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Targeting oxidative stress in preeclampsia

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ABSTRACT

Preeclampsia is a complex condition characterized by elevated blood pressure and organ damage involving kidneys or liver, resulting in significant morbidity and mortality for both the mother and the fetus. Increasing evidence suggests that oxidative stress, often caused by mitochondrial dysfunction within fetal trophoblast cells may play a major role in the development and progression of preeclampsia. Oxidative stress occurs as a result of an imbalance between the production of reactive oxygen species (ROS) and the capacity of antioxidant defenses, which can lead to placental cellular damage and endothelial cell dysfunction. Targeting oxidative stress appears to be a promising therapeutic approach that has the potential to improve both short- and long-term maternal and fetal outcomes, thus reducing the global burden of preeclampsia. The purpose of this review is to provide a comprehensive account of the mechanisms of oxidative stress in preeclampsia. Furthermore, it also examines potential interventions for reducing oxidative stress in preeclampsia, including natural antioxidant supplements, lifestyle modifications, mitochondrial targeting antioxidants, and pharmacological agents.

A better understanding of the mechanism of action of proposed therapeutic strategies targeting oxidative stress is essential for the identification of companion biomarkers and personalized medicine approaches for the development of effective treatments of preeclampsia.

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preeclampsia; oxidative stress; mitochondrial damage; trophoblasts; endothelial cells

Physiological placental development and aberrant placentation in preeclampsia

After conception, the fertilized oocyte grows and divides into a blastocyst, which embeds into the endometrium and begins to establish a blood supply for the developing infant (1). The blastocyst differentiates into the trophectoderm, which contains pluripotent cytotrophoblasts (CTBs) (2). As the placenta develops, the CTBs in the placental villi proliferate and differentiate either into a fused and multinucleated syncytiotrophoblast (STB) layer or invasive extravillous trophoblasts (EVTs) (3,4). The STB layer provides a protective barrier for nutrients and gases exchange between the maternal and fetal circulatory systems while producing hormones including human chorionic gonadotropin (hCG) (4). During pregnancy, EVTs invade the inner layers of the uterus and remodel the spiral uterine arteries. This is to maintain steady perfusion of the placental intervillous space and provide sufficient blood supply to the growing fetus through the formation of an extensive vascular network within the placental villi (5). The formation of newly formed blood vessels and the branching and elongation of existing vessels are tightly regulated by various factors (6). During early placental vasculogenesis, vascular endothelial growth factor (VEGF) and angiopoietin-1 stimulate endothelial cell proliferation and the establishment of new blood vessels (7,8). VEGF-mediated migration of endothelial cells is promoted by angiopoietin-2 (9,10). Additionally, estrogen and progesterone are released into the maternal circulation to support maternal cardiovascular adaptations to pregnancy along with the formation and maintenance of the placental vasculature (11–13).

The development of preeclampsia is believed to originate from inappropriate placentation (14). The pathogenic mechanisms that underlie this multisystem disorder are not well understood; however, a two-stage progression model has been proposed (15–17). Early-onset preeclampsia (EOP) is associated with an insufficient invasion of the EVTs and an inadequate remodeling of the spiral uterine arteries, leading to pulsatile perfusion of the placental bed, hypoxia-reperfusion injury, and subsequent stress on the STBs (15,18). During late-onset preeclampsia (LOP), placental growth restrictions, premature placental aging, or

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maternal cardiovascular risk factors result in the placenta being unable to meet the metabolic demands of the growing fetus, which can lead to STB stress (19–22). Both phenotypes of preeclampsia lead to the release of pro-inflammatory cytokines, an increase in the number of extracellular vesicles (EVs), reactive oxygen species (ROS), apoptotic debris, and anti-angiogenic factors into the systemic circulation (23–28). Consequently, maternal endothelial dysfunction and systemic inflammation emerge, resulting in decreased perfusion of the maternal organs, manifesting in multiple systemic symptoms of preeclampsia (19,28,29). A successful pregnancy depends on the tolerance by the maternal immune system of semi-allogeneic fetus and placenta (30–32). Anti-fetal rejection can be triggered by impaired immune tolerance and has been implicated in pregnancy complications, including preeclampsia (33–35). The invasive EVTs are in direct contact with uterine immune cells, including decidual natural killer cells (dNKs), macrophages, T cells, B cells, and dendritic cells (36). An EVT exhibits a unique combination of major histocompatibility complex type-1 molecules ligands, human leukocyte antigens (HLA) C, E, F, and G, in order to facilitate immune recognition (37,38). The inappropriate activation of the maternal immune system may affect trophoblast invasion and remodeling, initiating a cascade of events leading to preeclampsia (34,39). In addition, decidual stromal cells (DSCs) interact with trophoblasts and dNK cells to support trophoblast invasion and placental development. Dysregulation in their function can contribute to preeclampsia (40). Fibroblast cells synthesize and secrete components of the extracellular matrix, including collagen and fibronectin, which provide structural support to the placental tissue (41–43). Fibroblasts secrete growth factors including VEGF and transforming growth factor-beta (TGF-β), which are important for angiogenesis and trophoblast differentiation (41–43). Successful placentation during pregnancy involves a complex interplay between various cell types, including trophoblast cells, immune cells, stromal cells, endothelial cells, and fibroblast cells (43). Each cell type plays a crucial role in establishing and maintaining a healthy placenta, which is essential for proper fetal development and maternal health (41–43). Aberrant placentation, such as that seen in preeclampsia, involves dysfunction or maladaptation of these cells, leading to poor placental function and adverse pregnancy outcomes (41–43).

The role of mitochondrial function in placental development and growth

Mitochondria, as the energy-producing organelles, play a critical role in placental development and growth (44). Mitochondrial function is particularly important in STBs, enabling adequate communications at the maternal-fetal interface (45). This is achieved through the supply of required energy for syncytialization, nutrient transportation, hormone synthesis, and general metabolic processes within the placenta (44).

The process of oxidative phosphorylation (OXPHOS), which generates required cellular energy, constitutes a fundamental aspect of mitochondrial function during placental development (46). Mitochondrial OXPHOS facilitates adenosine triphosphate (ATP) production by transferring electrons along the electron transport chain (ETC) and synthesizing ATP via ATP synthase. ATP is essential for trophoblast proliferation, invasion, and vascular remodeling during early placental development (46). Disruptions in mitochondrial OXPHOS can lead to diminished ATP production, causing compromised placental development and impaired trophoblast proliferation (46–48).

In particular, mitochondria are responsible for nutrient transport and metabolism, processes essential for placental growth and optimal placental function (49). Mitochondrial enzymes including pyruvate dehydrogenase complex (PDHC) and carnitine palmitoyl transferase (CPT), facilitate the conversion of glucose and fatty acids, respectively, into acetyl-CoA, leading to energy production (50–53). Dysregulation in mitochondrial nutrient metabolism can adversely affect the STBs, impairing its ability to transport nutrients and gases efficiently, which in turn can impede placental growth and function (49). Apart from energy production and metabolism, mitochondria participate in apoptosis and regulate oxidative stress within trophoblast cells (54). Mitochondrial dysfunction can lead to excessive ROS generation, resulting in oxidative stress. ROS can potentially induce damage to cellular components such as lipids, proteins, and mitochondrial DNA (mtDNA), disrupting the delicate balance of cell signaling and homeostasis required for normal placental development (55,56). Additionally, mitochondrial dysfunction can initiate apoptotic signaling pathways, resulting in trophoblast cell death and adversely affecting placental growth (57).

MtDNA variations contribute to placental health, by encoding crucial ETC complex subunits which can influence mitochondrial function and energy production. Furthermore, modifications in mitochondrial dynamics, comprising fusion and fission processes, influence the morphology and function of mitochondria. Impairment in mitochondrial dynamics can compromise the integrity of the placenta, affecting nutrient transport, metabolism, and cellular function including

cellular differentiation, proliferation, and apoptosis (58,59).

Mitochondrial dysfunction of the placenta has been associated with the pathogenesis of various pregnancy complications, including preeclampsia, intrauterine growth restriction (IUGR) (60,61) and gestational diabetes mellitus (GDM) (62,63). These conditions are characterized by compromised placental development, altered nutrient metabolism, increased oxidative stress, and abnormal angiogenesis (64). Comprehending the mechanisms responsible for mitochondrial dysfunction in these pathological conditions is essential for identifying prospective therapeutic targets and developing interventions that can treat preeclampsia and improve maternal and fetal outcomes.

Furthermore, mitochondrial-derived peptides (MDPs) have recently gained attention for their role in placentation. MDPs originating from distinct segments of mitochondrial proteins, with the capacity to regulate mitochondrial biogenesis, oxidative stress response, inflammation, and apoptosis. Some MDPs, such as humanin and MOTS-c, have shown to have anti-apoptotic, anti-inflammatory, and metabolic regulatory properties (65). These peptides could potentially have implications for the development and growth of the placenta due to their anti-apoptotic properties, which help maintain trophoblast cell viability; their anti-inflammatory properties, which prevent excessive inflammatory responses linked to placental dysfunction; and their metabolic regulatory properties, which ensure efficient nutrient and energy supply essential for fetal development (65). Further research is needed to elucidate their specific roles in the placental tissue (66,67).

Recent progress in mitochondrial research methodologies, such as mitochondrial genome sequencing, proteomics, metabolomics, and functional assays, have made valuable tools available to study mitochondrial functions in placental development. These approaches enable the comprehensive characterization of mitochondrial modifications, functional changes, and metabolic adaptations within the placenta (68,69). Integrating these 'omics data with clinical observations and histological analyses can further enhance our comprehension of the significance of mitochondrial function in placental development and its impact on pregnancy outcomes.

General introduction on the pathogenesis of preeclampsia

Preeclampsia is a human-specific cardiovascular disorder of pregnancy characterized by the new onset of hypertension and proteinuria or other organ damage including IUGR diagnosed after the 20th week of gestation (70). EOP, diagnosed before 34 weeks of gestation, is associated with higher rates of maternal and fetal complications, and is often linked to abnormal placental development. This form of preeclampsia is associated with poor placental perfusion and inadequate spiral uterine artery remodeling, frequently leading to IUGR and the need for preterm delivery (71–73). In contrast, LOP, diagnosed from 34 weeks of gestation and comprising ~ 85% of all preeclampsia cases, is closely associated with poor maternal cardiovascular adaptations, rather than placental abnormalities. In LOP cases, fetal growth is typically less affected, allowing for term delivery and resulting in better overall pregnancy outcomes (71–73). Nevertheless, both EOP and LOP are the leading causes of morbidity and mortality of both mothers and babies in pregnancy. Long-term, individuals affected by preeclampsia in pregnancy have increased risk of developing cardiovascular, metabolic and neurological diseases, later in life (72). The offspring affected by preeclampsia have elevated risks of preterm birth, perinatal mortality, neurodevelopmental disabilities, and subsequent cardiovascular and metabolic disorders post-partum (74–76).

Preeclampsia is an enigmatic disorder in terms of its pathophysiology. There has been an increasing body of research suggesting that preeclampsia progresses through a series of stages. Placental insufficiency is primarily caused by genetic, environmental, and immunological factors during the first and the second trimesters of pregnancy (77–80) (Figure 1). Recent research has shown that dysregulation in mitochondrial homeostasis and dynamic function maintaining fission gene, dynamin-1-like (DNM1L) proteins, or fusion gene, mitofusin1 (MFN1), autophagy gene (ATG5) or macroautophagy gene, microtubule-associated protein 1 light chain 3β (MAP1LC3B), are responsible for placental dysfunction in preeclampsia (81–83). Diabetes mellitus, hyperglycemia, and chronic hypertension can significantly increase the morbidity of preeclampsia during pregnancy (84,85). Immunological factors and heightened inflammation often involving proinflammatory cytokines, tumor necrosis factor (TNF-α), interleukin-6 (IL-6), interleukin 1beta (IL-1β), and immune cells including natural killer cells (NK cells), T helper cells and macrophages can also contribute to preeclampsia progression (86) (Figure 1). In EOP, shallow trophoblast invasion caused by impaired spiral artery remodeling triggers placental ischemia-reperfusion injury (72). Oxidative stress and persistent hypoxia can cause a significant increase in anti-angiogenic proteins including soluble fms-like tyrosine kinase-1 (sFlt1)

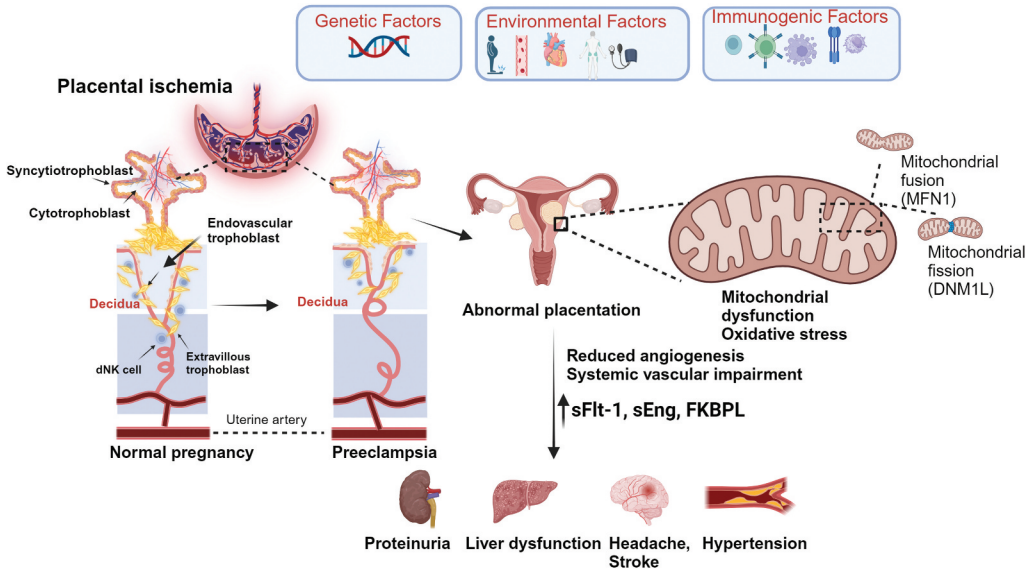

Figure 1. Schematic diagram of preeclampsia pathogenesis. Genetic factors, environmental factors and immunogenic factors are contributing factors to preeclampsia pathophysiology. Preeclampsia pathogenesis involves significant maternal trophoblast dysfunction and mitochondrial abnormality. In the beginning of pregnancy, the spiral uterine arteries are remodeled by trophoblast cells and dNK cells. An invasive subtype of trophoblasts, extravillous trophoblasts (EVTs) invade the spiral uterine arteries (SUAs) of the decidua in a tightly regulated fashion and replace the endothelial and muscle layers to reduce blood vessel resistance, resulting in unrestricted blood flow to the placenta and the fetus. However, in preeclampsia, the extent and depth of remodeling is shallower than in normal pregnancy. This impaired spiral uterine arteries remodeling is believed to play a key role in its pathogenesis, triggering a cascade of events including placental ischemia, inflammation and angiogenic imbalance. On the other hand, placental ischemia triggers mitochondrial dysfunction. Finally, it causes maternal syndromes such as proteinuria, liver dysfunction, headache, stroke, and hypertension. (created in https://BioRender.com).

and soluble endoglin (sEng) leading to angiogenic imbalance within the placenta (64). One emerging anti-angiogenic factor that is out of balance in preeclampsia belongs to the family of FK506 binding protein-like (FKBPL) or immunophilins, but is a divergent member of this group, with slightly different structures and functions (87–90). Recent research has shown that FKBPL in conjunction with its target cell membrane protein, CD44, has a promising potential as an early diagnostic biomarker of preeclampsia (91–94). The presence of angiogenic imbalance results in vascular syndrome, typical for preeclampsia that can induce proteinuria, liver dysfunction, headache, stroke, hypertension (95) and HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome (73). These features of preeclampsia or associated conditions can lead to pregnancy complications and pre-term birth (Figure 1).

The pathogenesis of preeclampsia involves a complex interplay of maternal, placental, and systemic factors, leading to endothelial dysfunction and impaired placental perfusion (96). Comprehending the fundamental mechanisms of preeclampsia is paramount in advancing the development of efficacious preventive and therapeutic approaches. Dysfunctional placentation and insufficient remodeling of the maternal spiral uterine arteries have been identified as significant etiological factors in the pathogenesis of preeclampsia (97). The placenta is crucial in the pathogenesis of preeclampsia because it secretes anti-angiogenic factors (sFlt-1, sEng) that antagonize pro-angiogenic factors VEGF, placental growth factor (PlGF) and promote vasoconstriction (86,95,98). Preeclampsia is linked to an amplified inflammatory response, which leads to endothelial activation, oxidative stress, and the release of factors (TNF-α, IL-6, IL-1β) perpetuating the inflammatory cascade (99,100). Increased ROS levels and impaired antioxidant defenses contribute to oxidative stress and endothelial dysfunction in preeclampsia (96,101). Our recent meta-analysis identified three key oxidative stress biomarkers, ischemia modified albumin (IMA), uric acid (UA) and malondialdehyde (MDA), with important roles in the pathogenesis of preeclampsia (102). These biomarkers have been implicated in abnormal placentation characterized by inadequate trophoblast invasion and remodeling of spiral uterine arteries (102). IMA is a marker of ischemic events, UA is a marker of non-enzymatic antioxidants, and MDA is a marker of lipid

peroxidation (102). Although UA typically has antioxidant properties, renal impairment can lead to reduced clearance and elevated UA levels. This increase transforms uric acid into a pro-oxidant, promoting oxidative stress and endothelial dysfunction, which can contribute to the development of preeclampsia (103). Thus, the dual role of UA in preeclampsia warrants close examination of its contribution to disease progression.

Endothelial dysfunction is a hallmark feature of preeclampsia that can cause impaired vasodilation, increase vascular permeability, and alter coagulation. Dysregulation of endothelial-derived factors, including nitric oxide (NO), endothelin-1 (ET-1), and prostacyclin, contributes to vasoconstriction and thrombotic events observed in preeclampsia. Furthermore, impaired endothelial cells secrete microparticles and facilitate platelet activation, exacerbating the prothrombotic condition (104). These abnormalities in the homeostatic system can contribute to systemic endothelial dysfunction and multiorgan damage observed in severe cases of preeclampsia. The most frequently affected organs include the liver, kidney, brain, and placenta.

The renin-angiotensin system (RAS) has also been implicated in the pathogenesis of preeclampsia. The disruption of the RAS with elevated levels of angiotensin II (Ang II) in the bloodstream and reduced levels of angiotensin-(1–7) [Ang-(1–7)], leads to vasoconstriction, inflammation, and oxidative stress commonly observed in preeclampsia. Moreover, autoantibodies targeting the angiotensin II type 1 receptor (AT1-AA) have been detected in preeclampsia, further implicating the role of the RAS in disease pathogenesis (105).

