beyond the metabolism

Nutritional insults during critical periods of gestation may thereby have a permanent effect on progeny (fetal, postnatal life and beyond) by affecting maternal nutritional status and fetal growth directly by determining the amount of nutrients available and indirectly the fetal endocrine system by signaling mechanisms across the placenta, and

epigenetically by modulating gene activity. Children born to obese mothers have a two-fold increased risk for childhood obesity [110], metabolic, cardiovascular, renal and neurological disorders later in life [111,112] at least in part due to early exposure to elevated glucose levels and impaired pancreatic function by acceleration of pancreatic β-cell maturation [113,114].

Besides metabolic risks, animal models of high-fat diet-induced obesity demonstrate that offspring display social impairments, anxiety and depressive phenotypes with cognitive impairment and hyperactivity [115]. In the similar manner, long-term longitudinal and associative studies have shown that children born to obese mothers have an increased risk to develop neuropsychiatric, mood disorders and increased risk of cognitive impairments [116,117] and at least 35 % of children with autism also suffer from childhood obesity [118]. The observed behavioral and cognitive deficits may be linked to cytokines in the maternal circulation that appears to modulate placental growth, function and microbiome; for example the IL-6. Because these, increased IL-6 in maternal obesity [119] or decreased expression in placenta [40] could significantly alter fetal serotonin balance, hypothalamic–pituitary–adrenal (HPA) axis and program life-long disease and neurocognitive disorders.

### 5.1. Take home message

During this review, several evidences shows that, mechanistically, placental adaptations drives the metabolic fetal (re)programming and reflects the dynamic physiological state allowing or not the tissue adaptation to environmental changes and responses to stress, whereas the inability to reprogram placental metabolism may result in severe risks phenotypes.

Placental axis in normal condition contributes for optimal fetal growth and development. Several adverse conditions that affect woman during pregnancy could lead to poor outcomes. This review shows that GDM can lead to macrosomia, hyperinsulinemia, hypoglycemia, and labor complication such as clavicle fractures, shoulder dystocia, and brachial plexus injuries. However, early treatment, before 20th weeks of gestation can lead to a better outcome. Considering both preeclampsia and cancer, they seem to lead to fetal growth restriction, lower placental weight, and smaller babies at birth. On the other hand, physical exercise, and healthy eating habits, with adequate macro and micronutrients, have been positively associated with various benefits for the health of both the mother and the newborn.

Indeed, recent studies suggest that maternal factors including pre-pregnancy BMI may trigger predict the development of offspring health complications more than only birthweight. The most of these complications pass by placental dynamics and adaptation to maternal milieu, a mechanism that we cannot control directly yet. However, the reduction of risk factors for chronic diseases from unhealthy diets and physical inactivity can be treated through public health actions. Monitor science and helps to understanding of the influences of diet and physical activity on health printing a positive impact to preventive interventions as well as develop, strengthen, and implement global, regional, national policies focused in reproductive age could improve the transgenerational effects of malnutrition.

## CRediT authorship contribution statement

**Bruna de Souza Lima**: Conceptualization; Data curation and Writing - original draft; **Ana Paula Varela Sanches, Josilene Lopes de Oliveira and Maíra Schuchter Ferreira**: Data curation and Writing - original draft; **Jane K. Cleal**: Writing - guidance, review & editing; **Leticia Ignacio-Souza**: Conceptualization, Funding acquisition; Writing - review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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