

# Pregnancy Metabolic Adaptation and Changes in Placental Metabolism in Preeclampsia

## Metabolische Anpassung in der Schwangerschaft und Stoffwechseländerungen der Plazenta bei Präeklampsie



### Authors

Yaxi Li<sup>1</sup>, Ling Ma<sup>1</sup>, Ruifen He<sup>1</sup>, Fei Teng<sup>1</sup>, Xue Qin<sup>1</sup>, Xiaolei Liang<sup>2</sup>, Jing Wang<sup>3</sup> 

### Affiliations

- 1 The First Clinical Medical College of Lanzhou University, Lanzhou, China
- 2 Department of Obstetrics and Gynecology, The First Hospital of Lanzhou University, Key Laboratory for Gynecologic Oncology Gansu Province, Lanzhou, China
- 3 The First Clinical Medical College of Lanzhou University, the First Hospital of Lanzhou University, Lanzhou City, Gansu Province, China

### Keywords

pregnancy, metabolic adaptation, preeclampsia, placenta, glucose, lipids, amino acids

### Schlüsselwörter

Schwangerschaft, metabolische Anpassung, Präeklampsie, Plazenta, Glukose, Lipide, Aminosäuren

received 8.5.2024

accepted after revision 24.8.2024

### Bibliography

Geburtsh Frauenheilk

DOI 10.1055/a-2403-4855

ISSN 0016-5751

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Georg Thieme Verlag KG, Rüdigerstraße 14,  
70469 Stuttgart, Germany

### Correspondence

Dr. Jing Wang

The First Clinical Medical College of Lanzhou University,  
the First Hospital of Lanzhou University

No. 1, Donggang West Road

730000 Lanzhou City, Gansu Province, China

wjdyx2008@126.com

### ABSTRACT

Pregnancy is a unique physiological state in which the maternal body undergoes a series of changes in the metabolism of glucose, lipids, amino acids, and other nutrients in order to adapt to the altered state of pregnancy and provide adequate nutrients for the fetus' growth and development. The metabolism of various nutrients is regulated by one another in order to maintain homeostasis in the body. Failure to adapt to the altered physiological conditions of pregnancy can lead to a range of pregnancy issues, including fetal growth limitation and preeclampsia. A failure of metabolic adaptation during pregnancy is linked to the emergence of preeclampsia. The treatment of preeclampsia by focusing on metabolic changes may provide new therapeutic alternatives.

### ZUSAMMENFASSUNG

Die Schwangerschaft ist ein einzigartiger physiologischer Zustand, in dem der Körper der Mutter verschiedene Veränderungen des Glukose-, Fett-, und Aminosäurestoffwechsels durchmacht, um sich an den veränderten Zustand der Schwangerschaft anzupassen und ausreichende Nährstoffe für das Wachstum und die Entwicklung des Fetus zur Verfügung zu stellen. Die Stoffwechselvorgänge der verschiedenen Nährstoffe regulieren sich gegenseitig, um die Homöostase im Körper aufrechtzuerhalten. Unterbleibt diese Anpassung an die veränderten physiologischen Bedingungen der Schwangerschaft, kann dies zu verschiedenen Problemen in der Schwangerschaft führen, beispielsweise eine fetale Wachstumsrestriktion oder Präeklampsie. Störungen der metabolischen Anpassung während der Schwangerschaft werden mit der Entstehung von Präeklampsie in Verbindung gebracht. Neue Ansätze zur Behandlung der Präeklampsie, bei denen das Augenmerk auf metabolische Veränderungen gerichtet wird, könnten neue therapeutische Alternativen bieten.

## Introduction

Preeclampsia (PE) is a common obstetric hypertensive disorder associated with acute maternal injury and long-term maternal and fetal complications, with a high and growing incidence in obstetrics (currently 3–5% worldwide) [1]. However, there is no cure for this often devastating condition of pregnancy, which is related to its complex pathogenesis [2]. Research has found that administering low-dose aspirin to high-risk groups in early pregnancy can prevent PE. Therefore, exploring the mechanisms of PE occurrence and effectively screening for high-risk factors in early pregnancy is crucial for promoting maternal health [3].

Research has found that the occurrence of PE is associated with many metabolic-related risk factors, such as common conditions like diabetes, obesity, and insulin resistance. Additionally, there are some lipid-related factors, such as elevated serum trans fatty acids and polyunsaturated fatty acids, as well as decreased levels of Omega-3 fatty acids [4]. A high intake of energy and sucrose in the diet is also related to an increased risk of preeclampsia [5].

The placenta, as a medium of maternal-fetal material exchange, is considered to be the origin of PE. During normal pregnancy, placental metabolism changes towards adaptation to fetal growth and development [6]. For example, a decrease in maternal responsiveness to insulin increases the availability of glucose to the fetus in late pregnancy. At the onset of PE, the placenta has reduced oxygen uptake and utilization, leading to impaired energy metabolism and unrelieved mild hypoxia, promoting the generation of an inflammatory response that leads to PE. Glucose and fatty acids act as energy substrates and regulate placental development through bioactive derivatives [7].

Current research generally suggests that the development of PE is associated with abnormal embryonic implantation and inadequate remodeling of the spiral arteries [8]. In early gestation, trophoblast cells invade the spiral arteries of the uterus, temporarily blocking them and creating a hypoxic environment by blocking placental blood flow. At around 10–12 weeks of gestation, the intra-arterial cellular plug is displaced and maternal blood perfuses the intervillous space and the placenta [9]. During this process, vascular smooth muscle and elastic material are replaced by inert fibrin material. A constant high volume and low flow rate of maternal blood to the fetus are ensured [10]. In PE, this remodeling process is disturbed, leading to dysfusion of the intrauterine placenta and oxidative stress of the placenta [11, 12]. Stressed trophoblasts release pro-inflammatory cytokines, reactive oxygen species, extracellular vesicles, and anti-angiogenic agents (e.g., sFLT1 and free fetal DNA) into the maternal circulation [9, 13, 14], causing maternal endothelial dysfunction and systemic multi-organ disease. Alterations in substance metabolism can also modulate disease development by influencing this process.

## Changes in Placental Metabolism

### Glycometabolism

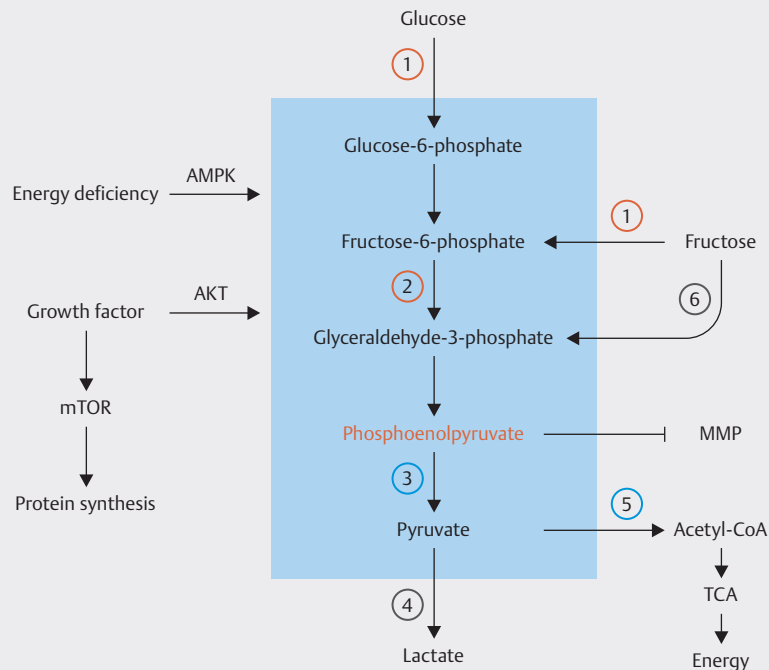
Glucose is one of the main energy sources in the human placenta and can produce a large amount of ATP, providing energy for material transportation, signal transduction, and protein synthesis. The glucose metabolism in the placenta is different from the

energy metabolism in other organs of the body. Even under the condition of sufficient oxygen, glucose in the placenta is still anaerobic glycolysis. Only about 20% of the glucose taken from maternal circulation is transported to the fetus, and 30% of it is converted into lactic acid through the placenta, which produces ATP and NADH [15]. As a general source of metabolic fuel, lactic acid can enter the fetus in an H<sup>+</sup>-dependent manner through the carrier on the basement membrane of the human placental trophoblast for energy metabolism and fatty acid synthesis [16]. Under the influence of lactate dehydrogenase, lactic acid can be transformed into pyruvic acid, which can function as an antioxidant in the body. Hydrogen peroxide can be directly inhibited by pyruvic acid through a non-enzymatic decarboxylation process. Pyruvic acid can also join the citric acid cycle. Citric acid is produced in greater amounts, which inhibits phosphofructokinase, allowing it to enter the pentose phosphate bypass and produce reduced coenzyme II (NADPH). This indirectly enhances the glutathione (GSH) antioxidant system's effectiveness and maintains redox homeostasis in cells [17, 18, 19].