In summary, the pathogenesis of preeclampsia is a multifactorial process involving interactions between maternal, placental, and systemic factors. Abnormal placentation, angiogenic imbalance, immune dysregulation, genetic susceptibility, oxidative stress and endothelial dysfunction collectively contribute to the development of preeclampsia. Given preeclampsia is a condition without a cure, a comprehensive understanding of these mechanisms is essential to advance the development of innovative therapeutic interventions and enhance the management of this potentially life-threatening condition.

Prediction and diagnosis of preeclampsia

Prediction and timely diagnosis of preeclampsia is vital for the effective management and improved outcomes of affected pregnancies. Various clinical, biochemical, and imaging markers have been utilized for prediction and diagnosis of preeclampsia, aiming to identify high-risk individuals and facilitate timely interventions (106,107). However, predicting and diagnosing preeclampsia accurately has been challenging due to inter-patient variability in symptoms and features, and its multifactorial and heterogenous nature.

Maternal demographic factors and medical history are essential in identifying pregnant individual at risk of preeclampsia. Advanced maternal age, nulliparity, obesity, preexisting chronic hypertension, type 1 or type 2 diabetes mellitus and a previous history of preeclampsia are associated with an increased risk of developing the condition (108,109).

Uterine artery Doppler ultrasound has demonstrated promise as a noninvasive imaging technique for predicting preeclampsia. A typical waveform, characterized by increased resistance and reduced diastolic flow, are associated with an increased risk of developing preeclampsia. Doppler ultrasound can reliably assess uteroplacental blood flow and vascular resistance, thereby assisting in predicting and identifying high-risk pregnancies (110).

Blood-based biochemical markers have been extensively investigated for their potential role in predicting and diagnosing preeclampsia. PlGF, a member of the VEGF family, is clinically utilized worldwide. Reduced PlGF levels during early pregnancy (i.e. the first trimester) have depicted predictive value for the subsequent occurrence of preeclampsia (111). Likewise, the involvement of sFlt-1, an anti-angiogenic protein, has been implicated in the pathophysiology of preeclampsia. Increased sFlt-1 levels and the sFlt-1/PlGF ratio have shown a reliable short-term predictive value of preeclampsia (112,113). In a prospective, multicenter, observational study, it was determined that a ratio of serum sFlt-1 to PlGF could be used to predict the presence or absence of preeclampsia in women with singleton pregnancies. An sFlt-1: PlGF ratio with a cut-off of > 38 was found to be an important predictor of preeclampsia. An sFlt-1:PlGF ratio above 38 had a positive predictive value of 36.7% with 66.2% sensitivity and 83.1% specificity for preeclampsia within 4 weeks, which informed its use as a rule-out than rule-on test (113). Another prospective multicenter study found that low plasma PlGF concentrations had high sensitivity (96%), negative predictive value (98%), and specificity (55%). A low PlGF plasma concentration with 0.87 area under the receiver operating characteristic (ROC) curve for predicting preeclampsia within 14 days, outperformed all other commonly used tests, whether used individually or in combination (112). In

addition to biomarkers for endothelial dysfunction, vascular cell adhesion molecules (VCAM-1), and pro-inflammatory cytokines (e.g., IL-6, and TNF-α) have been evaluated as predictors of and diagnostic indicator of preeclampsia (114–116). Based on ROC analysis, it was determined that VCAM-1 > 450 ng/ml was associated with a sensitivity of 79% and a specificity of 90% for the detection of severe preeclampsia and eclampsia in a case-control study of 60 participants (114). Researchers also reported using a small sample size that there was a significant difference in serum IL-6 concentrations between individuals with preeclampsia and healthy controls. The area under the curve (AUC) was 0.70, the odds ratio (OR) was approximately 2.82, sensitivity was 73%, and specificity was 64% (115). Furthermore, a significant increase in TNF-α concentrations was reported in African women with preeclampsia of varying severity compared to women with normotensive pregnancies (117). ROC curve analyses reported the AUC of 0.937 for the development of preeclampsia at a serum TNF-α cutoff level of >15.6 ng/mL, and the AUC of 0.978 for the severity of preeclampsia at a serum TNF-α cutoff level of >26.4 ng/mL (117).

FKBPL has emerged as a promising biomarker for prediction and diagnosis of preeclampsia. Recent studies have highlighted the significant role of FKBPL in modulating angiogenesis, inflammation, and endothelial dysfunction, all of which are critical factors contributing to the pathogenesis of preeclampsia (92,118,119). FKBPL plasma concentration is reduced at 20 weeks of gestation in women who proceeded to develop preeclampsia whereas it was increased in established preeclampsia. Its target protein, CD44, showed opposite trend in the prediction and diagnosis settings. Combining FKBPL and CD44 as the CD44/FKBPL ratio was deemed the optimal predictive tool at 20 weeks of gestation and for diagnosis of preeclampsia (91,94,120). FKBPL and CD44 biomarkers were also translated onto a highly sensitive point of care test based on up conversion nanoparticles showing the positive predictive value of 100% and the negative predictive value of 91% for EOP as well as 10-fold lower limit of detection for FKBPL compared to the frequently used ELISA assay (92). FKBPL has also shown utility as a determinant of cardiovascular disease (121) and its plasma concentration was increased in heart failure with preserved ejection fraction (HFpEF) compared to controls (122). It is well-known that cardiovascular disease is a long-term sequelae of preeclampsia (123) and therefore FKBPL could have a role as a diagnostic biomarkers during and post-pregnancy in this high-risk group.

The exploration of combining multiple markers and constructing prediction models has been undertaken to enhance the precision of preeclampsia diagnosis. These models incorporate various clinical, demographic, biochemical and imaging parameters to generate individualized risk assessments. Machine learning algorithms have been utilized to develop prediction models that accurately identify women at high risk of developing preeclampsia (124).

Despite the advancements, challenges still remain in ensuring accurate prediction and diagnosis of preeclampsia. Many proposed biomarkers lack the required sensitivity and specificity to be used as stand-alone diagnostic tests. Moreover, challenges arise from variations in study populations, diagnostic criteria, and the timing of sample collection, making it difficult to compare and validate the performance of different markers.

Whilst potentially costly to develop and run, a comprehensive approach encompassing clinical, biochemical, imaging, and multiple biomarkers is necessary to predict and diagnose all cases of preeclampsia. Combining demographic information, imaging parameters from uterine Doppler ultrasound, and biomarkers related to angiogenesis, endothelial dysfunction, inflammation, and metabolic alterations can enhance the accuracy of prediction and diagnosis of preeclampsia. Developing comprehensive risk assessment models and integrating emerging technologies can help identify high-risk pregnancies and implement timely interventions, ultimately improving maternal and fetal outcomes.

Current treatments for preeclampsia

Despite research into novel treatments for preeclampsia, the only current curative treatment is the removal of the placenta and delivery of the fetus. Symptoms of preeclampsia can be managed using antihypertensive agents (labetalol, methyldopa and/or nifedipine) and some prevention strategies include low dose aspirin (150 mg/day) before 16 weeks of gestation, calcium (<1 g/day) and vitamin D supplements, muscle resistance exercises (2.5–5 hours a week), and weight loss for overweight/obese mothers (70,125). It is now recognized that obesity is a major determinant of poor pregnancy outcomes. Given that there is a three-fold increased risk of developing preeclampsia when pregnant women have a high body mass index (BMI >30 kg/m^2), weight loss and exercise are encouraged to prevent disease onset in some cases (126–128). The most frequently clinically utilized preventative strategy for high-risk pregnant women is low-dose aspirin (80–150 mg/day) administered prior to 16 weeks of gestation (70). Studies have shown that aspirin can reduce

the risk of preterm preeclampsia (delivery before 37 weeks) by up to 62% (129,130).

More recently, statins have emerged as potential treatments for preeclampsia, and while statins are no longer labeled as Category X (contraindicated) according to the FDA, most patients should stop statins once they become pregnant. Nevertheless, statins may be beneficial for a small group of very high-risk pregnant women. Studies exploring statin use in preeclampsia have primarily utilized animal models or *in vitro* studies, with limited clinical trials such as the INOVASIA study (131,132). This small human trial evaluating pravastatin (40 mg/day) showed a promise in reducing rates of preterm preeclampsia (26.7% to 13.8%) and preterm birth (36% to 16%) by stabilizing blood pressure, proteinuria, and UA levels (131). Additionally, while statins primarily reduce cholesterol synthesis, leading to a substantial decrease in low-density lipoprotein (LDL) cholesterol and some increase in high-density lipoprotein (HDL) cholesterol, their effects on triglycerides are minimal. The primary rationale for considering statins in preeclampsia lies in their pleiotropic effects, which include antioxidant, anti-inflammatory, and general improvement in vascular health, with a potential to abrogate oxidative stress central to preeclampsia pathophysiology (132). A hypoglycemic agent, metformin, has been shown to reduce weight gain and the risk of preeclampsia in women with a BMI >35 kg/m^2 and to prolong gestation in women with preterm preeclampsia by almost a week without causing serious side effects (133). Other studies showed that calcium and vitamin D supplementation during pregnancy reduces the risk of preeclampsia (134,135). However, further research is needed to confirm these findings.

Clinically established preeclampsia is managed by reducing blood pressure to an acceptable level (<140/90 mm Hg) and preventing progression to eclampsia upon diagnosis (70) Many of the first line oral antihypertensive medications used to manage hypertension in the non-pregnant population, including angiotensin receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEi), are not considered safe for use during pregnancy (136). Consequently, older generation antihypertensive medications including methyldopa, labetalol, and nifedipine may be prescribed (137). In women with pre eclampsia, magnesium sulfate is used to prevent the development of eclamptic seizures, whereas corticosteroids, such as betamethasone, are routinely administered to encourage neonatal lung maturation, particularly in premature infants (138,139). As a result, they may not address the underlying pathology of pre-eclampsia, or prevent morbidity associated with preeclampsia complications during the second and early third trimesters.

Other studies have also suggested the use of glycerol trinitrate, its precursors, or L-arginine to restore nitric oxide levels and angiogenesis within the placenta and reduce oxidative stress can be used for prevention or treatment of preeclampsia (140–142).

The role of oxidative stress in preeclampsia

During healthy pregnancy, oxidative stress is increased, however in preeclampsia this is exacerbated leading to free radicals-induced damage of the endothelium, and maternal vascular dysfunction. Excessive oxidative stress contributes directly to impaired trophoblast invasion and endothelial dysfunction, two core pathophysiological features that can lead to placental dysfunction and preeclampsia (143). Overall, in preeclampsia, oxidative stress is driven by the imbalance between endogenous antioxidant system and free radicals, primarily ROS. Some typical ROS include NO, superoxide, hydrogen peroxide, hydroxyl radicals, and peroxynitrite (144). During normal gestation, ROS production is increased and necessary for the regulation of placental development and function, including trophoblast proliferation and migration, and angiogenesis (101). However, in preeclampsia, excessive ROS generation results in trophoblast dysfunction and shallower invasion, limiting blood flow to the placenta and impairing nutrient and oxygen exchange, which are essential for fetal growth (145). During cellular responses, ROS are rapidly captured by antioxidants (e.g., vitamin C and E) or metabolized by several antioxidant enzymes (e.g., superoxide dismutase (SOD), glutathione peroxidases (GPx), catalase, thioredoxins, and peroxiredoxins) (26,101,144,146,147). ROS (NO, hydrogen peroxide, hydroxyl radicals, and peroxynitrite), are generated through several pathways including mitochondrial aerobic metabolism, activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase (XO), cytochrome P450, and lipid peroxidation (101,148). NADPH oxidase catalyzes the production of free radicals, and it is found to be upregulated in placental tissues from individual with preeclampsia, particularly within the microvilli of STBs (148). As opposed to this, the NADPH oxidase isoform, NOX4, which is known to protect vascular function, is downregulated in the placental villous tissue in preeclampsia. This dysregulation contributes to endothelial dysfunction, as the altered ROS production damages vasculature, impairing their function and

contributing to hypertension and proteinuria in preeclampsia (149). Higher activity of XO was also recorded in plasma and CTBs in preeclampsia compared to healthy controls, which generates ROS through the use of oxygen as an electron acceptor (148). Markers of oxidative stress have been consistently shown to be increased in women with preeclampsia and small for gestational age (SGA) pregnancies, compared to healthy pregnancies (96,101,150). As described above, we assessed the diagnostic potential of oxidative stress biomarkers in a meta-analysis identifying three reliable oxidative stress markers, including IMA, UA, and MDA (96,102,151,152).

Oxidative stress, defined by an excess of ROS over antioxidant defenses, is increasingly recognized as a key driver of cellular senescence in the placenta, contributing to the pathogenesis of preeclampsia. Elevated ROS production under hypoxic or ischemic conditions damages cellular components, accelerating senescence, a process characterized by permanent cell cycle arrest and the secretion of pro-inflammatory factors collectively termed the senescence-associated secretory phenotype (SASP) (153). This senescence disrupts trophoblast proliferation and invasion, impairing the establishment of adequate maternal-fetal exchange essential for adequate placental function (154). Accumulation of senescent cells in the placenta is linked to heightened inflammatory pathways and endothelial dysfunction, which are hallmark features of preeclampsia. Elevated markers of oxidative stress and senescence, including p21 and p53, observed in preeclamptic placentae further underscore the connection between oxidative stress-induced senescence and disease pathology (155). Overall, oxidative stress contributes to placental dysfunction in preeclampsia by promoting senescence, inflammation, and impaired vascular health.

Furthermore, dysfunctional HDL particles in preeclampsia are increasingly recognized as contributors to oxidative stress due to their diminished antioxidant properties, which are typically facilitated by paraoxonase 1 (PON1) activity. Under normal conditions, HDL and PON1 are protective against oxidative stress by neutralizing lipid peroxides; however, in preeclampsia, HDL function is often impaired and PON1 activity is significantly reduced. These changes compromise the antioxidant defense, allowing increased levels of oxidized LDL and ROS to accumulate, which exacerbates endothelial dysfunction and inflammation (156). This pro-oxidative state damages the endothelium, contributing to the clinical features of preeclampsia, including high blood pressure and proteinuria, by disrupting vascular integrity and promoting inflammation.

When mitochondria become dysfunctional, they can become a major source of intracellular and extracellular oxidative stress, as demonstrated within placental tissues from individuals with preeclampsia (148,157). In preeclampsia, placental ischemia decreases mitochondrial respiration, resulting in increased ROS generation and an increase in mitochondrial oxidative stress in trophoblast cells. An abnormal expression of cytochrome C oxidase was also observed in mitochondria of pregnant women with preeclampsia (157).

Evidence of a link between preeclampsia and oxidative stress in animal models has also been established (101). Beauséjour et al. (2007) showed an increase in oxidative stress markers (8-iso-PGF (2alpha), TxB(2)/6-keto-PGF(1alpha) ratios, total TNF-alpha RNA expression, as well as the apoptotic index (Bax/Bcl-2 ratio) in pregnant rats who were fed sodium-supplemented diet compared to normal diet displaying some features of preeclampsia including increased blood pressure, decreased circulatory volume and diminished activity of the renin-angiotensin-aldosterone system (158). Another *in vivo* pregnancy study where pregnant rats were administered desoxycorticosterone acetate (DOCA) demonstrated that high blood pressure and sympathetic overactivity in preeclamptic rats are associated with increased ROS production through upregulating the expression of NOX4 in the rostral ventrolateral medulla (RVLM) (159).

Potential treatments targeting oxidative stress in preeclampsia

Oxidative stress, inflammation, immune and vascular dysfunction in the placenta as well as systemically in preeclampsia are hallmark features that researchers have sought to target using various therapeutic strategies. A major obstacle in the development of therapeutics for preeclampsia is the apprehension related to testing new agents in pregnant women without knowing whether these agents will adversely affect the fetus. Consequently, innovative therapies that have not been extensively tested in humans or pregnant individuals have been difficult to approve for use in clinical settings. Thus, repurposing drugs that are known to be safe in pregnancy is an attractive avenue for faster translation toward clinical use as potential treatments of preeclampsia. Preclinical and human trials investigating various pregnancy-safe agents through repurposing that can target key aberrant pathways in preeclampsia are underway for the prevention and treatment of preeclampsia (Figure 2) (**Table 1**)(**160**).

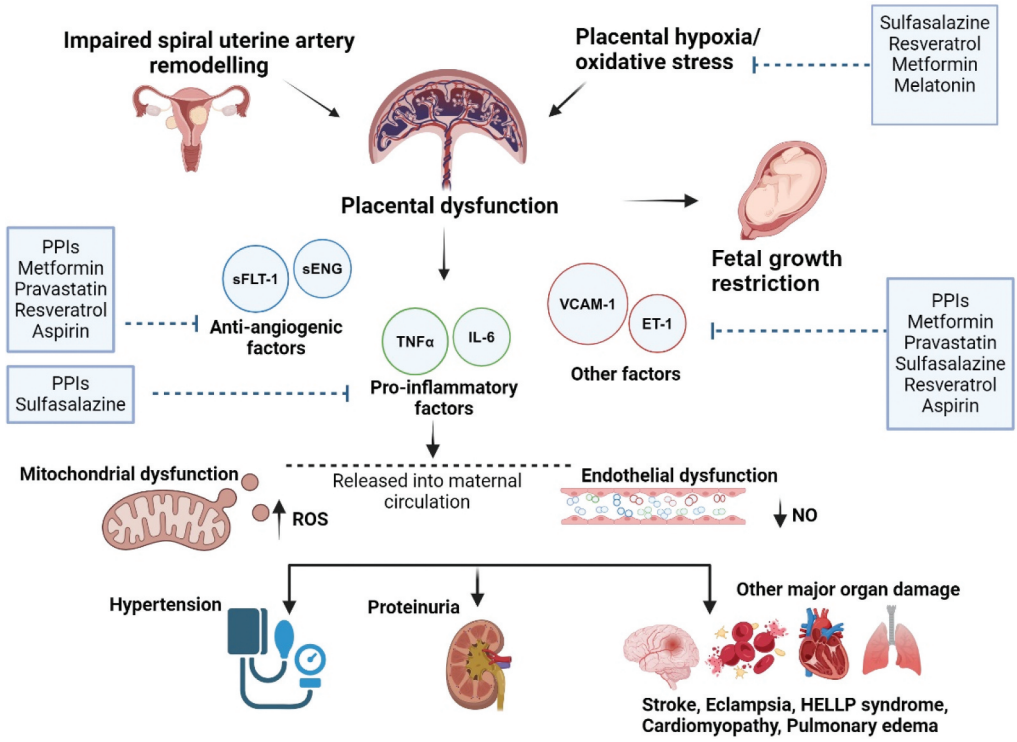

Figure 2. Schematic diagram depicting the factors involved in the development of preeclampsia and the therapeutic targets of several repurposed treatments. Oxidative stress and impaired spiral uterine artery remodeling play a major role in placental dysfunction leading to preeclampsia progression. Some repurposed drugs (PPIs, metformin, aspirin, resveratrol, pravastatin, sulfasalazine and melatonin) work by targeting anti-angiogenic, pro-inflammatory factors contribute to mitigate these complex diseases preeclampsia. (created in https://BioRender.com); *PPIs: proton pump inhibitors.*

Metformin

Metformin is an old-generation hypoglycemic drug that has been investigated over the last decade as a potential treatment for preeclampsia. Metformin's potential as a preeclampsia treatment extends beyond its hypoglycemic effects and it includes significant antioxidative properties. Metformin activates AMP-activated protein kinase (AMPK), which enhances mitochondrial function and reduces ROS production, helping to counteract oxidative stress (161). Studies have demonstrated that metformin inhibits the mitochondrial permeability transition pore, thereby reducing cell death and oxidative stress in conditions where mitochondria are stressed (161). Also, metformin prevents hyperglycemia-induced endothelial cell death by stabilizing the mitochondrial permeability transition, highlighting metformin's protective role against oxidative injury to endothelial cells, which is relevant to preeclampsia (162). Metformin is routinely prescribed for individuals with polycystic ovary syndrome or diabetes mellitus, as it increases cellular insulin uptake and reverses insulin resistance (163,164). More recently, metformin has been shown to abrogate endothelial dysfunction, hence it has cardio-protective effects in people with diabetes mellitus (163). Metformin has also been associated with reduced weight gain in women with GDM (165). One study demonstrated that the incidence of preeclampsia was reduced by 75% in obese pregnant women without diabetes mellitus who were treated with metformin compared to placebo (166). A meta-analysis conducted by Alqudah et al (2018) reported reduced risk of developing preeclampsia by ~ 30% in pregnant individuals with GDM or type 2 diabetes mellitus taking metformin compared to insulin alone, which was potentially attributed to reduced weight gain in the metformin group. Interestingly, the same meta-analysis did not find a significant difference between diet-controlled and metformin treated GDM groups (167). In a clinical trial conducted in South Africa, metformin extended the gestation age of delivery in EOP by an average of seven days compared to placebo (133). In addition to reducing the risk of premature birth, this finding may have implications for reducing the likelihood of perinatal health complications. Combined maternal, fetal, and neonatal outcomes as well as circulating levels of sFlt-1, PlGF, and sEng were similar between groups (133). Birth weight increased non-significantly in the metformin group, while length of stay in the neonatal unit decreased (133). There is an ongoing clinical trial (PI2 Trial is

Table 1. Summary of the findings of potential preventative and treatment strategies for preeclampsia.

