Thieme

Pregnancy Metabolic Adaptation and Changes in Placental Metabolism in Preeclampsia

Metabolische Anpassung in der Schwangerschaft und Stoffwechseländerungen der Plazenta bei Präeklampsie

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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 multiorgan disease. Alterations in substance metabolism can also modulate disease development by influencing this process.

Changes in Placental Metabolism

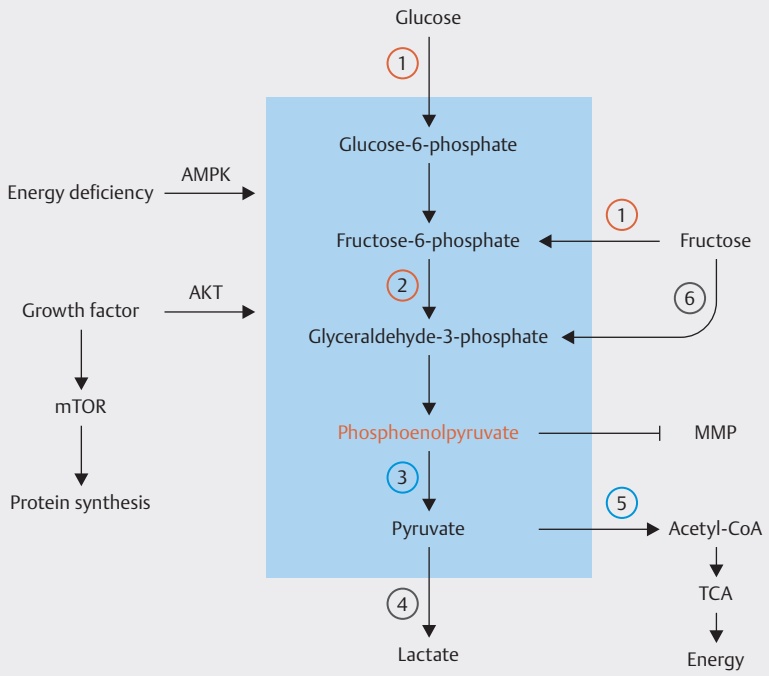
Glycometabolism

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^+-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 decarbonation 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.

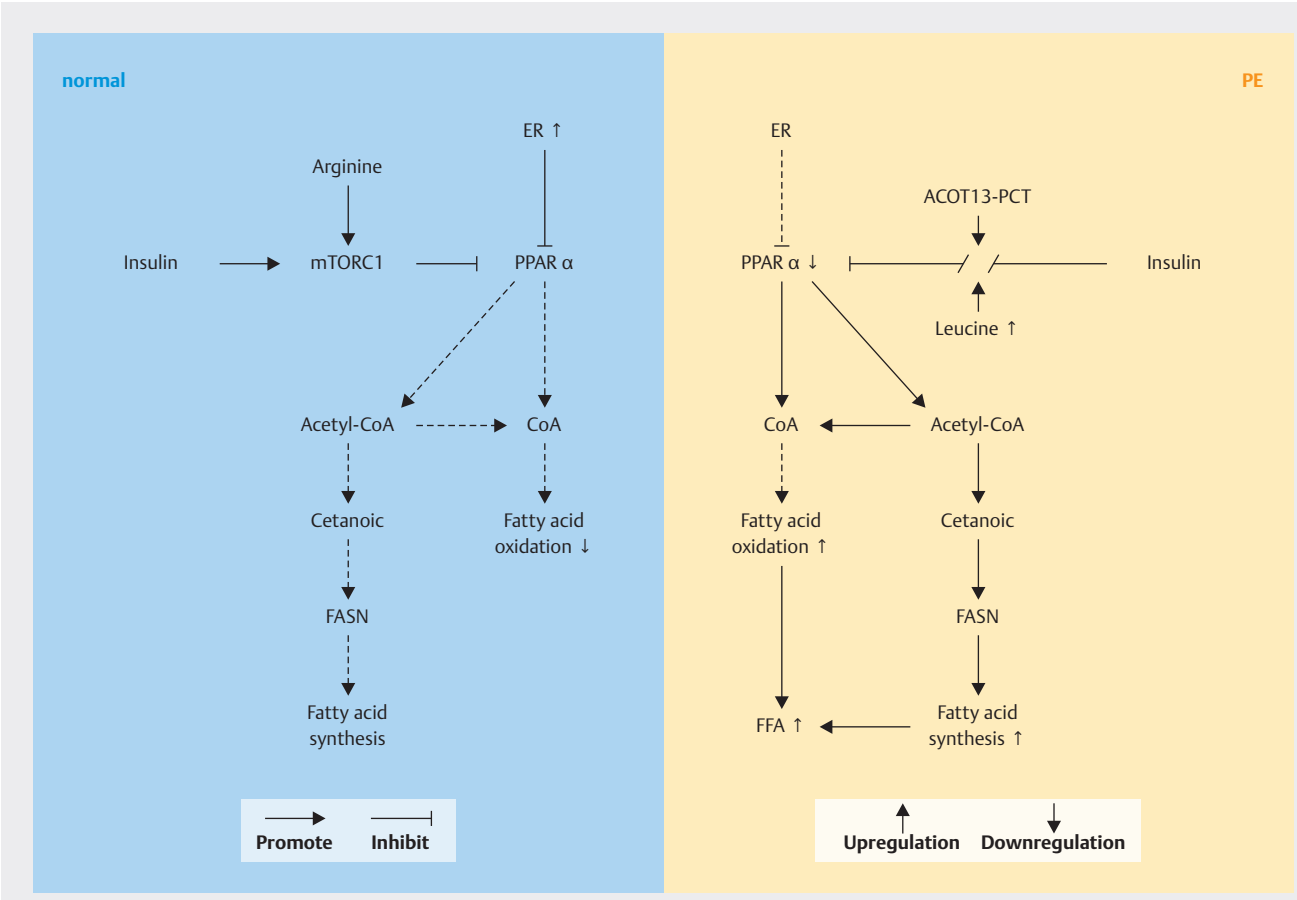
The development of the placenta, which is connected to trophoblast function, angiogenesis, endothelial damage, inflammation, ferroptosis, etc., is significantly influenced by ROS (reactive oxygen species) [26, 27, 28]. The hypoxic environment of the placenta increases the production of ROS in the mitochondria, 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 result 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



▶ **Fig. 2** Changes in lipid metabolism in PE. In PE, the content of free fatty acids in the body increases due to the changes in estrogen, insulin, ACOT13-PCTP, leucine, and arginine. ACOT13-PCTP = Acyl-CoA thioesterase 13 and phosphatidylcholine transfer protein complex; CoA = coenzyme A; ER = estrogen receptor; FASN = fatty acid synthase gene; FFA = free fatty acids; mTORC1 = mammalian target of rapamycin complex 1; PPARα = peroxisome proliferator-activated receptor α.

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 (S1 P). Both ceramide and S1 P 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 considered 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 α-ketoacid. The subsequent phase takes place in the mitochondria, where the branched chain ketone dehydrogenase complex (BCKDH) converts CoA and branched chain α 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 branch-chain α 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_6, and vitamin B_{12}. According to the current recommendations, supplementing with folic acid and vitamin B_{12} 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_1. A lack of vitamin B_1 will result in an accumulation of pyruvic acid and lactic acid. Vitamin B_6 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_6 deficiency [109, 110]. Additionally, research has shown that other B vitamins, like vitamin B_5, might raise CoA levels and delay PPARa activation. Vitamin B_5 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.

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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.

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