Some studies suggest that energy deficiency is related to the severity of preeclampsia [20]. Pyruvate dehydrogenase kinase 1 (PDK1) can phosphorylate pyruvic acid dehydrogenase (PDH) to inhibit its activity, and pyruvic acid is converted into Acetyl-CoA for further metabolism. Oxidative stress and hypoxia can boost PDK1 transcription [21], which leads to the accumulation of pyruvate and lactate [22]. Pyruvic acid dehydrogenase activity dropped, preventing pyruvic acid from entering the citric acid cycle, lowering citric acid production, and blocking the pentose phosphate pathway. At the same time, it impacts the production of acetyl-CoA and the antioxidant NADPH.

During placental energy metabolism in PE, the expression of several key enzymes, including hexokinase (HK) and phosphofructokinase (PFK), was upregulated, while several enzymes that catalyzed downstream reactions, such as pyruvate kinase and pyruvate dehydrogenase, were downregulated, and lactate dehydrogenase expression was not significantly altered. This means that the lactate metabolism pathway in the trophoblast is blocked, leading to the accumulation of phosphoenolpyruvate (PEP) (► **Fig. 1**). By blocking MMP, altering the remodeling of uterine spiral arteries, and impairing placental perfusion, PEP can prevent the invasion of trophoblasts [23].

The occurrence of preeclampsia is related to ischemia and hypoxia of the placenta, which leads to overactivation of trophoblast AMPK (AMP-activated protein kinase) and enhances trophoblast GLUT3 (glucose transporter 3) from the cytoplasm to the plasma membrane, thereby enhancing the placenta's uptake of glucose [23]. Thus, in the placenta during preeclampsia, glucose levels are markedly elevated. GLUT1 is primarily responsible for controlling the transplacental fetuses' glucose supply. The expression of GLUT1 is downregulated in the PE placenta [24], which also explains the reason why PE patients are prone to fetal growth restriction. The human body has the ability to adapt to changes in various complex factors, and when transplacental glucose transport decreases, system L and system A amino acid transport increases, as a compensatory mechanism to maintain normal fetal development [25].



► **Fig. 1** Changes in glucose metabolism in PE: ① hexokinase (HK) ② phosphofructokinase (PFK) ③ pyruvate kinase ④ LDH ⑤ pyruvate dehydrogenase ⑥ fructokinase. AMPK = Adenosine 5'-monophosphate (AMP)-activated protein kinase; AKT = protein kinase B; MMP = metalloproteinases; mTOR: mechanistic target of rapamycin; TCA = tricarboxylic acid cycle. In PE placenta, Hexokinase and Phosphofructokinase are upregulated, pyruvate kinase is downregulated, pyruvic acid dehydrogenase activity is reduced, and phosphoenolpyruvic acid accumulates. Red represents an upward adjustment, and blue represents a downward adjustment.

The development of the placenta, which is connected to trophoblast function, angiogenesis, endothelial damage, inflammation, ferroptosis, etc., is significantly influenced by ROS (reactive oxygen species) [26, 27, 28]. The hypoxic environment of the placenta increases the production of ROS in the mitochondria, causing PE-like symptoms. This is also demonstrated in a rat PE model by the administration of mitochondrial antioxidants, which can greatly enhance placental blood flow and placental development [29]. In mild PE, mitochondria can adapt by upregulating the oxidative phosphorylation pathway (OXPHOS) and antioxidant activity [30]. The production of ROS and the reduction of antioxidants lead to an imbalance in the body's oxidative/antioxidant system, leading to maternal inflammation.

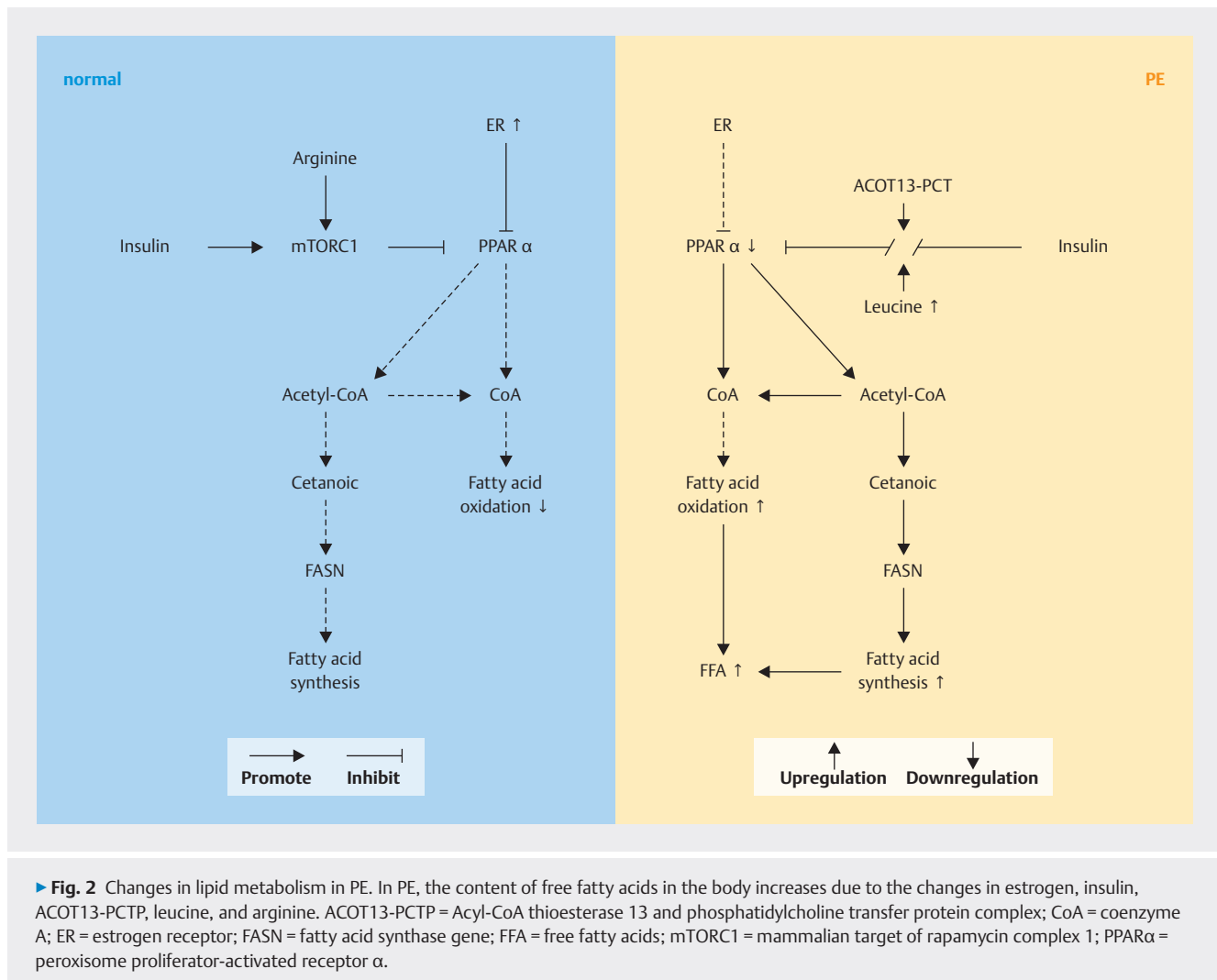
Some research also suggests that increased fructose metabolism contributes to the development of PE. When the embryo and placenta are hypoxic in the early stages of pregnancy, fructose is the perfect energy source [31, 32]. In a pregnant woman's body, any extra glucose is converted to fructose, and the two hexoses are then processed through aerobic glycolysis [33]. Large glucose accumulation in the placenta of PE increases fructose production. In vivo, fructose can be converted to uric acid [34, 35]. Uric acid can impair the aggressiveness of trophoblast cells, disrupt the remodeling of the uterine spiral arteries, hinder placental formation, and lead to ischemic and hypoxic conditions in the placenta. Additionally, ischemia and hypoxia in the fetus and placenta may stimulate the continued production of fructose [36]. This can re-

sult in further damage to the placenta, potentially leading it to enter an irreversible state.