Drugs	Study Types	Findings	References
Metformin	Clinical trials Meta-analyses RCTs	• In obese pregnant women without type 2 diabetes mellitus, metformin reduced preeclampsia by 75% • Extended gestational age of delivery in early-onset preeclampsia by an average of 7 days. • Metformin ± insulin reduces gestational weight gain and risk of preeclampsia by 30% compared to insulin only • Metformin + esomeprazole reduces endothelial dysfunction and sFlt-1 secretion	(133,166–168)
Low dose aspirin	*In vitro* studies Meta-analyses Clinical trials RCTs	• Prophylactic treatment for preeclampsia • Reduces incidence of preterm preeclampsia and IUGR • Non-steroid, anti-inflammatory, antiplatelet properties • Improves placental function and abrogates cytokines upregulation, apoptosis and premature trophoblast differentiation • Restores syncytiotrophoblast dysfunction	(173–176,178,179)
Resveratrol	*In vitro* studies Clinical trials *In vivo* studies	• Anti-oxidant, anti-inflammatory properties • Upregulates SIRT expression • Inhibits sFlt-1 and sEng secretion by primary trophoblasts and HUVECs • Reduces secretion of pro-inflammatory molecules and increases antioxidant molecule expression • Resveratrol inhibited pigment epithelium-derived factor (PEDF) by upregulating miR-363-3p expression, thereby further elevating the expression of VEGF in a rat model of preeclampsia. Furthermore, resveratrol was found to improve the viability, migration, and angiogenesis of Cocl2-induced hypoxic trophoblasts *in vitro*. • Resveratrol increases the velocity of blood flow in the uterine arteries and fetal weight in $COMT^{-/-}$ mice • Resveratrol + nifedipine therapy could be beneficial for preeclampsia management by attenuating hypertensive symptoms .	(179,180,182–184,187–189)
PPIs	Clinical trials *In vitro* studies	• Reduce inflammatory cytokine levels in the placenta and blood vessels • Inhibit sFlt-1, sEng and ET-1 secretion in women with confirmed or suspected preeclampsia • Higher dose of intravenous administration may be effective in pre-term preeclampsia • Good safety profile and no teratogenic reports	(190–192,195–197)
Sulfasalazine	Clinical trials *In vitro* studies	• Anti-inflammatory and antioxidant properties • Inhibits sFlt-1, sEng and PlGF secretion in primary trophoblast cells • Mitigates vascular dysfunction in primary endothelial cells and omental vessel • Inhibits anti-angiogenic factors, stimulates angiogenic factors, inhibits HO-1 and VCAM, and induces vasodilation • Sulfasalazine + Metformin at low dose significantly increase VEGFα expression and reduce ET-1 expression in primary endothelial cells	(160,198,200,201)
Pravastatin	Clinical trials *In vitro* studies *In vivo* studies	• Promising preventative treatment when used in early gestation in pregnancy • Early administration of pravastatin is associated with lower IUGR • Favorable safety profile compared to other statins • In a murine model of preeclampsia, pravastatin increased VEGF and PlGF expression in placenta and ameliorated symptoms of preeclampsia • In primary human tissue studies (purified cytotrophoblast cells and placental explants), pravastatin inhibits sFlt-1 and sEng production • Prevents vascular dysfunction by increasing eNOS within aortic endothelial cells in a mouse model of preeclampsia	(202,204–211)
Melatonin	Clinical trials *In vitro* studies *In vivo* studies	• Melatonin levels are reduced in preeclampsia • Reduces sFLT-1 secretion in primary trophoblasts but does not affect sFlt-1 secretion from placental explants or HUVECs • Inhibits oxidative stress but not vascular dysfunction • Reduces misfolded proteins transported by EVs from preeclamptic placentas • Reduces blood pressure • Antioxidant effects involve a release of Nrf2 gene • May have a protective effect on the developing brain of the fetus	(212–217)

RCT: randomized controlled trials.

a phase II, double blind, randomized controlled trial) assessing the efficacy of metformin in the treatment of preterm preeclampsia (between weeks 26 and 32) (PACTR201608001752102) (168). In this study, the primary outcome is the time from randomization to delivery. It is considered clinically relevant to have a five-day delivery delay. Secondary outcomes will include maternal and neonatal composite outcomes (168). Although additional trials are required, this study provides proof of concept for metformin as a

potential treatment of pre-term preeclampsia (168). Another trial is being conducted to prevent preeclampsia in women with Type 2 diabetes mellitus (NTC01353391). In this study, the primary outcome is a composite of fetal and neonatal outcomes. Several relevant outcomes related to maternal health and neonatal health were reported as secondary outcomes (169).

In terms of mechanisms, an *in vitro* study assessed the effects of metformin and esomeprazole on sEng and sFlt-1 secretion in primary placental cells, tissues, and endothelial cells (170). The findings showed that low dose metformin and esomeprazole together reduced endothelial dysfunction markers (VCAM-1, ET-1) and sFlt-1 secretion compared to using metformin alone (170). Metformin merits further investigation as a potential therapy for certain high-risk populations, including women with polycystic ovaries, diabetes mellitus, and obesity, A different study compared the combination of esomeprazole (40 mg) and metformin (1000 mg) with a placebo treatment for treatment of EOP (171). The purpose of this double-blind, randomized, placebo-controlled study was to determine whether combining metformin with esomeprazole could reduce sFlt-1 and sEng secretion as well as endothelial dysfunction (NCT03717701) (171). Another clinical trial investigating the use of metformin in pregnant women with type 1 diabetes mellitus is currently recruiting participants in North America (NCT03570632) (172). The aim of this trial is to determine whether daily oral metformin therapy initiated before 20 weeks' gestation reduces the frequency of hypertensive disorder of pregnancy (HDP) in women with type 1 diabetes mellitus compared to their usual care (172).

Aspirin

Low-dose aspirin (LDA; <150 mg/day) is used as a non-steroid anti-inflammatory drug with antiplatelet properties and it is the only prophylactic treatment used in the clinic for the prevention of preeclampsia. The administration of LDA early in pregnancy is an effective method for reducing the incidence of preterm preeclampsia (delivery before 37 weeks of gestation) and IUGR (173). In numerous meta-analyses of large cohort studies, LDA has shown to reduce the relative risk of developing preeclampsia by 19% in high-risk groups, and it is associated with a 7% reduction in the incidence of severe complications including preterm birth (174). The preventative low doses of aspirin used across different studies are varied ranging between 50 to 150 mg per day (175). One meta-analysis of 59 studies evaluating the effectiveness of various antiplatelet agents (LDA or dipyridamole), found pregnant individuals treated with anti-platelet agents were 17% less likely to develop preeclampsia and the numbers needed to treat (NNT) are estimated at 72 women in order to prevent one case of preeclampsia (175) Moreover, antiplatelet agents were found to reduce perinatal death by 15% and premature birth by 9% (175). Furthermore, a meta-analysis of 34 randomized controlled trials found that LDA significantly reduces the risk of preeclampsia in high-risk women when administered before 16 weeks gestation (176). In terms of LDA's mechanism of action, both antiplatelet and antioxidative effects have been reported. Aspirin exerts antioxidative effects by inhibiting lipid peroxidation and increasing nitric oxide (NO) bioavailability, which improves endothelial function (173,177). Additionally, an *in vitro* study showed that LDA or acetyl salicylic acid (5 μg/mL) increased PlGF production and restored preeclamptic serum-induced increase in the cytokines (activated leukocyte cell adhesion molecule, CXCL-16, and ErbB3) concentration, apoptosis markers, and premature trophoblast differentiation (178). Further evidence shows that aspirin ameliorates preeclampsia through restoring STB dysfunction, and reduces sFlt-1, which, when upregulated, causes vascular damage in preeclampsia (178,179). However, it is still unclear whether aspirin improves the shallow trophoblast invasion and remodeling of spiral uterine arteries observed mainly in EOP (179).

Resveratrol

As a member of the stilbene family of compounds, resveratrol (3, 5, 4'–trihydroxy stilbene) can be found in a variety of plants, including Polygonum Cuspidatum, grapes, wine, peanuts, blueberries, bilberries, and cranberries (68,180,181). Based on various preclinical experiments, resveratrol appears to be effective as a treatment of preeclampsia (181). It has been suggested that resveratrol's antioxidant properties are exerted through upregulating SIRT1 expression, thereby activating downstream antioxidant molecules. Consequently, resveratrol reduces the secretion of sFlt-1 and sEng by primary trophoblasts and human umbilical vein endothelial cells (HUVECs), which are increased in preeclampsia (180). In addition, it reduces pro-inflammatory cytokine, proteinase-activated receptor-2 (PAR-2), expression and increases antioxidant molecule expression, heme oxygenase-1 (HO-1), NADPH quinone oxidoreductase 1(NQO1), nuclear factor-erythroid 2 (NF-E2)-related factor 2 (Nrf2), glutathione (GSH), superoxide dismutase (SOD) and ARE (antioxidant responsive element) (181,182).

Evidence suggests that resveratrol regulates the functions of trophoblasts *in vitro* by activating the epithelial-mesenchymal transition (EMT) and Wnt signaling pathways (181,183).

In an *in vivo* model, resveratrol has shown the ability to alleviate the symptoms of pre-eclampsia, and reduce high blood pressure in hypertensive patients (180,184). One *in vivo* study created preeclampsia-like model using intraperitoneal injection of Ng-nitro-L-arginine methyl ester (L-NAME) in Sprague-Dawley rats. In this model, resveratrol inhibited pigment epithelium-derived factor (PEDF) by upregulating miR-363-3p expression, thereby further elevating the expression of VEGF in rats with preeclampsia-like symptoms (183). Furthermore, another finding from the same study showed that resveratrol improved the viability, migration, and angiogenesis of cobalt chloride (Cocl2)-induced hypoxic trophoblasts *in vitro* (183). Another study demonstrated that plasma from women who later developed preeclampsia induced increased heme oxygenase-1 (HO-1) production and reduced nitric oxide (NO) in endothelial cells (HUVECs). In contrast, no such changes were observed with plasma from women who had healthy pregnancies. Notably, increase in HO-1 and NO markers were abrogated by co-treatment with resveratrol (185). A co-treatment with the polyphenol (contained in chocolate) (186) and resveratrol also abrogated these changes and improved GSH levels (184). A separate study in Catechol-O-methyl transferase ($COMT^{-/-}$) knockout mice, which share many phenotypic characteristics of preeclampsia, found that resveratrol significantly increased the velocity of blood flow in the uterine arteries and the weight of the fetus in $COMT^{-/-}$ mice suggesting that it could be a promising therapeutic strategy for preeclampsia (187). A clinical trial (NCT01106170), that combined resveratrol treatment with phytochemicals (grape seed, green tea, a blend of quercetin, ginkgo biloba) reported a reduction of diastolic blood pressure, mean arterial pressure, and urinary nitrate and nitrite concentrations in participants with preeclampsia (188,189).

Proton pump inhibitors (PPIs)

PPIs are widely used to treat symptomatic gastric acid reflux by reducing acid secretion. Preclinical evidence suggests that PPIs may reduce preeclampsia symptoms (e.g., hemorrhage or stillbirth, or hypertension in pregnancy) and inflammatory cytokine levels in the placenta and blood vessels, as well as mitigate endothelial dysfunction (190,191). A study findings reported that in women with confirmed or suspected preeclampsia, PPIs showed a favorable pro-angiogenic profile by inhibiting sFlt-1, sEng, and ET-1 (191). A clinical trial conducted in Cape Town, South Africa, recruited 120 participants who were randomized to receive 40 mg of esomeprazole daily or a placebo in pregnancies with preterm preeclampsia. However, esomeprazole (40 mg) did not prolong gestation or decrease sFlt-1 circulating levels (192). In addition to these pro-angiogenic effects, PPIs have shown antioxidative potential by reducing oxidative stress and inflammatory markers, as observed in studies on endothelial cells and the gastrointestinal tract, potentially protecting vascular tissues from oxidative injury (193,194). The clinical studies demonstrated PPIs to be well tolerated and extensive safety data from very large cohorts confirmed that there are no teratogenic risks associated with their use, even when taken during the first trimester (160,195,196). An observational study of pregnant women exposed to PPIs for 8–45 days from the second trimester of pregnancy demonstrated a decreased circulating concentrations in sFlt-1, sEng, and ET-1 (160,195,197). Further clinical trials are necessary to assess the efficacy and safety of using PPIs as a prophylactic treatment to prevent the onset of preeclampsia, particularly in high-risk pregnant women, and to determine the optimal dosage, timing, and patient population.

Sulfasalazine

As explained above, preeclampsia is associated with increased abundance of pro-inflammatory cytokines that may contribute to endothelial dysfunction. Long-term evidence on sulfasalazine has demonstrated that it is safe to use in pregnancy, making it a promising candidate for preeclampsia treatment due to its anti-inflammatory and antioxidant properties. Besides treating arthritis and inflammatory bowel disease, sulfasalazine has also been used to treat auto-immune diseases (160,198). Sulfasalazine exerts antioxidative effects through its ability to increase the expression of heme oxygenase-1 (HO-1), an enzyme known for its protective role against oxidative stress. HO-1 reduces oxidative stress by neutralizing free radicals, which is particularly important in preventing oxidative damage to endothelial cells in preeclampsia (199). A study using primary human cytotrophoblast cells has shown that sulfasalazine reduced the secretion of sFlt-1 and sEng and increased the production of PlGF. In the same study, sulfasalazine mitigated vascular dysfunction and showed vasodilatory effects in primary endothelial cells and omental vessels (198). Sulfasalazine's antioxidant effects are further supported by its ability to decrease vascular cell adhesion molecule-1 (VCAM-1) levels, thereby reducing the risk of endothelial dysfunction in preeclampsia (198). A potential advantage of this

medication is that it has a potent anti-inflammatory properties, which may be helpful in resolving the placental and systemic inflammation associated with preeclampsia. Nevertheless, the pharmacokinetics of sulfasalazine in pregnancy is not fully understood, particularly in terms of absorption. To address this, a pharmacokinetic trial of sulfasalazine has been initiated among women with preterm preeclampsia in Australia (ACTRN12617000226303). This trial focused on determining the pharmacokinetics of sulfasalazine and its effect on the clinical and biochemical parameters of preeclampsia (160,200). Two preclinical studies using primary human cytotrophoblast cells, primary endothelial cells and omental vessels, showed that sulfasalazine decreases antiangiogenic factors (sFlt-1 and sENG), increases angiogenic factor (PlGF), increases HO-1, decreases VCAM-1, and induces vasodilation (160,198). The known safety profile of this drug during pregnancy and the positive results of preclinical studies support its progression into a clinical trial (160). The combination of metformin and low dose sulfasalazine significantly increased VEGFα expression and reduced TNF-α-induced ET-1 expression in primary endothelial cells, suggesting that treatment of preeclampsia may be improved by using this combinational therapy (201). Sulfasalazine's antioxidant and anti-inflammatory properties suggest it may help counteract the oxidative stress and inflammatory pathways central to preeclampsia pathogenesis. The potential of sulfasalazine as a therapeutic and preventive option for preeclampsia requires additional exploration through well-designed clinical trials (201).

Pravastatin

Pravastatin is currently being evaluated as a treatment for preeclampsia in several clinical trials due to its better safety profile compared with other statins (160,202). Recent systematic reviews and meta-analyses have deemed pravastatin as a promising preventative therapy for preeclampsia when used early in gestation (203–205). The meta-analysis established that pravastatin was ineffective for the prevention of preeclampsia when given after 35 weeks of gestation (203,206). However, when pravastatin therapy was given to mothers before 20 weeks of gestation, it was associated with the lower incidence of IUGR, neonatal intensive care unit (NICU) admissions, and premature delivery of neonates (203).

In a preclinical study, using an experimental murine model of preeclampsia following overexpressed sFlt-1 a lentiviral vector-mediated placenta-specific expression system resembling features including hypertension, proteinuria, and IUGR (207), pravastatin enhanced the expression of VEGF-like angiogenic factor (PlGF) and ameliorated the symptoms of preeclampsia including hypertension, proteinuria, and IUGR (207). Similarly, an *ex vivo* study with primary human tissues (purified cytotrophoblast cells and placental explants), demonstrated that pravastatin decreased sFlt-1 and sEng production, and abrogated endothelial dysfunction (132). In addition to its pro-angiogenic effects, pravastatin has been shown to exert antioxidant effects, reducing reactive oxygen species (ROS) and lipid peroxidation levels, thereby protecting endothelial cells from oxidative injury, a key factor in preeclampsia pathogenesis (207). Another study showed that pravastatin prevented vascular dysfunction in part by up-regulating isolated aortic endothelial nitric oxide synthase (eNOS) by approximately two-fold in an sFlt-1 overexpression mouse model of preeclampsia (208). However, in the StAmP trial (23410175), pravastatin treatment did not result in a reduction in circulating sFlt-1 concentration nor an increase in gestational age of delivery, in individuals with EOP. However, the study was underpowered and should potentially be carried out in a larger cohort of patients (204,209).