## Lipid metabolism

In the first and second trimesters of pregnancy, maternal lipid metabolism changes in the direction of promoting synthesis, while in the third trimester of pregnancy maternal lipid metabolism changes in the direction of decomposition [37]. There is a clear correlation between abnormal placental lipid metabolism and abnormal lipase activity and pregnancy disorders, and they are involved in various pregnancy pathologies, such as first-trimester miscarriage, endometrial cancer, and the development of preeclampsia [38, 39, 40, 41]. Patients with PE often have abnormal lipid metabolism before the onset of the disease, such as elevated levels of total cholesterol, non-HDL-C, and triglycerides in the third trimester, and decreased levels of high-density lipoprotein cholesterol (HDL-C). Increased cholesterol and fatty acid biosynthesis and decreased catabolism increase the risk of various metabolic diseases [42], but the pathogenic mechanisms have not been fully elucidated.

Cholesterol is one of the important compounds during pregnancy, maintaining the stability of cell membranes and membrane-related signaling pathways, and is also a precursor of bile acid and steroid hormones, which is involved in fetal growth and development. During the first trimester, maternal cholesterol synthesis increases due to changes in hormone levels. Cholesterol



is transported from the mother to the fetal circulation through the placenta. High-density lipoprotein cholesterol (HDL-C) levels are transiently elevated during normal pregnancy [43]. Protein ABCA1 (adenosine triphosphate-binding cassette transporter A1) mediates the efflux of cholesterol and other phospholipids, positively influences changes in lipid profiles and is involved in the construction of the HDL molecule [44], and the expression of ABCA1 is reduced in the placenta of preeclampsia [45], so HDL-C levels are reduced in PE placenta compared to non-HDL-C levels, but this result is controversial.

Lipids and fatty acids are key components in the metabolism of the placenta, which are key elements in metabolic processes and energy production and are involved in the development of the fetus and the maintenance of a normal pregnancy [46]. Excessive free fatty acids in the maternal circulation may be one of the important causes of PE. The normal placenta expresses more estrogen receptor (ER) mRNA, which can counteract the promoting effect of PPARα on fatty acid oxidation [47]. As a result, fatty acid oxidation is inhibited, and the fetus' supply of fatty acids is enhanced. This is a result of PPARα's ability to promote CoA synthesis [48]. ER mRNA expression levels, however, did not rise in PE

placentas. It is suggested that the placenta in PE patients may be in a state of inadequate energy supply, and that AMPK can be activated by a decrease in intracellular energy status [49], and that PPAR-γ coactivator-1α (PGC-1α) can be phosphorylated to mediate the expression of PPAR target genes. Insulin can reduce PPARα activity through the mTORC1 pathway [21, 49, 50, 51], but in PE, the inhibition will be blocked by an increase in the levels of the ACOT13-PCTP complex and leucine [52, 53] (► Fig. 2). This leads to increased fat oxidation in the placenta of PE, resulting in an increase in the level of free fatty acids in the maternal circulation.

### Production of bioactive lipid molecules

Lipid metabolism generates a variety of physiologically active lipid compounds, including eicosanoids, chemerin, sphingolipids, and others, in addition to energy and free fatty acids. Long-chain polyunsaturated fatty acids (LC-PUFAs) of the omega-3 (anti-inflammatory) and omega-6 (pro-inflammatory) series are essential for cellular metabolism and the regulation of gene expression involved in cellular homeostasis [54], and are precursors of eicosanoids, such as prostaglandins (PG), leukotrienes (LT), thrombox-

anes (TXA2), etc., which are involved in blood pressure regulation and play an important role in the growth and development of the placenta [55]. Decreased levels of omega-3 fatty acids and an increased omega-6/omega-3 ratio in PE mothers [56] may be one of the causes of maternal inflammation and placental dysfunction [57].

Chemerin (chemoattractin) is a small chemoattractant adipokine secreted mainly by adipose tissue that affects blood pressure, cholesterol levels, adipose tissue function, and insulin sensitivity [58, 59] and is involved in the development of insulin resistance. Both free fatty acids and high concentrations of insulin inhibit chemerin expression [60, 61]. In healthy pregnancies, serum chemerin levels increase significantly with increasing gestational age [62]. However, chemerin is overexpressed in the placental trophoblast of preeclampsia, which promotes lipid accumulation and insulin resistance in human trophoblast cells [59, 63, 64].

Sphingolipids are bioactive lipids that are physiologically implicated in cell growth, inflammation, immune and stress responses, cell adhesion and migration, angiogenesis, vascular function, and mitochondrial bioenergy [65], and can be hydrolyzed into ceramides, which are hydrolyzed into sphingosine (SPH) and fatty acids by ceramidase. Increased oxidative stress in the placenta in preeclampsia induces decreased lysosomal hydrolase activity and increased de novo synthesis, leading to ceramide overload [66], increased trophoblast autophagy and necroptosis, and mitochondrial homeostasis tilted toward fission, resulting in increased mitophagy [65]. In addition, SPH can be phosphorylated by SPHK to form hemolysphingolipid sphingosine-1-phosphate (S1P). Both ceramide and S1P control various signaling pathways involved in cell death, proliferation, migration, survival, and senescence [67] and are involved in the development of PE.

### Alterations in enzyme activity associated with fat metabolism

Lipoprotein-associated phospholipase A2 (LP-PLA2) can hydrolyze oxidized lecithin to generate free fatty acids and lysolecithin, and the level of LP-PLA2 in the placenta of preeclampsia is significantly increased. The binding of LP-PLA2 to low-density lipoprotein causes lipid metabolism disturbances, leading to placental atherosclerosis and decreased placental function [68].

In addition, these metabolites also play an important role during labor, mainly mediating processes such as myometrial contraction [69]. However, endocannabinoid levels are significantly reduced in patients with PE [70], which may adversely affect fetal brain development. Diacylglycerol lipase (DAGL) p-diacylglycerol (DAG) has sn-1-specific hydrolytic activity and can catalyze the hydrolysis of DAG to 2-arachidonoylglycerol (2-AG), which is the most abundant endocannabinoid in tissues [71]. During the last trimester of pregnancy and the first 18 months after birth, arachidonic acid is preferentially and rapidly deposited in the cerebral cortex to participate in fetal brain development [72].

### Amino acid metabolism

The development of the fetus is directly dependent on the availability of amino acids, which are the second-most significant nutrient that crosses the placenta [73]. 32% of the energy needed

by sheep fetuses is used by amino acid oxidation [74]. Protein in food serves a variety of biological and metabolic purposes. Aside from being a crucial part of proteins, amino acids also play a role in the control of blood pressure (BP), lipid metabolism, food intake, and immunological function [75]. During the early stages of embryonic development, amino acids are also essential regulatory elements for cell function and energy metabolism [76]. Early in pregnancy, protein metabolism is similar to that of non-pregnant women; in mid- and late-pregnancy, protein synthesis increased by 15% and 25%, respectively [77]. This indicates that the mother's need for amino acids increases over the course of pregnancy. Amino acid intake and synthesis may be inadequate. PE patients' serum levels of isoleucine, glutamine, lysine, proline, histidine, phenylalanine, and alanine were lower at all stages of pregnancy as compared to the control group of healthy pregnancies [78].

In the organism, amino acids perform numerous intricate physiological processes. The mother's body may modify the balance of different amino acids to adapt to pregnancy. In a healthy pregnancy, the mother's protein decomposition increases, and keto amino acids and branched-chain amino acids are metabolized in the liver and surrounding tissues [79]. Amino acids are transported to the fetus through the placenta and participate in fetal growth [49]. According to research, the System A transporter protein (SLC38) could regulate the intake and supply of non-essential neutral amino acids. SLC38A4 knockout can cause significant placental dysplasia and weight loss in the placenta and fetus [80]. This demonstrates the significance of amino acids in the development and growth of the fetus and placenta.

*Homocysteine* (Hct) is a sulfur-containing essential amino acid produced primarily by the demethylation of dietary methionine, which is associated with oxidative stress and inflammatory responses and is required for the growth of human cells and tissues [81]. Early pregnancy is when Hct first starts to decline; mid pregnancy is when it reaches its lowest point; and late pregnancy is when it gradually rises to the level of early pregnancy [82]. Throughout pregnancy, the amount of Hct decreased in comparison to non-pregnancy. However, compared to non-PE patients, PE patients have higher levels of Hct [83]. Patients with severe PE had considerably greater levels of maternal and fetal serum Hct compared to those with mild PE [84].

By encouraging apoptosis, Hct can lead to placental malfunction. Hct can cause the apoptosis of trophoblasts in primary human placental trophoblasts (36 weeks of pregnancy) and considerably lower the release of human chorionic gonadotropin, according to in vitro research [85]. As a result, Hct can influence the development of preeclampsia by impairing trophoblast and vascular endothelial cell function.

Tryptophan is an essential amino acid for the human body that needs to be obtained from food. According to some researchers, the metabolism of tryptophan may be a key metabolic pathway involved in the development of preeclampsia. Tryptophan is a kynurenine pathway (KP) precursor metabolite that is converted to kynurenine by the enzyme indolamine 2,3-dioxygenase (IDO), which regulates vascular tone, energy metabolism, and immunological tolerance [86]. Studies indicate that placentas affected by PE produce less kynurenine compared to healthy placentas, which

may be linked to reduced IDO expression in PE placentas [87]. Furthermore, an increased kynurenine/tryptophan ratio in the placenta of patients with PE is associated with a significant decrease in tryptophan concentrations [88].

At the same time, the synthesis of serotonin also began with tryptophan. Under the regulation of tetrahydrobiopterin-dependent tryptophan hydroxylase, tryptophan is transformed into 5-hydroxytryptophan, which is then further decarboxylated to produce serotonin (5-hydroxytryptamine) [2]. Many immune cells, including dendritic cells, mast cells, T cells, B cells, macrophages, etc., have serotonin receptors [89]. Placental trophoblasts have 5-hydroxytryptamine transporters, which can control blood flow across the placental vascular bed. Additionally, 5-hydroxytryptamine can regulate PE by modulating trophoblast activity and proliferation through HTRA2 [90].

*Arginine* is a crucial nitric oxide donor. L-arginine supplementation during pregnancy can prevent the occurrence of preeclampsia, lower blood pressure, and lessen the need for antihypertensive medicines in women with hypertensive disorders [91]. According to several studies, arginine supplementation can lower endothelin-1 levels, which will enhance vascular function [92, 93]. Arginine stimulates the proliferation, migration, differentiation, and translation of mRNAs necessary for the formation and development of the conceptus by activating the mechanistic target of rapamycin (mTOR) signaling pathway [33]. In addition, arginine is also involved in the urea cycle and polyamine metabolism, regulates cell function, and is crucial to the growth and development of pregnancy [94]. Preeclampsia risk can also be predicted in early pregnancy using the single metabolite and amino acid ratio connected to the arginine bioavailability and nitric oxide synthase pathways [95].

*Glycine* is a non-essential amino acid for the human body. It participates in the production of bilirubin, creatine, and heme in the body [96] and is essential for the fetus's growth and development. Due to increased demand, the body's glycine flux falls during pregnancy, particularly in late pregnancy, when glycine synthesis is relatively insufficient. L-serine is absorbed in the placenta of sheep and transformed into glycine by serine hydroxymethyltransferase (SHMT). However, SHMT activity is 24 times lower in the human placenta than it is in sheep, suggesting that SHMT may not be the primary mechanism for glycine synthesis in the human placenta [97, 98]. According to clinical studies, increasing glycine intake in late pregnancy resulted in lower serum levels of Hct, ornithine, histidine, and urea [99].

*Glutathione*, which is produced by glutamic acid, cysteine, and glycine, is a crucial part of the human antioxidant system. Inadequate glycine can inhibit glutathione synthesis [100]. An imbalance in the body's oxidative/antioxidant system can impair trophoblast function and is an important cause of PE. Furthermore, glutamate from the fetal circulation may be taken up, changed into glutamine in the placenta, and then returned to the fetal circulation. Glutamate is the primary excitatory neurotransmitter in the central nervous system of mammals, and large amounts can be harmful to the fetal nervous system [49, 101].

The requirement for essential amino acids such as threonine, lysine, isoleucine, and phenylalanine rises in the third trimester of pregnancy compared to the first [102, 103, 104]. Lysine is consid-

ered to be beneficial for human growth, boost the immune system, and improve the functioning of the central nervous system. The formation of bone collagen depends in part on lysine [105]. Lysine and phenylalanine levels were considerably lower in PE patients. Furthermore, lysine is an important protein acetylation site, and the site can control the incidence of PE by modulating lysine acetylation.

The complete catabolism of *isoleucine*, *leucine*, and *valine* requires many enzymatic steps, most of which occur in mitochondria. In the placenta, branched-chain aminotransferase (BCAT) catalyzes their conversion to branched-chain  $\alpha$ -ketoacid. The subsequent phase takes place in the mitochondria, where the branched chain ketone dehydrogenase complex (BCKDH) converts CoA and branched chain  $\alpha$  ketonic acid into ketoacyl coenzyme A [106]. BCKDH is deactivated by branched-chain ketoacid dehydrogenase kinase. In PE, there is an increase in BCAT1 and branched-chain ketoacid dehydrogenase expression, which causes branched-chain  $\alpha$  ketoacid accumulation. At the same time, CoA deficiency also causes an increase in ketoacid concentration by decreasing the flux of branched-chain ketoacid dehydrogenase, which results in oxidative stress in the mitochondria. Screening for elevated sphingosine-1-phosphate and isoketovalerate at 14 to 16 weeks' gestation may be early risk factors for hypertension and acidosis, as they imply an already stressed placenta [21].

## Other metabolic changes

Vitamin D levels in the mother can influence placental function and the differentiation and invasion of trophoblasts by controlling immunological and anti-inflammatory responses. Preeclamptic pregnant women have relatively low vitamin D levels [55, 107]. By increasing the formation of Hct in one carbon metabolism and altering fatty acid metabolism, vitamin D deficiency during pregnancy may enhance oxidative stress. Hct production is regulated by the enzyme cystathionine beta synthase (CBS), which also controls one-carbon metabolism. Lack of vitamin D will cause CBS expression to decline, which will cause hyperhomocysteinemia [83].

Water-soluble B vitamins play a crucial role as substrates and coenzyme factors in the transfer of carbon groups during carbon metabolism [108]. There is a lot of research on folic acid, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub>. According to the current recommendations, supplementing with folic acid and vitamin B<sub>12</sub> in the early stages of pregnancy helps avoid pregnancy disorders, encourage the development of the fetal neurological system, and lessen complications. Pyruvic acid dehydrogenase contains vitamin B<sub>1</sub>. A lack of vitamin B<sub>1</sub> will result in an accumulation of pyruvic acid and lactic acid. Vitamin B<sub>6</sub> is implicated not only in Hct metabolism but also in canine uric acid metabolism. The synthesis of serotonin, melatonin, etc. will be hampered by a vitamin B<sub>6</sub> deficiency [109, 110]. Additionally, research has shown that other B vitamins, like vitamin B<sub>5</sub>, might raise CoA levels and delay PPAR $\alpha$  activation. Vitamin B<sub>5</sub> is mostly obtained from the gut flora [21].

## Conclusion

Pregnancy is an adaptation process; from fetal implantation to fetal delivery, the mother makes modifications to protect her and to adapt to the fetal growth and development. Mothers can adjust

to their pregnant state in an essential way through metabolic reprogramming. According to studies, reprogramming of the metabolism of sugar, fatty acids, and amino acids plays a role in appropriate embryonic growth and development. The occurrence of pregnancy complications such as pregnancy-induced hypertension, pregnancy-induced diabetes, PE, and other metabolic diseases during pregnancy is related to the impairment of metabolic homeostasis [111]. In vivo gene and protein regulation is amplified by metabolic alterations, which have a direct impact on preeclampsia symptoms as well as fetal growth and development. Gene expression and protein regulation can also be impacted by abnormal quantities of metabolites over the same period.