A further advantage of pravastatin is that it is hydrophilic and hence it does not cross the placenta readily, which reduces teratogenic risks (160,204,205). Compared to other statins including rosuvastatin and simvastatin, pravastatin is less toxic to endothelial cells at high doses (160). Despite the fact that simvastatin and rosuvastatin have been shown to be more effective than different generation statins (pravastatin, and atorvastatin) in people with cardiovascular diseases and to be able to reduce sFlt-1, ET-1, and oxidative stress in preeclampsia models, their endothelial cell toxicity deems them less desirable than pravastatin, making pravastatin a safer choice (210,211). Therefore, taking into the account both safety and efficacy, pravastatin is likely the most promising treatment for preeclampsia, compared to other statins (160).

Melatonin

As an endogenous hormone and antioxidant, melatonin is produced by the pineal gland and the placenta (160,212–214). There is evidence that melatonin plays a role in the pathogenesis of preeclampsia, given that women with preeclampsia have significantly lower melatonin plasma concentration with lower expression of melatonin receptors within the placental tissue (215,216). A meta-analysis determined that lower concentration of melatonin in individuals with preeclampsia was positively correlated to the severity of the condition (216). In an *in vitro* study, melatonin was found to reduce sFlt-1 secretion from primary

trophoblasts. However, it did not affect the secretion of sFlt-1 or sEng from either placental explants or HUVECs. The study also determined that melatonin did not restore TNF-α-induced VCAM-1 and ET-1 overexpression in endothelial cells. The results of this study indicate that while melatonin treatment reduces oxidative stress, it does not target all sources of vascular dysfunction (213). The results of another *in vitro* study indicated that melatonin could reduce misfolded proteins transported by extracellular vesicles (EVs) from preeclamptic placentas. In addition, it inhibits the ability of these EVs to activate endothelial cells (212). As preeclampsia is associated with widespread vascular dysfunction, peripheral vasoconstriction may result in maternal hypertension (213). Given that melatonin has demonstrated antihypertensive effects, it could be used for symptomatic management of preeclampsia that also targets the root cause of the disease (214). Researchers demonstrated that the antioxidant response element of safeguarding genes is activated when melatonin releases Nrf2 from Kelch-like ECH-associated protein 1 (KEAP-1). ROS are neutralized by these proteins through cellular redox reactions. Melatonin is therefore able to improve vascular function by reducing vasoconstriction, reducing capillary leakage, and enhancing placental function. It has also been suggested that melatonin may directly protect the developing brain of the fetus (214). In the PAMPR open-label, single-arm trial, melatonin prolonged gestational age of delivery by 6 ± 2.3 days and reduced the need for increasing antihypertensives following the diagnosis of preeclampsia (217). Inan *in vitro* xanthine/xanthine oxidase (X/XO) placental explant model, melatonin mitigated TNFα-induced VCAMs increased expression and preserved endothelial monolayer integrity without altering other markers of endothelial activation or dysfunction (217). On the other hand, during a phase I trial including 20 women with preeclampsia, melatonin was found to mitigate maternal endothelial pro-oxidant injury and could therefore serve as an effective adjuvant therapy for women with severe preeclampsia, and improving clinical outcomes (160,217). Further preclinical and clinical studies should be conducted to investigate the efficacy and mechanism of action of melatonin in preeclampsia.

Mesenchymal stem/stromal cells (MSCs) and EVs as an emerging treatment for preeclampsia

MSCs can be derived from bone marrow, adipose tissue, the pancreas, the placenta, or the umbilical cord (218–220). Due to their multipotency, these cells can differentiate into multiple cell lineages, though their therapeutic effects appears to be influenced by their ability to communicate with target cells through their secretome, which is dominated by EVs (218–221). In preclinical models of inflammatory injury-related diseases including osteoarthritis, rheumatoid arthritis, stroke, Alzheimer's disease, cardiovascular disease, and preeclampsia, MSCs have demonstrated promising results (219) (Figure 3).

Recent studies have investigated the therapeutic potential of MSCs in preeclampsia due to their immunomodulatory, anti-inflammatory, antioxidant, and proangiogenic properties (219). MSCs are multipotent mesodermal cells that can give rise to stromal cell lineages (222). Trophic factors released by MSCs have been identified to have cytoprotective (anti-apoptotic and pro-mitotic), anti-inflammatory and anti-fibrotic effects whilst promoting endogenous tissue regeneration and vascularization in various contexts (223). MSCs also have antioxidant effects, as they can secrete enzymes including superoxide dismutase (SOD) and catalase, which help neutralize ROS and reduce oxidative damage in preeclampsia (224). Trophic factors of interest commonly secreted by MSCs include transforming growth factor-b-1 (TGF-b-1), TNF-α, PGE2, IFN-γ, hepatocyte growth factor (HGF), fibroblast growth factor (FGF), indoleamine-pyrrole 2,3-dioxygenase (IDO), VEGF-A, and nitric oxide (225). Research into preeclampsia has also unveiled that placental-derived MSCs from individuals with preeclampsia differ from healthy pregnancies and this abnormal placental MSC function could be a contributing factor for the onset of preeclampsia (226). Placental MSCs express higher levels of CD34, CD44, and leukemia inhibitory factor (LIF) within decidua in the presence of preeclampsia compared to normotensive patients (227). Microarray studies have identified several decidual MSCs (dMSCs)-derived miRNAs that are upregulated in preeclampsia suggesting that differential miRNA expression may be involved in the development of preeclampsia (228,229). One study confirmed that the overexpression of miR-16 resulted in reduced migration and proliferation of normotensive pregnancy-derived MSCs and affected the vascularization capacity of HUVECs in addition to a reduction in the migratory capacity of trophoblast cells. Furthermore, miR-136 and miR-494 have been found to be highly expressed in dMSCs from individual with preeclampsia, and both miRNAs have been linked to increased apoptosis and suppression of the angiogenic activity of HUVECs (230,231).

However, due to their proangiogenic and antioxidant properties, healthy MSCs have emerged as a promising resource for treatment of preeclampsia

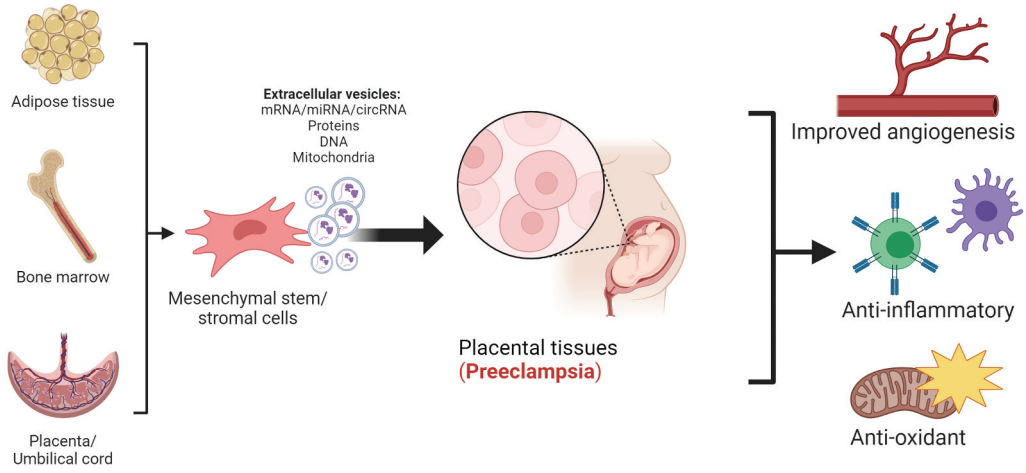

Figure 3. Schematic illustrating the application of MSCs derived EVs in treating preeclampsia. MSCs exert therapeutic effects by secreting EVs that contain mRNAs, miRNAs, circRNA, DNA, proteins, and organelles including mitochondria. MSCs can treat pre eclampsia by improving angiogenesis, immunomodulation, and redox regulation through their EVs. Figure adapted from Suvakov et al, 2020 (219). Created in https://BioRender.com.

(219,226). A study performed on preeclamptic placental villous explants showed that placenta-derived-MSC conditioned media had anti-inflammatory and pro-angiogenic effects, reducing the expression of macrophage-migration inhibitory factor (MIF), TNF-α, IL-6 and sFlt-1 (232). Studies in rat and mouse models of preeclampsia have shown that MSCs can reduce symptoms of preeclampsia including blood pressure and proteinuria by targeting the inflammatory response resulting in decreased TNF-α and other inflammatory cytokines (233,234). More recently, a study published in 2020, showed that MSCs-conditioned media enhanced trophoblast migration in both hypoxia and normoxia, and promoted tubule formation of endothelial cells in association with reduced expression of an anti-angiogenic factor, FKBPL, and increased CD44 expression (91).

In recent years, EVs have been identified as key messengers in intercellular communication with anti-inflammatory and antioxidant functions. MSC-derived EVs carry antioxidant enzymes and miRNAs that reduce ROS levels in endothelial and placental cells, offering protection against oxidative stress-related damage in preeclampsia (235). A great variety of mammalian cell types including MSCs are capable of constitutively releasing EVs into their environment (236,237). Given their anti-inflammatory and trophic effects, MSC-EVs have gained interest for their potential as cell-free therapeutic treatment presenting lower risks than cell-based therapy and relative ease of manufacture, processing and storage (220,236,238). In the context of preeclampsia, MSC-EVs have been studied in both animal and human *in vitro* models. In a heme oxygenase (Hmox1) null mutant mouse model of preeclampsia, MSC-EVs were found to modify the markers of inflammation in the pregnant uterus in addition to improving fetal lung branching (239). In the same model, MSC-EVs were reported to modify markers of oxidative stress in the pregnant uterus and enhance antioxidant defense, reducing oxidative injury in placental and fetal tissues (235) as well as abrogate fetal loss and fetal growth restriction, improve the spiral uterine artery remodeling process, and ameliorate the maternal preeclampsia-like symptoms (240). In the rat L-NAME (N^G-nitro-l-arginine methyl ester)-induced model of preeclampsia, MSC-EVs led to a reduction in blood pressure and proteinuria, improved the placental and fetal development, reduced resorption rate, increased expression of angiogenic markers, reduced cell apoptosis, and decreased sFlt-1 levels (241). In a human cell culture model of preeclampsia, dMSCs-EVs treatment increased HUVECs attachment and proliferation and reduced the expression of pro-inflammatory IL-6 cytokine (242). Furthermore, the addition of dMSCs-EVs to preeclampsia serum treated HUVECs resulted in a significant reduction in lipid peroxidation, indicating a decrease in oxidative stress, which is crucial for improving endothelial health in preeclampsia (242). Lastly, a study on the effects of amnion-derived EVs on cultured trophoblasts cells, resulted in an increase of trophoblast proliferation and autophagy under hypoxic conditions. Researchers were able to pinpoint this to the downregulation of EZH2 which resulted in inactivation of the mTOR signaling pathway (243).

Overall, MSC-derived EVs represent a promising avenue for preeclampsia treatment due to their safety, lower immunogenicity compared to cell-based therapies, ease of manufacturing, storage and transport, and therapeutic effects and mechanisms that target the key root causes of preeclampsia.

Mitochondria targeting therapies

There are currently no treatments that can cure preeclampsia (68,82). Antihypertensive drugs are commonly used to manage clinical symptoms in pregnant individuals with preeclampsia. However, these treatments are not designed to prolong gestation or mitigate the impacts of preeclampsia on fetal development and growth, as they do not address the underlying disease mechanisms (68,244). One of the reasons for the lack of effective treatment for preeclampsia is poorly understood mechanisms of pathogenesis. However, research has established that mitochondrial dysfunction within the trophoblast cells in the placenta from women with preeclampsia was associated with impaired energy metabolism, redox imbalances, dysregulation of mitochondrial biogenesis and dynamics, accumulation of mitochondrial DNA, abnormal mitophagy and autophagy, as well as cell senescence and apoptosis (245). Therefore, targeting mitochondrial function, a hallmark feature of preeclampsia, could potentially halt disease progression (68,82). Mitochondrial ROS production induced by hypoxia plays a significant role in placental dysfunction and preeclampsia. Traditional antioxidant therapies (vitamin C, vitamin E) have not been effective in preventing preeclampsia due to their inability to specifically target mitochondrial ROS (mtROS) and other ROS forms (246,247). In the DAPIT study (ISRCTN27214045) including pregnant women with type 1 diabetes although vitamin C and E did not decrease the incidence of preeclampsia overall, sub analyses in participants with low levels of antioxidant status showed beneficial results (248). Recent studies, however, have shown promising results with various antioxidant therapies that specifically target mitochondrial ROS-induced placental dysfunction (56,68,82,246,249). Some of the mitochondria targeting antioxidants are described below.

Coenzyme Q10 or CoQ10

Interventional study in humans have found that CoQ10, a key component of the mitochondrial electron transport chain, could be a promising treatment for preeclampsia (82,250). In preeclampsia there is a significant reduction in plasma concentration of CoQ10 (251). However, another study shows that CoQ10 concentration in placental mitochondria from individuals with preeclampsia were reported to be increased (252). This is due to increased ROS production in the placenta in the presence of preeclampsia, which suggests compensatory accumulation (252). A randomized, double-blind, placebo-controlled study was conducted to assess the safety and effectiveness of daily oral administration of 200mg CoQ10 from 20 weeks of gestation until delivery (250). The study concluded that supplementation with CoQ10 was associated with reduced preeclampsia risks reporting the incidence of preeclampsia of 25.6% in the placebo group compared to 14.4% in CoQ10 treatment groups. The high incidence of preeclampsia in this study is due to the recruitment of women at increased risk, including those with Type 2 diabetes mellitus. The significant reduction in preeclampsia rates with CoQ10 supplementation highlights its potential as a preventative measure in high-risk pregnancies, particularly among women with pre-gestational diabetes mellitus (56,148,250). A meta-analysis of randomized controlled trials investigating the effects of CoQ10 compared with placebo on endothelial function demonstrated a significant improvement in endothelial function assessed peripherally by flow-mediated dilatation in the presence of CoQ10. (253). Althought this meta-analysis included participants with and without cardiovascular disease, this is relevant to preeclampsia given endothelial dysfunction is a hallmark feature of its pathogenesis. Although CoQ10 shows some promising therapeutic effects in preeclampsia, the exact mechanism is still not fully understood. Some evidence suggests that CoQ10 could increase the total antioxidant capacity, which could decrease ROS and reactive nitrogen species (RNS) levels in preeclampsia (56).

Mito Q

MitoQ is a pharmaceutical compound developed by linking a quinone moiety to a triphenylphosphonium (TPP) moiety through a 10-carbon chain, which allows it to target mitochondria effectively (254). Once inside the mitochondria, MitoQ is converted into ubiquinol by mitochondrial complex II. As an antioxidant, ubiquinol neutralizes free radicals and can be continuously recycled within mitochondria to maintain a required level of antioxidant activity (68,246). MitoQ is another mitochondrial targeting antioxidant capable of abrogating mitochondrial oxidative stress and hypertension in preeclampsia (246). The MitoQ treatment increased placental maternal blood space surface area and volume in a rat model of unfolded protein response (UPR) while inhibiting activation of mitochondrial and endoplasmic reticulum stress, and preventing downstream effects that can damage cells and organelle (255). It has

been shown that MitoQ accumulates within the placental tissue following its administration in rats (249,256). An animal model of prenatal hypoxia has shown that MitoQ treatment prevents hypoxia-induced reduction in mitochondrial activity and increase in placental ROS (249,255–259). MitoQ has been shown to improve fetal growth in rats in hypoxia-induced model of fetal growth restriction (249,256). A study evaluating whether MitoQ bound to drug-loaded γ-PGA-Phe nanoparticles (NPs) would prevent it from crossing the placenta and affecting fetal development, reported that NP-bound MitoQ prevented placental oxidative stress, improved fetal weight, and protected the fetal brain in a hypoxic pregnancy rat model (11% oxygen: gestational day (GD) 16–21) (256). Furthermore, in the rat reduced uterine perfusion pressure (RUPP) model, MitoQ has also been shown to improve electron transport chain (ETC) function, reduce mean arterial pressure, and restore fetal growth (249,260). However, precaution should be taken when considering antioxidants as preventative measure for preeclampsia, as a rodent study reported that MitoQ administration early in pregnancy could impair normal placenta development through the reduction of physiological ROS (45,68).

MitoTEMPO

MitoTEMPO is another widely used mitochondrion targeting antioxidant containing piperidine nitroxide (Tempo). It mimics SOD and catalyzes the dismutation of the superoxide radicals into molecular oxygen and hydrogen peroxide within the mitochondria (56,68,81,246). Previous preclinical studies have shown that MitoTEMPO significantly reduces maternal blood pressure and increases both placental and fetal weight in the rat RUPP model of preeclampsia (56,68,260). A study in a placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) dysfunction-induced preeclampsia-like rat model resembling preeclampsia and mitochondrial dysfunction of EVTs, found that MitoTEMPO improved both the stability of placental mitochondrial DNA and mitochondrial dynamics (68,261). HUVECs treated with serum from women with preeclampsia, in the presence of MitoTEMPO have also shown a significant reduction in mitochondrial ROS, mitochondrial uncoupling protein 1, and Toll-like Receptor activity (81,246). Further evidence from *in vitro* studies shows that MitoTEMPO maintains mitochondrial function and reduces the effect of hydrogen peroxide on cell death (262). MitoTEMPO has been tested in humans and is reported to have a favorable safety profile (68,81,262–264), however no data is currently available with regards to pregnancy.

Ergothioneine

As a water-soluble amino acid and derivative of histidine, L-Ergothioneine (ERG) has been shown to possess radical-scavenging properties (56,265–269). Ergothioneine accumulates in mitochondria via its specific transporter, OCTN1 (also known as SLC22A4), which enables it to concentrate in mitochondrial compartments where it exerts protective effects against oxidative damage (270). In a number of pathologies (ischemic kidney and liver), ERG has been tested for its therapeutic potential and there is evidence that it accumulates in mitochondria exerting anti-oxidant effects (56,265,267,269,271–274). When ERG was tested *in vivo* using the rat RUPP model of preeclampsia, a number of phenotypic features of EOP were alleviated by ERG treatment, including hypertension, fetal growth restriction, and increased sFlt-1 concentration or metabolites associated with inflammation. The accumulation of ERG in mitochondria allows it to directly scavenge mitochondrial ROS, contributing to increased antioxidant levels and reduced inflammation (275,276). Although promising, further studies are needed to validate the therapeutic potential of ERG in preeclampsia.