Nutrient signal sensing is a key factor in whole-body metabolic homeostasis. The placenta acts as a “nutrient sensor” that regulates its own nutrient transport activities [49, 112]. Acetyl-CoA is an intermediate molecule in energy metabolism; glucose, lipids, and amino acids can all be converted to acetyl-CoA to produce energy [20]. Acetyl-CoA is used as an intermediate between the three and can also be converted to each other. In addition, acetyl-CoA can produce CoA and cetanoic acid, which are widely involved in fatty acid and amino acid metabolism. The placenta can convert ingested nutrients into other forms that provide substrates for placental metabolism and fetal growth [113]. For example, sugar metabolism intermediates can synthesize some amino acids under the catalysis of enzymes. This is also supported by the finding that glycogenic amino acids decrease during fasting pregnancy [103]. The synthesis and catabolism of sugars, lipids, and amino acids are interrelated and regulated by glycolysis and the tricarboxylic acid cycle.

The development of PE is not solely due to the metabolic changes of a single substance, but rather the interaction of multiple substances that disrupt the body’s physiological balance. Addressing nutritional deficiencies during pregnancy may help correct the metabolic imbalances in women with PE. Studies indicate that providing certain nutrients during pregnancy can positively influence the onset and progression of PE. For instance, taking individual supplements of vitamin D, calcium, omega-3 fatty acids, and long-term low-dose L-arginine (3 g/6.6 g/d) in early pregnancy can help prevent PE and improve negative outcomes like low birth weight [5, 114, 115]. Supplementing multiple micronutrients (MMN) (including various vitamins, copper, iron, zinc, etc.) [116] can also help prevent the occurrence of PE. While balanced protein supplements do not protect against PE, they can reduce the risk of stillbirth [114]. However, nutrient supplementation during pregnancy may also lead to negative effects. Research has shown that combining vitamin C and vitamin E does not prevent PE and may even worsen its occurrence [117, 118]. Given the complexity of human metabolism, the use of metabolic therapy should be approached with caution.

## Funding information

ldyyyn2022-16 | The First Hospital of Lanzhou University |

## Contributors' Statement

Yaxi Li prepared the manuscript. Jing Wang and Xiaolei Liang provided writing guidance. Qinying Zhu and Fei Teng revised the manuscript. Ruifen He and Ling Ma provided drawing guidance. All authors have approved the final manuscript.

## Conflict of Interest

The authors declare that they have no conflict of interest.

## References

- [1] Wang Y, Li B, Zhao Y. Inflammation in Preeclampsia: Genetic Biomarkers, Mechanisms, and Therapeutic Strategies. *Front Immunol* 2022; 13: 883404. DOI: 10.3389/fimmu.2022.883404
- [2] Gumusoglu S, Scroggins S, Vignato J et al. The Serotonin-Immune Axis in Preeclampsia. *Curr Hypertens Rep* 2021; 23: 37. DOI: 10.1007/s11906-021-01155-4
- [3] Amylidi-Mohr S, Kubias J, Neumann S et al. Reducing the Risk of Preterm Preeclampsia: Comparison of Two First Trimester Screening and Treatment Strategies in a Single Centre in Switzerland. *Geburtshilfe Frauenheilkd* 2021; 81: 1354–1361. DOI: 10.1055/a-1332-1437
- [4] Hart NR. Paradoxes: Cholesterol and Hypoxia in Preeclampsia. *Biomolecules* 2024; 14. DOI: 10.3390/biom14060691
- [5] Middleton P, Gomersall JC, Gould JF et al. Omega-3 fatty acid addition during pregnancy. *Cochrane Database Syst Rev* 2018(11): CD003402. DOI: 10.1002/14651858.CD003402.pub3
- [6] Tain YL, Hsu CN. The Impact of Nutrient Intake and Metabolic Wastes during Pregnancy on Offspring Hypertension: Challenges and Future Opportunities. *Metabolites* 2023; 13: 418. DOI: 10.3390/metabo13030418
- [7] Hu M, Li J, Baker PN et al. Revisiting preeclampsia: a metabolic disorder of the placenta. *FEBS J* 2022; 289: 336–354. DOI: 10.1111/febs.15745
- [8] Amylidi-Mohr S, Kubias J, Neumann S et al. Reducing the Risk of Preterm Preeclampsia: Comparison of Two First Trimester Screening and Treatment Strategies in a Single Centre in Switzerland. *Geburtshilfe Frauenheilkd* 2021; 81: 1354–1361. DOI: 10.1055/a-1332-1437
- [9] Dimitriadis E, Rolnik DL, Zhou W et al. Pre-eclampsia. *Nat Rev Dis Primers* 2023; 9: 8. DOI: 10.1038/s41572-023-00417-6
- [10] Burton GJ, Jauniaux E. The cytotrophoblastic shell and complications of pregnancy. *Placenta* 2017; 60: 134–139. DOI: 10.1016/j.placenta.2017.06.007
- [11] Redman CW, Sargent IL, Staff AC. IFPA Senior Award Lecture: making sense of pre-eclampsia – two placental causes of preeclampsia? *Placenta* 2014; 35: S20–S25. DOI: 10.1016/j.placenta.2013.12.008
- [12] Broekhuizen M, de Vries R, Smits MAW et al. Pentoxifylline as a therapeutic option for pre-eclampsia: a study on its placental effects. *Br J Pharmacol* 2022; 179: 5074–5088. DOI: 10.1111/bph.15931
- [13] Marlatt KL, Redman LM, Beyl RA et al. Racial differences in body composition and cardiometabolic risk during the menopause transition: a prospective, observational cohort study. *Am J Obstet Gynecol* 2020; 222: 365.e1–365.e18. DOI: 10.1016/j.ajog.2019.09.051
- [14] Pankiewicz K, Fijałkowska A, Issat T et al. Insight into the Key Points of Preeclampsia Pathophysiology: Uterine Artery Remodeling and the Role of MicroRNAs. *Int J Mol Sci* 2021; 22: 3132. DOI: 10.3390/ijms22063132
- [15] Gu W, Jones CT, Harding JE. Metabolism of glucose by fetus and placenta of sheep. The effects of normal fluctuations in uterine blood flow. *J Dev Physiol* 1987; 9: 369–389