AP39

AP39 is an emerging antioxidant treatment that acts as a mitochondria-targeted hydrogen sulfide (H2S) donor (249,277). In a study, using a model of primary human trophoblast cell culture where hypoxia increased mitochondrial ROS production and sFlt-1 concentration, AP39 inhibited ROS production, reduced HIF-1α protein expression, and decreased sFlt-1 production. Additionally, AP39 was capable of modulating mitochondrial bioenergy that led to the reversal of oxidative stress and antiangiogenic responses in trophoblasts following hypoxia exposure, while also enhancing cytochrome c oxidase (COX) activity (249,277). Similarly, AP39 was able to abrogate anti-angiogenic impact of increased sFlt-1 production in primary human trophoblast cell culture model and restore mitochondrial bioenergetics in hypoxic environment. A study found that inhibition of cystathionine γ-lyase (CSE) increases the release of sFlt-1 and sEng in response to H2S dysregulation in endothelial cells. It was also investigated whether these effects are related to CSE-induced production of sFlt-1 and sEng in endothelial cells. They found that low CSE increased the emphasis on glycolysis and the production of mitochondrial superoxide. According to this study, AP39, a mitochondrial-targeted H2S donor, was able to suppress preeclampsia-

induced endothelial dysfunction caused by sFlt-1 (278). AP39 was shown to improve mitochondrial function in human primary trophoblasts by targeting H2S, which acts as a replacement electron transport component and ATP generator in mitochondria, at the concentrations tested, i.e. 50μM (277). The mitochondrial electron transport rate can be increased by H2S at low concentrations via direct electron donation, an increase in mitochondrial cAMP levels, direct activation of ATP synthase, and mitochondrial antioxidant effects (277). Conversely, a higher concentration of H2S inhibits mitochondrial function through mitochondrial complex IV (277). It is important to use AP39 at the appropriate concentrations, to achieve beneficial cellular effects within the placenta via direct mitochondrial protection, as well as through stimulation of complex IV, in turn modulating mitochondrial ROS production (277). This mechanism of action could be favorable for the treatment of preeclampsia, however the safety profile of AP39 in pregnancy is still not established.

Micronutrients supplements as a therapy for preeclampsia

Recently, micronutrients including vitamins A, B6, B12, C, D, E, folate, selenium and zinc have emerged as key determinants of pregnancy outcome and are implicated in modulating maternal and fetal metabolism, oxidative stress, and placentation (56,279,280). During pregnancy, these micronutrients can enhance the maternal capacity to manage heightened oxidative stress (280–282). However, the use of vitamin A is restricted during pregnancy due to potential teratogenic effects, especially when consumed in doses exceeding the recommended daily allowance (RDA) of 2,500–3,000 IU. Excessive intake of vitamin A has been associated with an increased risk of congenital malformations, and therefore, supplementation should be carefully managed (283). The inflammatory and oxidative stress state of pregnancy may be worsened by the deficiencies in folate, selenium, vitamin C, and vitamin E, potentially contributing to endothelial dysfunction and clinical manifestations of preeclampsia (280,284). Unlike other micronutrients, vitamins B6 and B12 do not directly combat oxidative stress but play essential roles in cellular metabolism and homocysteine regulation. Elevated homocysteine levels, which vitamins B6 and B12 help reduce, are associated with endothelial dysfunction and may indirectly contribute to the risk of preeclampsia (285). Vitamin D possesses immunomodulatory properties that could influence the maintenance of pregnancy. In addition to its immunomodulatory effects, vitamin D has antioxidant properties that may help reduce oxidative stress in preeclampsia. Vitamin D's active form, calcitriol, has been shown to inhibit ROS production and improve antioxidant defenses, which is critical in mitigating oxidative damage to placental and endothelial cells (286). There may be a potential benefit in ensuring that vitamin D status and consumption is adequate in pregnancy to prevent preeclampsia (280,284). The Norwegian Mother and Child Cohort Study examined the association between Vitamin D intake during pregnancy and preeclampsia among 23,423 nulliparous pregnant women. In this study, they reported a reduced odds ratio of 0.76 (95% CI 0.60–0.95) for preeclampsia in women with a total vitamin D intake of 15–20 micrograms per day compared to women with an intake of less than 5 micrograms per day. Additionally, women taking 10–15 micrograms of vitamin D per day were found to have decreased the risk of preeclampsia by 27% (OR 0.73; 95% CI 0.58–0.92) compared with women taking no vitamin D supplementation (280,284). Despite this, no correlation was found between vitamin D intake from diet alone and the risk of preeclampsia (280,284). The antioxidant properties of vitamins C and E help scavenge free radicals and reduce cellular damage caused by ROS (280). A significant reduction in preterm birth risk following supplementation of vitamin C and E in pregnant women as part of clinical trial was conducted in the UK (287). In contrast, a multicentre trial was conducted in Australia and New Zealand, involving 1,877 nulliparous women found no significant difference in the risk of preeclampsia, IUGR, infant death or other serious outcomes in infants (288). Thus, it is difficult to draw a conclusion whether preeclampsia may be successfully prevented or treated with a single or multiple micronutrients as there may be diverse factors playing a role in the pathogenesis of preeclampsia including the baseline micronutrient status in women prior to or during pregnancy. However, a larger study by researchers examined whether the use of multivitamins and minerals during pregnancy may reduce the risk of preeclampsia. The analysis included 2,261 pregnancies, with preeclampsia occurring in 1.95% of cases. A body mass index (BMI) of ≥ 25 was linked to a 1.97-fold increase in the risk of preeclampsia. Additionally, first-trimester multivitamin use, reported by 31.8% of women, was associated with a 67% reduction in preeclampsia risk after adjustment (56,289).

Future perspectives

To effectively manage preeclampsia, it is important to address the heightened oxidative stress because it plays an important role in the pathophysiology of the condition, contributing to endothelial dysfunction and inflammation, and leading to placental

dysfunction (155,290). In addition, it is important to note that although addressing oxidative stress may be beneficial in the clinical management of preeclampsia, it is generally part of a comprehensive treatment plan that includes monitoring blood pressure, managing the symptoms, and, in severe cases, delivering the baby to avoid complications for the mother and the baby (291–293).

Targeting oxidative stress in preeclampsia presents several challenges. Although many compounds reduce oxidative stress *in vitro*, delivering these agents effectively to placental or vascular tissues *in vivo* is difficult due to poor solubility, rapid metabolism, and limited permeability. Additionally, a lack of reliable oxidative stress biomarkers complicates treatment monitoring (294) however, meta-analyses have identified promising candidates, including IMA, UA, and MDA (96,295). Developing therapies that maximize efficacy and minimize off-target effects is crucial, as is exploring optimal combination of treatments for synergistic benefits. While emerging therapies show potential, further research is essential to confirm their safety and efficacy for preeclampsia. Recent evidence suggests using preclinical models that potential modulators of mitochondrial mitophagy could be used to prevent preeclampsia. The optimal level of mitochondrial mitophagy promotes trophoblast cell survival, while imbalance leads to apoptosis (68,82). Researchers are attempting to develop new drugs that can control the expression of target proteins involved in the regulation of mitochondrial dynamics and mitophagy (e.g., BNIP3, TFAM, DRAM1, MFN1, MFN2, OPA1, and DRP1). Examples include the quinazolinone derivative known as mitochondrial division inhibitor-1 (Mdivi-1), an inhibitor of dynamin related protein 1 (DRP1) (82). Mdivi-1 works by inhibiting DRP1, a key regulator of mitochondrial fission, which prevents excessive mitochondrial fragmentation. By stabilizing mitochondrial morphology, Mdivi-1 preserves mitochondrial function, reduces oxidative stress, and prevents downstream cascade leading to cell apoptosis, therefore showing potential for targeting mechanisms implicated in preeclampsia pathology (296) (297,298). This has led to the development of pharmacological modulators of mitochondrial dynamics and mitophagy, which offer great potential for advancing basic research and clinical translation in preeclampsia treatment.

Effective preeclampsia treatment could be developed and implemented through interdisciplinary collaboration and innovative technologies. Given that preeclampsia is a multifactorial disorder, we need experts from the obstetrics, gynecology, cardiology, genetics, immunology, and placental biology research fields to collaborate and share knowledge across disciplines to design appropriate studies that will evaluate the appropriateness of various antioxidant treatments. This holistic approach provides an opportunity to better understand the underlying mechanisms, identify risk factors, and formulate effective prevention and treatment plans (203,294,299,300). Researchers from various STEM disciplines should also lead the development of innovative technologies including novel biomarkers, genetic screening, as well as advanced imaging of placental morphology and diagnostic platforms that can contribute to the early detection and diagnosis of preeclampsia. More reliable panel of biomarkers detectable in the blood (invasively) or saline/urine (non-invasively) should be developed to predict and diagnose preeclampsia before symptoms manifestation. This approach could lead to implementation of safe and effective preventative therapies for preeclampsia therefore reducing associated complications through timely clinical intervention and management.

As a treatment approach for heterogenous conditions such as preeclampsia, personalized medicine holds great promise. Personalized medicine allows treatment plans to be tailored according to the characteristics of the individual patients upon diagnosed. Treatment decisions are influenced by variables including preeclampsia phenotype and severity, gestational age, and the presence of other medical conditions. It is important to note that personalized medicine considers not only genetic factors but also lifestyle and environmental factors that have the potential to influence preeclampsia risk and progression.

(301). There are a number of considerations when it comes to translating promising preclinical findings into clinical practice for preeclampsia. Preclinical studies often rely on animal models that mimic preeclampsia, but the translational relevance of these models to human preeclampsia is often questioned due to interspecies differences and limitations in replicating the full spectrum of the human diseases, while the ethical complexities of testing new treatments in pregnant women still exist (302,303). Better *in vitro* models are needed to increase our understanding of preeclampsia pathogenesis toward developing improved predictive, diagnostic, and therapeutic options, and ensuring that pregnant individuals and their offspring receive better support and care.

Conclusions

In summary, oxidative stress plays a significant role in the development and progression of preeclampsia, a leading cause of morbidity and mortality in pregnancy (304). Current research has identified several potential strategies to reduce oxidative stress through the use of clinically available or novel antioxidants and micronutrients (203). A number of these therapies have been repurposed, however further research is still necessary to validate

these approaches in preeclampsia and to gain a better understanding of their mechanisms of action in pregnancy settings. The development of targeted therapies for preeclampsia and further research into the mechanisms of oxidative stress hold significant promise for improving outcomes for both mothers and their offspring (123,305). However, conducting clinical trials to test potential treatments for preeclampsia is hindered by the difficulty in recruiting pregnant women. Pregnant women have been routinely excluded from pharmaceutical trials because of the widespread concern about drugs harming the fetus. However, there is still scarce evidence on medication safety and efficacy during pregnancy. According to a systematic review, theoretically informed strategies can facilitate the engagement, participation, and trust of pregnant and lactating women in clinical trials. Nevertheless, this is accomplished by linking identified risk factors to a framework for behavioral change (306). Although significant progress has been made in understanding the etiology and pathogenesis of preeclampsia, there are still many gaps that require multidisciplinary effort. Developing targeted treatments with antioxidant capacity that are safe to use in pregnancy, is of a critical importance in order to reduce both short- and long-term burden of preeclampsia. This will require joint global effort, that includes sharing of knowledge and resources and conducting large and robust multicentre clinical trials in pregnant women.

Article Highlights

Oxidative stress and mitochondrial dysfunction play a key role in the pathogenesis of preeclampsia. This review provides comprehensive account of oxidative stress mechanisms relevant to preeclampsia Targeted treatments including antioxidant supplements, lifestyle modifications, mitochondrial targeting antioxidants and pharmacological agents to counteract oxidative stress in preeclampsia are discussed.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

[1] Yusuf SK, Kristin MA. Embryology, week 1. StatPearls [Internet]. 2023. PMID: 32119449. Apr 17.
[2] Emiliani S, Delbaere A, Devreker F, et al. Embryo–maternal interactive factors regulating the implantation process: implications in assisted reproductive treatment. Reprod Biomed Online. 2005 Jan;10(4):527–540. doi: 10.1016/S1472-6483(10)60831-0
[3] Davies J, Pollheimer J, Yong HEJ, et al. Epithelial-mesenchymal transition during extravillous trophoblast differentiation. Cell Adh Migr. 2016 May 3;10(3):310–321. doi: 10.1080/19336918.2016.1170258
[4] Hoshina M, Boothby M, Hussa R, Pattillo R, Camel HM, Boime I. Linkage of human chorionic gonadotrophin and placental lactogen biosynthesis to trophoblast differentiation and tumorigenesis. Placenta. 1985 Mar;6(2):163–172. doi: 10.1016/S0143-4004(85)80066-7
[5] Pereira RD, De Long NE, Wang RC, et al. Angiogenesis in the placenta: the role of reactive oxygen species signaling. Biomed Res Int. 2015;2015:1–12. doi: 10.1155/2015/814543
[6] Chen D, Zheng J. Regulation of placental angiogenesis. Microcirculation. 2014 Jan 3;21(1):15–25. doi: 10.1111/micc.12093
[7] Pérez-Gutiérrez L, Ferrara N. Biology and therapeutic targeting of vascular endothelial growth factor a. Nat Rev Mol Cell Biol. 2023 Nov 25;24(11):816–834. doi: 10.1038/s41580-023-00631-w
[8] Witzenbichler B, Maisonpierre PC, Jones P, et al. Chemotactic properties of angiopoietin-1 and -2, ligands for the endothelial-specific receptor tyrosine kinase Tie2. J Biol Chem. 1998 Jul;273(29):18514–18521. doi: 10.1074/jbc.273.29.18514
[9] Dunk C, Shams M, Nijjar S, et al. Angiopoietin-1 and angiopoietin-2 activate trophoblast tie-2 to promote growth and migration during placental development. Am J Pathol. 2000 Jun;156(6):2185–2199. doi: 10.1016/S0002-9440(10)65089-4
[10] Geva E, Ginzinger DG, Zaloudek CJ, et al. Human placental vascular development: vasculogenic and angiogenic (branching and nonbranching) transformation is regulated by vascular endothelial growth factor-a, angiopoietin-1, and angiopoietin-2. J Clin

Endocrinol Metab. 2002 Sep;87(9):4213–4224. doi: 10.1210/jc.2002-020195

[11] Costa MA. The endocrine function of human placenta: an overview. Reprod Biomed Online. 2016 Jan;32(1):14–43. doi: 10.1016/j.rbmo.2015.10.005

[12] Cuffe JSM, Holland O, Salomon C, et al. Review: placental derived biomarkers of pregnancy disorders. Placenta. 2017 Jun;54:104–110. doi: 10.1016/j.placenta.2017.01.119

[13] Record M. Intercellular communication by exosomes in placenta: a possible role in cell fusion? Placenta. 2014 May;35(5):297–302. doi: 10.1016/j.placenta.2014.02.009

[14] Umapathy A, Chamley LW, James JL. Reconciling the distinct roles of angiogenic/anti-angiogenic factors in the placenta and maternal circulation of normal and pathological pregnancies. Angiogenesis. 2020 May 9;23(2):105–117. doi: 10.1007/s10456-019-09694-w

[15] Lyall F, Robson SC, Bulmer JN. Spiral artery remodeling and trophoblast invasion in preeclampsia and fetal growth restriction. Hypertension. 2013 Dec;62(6):1046–1054. doi: 10.1161/HYPERTENSIONAHA.113.01892

[16] Staff AC. The two-stage placental model of preeclampsia: an update. J Reprod Immunol. 2019 Sep;134–135:1–10. doi: 10.1016/j.jri.2019.07.004

[17] Tateishi A, Ohira S, Yamamoto Y, et al. Histopathological findings of pregnancy-induced hypertension: histopathology of early-onset type reflects two-stage disorder theory. Virchows Arch. 2018 Apr 9;472(4):635–642. doi: 10.1007/s00428-018-2315-3

[18] Gerretsen G, Huisjes HJ, Elema JD. Morphological changes of the spiral arteries in the placentae bed in relation to pre-eclampsia and fetal growth retardation. BJOG An Int J Obstet Gynaecol. 1981 Sep 23;88(9):876–881. doi: 10.1111/j.1471-0528.1981.tb02222.x

[19] Burton GJ, Redman CW, Roberts JM, et al. Pre-eclampsia: pathophysiology and clinical implications. BMJ. 2019 Jul 15:l2381. doi: 10.1136/bmj.l2381

[20] Rana S, Lemoine E, Granger JP, et al. Preeclampsia. Circ Res. 2019 Mar 29;124(7):1094–1112. doi: 10.1161/CIRCRESAHA.118.313276

[21] Redman CWG, Staff AC, Roberts JM. Syncytiotrophoblast stress in preeclampsia: the convergence point for multiple pathways. Am J Obstet Gynecol. 2022 Feb;226(2):S907–27. doi: 10.1016/j.ajog.2020.09.047

[22] Redman CWG, Staff AC. Preeclampsia, biomarkers, syncytiotrophoblast stress, and placental capacity. Am J Obstet Gynecol. 2015 Oct;213(4):S9.e1–SS9.e4. doi: 10.1016/j.ajog.2015.08.003

[23] Burton GJ, Woods AW, Jauniaux E, et al. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta. 2009 Jun;30(6):473–482. doi: 10.1016/j.placenta.2009.02.009

[24] Holland O, Dekker Nitert M, Gallo LA, et al. Review: placental mitochondrial function and structure in gestational disorders. Placenta. 2017 Jun;54:2–9. doi: 10.1016/j.placenta.2016.12.012

[25] Hubel CA. Oxidative stress in the pathogenesis of preeclampsia. Proc Soc Exp Biol Med. 1999 Dec;222(3):222–235. doi: 10.1046/j.1525-1373.1999.d01-139.x

[26] Myatt L, Cui X. Oxidative stress in the placenta. Histochem Cell Biol. 2004 Oct 10;122(4):369–382. doi: 10.1007/s00418-004-0677-x

[27] 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 Mar 19;22(6):3132. doi: 10.3390/ijms22063132

[28] Tannetta D, Masliukaite I, Vatish M, et al. Update of syncytiotrophoblast derived extracellular vesicles in normal pregnancy and preeclampsia. J Reprod Immunol. 2017 Feb;119:98–106. doi: 10.1016/j.jri.2016.08.008

[29] Kroll J, Waltenberger J. VEGF-A induces expression of eNOS and iNOS in endothelial cells via VEGF receptor-2 (KDR). Biochem Biophys Res Commun. 1998 Nov;252(3):743–746. doi: 10.1006/bbrc.1998.9719

[30] Erlebacher A. Mechanisms of T cell tolerance towards the allogeneic fetus. Nat Rev Immunol. 2013 Jan 14;13(1):23–33. doi: 10.1038/nri3361

[31] Koch CA, Platt JL. Natural mechanisms for evading graft rejection: the fetus as an allograft. Springer Semin Immunopathol. 2003 Sep 1;25(2):95–117. doi: 10.1007/s00281-003-0136-0

[32] Rowe JH, Ertelt JM, Xin L, et al. Pregnancy imprints regulatory memory that sustains anergy to fetal antigen. Nature. 2012 Oct 26;490(7418):102–106. doi: 10.1038/nature11462

[33] Benzon S, Zekić Tomaš S, Benzon Z, et al. Involvement of T lymphocytes in the placentae with villitis of unknown etiology from pregnancies complicated with preeclampsia. J Matern Neonatal Med. 2016 Apr 2;29(7):1055–1060. doi: 10.3109/14767058.2015.1032239

[34] Cornelius DC. Preeclampsia: from inflammation to immunoregulation. Clin Med Insights Blood Disord. 2018 Jan 1;11:1179545X1775232. doi: 10.1177/1179545X17752325

[35] Labarrere C, Althabe O. Chronic villitis of unknown etiology and maternal arterial lesions in preeclamptic pregnancies. Eur J Obstet Gynecol Reprod Biol. 1985 Jul;20(1):1–11. doi: 10.1016/0028-2243(85)90077-2

[36] Faas MM, de Vos P. Uterine NK cells and macrophages in pregnancy. Placenta. 2017 Aug;56:44–52. doi: 10.1016/j.placenta.2017.03.001

[37] Papúchová H, Meissner TB, Li Q, et al. The dual role of HLA-C in tolerance and immunity at the maternal-fetal interface. Front Immunol. 2019 Dec 9;10. doi: 10.3389/fimmu.2019.02730

[38] Parham P, Moffett A. Variable NK cell receptors and their MHC class I ligands in immunity, reproduction and human evolution. Nat Rev Immunol. 2013 Feb 21;13(2):133–144. doi: 10.1038/nri3370

[39] Ribeiro VR, Romao-Veiga M, Romagnoli GG, et al. Association between cytokine profile and transcription factors produced by T-cell subsets in early- and late-onset pre-eclampsia. Immunol. 2017 Sep 19;152(1):163–173. doi: 10.1111/imm.12757

[40] Murata H, Tanaka S, Okada H. The regulators of human endometrial stromal cell decidualization. Biomolecul. 2022 Sep 10;12(9):1275. doi: 10.3390/biom12091275

[41] Campbell KA, Colacino JA, Puttabyatappa M, et al. Placental cell type deconvolution reveals that cell proportions drive preeclampsia gene expression differences. Commun Biol. 2023 Mar 13;6(1):264. doi: 10.1038/s42003-023-04623-6

[42] Elizabeth JH, Bordoni B. Embryology, placenta. StatPearls [Internet]. 2023. PMID: 31869098. May 1.