- [16] Inuyama M, Ushigome F, Emoto A et al. Characteristics of L-lactic acid transport in basal membrane vesicles of human placental syncytiotrophoblast. *Am J Physiol Cell Physiol* 2002; 283: C822–C830. DOI: 10.1152/ajpcell.00545.2001
- [17] Yin H, Li J, Tian J et al. Uterine pyruvate metabolic disorder induced by silica nanoparticles act through the pentose phosphate pathway. *J Hazard Mater* 2021; 412: 125234. DOI: 10.1016/j.jhazmat.2021.125234
- [18] Yi-jie G, Shu-zhe D. Anti-oxidation of Pyruvate. *Chinese Journal of Tissue Engineering Research* 2006; 10: 141–143
- [19] Liu Y, Peng W, Qi H-B. [Glucose Metabolism-Derived Nicotinamide Adenine Dinucleotide Phosphate in Late-Onset Preeclampsia Placenta Tissue and Its Correlation with Oxidative Stress]. *Sichuan Da Xue Xue Bao Yi Xue Ban* 2022; 53: 1028–1032. DOI: 10.12182/20221160212
- [20] Aye ILMH, Aiken CE, Charnock-Jones DS et al. Placental energy metabolism in health and disease-significance of development and implications for preeclampsia. *Am J Obstet Gynecol* 2022; 226: S928–S944. DOI: 10.1016/j.ajog.2020.11.005
- [21] Hodgman C, Khan GH, Atiomo W. Coenzyme A Restriction as a Factor Underlying Pre-Eclampsia with Polycystic Ovary Syndrome as a Risk Factor. *Int J Mol Sci* 2022; 23: 2785. DOI: 10.3390/ijms23052785
- [22] Bloxam DL, Bullen BE, Walters BN et al. Placental glycolysis and energy metabolism in preeclampsia. *Am J Obstet Gynecol* 1987; 157: 97–101. DOI: 10.1016/s0002-9378(87)80354-x
- [23] Xu P, Zheng Y, Liao J et al. AMPK regulates homeostasis of invasion and viability in trophoblasts by redirecting glucose metabolism: Implications for pre-eclampsia. *Cell Prolif* 2023; 56: e13358. DOI: 10.1111/cpr.13358
- [24] Lüscher BP, Marini C, Joerger-Messerli MS et al. Placental glucose transporter (GLUT)-1 is down-regulated in preeclampsia. *Placenta* 2017; 55: 94–99. DOI: 10.1016/j.placenta.2017.04.023
- [25] Ganguly A, Collis L, Devaskar SU. Placental glucose and amino acid transport in calorie-restricted wild-type and Glut3 null heterozygous mice. *Endocrinology* 2012; 153: 3995–4007. DOI: 10.1210/en.2011-1973
- [26] Yang Y, Jin H, Qiu Y et al. Reactive Oxygen Species are Essential for Placental Angiogenesis During Early Gestation. *Oxid Med Cell Longev* 2022; 2022: 4290922. DOI: 10.1155/2022/4290922
- [27] Liao T, Xu X, Ye X et al. DJ-1 upregulates the Nrf2/GPX4 signal pathway to inhibit trophoblast ferroptosis in the pathogenesis of preeclampsia. *Sci Rep* 2022; 12: 2934. DOI: 10.1038/s41598-022-07065-y
- [28] Goutami L, Jena SR, Swain A et al. Pathological Role of Reactive Oxygen Species on Female Reproduction. *Adv Exp Med Biol* 2022; 1391: 201–220. DOI: 10.1007/978-3-031-12966-7\_12
- [29] Long J, Huang Y, Tang Z et al. Mitochondria Targeted Antioxidant Significantly Alleviates Preeclampsia Caused by 11 $\beta$ -HSD2 Dysfunction via OPA1 and MtDNA Maintenance. *Antioxidants (Basel)* 2022; 11: 1505. DOI: 10.3390/antiox11081505
- [30] Holland OJ, Cuffe JSM, Dekker Nitert M et al. Placental mitochondrial adaptations in preeclampsia associated with progression to term delivery. *Cell Death Dis* 2018; 9: 1150. DOI: 10.1038/s41419-018-1190-9
- [31] Nakagawa T, Lanaspas MA, Millan IS et al. Fructose contributes to the Warburg effect for cancer growth. *Cancer Metab* 2020; 8: 16. DOI: 10.1186/s40170-020-00222-9
- [32] Lanaspas MA, Ishimoto T, Cicerchi C et al. Endogenous fructose production and fructokinase activation mediate renal injury in diabetic nephropathy. *J Am Soc Nephrol* 2014; 25: 2526–2538. DOI: 10.1681/ASN.2013080901
- [33] Bazer FW, Seo H, Wu G et al. Interferon tau: Influences on growth and development of the conceptus. *Theriogenology* 2020; 150: 75–83. DOI: 10.1016/j.theriogenology.2020.01.069
- [34] Seval MM, Karabulut HG, Tükün A et al. Cell free fetal DNA in the plasma of pregnant women with preeclampsia. *Clin Exp Obstet Gynecol* 2015; 42: 787–791
- [35] de Jong CL, Paarlberg KM, van Geijn HP et al. Decreased first trimester uric acid production in future preeclamptic patients. *J Perinat Med* 1997; 25: 347–352. DOI: 10.1515/jpme.1997.25.4.347
- [36] Nakagawa T, Ana A-H, Kosugi T et al. Fructose might be a clue to the origin of preeclampsia insights from nature and evolution. *Hypertens Res* 2023; 46: 646–653. DOI: 10.1038/s41440-022-01121-w
- [37] Ting L, Tao D. Maternal lipid metabolism and fetal growth. *Chinese Journal of Practical Gynecology and Obstetrics* 2018; 34: 963–966. DOI: 10.19538/j.fk2018090104
- [38] Szczuko M, Kikut J, Komornik N et al. The Role of Arachidonic and Linoleic Acid Derivatives in Pathological Pregnancies and the Human Reproduction Process. *Int J Mol Sci* 2020; 21: 9628. DOI: 10.3390/ijms21249628
- [39] Wojcik-Baszko D, Charkiewicz K, Laudanski P. Role of dyslipidemia in preeclampsia-A review of lipidomic analysis of blood, placenta, syncytiotrophoblast microvesicles and umbilical cord artery from women with preeclampsia. *Prostaglandins Other Lipid Mediat* 2018; 139: 19–23. DOI: 10.1016/j.prostaglandins.2018.09.006
- [40] Fügedi G, Molnár M, Rigó J et al. Increased placental expression of cannabinoid receptor 1 in preeclampsia: an observational study. *BMC Pregnancy Childbirth* 2014; 14: 395. DOI: 10.1186/s12884-014-0395-x
- [41] Maccarrone M, Bisogno T, Valensise H et al. Low fatty acid amide hydrolase and high anandamide levels are associated with failure to achieve an ongoing pregnancy after IVF and embryo transfer. *Mol Hum Reprod* 2002; 8: 188–195. DOI: 10.1093/molehr/8.2.188
- [42] Liu N, Guo Y-N, Wang X-J et al. Copy Number Analyses Identified a Novel Gene: APOBEC3A Related to Lipid Metabolism in the Pathogenesis of Preeclampsia. *Front Cardiovasc Med* 2022; 9: 841249. DOI: 10.3389/fcvm.2022.841249
- [43] Zeljković A, Ardalić D, Vekić J et al. Effects of Gestational Diabetes Mellitus on Cholesterol Metabolism in Women with High-Risk Pregnancies: Possible Implications for Neonatal Outcome. *Metabolites* 2022; 12: 959. DOI: 10.3390/metabo12100959
- [44] Wolski H, Ożarowski M, Kurzawińska G et al. Expression of ABCA1 Transporter and LXRA/LXRB Receptors in Placenta of Women with Late Onset Preeclampsia. *J Clin Med* 2022; 11: 4809. DOI: 10.3390/jcm11164809
- [45] Baumann M, Körner M, Huang X et al. Placental ABCA1 and ABCG1 expression in gestational disease: Pre-eclampsia affects ABCA1 levels in syncytiotrophoblasts. *Placenta* 2013; 34: 1079–1086. DOI: 10.1016/j.placenta.2013.06.309
- [46] Berger N, van der Wel T, Hirschmugl B et al. Inhibition of diacylglycerol lipase  $\beta$  modulates lipid and endocannabinoid levels in the ex vivo human placenta. *Front Endocrinol (Lausanne)* 2023; 14: 1092024. DOI: 10.3389/fendo.2023.1092024
- [47] Yoon M. PPAR $\alpha$  in Obesity: Sex Difference and Estrogen Involvement. *PPAR Res* 2010; 2010: 584296. DOI: 10.1155/2010/584296
- [48] Ramaswamy G, Karim MA, Murti KG et al. PPAR $\alpha$  controls the intracellular coenzyme A concentration via regulation of PANK1 $\alpha$  gene expression. *J Lipid Res* 2004; 45: 17–31. DOI: 10.1194/jlr.M300279-JLR200
- [49] Cleal JK, Lewis RM. The mechanisms and regulation of placental amino acid transport to the human foetus. *J Neuroendocrinol* 2008; 20: 419–426. DOI: 10.1111/j.1365-2826.2008.01662.x
- [50] Sugden MC, Caton PW, Holness MJ. PPAR control: it's SIRTainly as easy as PGC. *J Endocrinol* 2010; 204: 93–104. DOI: 10.1677/JOE-09-0359
- [51] Blanchard P-G, Festuccia WT, Houde VP et al. Major involvement of mTOR in the PPAR $\gamma$ -induced stimulation of adipose tissue lipid uptake and fat accretion. *J Lipid Res* 2012; 53: 1117–1125. DOI: 10.1194/jlr.M021485
- [52] Nie C, He T, Zhang W et al. Branched Chain Amino Acids: Beyond Nutrition Metabolism. *Int J Mol Sci* 2018; 19: 954. DOI: 10.3390/ijms19040954