[43] Knöfler M, Haider S, Saleh L, et al. Human placenta and trophoblast development: key molecular mechanisms and model systems. Cell Mol Life Sci. 2019 Sep 3;76(18):3479–3496. doi: 10.1007/s00018-019-03104-6

[44] Sferruzzi-Perri AN, Higgins JS, Vaughan OR, et al. Placental mitochondria adapt developmentally and in response to hypoxia to support fetal growth. Proc Natl Acad Sci USA. 2019 Jan 29;116(5):1621–1626. doi: 10.1073/pnas.1816056116

[45] Yang Y, Xu P, Zhu F, et al. The potent antioxidant MitoQ protects against preeclampsia during late gestation but increases the risk of preeclampsia when administered in early pregnancy. Antioxid Redox Signal. 2021 Jan 10;34(2):118–136. doi: 10.1089/ars.2019.7891

[46] Lu M, Sferruzzi-Perri AN. Placental mitochondrial function in response to gestational exposures. Placenta. 2021 Jan;104:124–137. doi: 10.1016/j.placenta.2020.11.012

[47] Olszewska A, Szewczyk A. Mitochondria as a pharmacological target: magnum overview. IUBMB Life. 2013 Mar 25;65(3):273–281. doi: 10.1002/iub.1147

[48] McClements L, Richards C, Patel N, et al. Impact of reduced uterine perfusion pressure model of preeclampsia on metabolism of placenta, maternal and fetal hearts. Sci Rep. 2022 Jan 21;12(1):1111. doi: 10.1038/s41598-022-05120-2

[49] Rodríguez-Cano AM, Calzada-Mendoza CC, Estrada-Gutierrez G, et al. Nutrients, Mitochondrial Function, And Perinatal Health. Nutr. 2020 Jul 21;12(7):2166. doi: 10.3390/nu12072166

[50] Patel MS, Nemeria NS, Furey W, et al. The pyruvate dehydrogenase complexes: structure-based function and regulation. J Biol Chem. 2014 Jun;289(24):16615–16623. doi: 10.1074/jbc.R114.563148

[51] Houten SM, Wanders RJA. A general introduction to the biochemistry of mitochondrial fatty acid β-oxidation. J Of Inher Metab Disea. 2010 Oct 2;33(5):469–477. doi: 10.1007/s10545-010-9061-2

[52] Kuszak AJ, Espey MG, Falk MJ, et al. Nutritional interventions for mitochondrial OXPHOS deficiencies: mechanisms and model systems. Annu Rev Pathol Mech Dis. 2018 Jan 24;13(1):163–191. doi: 10.1146/annurev-pathol-020117-043644

[53] Ramsey PS, Biggio JR. Carnitine palmitoyltransferase deficiency in pregnancy. J Matern Neonatal Med. 2005 Nov 1;18(5):357–359. doi: 10.1080/14767050500275861

[54] Vangrieken P, Al-Nasiry S, Bast A, et al. Placental mitochondrial abnormalities in preeclampsia. Reprod Sci. 2021 Aug 1;28(8):2186–2199. doi: 10.1007/s43032-021-00464-y

[55] Fisher JJ, Bartho LA, Perkins AV, et al. Placental mitochondria and reactive oxygen species in the physiology and pathophysiology of pregnancy. Clin Exp Pharma Physio. 2020 Jan 15;47(1):176–184. doi: 10.1111/1440-1681.13172

[56] Marín R, Chiarello DI, Abad C, et al. Oxidative stress and mitochondrial dysfunction in early-onset and late-onset preeclampsia. Biochim Biophys Acta - Mol Basis Dis. 2020 Dec;1866(12):165961. doi: 10.1016/j.bbadis.2020.165961

[57] Mammucari C, Rizzuto R. Signaling pathways in mitochondrial dysfunction and aging. Mech Ageing Dev. 2010 Jul;131(7–8):536–543. doi: 10.1016/j.mad.2010.07.003

[58] Cowell W, Brunst K, Colicino E, et al. Placental mitochondrial DNA mutational load and perinatal outcomes: findings from a multi-ethnic pregnancy cohort. Mitochondrion. 2021 Jul;59:267–275. doi: 10.1016/j.mito.2021.06.006

[59] Díaz M, Aragonés G, Sánchez-Infantes D, et al. Mitochondrial DNA in placenta: associations with fetal growth and superoxide dismutase activity. Horm Res Paediatr. 2014;82(5):303–309. doi: 10.1159/000366079

[60] Mandò C, De Palma C, Stampalija T, et al. Placental mitochondrial content and function in intrauterine growth restriction and preeclampsia. Am J Physiol Metab. 2014 Feb 15;306(4):E404–13.

[61] Naha R, Anees A, Chakrabarty S, et al. Placental mitochondrial DNA mutations and copy numbers in intrauterine growth restricted (IUGR) pregnancy. Mitochondrion. 2020 Nov;55:85–94. doi: 10.1016/j.mito.2020.08.008

[62] Sobrevia L, Valero P, Grismaldo A, et al. Mitochondrial dysfunction in the fetoplacental unit in gestational diabetes mellitus. Biochim Biophys Acta - Mol Basis Dis. 2020 Dec;1866(12):165948. doi: 10.1016/j.bbadis.2020.165948

[63] Fisher JJ, Vanderpeet CL, Bartho LA, et al. Mitochondrial dysfunction in placental trophoblast cells experiencing gestational diabetes mellitus. J Physiol. 2021 Feb 15;599(4):1291–1305. doi: 10.1113/JP280593

[64] Aouache R, Biquard L, Vaiman D, et al. Oxidative stress in preeclampsia and placental diseases. Int J Mol Sci. 2018 May 17;19(5):1496. doi: 10.3390/ijms19051496

[65] Merry TL, Chan A, Woodhead JST, et al. Mitochondrial-derived peptides in energy metabolism. Am J Physiol Metab. 2020 Oct 1;319(4):E659–66. doi: 10.1152/ajpendo.00249.2020

[66] Miller B, Kim SJ, Kumagai H, et al. Mitochondria-derived peptides in aging and healthspan. J Clin Invest. 2022 May 2;132(9). doi: 10.1172/JCI158449

[67] Ruiz D, Santibañez M, Lavín BA, et al. Evolution of mitochondrially derived peptides humanin and MOTSc, and changes in insulin sensitivity during early gestation in women with and without gestational diabetes. J Clin Med. 2022 May 26;11(11):3003. doi: 10.3390/jcm11113003

[68] Jahan F, Vasam G, Green AE, et al. Placental mitochondrial function and dysfunction in preeclampsia. Int J Mol Sci. 2023 Feb 20;24(4):4177. doi: 10.3390/ijms24044177

[69] Jiang Y, Wang X. Comparative mitochondrial proteomics: perspective in human diseases. J Hematol Oncol. 2012 Dec 18;5(1):11. doi: 10.1186/1756-8722-5-11

[70] Shanmugalingam R, Barrett HL, Beech A, et al. A summary of the 2023 society of obstetric medicine of Australia and New Zealand (SOMANZ) hypertension in pregnancy guideline. Med J Aust. 2024 Jun 17;220(11):582–591. doi: 10.5694/mja2.52312

[71] Magee LA, Pels A, Helewa M, et al. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens An Int J Women's Cardiovasc Heal. 2014 Apr;4(2):105–145. doi: 10.1016/j.preghy.2014.01.003

[72] Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. Am J Obstet Gynecol. 2013 Dec;209(6):.e544.1–.e544.12. doi: 10.1016/j.ajog.2013.08.019

[73] Phipps E, Prasanna D, Brima W, et al. Preeclampsia: updates in pathogenesis, definitions, and guidelines. Clin J Am Soc Nephrol. 2016 Jun;11(6):1102–1113. doi: 10.2215/CJN.12081115

[74] Poon LC, Magee LA, Verlohren S, et al. A literature review and best practice advice for second and third trimester risk stratification, monitoring, and management of pre-eclampsia. Int J Gynecol Obstet. 2021 Jul 29;154(S1):3–31. doi: 10.1002/ijgo.13763

[75] Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Heal. 2014 Jun;2(6):e323–33. doi: 10.1016/S2214-109X(14)70227-X

[76] Lazar S, Rayner B, Lopez Campos G, et al. Mechanisms of heart failure with preserved ejection fraction in the presence of diabetes mellitus. Transl Metab Syndr Res. 2020;3:1–5. doi: 10.1016/j.tmsr.2020.04.002

[77] Huppertz B. Placental origins of preeclampsia. Hypertension. 2008 Apr;51(4):970–975. doi: 10.1161/HYPERTENSIONAHA.107.107607

[78] Palei AC, Spradley FT, Warrington JP, et al. Pathophysiology of hypertension in pre-eclampsia: a lesson in integrative physiology. Acta Physiol. 2013 Jul 7;208(3):224–233. doi: 10.1111/apha.12106

[79] Romero R, Chaiworapongsa T. Preeclampsia: a link between trophoblast dysregulation and an antiangiogenic state. J Clin Invest. 2013 Jul 1;123(7):2775–2777. doi: 10.1172/JCI70431

[80] Ives CW, Sinkey R, Rajapreyar I, et al. Preeclampsia—pathophysiology and clinical presentations. J Am Coll Cardiol. 2020 Oct;76(14):1690–1702.

[81] McCarthy C, Kenny LC. Therapeutically targeting mitochondrial redox signalling alleviates endothelial dysfunction in preeclampsia. Sci Rep. 2016 Sep 8;6(1):32683. doi: 10.1038/srep32683

[82] Kobayashi H, Yoshimoto C, Matsubara S, et al. An integral role of mitochondrial function in the pathophysiology of preeclampsia. Mol Biol Rep. 2024 Dec 23;51(1):330. doi: 10.1007/s11033-024-09285-z

[83] Hu XQ, Zhang L. Mitochondrial dysfunction in the pathogenesis of preeclampsia. Curr Hypertens Rep. 2022 Jun 7;24(6):157–172. doi: 10.1007/s11906-022-01184-7

[84] Poon LC, Shennan A, Hyett JA, et al. The international federation of gynecology and obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. Int J Gynecol Obstet. 2019 May 20;145(S1):1–33. doi: 10.1002/ijgo.12802

[85] Fox R, Kitt J, Leeson P, et al. Preeclampsia: risk factors, diagnosis, management, and the cardiovascular impact on the offspring. J Clin Med. 2019 Oct 4;8(10):1625. doi: 10.3390/jcm8101625

[86] Maynard SE, Karumanchi SA. Angiogenic factors and preeclampsia. Semin Nephrol. 2011 Jan;31(1):33–46. doi: 10.1016/j.semnephrol.2010.10.004

[87] McClements L, Annett S, Yakkundi A, et al. FKBPL and its peptide derivatives inhibit endocrine therapy resistant cancer stem cells and breast cancer metastasis by down-regulating DLL4 and Notch4. BMC Cancer. 2019 Dec 11;19(1):351. doi: 10.1186/s12885-019-5500-0

[88] McClements L, Yakkundi A, Papaspyropoulos A, et al. Targeting treatment-resistant breast cancer stem cells with FKBPL and Its peptide derivative, AD-01, via the CD44 pathway. Clin Cancer Res. 2013 Jul 15;19(14):3881–3893. doi: 10.1158/1078-0432.CCR-13-0595

[89] Yakkundi A, Bennett R, Hernández-Negrete I, et al. FKBPL is a critical antiangiogenic regulator of developmental and pathological angiogenesis. Arterioscler Thromb Vasc Biol. 2015 Apr;35(4):845–854. doi: 10.1161/ATVBAHA.114.304539

[90] Valentine A, O'Rourke M, Yakkundi A, et al. FKBPL and peptide derivatives: novel biological agents that inhibit angiogenesis by a CD44-dependent mechanism. Clin Cancer Res. 2011 Mar 1;17(5):1044–1056. doi: 10.1158/1078-0432.CCR-10-2241

[91] Todd N, McNally R, Alqudah A, et al. Role of a novel angiogenesis FKBPL-CD44 pathway in preeclampsia risk stratification and mesenchymal stem cell treatment. J Clin Endocrinol Metab. 2021 Jan 1;106(1):26–41. doi: 10.1210/clinem/dgaa403

[92] Masoumeh Ghorbanpour S, Wen S, Kaitu'u-Lino TJ, et al. Quantitative point of care tests for timely diagnosis of early-onset preeclampsia with high sensitivity and specificity. Angew Chem Int Ed. 2023 Jun 26;62(26). doi: 10.1002/anie.202301193

[93] Ghorbanpour SM, Richards C, Pienaar D, et al. A placenta-on-a-chip model to determine the regulation of FKBPL and galectin-3 in preeclampsia. Cell Mol Life Sci. 2023 Feb 18;80(2):44. doi: 10.1007/s00018-022-04648-w

[94] McNally R, Alqudah A, McErlean EM, et al. Non-viral gene delivery utilizing RALA modulates sFlt-1 secretion, important for preeclampsia. Nanomed (Lond). 2021 Sep 26;16(22):1999–2012. doi: 10.2217/nnm-2021-0180

[95] Wang A, Rana S, Karumanchi SA. Preeclampsia: the role of angiogenic factors in its pathogenesis. Physiol. 2009 Jun;24(3):147–158. doi: 10.1152/physiol.00043.2008

[96] Chiarello DI, Abad C, Rojas D, et al. Oxidative stress: normal pregnancy versus preeclampsia. Biochim Biophys Acta - Mol Basis Dis. 2020 Feb;1866(2):165354. doi: 10.1016/j.bbadis.2018.12.005

[97] Roberts JM. Pathophysiology of ischemic placental disease. Semin Perinatol. 2014 Apr;38(3):139–145. doi: 10.1053/j.semperi.2014.03.005

[98] Cerdeira AS, Karumanchi SA. Angiogenic factors in preeclampsia and related disorders. Cold Spring Harb Perspect Med. 2012 Nov 1;2(11):a006585–a006585. doi: 10.1101/cshperspect.a006585

[99] Martínez-Varea A, Pellicer B, Perales-Marín A, et al. Relationship between maternal immunological response during pregnancy and onset of preeclampsia. J Immunol Res. 2014;2014:1–15. doi: 10.1155/2014/210241

[100] Geldenhuys J, Rossouw TM, Lombaard HA, et al. Disruption in the regulation of immune responses in the placental subtype of preeclampsia. Front Immunol. 2018 Jul 20;9. doi: 10.3389/fimmu.2018.01659

[101] Phoswa WN, Khaliq OP, Jakovljevic V. The role of oxidative stress in hypertensive disorders of pregnancy (preeclampsia, gestational hypertension) and metabolic disorder of pregnancy (gestational diabetes mellitus). Oxid Med Cell Longev. 2021 May 31;2021 (1):1–10. doi: 10.1155/2021/5581570

[102] Afrose D, Chen H, Ranashinghe A, et al. The diagnostic potential of oxidative stress biomarkers for preeclampsia: systematic review and meta-analysis. Biol Sex Differ. 2022 Jun 4;13(1):26. doi: 10.1186/s13293-022-00436-0

[103] Maynard S, Epstein FH, Karumanchi SA. Preeclampsia and angiogenic imbalance. Annu Rev Med. 2008 Feb 1;59(1):61–78. doi: 10.1146/annurev.med.59.110106.214058

[104] Lamarca B. Endothelial dysfunction. An important mediator in the pathophysiology of hypertension during pre-eclampsia. Minerva Ginecol. 2012 Aug;64 (4):309–320.

[105] Leal CRV, Costa LB, Ferreira GC, et al. Renin-angiotensin system in normal pregnancy and in preeclampsia: a comprehensive review. Pregnancy Hypertens. 2022 Jun;28:15–20. doi: 10.1016/j.preghy.2022.01.011

[106] MacDonald TM, Walker SP, Hannan NJ, et al. Clinical tools and biomarkers to predict preeclampsia. EBioMedicine. 2022 Jan;75:103780. doi: 10.1016/j.ebiom.2021.103780

[107] Sroka D, Verlohren S. Short term prediction of preeclampsia. Matern Med. 2021 Apr;3(2):107–115. doi: 10.1097/FM9.0000000000000097

[108] Al-Rubaie ZTA, Hudson HM, Jenkins G, et al. Prediction of pre-eclampsia in nulliparous women using routinely collected maternal characteristics: a model development and validation study. BMC Pregnancy Childbirth. 2020 Dec 6;20(1):23. doi: 10.1186/s12884-019-2712-x

[109] R K. Socio-demographic and other risk factors of pre eclampsia at a tertiary care hospital, Karnataka: case control study. J Clin DIAGNOSTIC Res. 20 Sep 2014;8(9): JC01–4. doi:10.7860/JCDR/2014/10255.4802.