- [53] Kawano Y, Ersoy BA, Li Y et al. Thioesterase Superfamily Member 2 (Them2) and Phosphatidylcholine Transfer Protein (PC-TP) Interact To Promote Fatty Acid Oxidation and Control Glucose Utilization. *Mol Cell Biol* 2014; 34: 2396–2408. DOI: 10.1128/MCB.01601-13
- [54] Basak S, Duttaroy AK. Effects of fatty acids on angiogenic activity in the placental extravillous trophoblast cells. *Prostaglandins Leukot Essent Fatty Acids* 2013; 88: 155–162. DOI: 10.1016/j.plefa.2012.10.001
- [55] Nema J, Randhir K, Wadhvani N et al. Maternal vitamin D deficiency reduces docosahexaenoic acid, placental growth factor and peroxisome proliferator activated receptor gamma levels in the pup brain in a rat model of preeclampsia. *Prostaglandins Leukot Essent Fatty Acids* 2021; 175: 102364. DOI: 10.1016/j.plefa.2021.102364
- [56] Godhamgaonkar AA, Wadhvani NS, Joshi SR. Exploring the role of LC-PUFA metabolism in pregnancy complications. *Prostaglandins Leukot Essent Fatty Acids* 2020; 163: 102203. DOI: 10.1016/j.plefa.2020.102203
- [57] Godhamgaonkar AA, Wadhvani NS, Joshi SR. Exploring the role of LC-PUFA metabolism in pregnancy complications. *Prostaglandins Leukot Essent Fatty Acids* 2020; 163: 102203. DOI: 10.1016/j.plefa.2020.102203
- [58] Recinella L, Orlando G, Ferrante C et al. Adipokines: New Potential Therapeutic Target for Obesity and Metabolic, Rheumatic, and Cardiovascular Diseases. *Front Physiol* 2020; 11: 578966. DOI: 10.3389/fphys.2020.578966
- [59] Tan L, Ouyang Z, Chen Z et al. Adipokine chemerin overexpression in trophoblasts leads to dyslipidemia in pregnant mice: implications for preeclampsia. *Lipids Health Dis* 2023; 22: 12. DOI: 10.1186/s12944-023-01777-4
- [60] Tan SK, Mahmud I, Fontanesi F et al. Obesity-Dependent Adipokine Chemerin Suppresses Fatty Acid Oxidation to Confer Ferroptosis Resistance. *Cancer Discov* 2021; 11: 2072–2093. DOI: 10.1158/2159-8290.CD-20-1453
- [61] Zhu L, Huang J, Wang Y et al. Chemerin causes lipid metabolic imbalance and induces passive lipid accumulation in human hepatoma cell line via the receptor GPR1. *Life Sci* 2021; 278: 119530. DOI: 10.1016/j.lfs.2021.119530
- [62] Yu M, Yang Y, Huang C et al. Chemerin: A Functional Adipokine in Reproductive Health and Diseases. *Biomedicines* 2022; 10: 1910. DOI: 10.3390/biomedicines10081910
- [63] Carlino C, Trotta E, Stabile H et al. Chemerin regulates NK cell accumulation and endothelial cell morphogenesis in the decidua during early pregnancy. *J Clin Endocrinol Metab* 2012; 97: 3603–3612. DOI: 10.1210/jc.2012-1102
- [64] Tan L, Chen Z, Sun F et al. Placental trophoblast-specific overexpression of chemerin induces preeclampsia-like symptoms. *Clin Sci (Lond)* 2022; 136: 257–272. DOI: 10.1042/CS20210989
- [65] Klemetti MM, Alahari S, Post M et al. Distinct Changes in Placental Ceramide Metabolism Characterize Type 1 and 2 Diabetic Pregnancies with Fetal Macrosomia or Preeclampsia. *Biomedicines* 2023; 11: 932. DOI: 10.3390/biomedicines11030932
- [66] Melland-Smith M, Ermini L, Chauvin S et al. Disruption of sphingolipid metabolism augments ceramide-induced autophagy in preeclampsia. *Autophagy* 2015; 11: 653–669. DOI: 10.1080/1548627.2015.1034414
- [67] Ying L, Tippetts TS, Chaurasia B. Ceramide dependent lipotoxicity in metabolic diseases. *NHA* 2019; 5: 1–12. DOI: 10.3233/NHA-170032
- [68] Wang J, Dong X, Wu H-Y et al. Relationship of Placental and Serum Lipoprotein-Associated Phospholipase A2 Levels with Hypertensive Disorders of Pregnancy. *Int J Womens Health* 2022; 14: 797–804. DOI: 10.2147/IJWH.S361859
- [69] Phillips RJ, Fortier MA, López Bernal A. Prostaglandin pathway gene expression in human placenta, amnion and choriondecidua is differentially affected by preterm and term labour and by uterine inflammation. *BMC Pregnancy Childbirth* 2014; 14: 241. DOI: 10.1186/1471-2393-14-241
- [70] Maia J, Fonseca BM, Teixeira N et al. The fundamental role of the endocannabinoid system in endometrium and placenta: implications in pathophysiological aspects of uterine and pregnancy disorders. *Hum Reprod Update* 2020; 26: 586–602. DOI: 10.1093/humupd/dmaa005
- [71] Bisogno T, Howell F, Williams G et al. Cloning of the first sn1-DAG lipases points to the spatial and temporal regulation of endocannabinoid signaling in the brain. *J Cell Biol* 2003; 163: 463–468. DOI: 10.1083/jcb.200305129
- [72] Basak S, Mallick R, Banerjee A et al. Maternal Supply of Both Arachidonic and Docosahexaenoic Acids Is Required for Optimal Neurodevelopment. *Nutrients* 2021; 13: 2061. DOI: 10.3390/nu13062061
- [73] Herrera E. Lipid metabolism in pregnancy and its consequences in the fetus and newborn. *Endocrine* 2002; 19: 43–55. DOI: 10.1385/ENDO:19:1:43
- [74] Faichney CJ, White GA. Effects of maternal nutritional status on fetal and placental growth and on fetal urea synthesis in sheep. *Aust J Biol Sci* 1987; 40: 365–377. DOI: 10.1071/bi9870365
- [75] Jahan-Mihan A, Luhovyy BL, El Khoury D et al. Dietary proteins as determinants of metabolic and physiologic functions of the gastrointestinal tract. *Nutrients* 2011; 3: 574–603. DOI: 10.3390/nu3050574
- [76] Wang X, Luo W, Tan D et al. Positive regulation of placentation by L-amino acid transporter-1 (lat1) in pregnant mice. *Int J Clin Exp Pathol* 2017; 10: 9551–9558
- [77] Felig P, Kim YJ, Lynch V et al. Amino acid metabolism during starvation in human pregnancy. *J Clin Invest* 1972; 51: 1195–1202
- [78] Dasgupta S, Subramani E, Mitra I et al. Discovery of novel metabolic signatures for early identification of women at risk of developing gestational hypertension. *Metabolomics* 2023; 19: 50. DOI: 10.1007/s11306-023-02012-y
- [79] Pappa KI, Vlachos G, Theodora M et al. Intermediate metabolism in association with the amino acid profile during the third trimester of normal pregnancy and diet-controlled gestational diabetes. *Am J Obstet Gynecol* 2007; 196: 65.e1–65.e5. DOI: 10.1016/j.ajog.2006.06.094
- [80] Kadife E, Harper A, De Alwis N et al. SLC38A4 Amino Acid Transporter Expression Is Significantly Lower in Early Preterm Intrauterine Growth Restriction Complicated Placentas. *Int J Mol Sci* 2022; 24: 403. DOI: 10.3390/ijms24010403
- [81] Hermann A, Sitdikova G. Homocysteine: Biochemistry, Molecular Biology and Role in Disease. *Biomolecules* 2021; 11: 737. DOI: 10.3390/biom11050737
- [82] Memon SI, Acharya NS. The Association Between Serum Homocysteine Levels and Placenta-Mediated Complications: A Narrative Review. *Cureus* 2022; 14: e31305. DOI: 10.7759/cureus.31305
- [83] Nandi AA, Wadhvani NS, Joshi SR. Altered metabolic homeostasis between vitamin D and long chain polyunsaturated fatty acids in preeclampsia. *Med Hypotheses* 2017; 100: 31–36. DOI: 10.1016/j.mehy.2017.01.009
- [84] Acilmis YG, Dikensoy E, Kutlar AI et al. Homocysteine, folic acid and vitamin B12 levels in maternal and umbilical cord plasma and homocysteine levels in placenta in pregnant women with pre-eclampsia. *J Obstet Gynaecol Res* 2011; 37: 45–50. DOI: 10.1111/j.1447-0756.2010.01317.x
- [85] Di Simone N, Maggiano N, Caliandro D et al. Homocysteine induces trophoblast cell death with apoptotic features. *Biol Reprod* 2003; 69: 1129–1134. DOI: 10.1095/biolreprod.103.015800
- [86] Broekhuizen M, Klein T, Hitzler E et al. I-Tryptophan-Induced Vasodilation Is Enhanced in Preeclampsia: Studies on Its Uptake and Metabolism in the Human Placenta. *Hypertension* 2020; 76: 184–194. DOI: 10.1161/HYPERTENSIONAHA.120.14970
- [87] Keaton SA, Heilman P, Bryleva EY et al. Altered Tryptophan Catabolism in Placentas From Women With Pre-eclampsia. *Int J Tryptophan Res* 2019; 12: 1178646919840321. DOI: 10.1177/1178646919840321

- [88] van Zundert SK, Broekhuizen M, Smit AJ et al. The Role of the Kynurenine Pathway in the (Patho) physiology of Maternal Pregnancy and Fetal Outcomes: A Systematic Review. *Int J Tryptophan Res* 2022; 15: 11786469221135545. DOI: 10.1177/11786469221135545
- [89] Herr N, Bode C, Duerschmied D. The Effects of Serotonin in Immune Cells. *Front Cardiovasc Med* 2017; 4: 48. DOI: 10.3389/fcvm.2017.00048
- [90] Hadden C, Fahmi T, Cooper A et al. Serotonin transporter protects the placental cells against apoptosis in caspase 3-independent pathway. *J Cell Physiol* 2017; 232: 3520–3529. DOI: 10.1002/jcp.25812
- [91] Menichini D, Feliciello L, Neri I et al. L-Arginine supplementation in pregnancy: a systematic review of maternal and fetal outcomes. *J Matern Fetal Neonatal* 2023; 36: 2217465. DOI: 10.1080/14767058.2023.2217465
- [92] Tong S, Kaitu'u-Lino TJ, Hastie R et al. Pravastatin, proton-pump inhibitors, metformin, micronutrients, and biologics: new horizons for the prevention or treatment of preeclampsia. *Am J Obstet Gynecol* 2022; 226: S1157–S1170. DOI: 10.1016/j.ajog.2020.09.014
- [93] Vadillo-Ortega F, Perichart-Perera O, Espino S et al. Effect of supplementation during pregnancy with L-arginine and antioxidant vitamins in medical food on pre-eclampsia in high risk population: randomised controlled trial. *BMJ* 2011; 342: d2901. DOI: 10.1136/bmj.d2901
- [94] Gong S, Sovio U, Aye IL et al. Placental polyamine metabolism differs by fetal sex, fetal growth restriction, and preeclampsia. *JCI Insight* 2018; 3: e120723. DOI: 10.1172/jci.insight.120723
- [95] Tuytten R, Syngelaki A, Thomas G et al. First-trimester preterm preeclampsia prediction with metabolite biomarkers: differential prediction according to maternal body mass index. *Am J Obstet Gynecol* 2023; 229: 55.e1–55.e10. DOI: 10.1016/j.ajog.2022.12.012
- [96] Wang W, Wu Z, Dai Z et al. Glycine metabolism in animals and humans: implications for nutrition and health. *Amino Acids* 2013; 45: 463–477. DOI: 10.1007/s00726-013-1493-1
- [97] Geddie G, Moores R, Meschia G et al. Comparison of leucine, serine and glycine transport across the ovine placenta. *Placenta* 1996; 17: 619–627. DOI: 10.1016/s0143-4004(96)80080-4
- [98] Lewis RM, Godfrey KM, Jackson AA et al. Low serine hydroxymethyltransferase activity in the human placenta has important implications for fetal glycine supply. *J Clin Endocrinol Metab* 2005; 90: 1594–1598. DOI: 10.1210/jc.2004-0317
- [99] Rasmussen BF, Ennis MA, Dyer RA et al. Glycine, a Dispensable Amino Acid, Is Conditionally Indispensable in Late Stages of Human Pregnancy. *J Nutr* 2021; 151: 361–369. DOI: 10.1093/jn/nxaa263
- [100] Friesen RW, Novak EM, Hasman D et al. Relationship of dimethylglycine, choline, and betaine with oxoproline in plasma of pregnant women and their newborn infants. *J Nutr* 2007; 137: 2641–2646. DOI: 10.1093/jn/137.12.2641
- [101] Bradford HF, Young AM, Crowder JM. Continuous glutamate leakage from brain cells is balanced by compensatory high-affinity reuptake transport. *Neurosci Lett* 1987; 81: 296–302. DOI: 10.1016/0304-3940(87)90399-5
- [102] Payne M, Stephens T, Lim K et al. Lysine Requirements of Healthy Pregnant Women are Higher During Late Stages of Gestation Compared to Early Gestation. *J Nutr* 2018; 148: 94–99. DOI: 10.1093/jn/nxx034
- [103] Elango R, Ball RO. Protein and Amino Acid Requirements during Pregnancy. *Adv Nutr* 2016; 7: 839S–844S. DOI: 10.3945/an.115.011817
- [104] Levesque CL, Moehn S, Pencharz PB et al. The threonine requirement of sows increases in late gestation. *J Anim Sci* 2011; 89: 93–102. DOI: 10.2527/jas.2010-2823
- [105] Shrestha N, Melvin SD, McKeating DR et al. Sex-Specific Differences in Lysine, 3-Hydroxybutyric Acid and Acetic Acid in Offspring Exposed to Maternal and Postnatal High Linoleic Acid Diet, Independent of Diet. *Int J Mol Sci* 2021; 22: 10223. DOI: 10.3390/ijms221910223
- [106] Brosnan JT, Brosnan ME. Branched-chain amino acids: enzyme and substrate regulation. *J Nutr* 2006; 136: 2075–2115. DOI: 10.1093/jn/136.12.075
- [107] Feng Y, Lian X, Guo K et al. A comprehensive analysis of metabolomics and transcriptomics to reveal major metabolic pathways and potential biomarkers of human preeclampsia placenta. *Front Genet* 2022; 13: 1010657. DOI: 10.3389/fgene.2022.1010657
- [108] Deepa R, Mandal S, Van Schayck OCP et al. Vitamin B6 Levels and Impaired Folate Status but Not Vitamin B12 Associated with Low Birth Weight: Results from the MAASTH Birth Cohort in South India. *Nutrients* 2023; 15. DOI: 10.3390/nu15071793
- [109] Bjørke-Monsen A-L, Varsi K, Ulvik A et al. A Vegetarian Diet Significantly Changes Plasma Kynurenine Concentrations. *Biomolecules* 2023; 13: 391. DOI: 10.3390/biom13020391
- [110] Ueland PM, Ulvik A, Rios-Avila L et al. Direct and Functional Biomarkers of Vitamin B6 Status. *Annu Rev Nutr* 2015; 35: 33–70. DOI: 10.1146/annurev-nutr-071714-034330
- [111] Tanaka M, Itoh H. Hypertension as a Metabolic Disorder and the Novel Role of the Gut. *Curr Hypertens Rep* 2019; 21: 63. DOI: 10.1007/s11906-019-0964-5
- [112] Kniss DA, Shubert PJ, Zimmerman PD et al. Insulinlike growth factors. Their regulation of glucose and amino acid transport in placental trophoblasts isolated from first-trimester chorionic villi. *J Reprod Med* 1994; 39: 249–256
- [113] Vaughan OR, Fowden AL. Placental metabolism: substrate requirements and the response to stress. *Reprod Domest Anim* 2016; 51 (Suppl 2): 25–35. DOI: 10.1111/rda.12797
- [114] Kinshella MW, Omar S, Scherbinsky K et al. Effects of Maternal Nutritional Supplements and Dietary Interventions on Placental Complications: An Umbrella Review, Meta-Analysis and Evidence Map. *Nutrients* 2021; 13: 472. DOI: 10.3390/nu13020472
- [115] Weckman AM, McDonald CR, Baxter JB et al. Perspective: L-arginine and L-citrulline Supplementation in Pregnancy: A Potential Strategy to Improve Birth Outcomes in Low-Resource Settings. *Adv Nutr* 2019; 10: 765–777. DOI: 10.1093/advances/nmz015
- [116] da Silva Lopes K, Ota E, Shakya P et al. Effects of nutrition interventions during pregnancy on low birth weight: an overview of systematic reviews. *BMJ Glob Health* 2017; 2: e000389. DOI: 10.1136/bmjgh-2017-000389
- [117] Rahimi R, Nikfar S, Rezaie A et al. A meta-analysis on the efficacy and safety of combined vitamin C and E supplementation in preeclamptic women. *Hypertens Pregnancy* 2009; 28: 417–434. DOI: 10.3109/10641950802629667
- [118] Villar J, Purwar M, Merialdi M et al. World Health Organisation multicentre randomised trial of supplementation with vitamins C and E among pregnant women at high risk for pre-eclampsia in populations of low nutritional status from developing countries. *BJOG* 2009; 116: 780–788. DOI: 10.1111/j.1471-0528.2009.02158.x