[110] Mojgan Barati M, Shahbazian N, Ahmadi L. Diagnostic evaluation of uterine artery Doppler sonography for the prediction of adverse pregnancy outcomes. J Res Med Sci. 2014 Jun;19(6):515–519.

[111] Chen H, Aneman I, Nikolic V, et al. Maternal plasma proteome profiling of biomarkers and pathogenic mechanisms of early-onset and late-onset preeclampsia. Sci Rep. 2022 Nov 9;12(1):19099. doi: 10.1038/s41598-022-20658-x

[112] Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia. Circulation. 2013 Nov 5;128 (19):2121–2131. doi: 10.1161/CIRCULATIONAHA.113.003215

[113] Zeisler H, Llurba E, Chantraine F, et al. Predictive value of the sFlt-1: PlGF ratio in women with suspected preeclampsia. N Engl J Med. 2016 Jan 7;374 (1):13–22. doi: 10.1056/NEJMoa1414838

[114] Budak E, Madazli R, Aksu M, et al. Vascular cell adhesion molecule-1 (VCAM-1) and leukocyte activation in pre-eclampsia and eclampsia. Int J Gynecol Obstet. 1998 Nov 21;63(2):115–121. doi: 10.1016/S0020-7292(98)00138-6

[115] Gencheva D, Nikolov F, Uchikova E, et al. Interleukin-6 and its correlations with maternal characteristics and echocardiographic parameters in pre-eclampsia, gestational hypertension and normotensive pregnancy. Cardiovasc J Afr. 2022 Apr 30;33 (2):27–35. doi: 10.5830/CVJA-2021-040

[116] Mihu D, Razvan C, Malutan A, et al. Evaluation of maternal systemic inflammatory response in preeclampsia. Taiwan J Obstet Gynecol. 2015 Apr;54 (2):160–166. doi: 10.1016/j.tjog.2014.03.006

[117] Adenekan MA, Oluwole AA, Olorunfemi G, et al. Maternal tumour necrosis factor-alpha levels in pre-eclamptic pregnancies in Lagos, South-West Nigeria. Pregnancy Hypertens. 2022 Dec;30:198–203. doi: 10.1016/j.preghy.2022.10.011

[118] Yakkundi A, McCallum L, O'Kane A, et al. The anti-migratory effects of FKBPL and Its peptide derivative, AD-01: regulation of CD44 and the cytoskeletal pathway. PLoS One. 2013 Feb 15;8(2):e55075. doi: 10.1371/journal.pone.0055075

[119] Annett SL, Spence S, Garciarena C, et al. The immunophilin protein FKBPL and its peptide derivatives are novel regulators of vascular integrity and inflammation via nf-κB signaling. SSRN Electron J. 2021. doi: 10.2139/ssrn.3858052

[120] Richards C, Sesperez K, Chhor M, et al. Characterisation of cardiac health in the reduced uterine perfusion pressure model and a 3D cardiac spheroid model, of preeclampsia. Biol Sex Differ. 2021 Dec 20;12(1):31. doi: 10.1186/s13293-021-00376-1

[121] Januszewski AS, Watson CJ, O'Neill V, et al. FKBPL is associated with metabolic parameters and is a novel determinant of cardiovascular disease. Sci Rep. 2020 Dec 10;10(1):21655. doi: 10.1038/s41598-020-78676-6

[122] Chhor M, Chen H, Jerotić D, et al. FK506-binding protein like (FKBPL) has an important role in heart failure with preserved ejection fraction pathogenesis with potential diagnostic utility. Biomolecules. 2023 Feb 18;13(2):395. doi: 10.3390/biom13020395

[123] Dimitriadis E, Rolnik DL, Zhou W, et al. Pre-eclampsia. Nat Rev Dis Prim. 2023 Feb 16;9(1):8. doi: 10.1038/s41572-023-00417-6

[124] Wright D, Syngelaki A, Akolekar R, et al. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. Am J Obstet Gynecol. 2015 Jul;213(1):.e62.1–.e62.10. doi: 10.1016/j.ajog.2015.02.018

[125] Berzan E, Doyle R, Brown CM. Treatment of preeclampsia: current approach and future perspectives. Curr Hypertens Rep. 2014 Sep 19;16(9):473. doi: 10.1007/s11906-014-0473-5

[126] Paulsen CP, Bandak E, Edemann-Callesen H, et al. The effects of exercise during pregnancy on gestational diabetes mellitus, preeclampsia, and spontaneous abortion among healthy women—a systematic review and meta-analysis. Int J Environ Res Public Health. 2023 Jun 6;20(12):6069. doi: 10.3390/ijerph20126069

[127] Poniedziałek-Czajkowska E, Mierzyński R, Leszczyńska-Gorzelak B. Preeclampsia and obesity—the preventive role of exercise. Int J Environ Res Public Health. 2023 Jan 10;20(2):1267. doi: 10.3390/ijerph20021267

[128] Roberts JM, Bodnar LM, Patrick TE, et al. The role of obesity in preeclampsia. Pregnancy Hypertens An Int J Women's Cardiovasc Heal. 2011 Jan;1(1):6–16. doi: 10.1016/j.preghy.2010.10.013

[129] Askie LM, Duley L, Henderson-Smart DJ, et al. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet. 2007 May;369(9575):1791–1798. doi: 10.1016/S0140-6736(07)60712-0

[130] Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med. 2017 Aug 17;377(7):613–622. doi: 10.1056/NEJMoa1704559

[131] Akbar MIA, Azis MA, Riu DS, et al. INOVASIA study: a multicenter randomized clinical trial of pravastatin to prevent preeclampsia in high-risk patients. Am J Perinatol. 2022 Mar 15;41(9):1203–1211. doi: 10.1055/a-1798-1925

[132] Brownfoot FC, Tong S, Hannan NJ, et al. Effects of pravastatin on human placenta, endothelium, and women with severe preeclampsia. Hypertension. 2015 Sep;66(3):687–697. doi: 10.1161/HYPERTENSIONAHA.115.05445

[133] Cluver CA, Hiscock R, Decloedt EH, et al. Use of metformin to prolong gestation in preterm pre-eclampsia: randomised, double blind, placebo controlled trial. BMJ. 2021 Sep 22:n2103. doi: 10.1136/bmj.n2103

[134] Bodnar LM, Catov JM, Simhan HN, et al. Maternal vitamin D deficiency increases the risk of preeclampsia. The J Clin Endocrinol & Metab. 2007 Sep 1;92(9):3517–3522. doi: 10.1210/jc.2007-0718

[135] Hofmeyr GJ, Lawrie TA, Atallah ÁN, et al. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2018 Oct 1;2018(10). doi: 10.1002/14651858.CD001059.pub5

[136] Bullo M, Tschumi S, Bucher BS, et al. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists. Hypertension. 2012 Aug;60(2):444–450. doi: 10.1161/HYPERTENSIONAHA.112.196352

[137] Easterling T, Mundle S, Bracken H, et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. Lancet. 2019 Sep;394(10203):1011–1021. doi: 10.1016/S0140-6736(19)31282-6

[138] Roberts D, Brown J, Medley N, et al. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017 Mar 21. doi: 10.1002/14651858.CD004454.pub3

[139] Smith JM, Lowe RF, Fullerton J, et al. An integrative review of the side effects related to the use of magnesium sulfate for pre-eclampsia and eclampsia management. BMC Pregnancy Childbirth. 2013 Dec 5;13(1):34. doi: 10.1186/1471-2393-13-34

[140] George EM, Arany M, Cockrell K, et al. Induction of heme oxygenase-1 attenuates sFlt-1-induced hypertension in pregnant rats. Am J Physiol Integr Comp Physiol. 2011 Nov;301(5):R1495–500. doi: 10.1152/ajpregu.00325.2011

[141] Meher S, Duley L. Nitric oxide for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2007 Apr 18;2010(2). doi: 10.1002/14651858.CD006490

[142] Wang Z, Wang P, Liu H, et al. Maternal adiposity as an independent risk factor for pre-eclampsia: a meta-analysis of prospective cohort studies. Obes Rev. 2013 Jun 26;14(6):508–521. doi: 10.1111/obr.12025

[143] Chang CW, Wakeland AK, Parast MM. Trophoblast lineage specification, differentiation and their regulation by oxygen tension. J Endocrinol. 2018 Jan;236(1):R43–56. doi: 10.1530/JOE-17-0402

[144] Kalyanaraman B. Teaching the basics of redox biology to medical and graduate students: oxidants, antioxidants and disease mechanisms. Redox Biol. 2013;1(1):244–257. doi: 10.1016/j.redox.2013.01.014

[145] Kornacki J, Olejniczak O, Sibiak R, et al. Pathophysiology of pre-eclampsia—two theories of the development of the disease. Int J Mol Sci. 2023 Dec 25;25(1):307. doi: 10.3390/ijms25010307

[146] Lappas M, Mittion A, Permezel M. In response to oxidative stress, the expression of inflammatory cytokines and antioxidant enzymes are impaired in placenta, but not adipose tissue, of women with gestational diabetes. J Endocrinol. 2010 Jan;204(1):75–84. doi: 10.1677/JOE-09-0321

[147] Matsubara K, Matsubara Y, Hyodo S, et al. Role of nitric oxide and reactive oxygen species in the pathogenesis of preeclampsia. J Obstet Gynaecol Res. 2010 Apr 25;36(2):239–247. doi: 10.1111/j.1447-0756.2009.01128.x

[148] Han C, Huang P, Lyu M, et al. Oxidative stress and preeclampsia-associated prothrombotic state. Antioxidants. 2020 Nov 17;9(11):1139. doi: 10.3390/antiox9111139

[149] Myatt L, Webster RP. Vascular biology of preeclampsia. J Thromb Haemost. 2009 Mar;7(3):375–384. doi: 10.1111/j.1538-7836.2008.03259.x

[150] SÃ¡nchez-Aranguren LC, Prada CE, RiaÃ±o-Medina CE, et al. Endothelial dysfunction and preeclampsia: role of oxidative stress. Front Physiol. 2014 Oct 10;5. doi: 10.3389/fphys.2014.00372

[151] Shevtsova A, Gordiienko I, Tkachenko V, et al. Ischemia-modified albumin: origins and clinical implications. Dis Markers. 2021 Jul 19;2021:1–18. doi: 10.1155/2021/9945424

[152] Khaliq OP, Konoshita T, Moodley J, et al. The role of uric acid in preeclampsia: Is uric acid a causative factor or a sign of preeclampsia? Curr Hypertens Rep. 2018 Sep 10;20(9):80. doi: 10.1007/s11906-018-0878-7

[153] Burton GJ, Yung HW, Cindrova-Davies T, et al. Placental endoplasmic reticulum stress and oxidative stress in the pathophysiology of unexplained intrauterine growth restriction and early onset preeclampsia. Placenta. 2009 Mar;30:43–48. doi: 10.1016/j.placenta.2008.11.003

[154] Saito S, Nakashima A. A review of the mechanism for poor placentation in early-onset preeclampsia: the role of autophagy in trophoblast invasion and vascular remodeling. J Reprod Immunol. 2014 Mar;101–102:80–88. doi: 10.1016/j.jri.2013.06.002

[155] Gupta S, Agarwal A, Sharma RK. The role of placental oxidative stress and lipid peroxidation in preeclampsia. Obstet Gynecol Surv. 2005 Dec;60(12):807–816. doi: 10.1097/01.ogx.0000193879.79268.59

[156] Belo L, Santossilva A, Caslake M, et al. Oxidized-ldl levels in normal and pre-eclamptic pregnancies: contribution of LDL particle size. Atherosclerosis. 2005 Nov;183(1):185–186. doi: 10.1016/j.atherosclerosis.2005.06.028

[157] Lian R, Zhu BS, Zeng X. An update review of the pathogenesis hypothesis in Preeclampsia. Clin Exp Obstet Gynecol. 2022 Jul 22;49(8):170. doi: 10.31083/j.ceog4908170

[158] Beauséjour A, Bibeau K, Lavoie JC, et al. Placental oxidative stress in a rat Model of preeclampsia. Placenta. 2007 Jan;28(1):52–58. doi: 10.1016/j.placenta.2005.12.003

[159] Yan JQ, Huang F, Hao F, et al. Oxidative stress in the rostral ventrolateral medulla contributes to cardiovascular regulation in preeclampsia. Front Physiol. 2017 Oct 4;8. doi: 10.3389/fphys.2017.00772

[160] de Alwis N, Binder NK, Beard S, et al. Novel approaches to combat preeclampsia: from new drugs to innovative delivery. Placenta. 2020 Dec;102:10–16. doi: 10.1016/j.placenta.2020.08.022

[161] Guigas B, Detaille D, Chauvin C, et al. Metformin inhibits mitochondrial permeability transition and cell death: a pharmacological *in vitro* study. Biochem J. 2004 Sep 15;382(3):877–884. doi: 10.1042/BJ20040885

[162] Detaille D, Guigas B, Chauvin C, et al. Metformin prevents high-glucose–Induced endothelial cell death through a mitochondrial permeability transition-dependent process. Diabetes. 2005 Jul 1;54(7):2179–2187. doi: 10.2337/diabetes.54.7.2179

[163] Nafisa A, Gray SG, Cao Y, et al. Endothelial function and dysfunction: impact of metformin. Pharmacol Ther. 2018 Dec;192:150–162. doi: 10.1016/j.pharmthera.2018.07.007

[164] Seli E. Should patients with polycystic ovarian syndrome be treated with metformin? Hum Reprod. 2002 Sep 1;17(9):2230–2236. doi: 10.1093/humrep/17.9.2230

[165] Tertti K, Laine K, Ekblad U, et al. The degree of fetal metformin exposure does not influence fetal outcome in gestational diabetes mellitus. Acta Diabetol. 2014 Oct 16;51(5):731–738. doi: 10.1007/s00592-014-0570-6

[166] Ma'ayeh M, Rood KM, Kniss D, et al. Novel interventions for the prevention of preeclampsia. Curr Hypertens Rep. 2020 Feb 12;22(2):17. doi: 10.1007/s11906-020-1026-8

[167] Alqudah A, McKinley MC, McNally R, et al. Risk of pre-eclampsia in women taking metformin: a systematic review and meta-analysis. Diabet Med. 2018 Feb 14;35(2):160–172. doi: 10.1111/dme.13523

[168] Cluver C, Walker SP, Mol BW, et al. A double blind, randomised, placebo-controlled trial to evaluate the efficacy of metformin to treat preterm pre-eclampsia (PI2 trial): study protocol. BMJ Open. 2019 Apr 24;9(4):e025809. doi: 10.1136/bmjopen-2018-025809

[169] Feig DS, Donovan LE, Zinman B, et al. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2020 Oct;8(10):834–844. doi: 10.1016/S2213-8587(20)30310-7

[170] Kaitu'u-Lino TJ, Brownfoot FC, Beard S, et al. Combining metformin and esomeprazole is additive in reducing sFlt-1 secretion and decreasing endothelial dysfunction – implications for treating preeclampsia. PLoS One. 2018 Feb 21;13(2):e0188845. doi: 10.1371/journal.pone.0188845

[171] NCT03717701. Metformin and esomeprazole in treatment of early onset preeclampsia 2018 Oct 22. ClinicalTrials.gov.

[172] NCT03570632. Metformin for preeclampsia prevention in pregnant women with type 1 diabetes mellitus. ClinicalTrials.gov. 2024 Dec 14.

[173] Bujold E, Roberge S, Lacasse Y, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy. Obstet Gynecol. 2010 Aug;116(2):402–414. doi: 10.1097/AOG.0b013e3181e9322a

[174] Antiplatelet agents for prevention of pre-eclampsia and its consequences: a systematic review and individual patient data meta-analysis. BMC Pregnancy Childbirth. 2005 Dec 18;5(1):7. doi: 10.1186/1471-2393-5-7

[175] Duley L, Meher S, Hunter KE, et al. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2019 Oct 30;2019(10). doi: 10.1002/14651858.CD004659.pub3

[176] Duley L, Henderson-Smart DJ, Meher S, et al. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2007 Apr 18. doi: 10.1002/14651858.CD004659.pub2

[177] Roberge S, Odibo AO, Bujold E. Aspirin for the prevention of preeclampsia and intrauterine growth restriction. Clin Lab Med. 2016 Jun;36(2):319–329. doi: 10.1016/j.cll.2016.01.013

[178] Panagodage S, Yong HEJ, Da Silva Costa F, et al. Low-dose acetylsalicylic acid treatment modulates the production of cytokines and improves trophoblast function in an in vitro model of early-onset preeclampsia. Am J Pathol. 2016 Dec;186(12):3217–3224.

[179] Su MT, Wang CY, Tsai PY, et al. Aspirin enhances trophoblast invasion and represses soluble fms-like tyrosine kinase 1 production. J Hypertens. 2019 Dec;37(12):2461–2469. doi: 10.1097/HJH.0000000000002185

[180] Liu Z, Wang C, Pei J, et al. SIRT1: a novel protective molecule in pre-eclampsia. Int J Med Sci. 2022;19(6):993–1002.

[181] Wang P, Xi Huang C, Gao J-J, et al. Resveratrol induces SIRT1-dependent autophagy to prevent H2O2-induced oxidative stress and apoptosis in HTR8/SVneo cells. Placenta. 2020 Feb;91:11–18. doi: 10.1016/j.placenta.2020.01.002

[182] Al-Ani B. Resveratrol inhibits proteinase-activated receptor-2-induced release of soluble vascular endothelial growth factor receptor-1 from human endothelial cells. Excli J. 2013;12:598–604.

[183] Liu J, Yao L, Wang Y. Resveratrol alleviates preeclampsia-like symptoms in rats through a mechanism involving the miR-363-3p/PEDF/VEGF axis. Microvasc Res. 2023 Mar;146:104451. doi: 10.1016/j.mvr.2022.104451

[184] Poudel R, Stanley JL, Rueda-Clausen CF, et al. Effects of resveratrol in pregnancy using murine models with reduced blood supply to the uterus. PLoS One. 2013 May 8;8(5):e64401. doi: 10.1371/journal.pone.0064401

[185] Caldeira-Dias M, Montenegro MF, Bettiol H, et al. Resveratrol improves endothelial cell markers impaired by plasma incubation from women who subsequently develop preeclampsia. Hypertens Res. 2019 Aug 6;42(8):1166–1174. doi: 10.1038/s41440-019-0243-5

[186] Triche EW, Grosso LM, Belanger K, et al. Chocolate consumption in pregnancy and reduced likelihood of preeclampsia. Epidemiology. 2008 May;19(3):459–464. doi: 10.1097/EDE.0b013e31816a1d17

[187] Ding J, Kang Y, Fan Y, et al. Efficacy of resveratrol to supplement oral nifedipine treatment in pregnancy-induced preeclampsia. Endocr Connect. 2017 Nov;6(8):595–600. doi: 10.1530/EC-17-0130

[188] Biesinger S, Michaels HA, Quadros AS, et al. A combination of isolated phytochemicals and botanical extracts lowers diastolic blood pressure in a randomized controlled trial of hypertensive subjects. Eur J Clin Nutr. 2016 Jan 10;70(1):10–16. doi: 10.1038/ejcn.2015.88

[189] NCT01106170. Efficacy of provex CV supplement to reduce inflammation cytokines and blood pressure. ClinicalTrials.gov. 2010 Apr 15.

[190] Ka Atwa, Zm, Ibrahim, M, Elshaer. Role of Esomeprazole in Early Preeclampsia: A Randomized Controlled Trial Austin Journal of Obstetrics and Gynecology. Aug 6 2021;8(6):1189. doi:10.26420/austinobstetgynecol.2021.1189.

[191] Saleh L, Samantar R, Garrelds IM, et al. Low soluble fms-like tyrosine kinase-1, endoglin, and endothelin-1 levels in women with confirmed or suspected preeclampsia using proton pump inhibitors. Hypertension. 2017 Sep;70(3):594–600. doi: 10.1161/HYPERTENSIONAHA.117.09741

[192] Cluver CA, Hannan NJ, van Papendorp E, et al. Esomeprazole to treat women with preterm preeclampsia: a randomized placebo controlled trial. Am J Obstet Gynecol. 2018 Oct;219(4):.e388.1–.e388.17. doi: 10.1016/j.ajog.2018.07.019

[193] Yoshida N. Inflammation and oxidative stress in gastroesophageal reflux disease. J Clin Biochem Nutr. 2007;40(1):13–23. doi: 10.3164/jcbn.40.13

[194] Nolde M, Bahls M, Friedrich N, et al. Association of proton pump inhibitor use with endothelial function and metabolites of the nitric oxide pathway: a cross-sectional study. Pharmacother J Hum Pharmacol Drug Ther. 2021 Feb 4;41(2):198–204. doi: 10.1002/phar.2504

[195] Matok I, Levy A, Wiznitzer A, et al. The safety of fetal exposure to proton-pump inhibitors during pregnancy. Dig Dis Sci. 2012 Mar 30;57(3):699–705. doi: 10.1007/s10620-011-1940-3

[196] Onda K, Tong S, Beard S, et al. Proton pump inhibitors decrease soluble fms-like tyrosine kinase-1 and soluble endoglin secretion, decrease hypertension, and rescue endothelial dysfunction. Hypertens. 2017 Mar;69(3):457–468. doi: 10.1161/HYPERTENSIONAHA.116.08408

[197] Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. N Engl J Med. 2010 Nov 25;363(22):2114–2123. doi: 10.1056/NEJMoa1002689

[198] Brownfoot FC, Hannan NJ, Cannon P, et al. Sulfasalazine reduces placental secretion of antiangiogenic factors, up-regulates the secretion of placental growth factor and rescues endothelial dysfunction. EBioMedicine. 2019 Mar;41:636–648. doi: 10.1016/j.ebiom.2019.02.013

[199] Ryter SW, Alam J, Choi AMK. Heme oxygenase-1/Carbon monoxide: from basic science to therapeutic applications. Physiol Rev. 2006 Apr;86(2):583–650. doi: 10.1152/physrev.00011.2005

[200] Sakowicz A, Bralewska M, Rybak-Krzyszkowska M, et al. New ideas for the prevention and treatment of preeclampsia and their molecular inspirations. Int J Mol Sci. 2023 Jul 28;24(15):12100. doi: 10.3390/ijms241512100

[201] Brownfoot FC, Hastie R, Hannan NJ, et al. Combining metformin and sulfasalazine additively reduces the secretion of antiangiogenic factors from the placenta: implications for the treatment of preeclampsia. Placenta. 2020 Jun;95:78–83. doi: 10.1016/j.placenta.2020.04.010

[202] NCT01717586, The university of texas medical branch Galveston. Pravastatin for prevention of preeclampsia (statin). Clin Trials Gov. 2023 March 22.

[203] Mészáros B, Veres DS, Nagyistók L, et al. Pravastatin in preeclampsia: a meta-analysis and systematic

review. Front Med. 2023 Jan 13;9. doi: 10.3389/fmed.2022.1076372

[204] Costantine M. Pravastatin to ameliorate early-onset pre-eclampsia: promising but not there yet. BJOG An Int J Obstet Gynaecol. 2020 Mar 6;127(4):489–489. doi: 10.1111/1471-0528.16067

[205] Girardi G. Pravastatin to treat and prevent preeclampsia. Preclinical and clinical studies. J Reprod Immunol. 2017 Nov;124:15–20. doi: 10.1016/j.jri.2017.09.009

[206] Döbert M, Varouxaki AN, Mu AC, et al. Pravastatin versus placebo in pregnancies at high risk of term preeclampsia. Circulation. 2021 Aug 31;144(9):670–679. doi: 10.1161/CIRCULATIONAHA.121.053963

[207] Kumasawa K, Ikawa M, Kidoya H, et al. Pravastatin induces placental growth factor (PGF) and ameliorates preeclampsia in a mouse model. Proc Natl Acad Sci USA. 2011 Jan 25;108(4):1451–1455. doi: 10.1073/pnas.1011293108

[208] Fox KA, Longo M, Tamayo E, et al. Effects of pravastatin on mediators of vascular function in a mouse model of soluble Fms-like tyrosine kinase-1–induced preeclampsia. Am J Obstet Gynecol. 2011 Oct;205(4):.e366.1–.e366.5.

[209] Ahmed A, Williams D, Cheed V, et al. Pravastatin for early-onset pre-eclampsia: a randomised, blinded, placebo-controlled trial. BJOG An Int J Obstet Gynaecol. 2020 Mar 14;127(4):478–488. doi: 10.1111/1471-0528.16013

[210] Brownfoot FC, Tong S, Hannan NJ, et al. Effects of simvastatin, rosuvastatin and pravastatin on soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sENG) secretion from human umbilical vein endothelial cells, primary trophoblast cells and placenta. BMC Pregnancy Childbirth. 2016 Dec 20;16(1):117. doi: 10.1186/s12884-016-0902-3

[211] de Alwis N, Beard S, Mangwiro YT, et al. Pravastatin as the statin of choice for reducing pre-eclampsia-associated endothelial dysfunction. Pregnancy Hypertens. 2020 Apr;20:83–91. doi: 10.1016/j.preghy.2020.03.004

[212] Tang Y, Groom K, Chamley L, et al. Melatonin, a potential therapeutic agent for preeclampsia, reduces the extrusion of toxic extracellular vesicles from pre-eclamptic placentae. Cells. 2021 Jul 27;10(8):1904. doi: 10.3390/cells10081904

[213] Hannan NJ, Binder NK, Beard S, et al. Melatonin enhances antioxidant molecules in the placenta, reduces secretion of soluble fms-like tyrosine kinase 1 (sFLT) from primary trophoblast but does not rescue endothelial dysfunction: an evaluation of its potential to treat preeclampsia. PLoS One. 2018 Apr 11;13(4):e0187082. doi: 10.1371/journal.pone.0187082

[214] Langston-Cox A, Marshall SA, Lu D, et al. Melatonin for the management of preeclampsia: a review. Antioxidants. 2021 Mar 3;10(3):376. doi: 10.3390/antiox10030376

[215] Zeng K, Gao Y, Wan J, et al. The reduction in circulating levels of melatonin may be associated with the development of preeclampsia. J Hum Hypertens. 2016 Nov 2;30(11):666–671. doi: 10.1038/jhh.2016.37

[216] Dou Y, Lin B, Cheng H, et al. The reduction of melatonin levels is associated with the development of preeclampsia: a meta-analysis. Hypertens Pregnancy. 2019 Apr 3;38(2):65–72. doi: 10.1080/10641955.2019.1581215

[217] Hobson SR, Gurusinghe S, Lim R, et al. Melatonin improves endothelial function in vitro and prolongs pregnancy in women with early-onset preeclampsia. J Pineal Res. 2018 Oct;65(3). doi: 10.1111/jpi.12508

[218] Fu L, Liu Y, Zhang D, et al. Beneficial effect of human umbilical cord-derived mesenchymal stem cells on an endotoxin-induced rat model of preeclampsia. Exp Ther Med. 2015 Nov;10(5):1851–1856. doi: 10.3892/etm.2015.2742

[219] Suvakov S, Richards C, Nikolic V, et al. Emerging therapeutic potential of mesenchymal stem/stromal cells in preeclampsia. Curr Hypertens Rep. 2020 May 14;22(5):37. doi: 10.1007/s11906-020-1034-8

[220] Ryan ST, Hosseini-Beheshti E, Afrose D, et al. Extracellular vesicles from mesenchymal stromal cells for the treatment of inflammation-related conditions. Int J Mol Sci. 2021 Mar 16;22(6):3023. doi: 10.3390/ijms22063023

[221] da Silva Meirelles L, Fontes AM, Covas DT, et al. Mechanisms involved in the therapeutic properties of mesenchymal stem cells. Cytokine Growth Factor Rev. 2009 Oct;20(5–6):419–427. doi: 10.1016/j.cytogfr.2009.10.002

[222] Jovic D, Yu Y, Wang D, et al. A brief overview of global trends in MSC-Based cell therapy. STEM Cell Rev And Rep. 2022 Jun 28;18(5):1525–1545. doi: 10.1007/s12015-022-10369-1

[223] Gnecchi M, Danieli P, Malpasso G et al. Paracrine mechanisms of mesenchymal stem cells in tissue repair. In. 2016:1416:123–146. doi: 10.1007/978-1-4939-3584-0_7.

[224] Bagno L, Hatzistergos KE, Balkan W, et al. Mesenchymal stem cell-based therapy for cardiovascular disease: progress and challenges. Mol Ther. 2018 Jul;26(7):1610–1623. doi: 10.1016/j.ymthe.2018.05.009

[225] Kuraitis D, Giordano C, Ruel M, et al. Exploiting extracellular matrix-stem cell interactions: a review of natural materials for therapeutic muscle regeneration. Biomater. 2012 Jan;33(2):428–443. doi: 10.1016/j.biomaterials.2011.09.078

[226] Kusuma GD, Georgiou HM, Perkins AV. Mesenchymal stem/stromal cells and their role in oxidative stress associated with preeclampsia. Yale J Biol Med. 2022 Mar 31;95(1):115–127. doi: 10.1016/s0301-2115(00)00423-1

[227] Benian A, Uzun H, Aydın S, et al. Placental stem cell markers in pre-eclampsia. Intl J Gynecology & Obste. 2008 Mar 28;100(3):228–233. doi: 10.1016/j.ijgo.2007.09.023

[228] Wang Y, Fan H, Zhao G, et al. miR-16 inhibits the proliferation and angiogenesis-regulating potential of mesenchymal stem cells in severe pre-eclampsia. FEBS J. 2012 Dec 22;279(24):4510–4524. doi: 10.1111/febs.12037

[229] Zhao G, Zhou X, Chen S, et al. Differential expression of microRNAs in decidua-derived mesenchymal stem

cells from patients with pre-eclampsia. J Biomed Sci. 2014 Dec 19;21(1):81. doi: 10.1186/s12929-014-0081-3
[230] Ji L, Zhang L, Li Y, et al. MiR-136 contributes to pre-eclampsia through its effects on apoptosis and angiogenesis of mesenchymal stem cells. Placenta. 2017 Feb;50:102–109. doi: 10.1016/j.placenta.2017.01.102
[231] Chen S, Zhao G, Miao H, et al. MicroRNA-494 inhibits the growth and angiogenesis-regulating potential of mesenchymal stem cells. FEBS Lett. 2015 Mar 12;589(6):710–717. doi: 10.1016/j.febslet.2015.01.038
[232] Nuzzo AM, Giuffrida D, Piccoli E, et al. Anti-inflammatory and pro-angiogenic effects of placental mesenchymal stromal cells conditioned media on pre-eclamptic placental tissue. Placenta. 2014 Sep;35(9):A87. doi: 10.1016/j.placenta.2014.06.280
[233] Liu L, Zhao G, Fan H, et al. Mesenchymal stem cells ameliorate Th1-induced pre-eclampsia-like symptoms in mice via the suppression of tnf-α expression. PLoS One. 2014 Feb 18;9(2):e88036. doi: 10.1371/journal.pone.0088036
[234] Wang LL, Yu Y, Guan HB, et al. Effect of human umbilical cord mesenchymal stem cell transplantation in a rat model of preeclampsia. Reprod Sci. 2016 Aug 30;23(8):1058–1070. doi: 10.1177/1933719116630417
[235] Schuster J, Cheng S, Padbury J, et al. Placental extracellular vesicles and pre-eclampsia. Am J Reprod Immunol. 2021 Feb 18;85(2). doi: 10.1111/aji.13297
[236] Rani S, Ryan AE, Griffin MD, et al. Mesenchymal stem cell-derived extracellular vesicles: toward cell-free therapeutic applications. Mol Ther. 2015 May;23(5):812–823. doi: 10.1038/mt.2015.44
[237] Yeo RWY, Lai RC, Zhang B, et al. Mesenchymal stem cell: an efficient mass producer of exosomes for drug delivery. Adv Drug Deliv Rev. 2013 Mar;65(3):336–341. doi: 10.1016/j.addr.2012.07.001
[238] Varderidou-Minasian S, Lorenowicz MJ. Mesenchymal stromal/stem cell-derived extracellular vesicles in tissue repair: challenges and opportunities. Theranostics. 2020;10(13):5979–5997. doi: 10.7150/thno.40122
[239] Taglauer ES, Fernandez-Gonzalez A, Willis GR, et al. Antenatal mesenchymal stromal cell extracellular vesicle therapy prevents preeclamptic lung injury in mice. Am J Respir Cell Mol Biol. 2022 Jan;66(1):86–95. doi: 10.1165/rcmb.2021-0307OC
[240] Taglauer ES, Fernandez-Gonzalez A, Willis GR, et al. Mesenchymal stromal cell-derived extracellular vesicle therapy prevents preeclamptic physiology through intrauterine immunomodulation†. Biol Reprod. 2021 Feb 11;104(2):457–467. doi: 10.1093/biolre/ioaa198
[241] Xiong ZH, Wei J, Lu MQ, et al. Protective effect of human umbilical cord mesenchymal stem cell exosomes on preserving the morphology and angiogenesis of placenta in rats with preeclampsia. Biomed Pharmacother. 2018 Sep;105:1240–1247.
[242] Zheng S, Shi A, Hill S, et al. Decidual mesenchymal stem/stromal cell-derived extracellular vesicles ameliorate endothelial cell proliferation, inflammation, and oxidative stress in a cell culture model of preeclampsia. Pregnancy Hypertens. 2020 Oct;22:37–46. doi: 10.1016/j.preghy.2020.07.003
[243] Chu Y, Chen W, Peng W et al. Amnion-derived mesenchymal stem cell exosomes-mediated autophagy promotes the survival of trophoblasts under hypoxia through mTOR pathway by the downregulation of EZH2. Front Cell Dev Biol. 2020 Nov 11;8:545852 doi: 10.3389/fcell.2020.545852.
[244] Duley L. Pre-eclampsia and the hypertensive disorders of pregnancy. Br Med Bull. 2003 Dec 1;67(1):161–176. doi: 10.1093/bmb/ldg005
[245] Spinelli JB, Haigis MC. The multifaceted contributions of mitochondria to cellular metabolism. Nat Cell Biol. 2018 Jul 27;20(7):745–754. doi: 10.1038/s41556-018-0124-1
[246] Smith AN, Wang X, Thomas DG, et al. The role of mitochondrial dysfunction in preeclampsia: causative factor or collateral damage? Am J Hypertens. 2021 May 22;34(5):442–452. doi: 10.1093/ajh/hpab003
[247] Kent A. Antioxidants and preeclampsia. Rev Obs Gynecol. 2010;3(2):72–73.
[248] McCance DR, Holmes VA, Maresh MJ, et al. Vitamins C and E for prevention of pre-eclampsia in women with type 1 diabetes (DAPIT): a randomised placebo-controlled trial. Lancet. 2010 Jul;376(9737):259–266. doi: 10.1016/S0140-6736(10)60630-7
[249] Hu XQ, Zhang L. Hypoxia and mitochondrial dysfunction in pregnancy complications. Antioxidants. 2021 Mar 8;10(3):405. doi: 10.3390/antiox10030405
[250] Teran E, Hernandez I, Nieto B, et al. Coenzyme Q10 supplementation during pregnancy reduces the risk of pre-eclampsia. Intl J Gynecology & Obste. 2009 Apr 19;105(1):43–45. doi: 10.1016/j.ijgo.2008.11.033
[251] Teran E, Racines-Orbe M, Vivero S, et al. Preeclampsia is associated with a decrease in plasma coenzyme Q10 levels. Free Radic Biol Med. 2003 Dec;35(11):1453–1456. doi: 10.1016/j.freeradbiomed.2003.08.004
[252] Teran E, Vivero S, Racines-Orbe M, et al. Coenzyme Q_{10} is increased in placenta and cord blood during preeclampsia. Biofactors. 2005 Jan 19;25(1–4):153–-158. doi: 10.1002/biof.5520250117
[253] Gao L, Mao Q, Cao J, et al. Effects of coenzyme Q10 on vascular endothelial function in humans: a meta-analysis of randomized controlled trials. Atherosclerosis. 2012 Apr;221(2):311–316. doi: 10.1016/j.atherosclerosis.2011.10.027
[254] Murphy MP, Smith RAJ. Targeting antioxidants to mitochondria by conjugation to lipophilic cations. Annu Rev Pharmacol Toxicol. 2007 Feb 1;47(1):629–656. doi: 10.1146/annurev.pharmtox.47.120505.105110
[255] Nuzzo AM, Camm EJ, Sferruzzi-Perri AN, et al. Placental adaptation to early-onset hypoxic pregnancy and mitochondria-targeted antioxidant therapy in a rodent model. Am J Pathol. 2018 Dec;188(12):2704–2716. doi: 10.1016/j.ajpath.2018.07.027
[256] Phillips TJ, Scott H, Menassa DA, et al. Treating the placenta to prevent adverse effects of gestational hypoxia on fetal brain development. Sci Rep. 2017 Aug 22;7(1):9079. doi: 10.1038/s41598-017-06300-1
[257] Aljunaidy MM, Morton JS, Kirschenman R, et al. Maternal treatment with a placental-targeted antioxidant (MitoQ) impacts offspring cardiovascular

function in a rat model of prenatal hypoxia. Pharmacol Res. 2018 Aug;134:332–342. doi: 10.1016/j.phrs.2018.05.006

[258] Ganguly E, Kirschenman R, Spaans F, et al. Nanoparticle-encapsulated antioxidant improves placental mitochondrial function in a sexually dimorphic manner in a rat model of prenatal hypoxia. FASEB J. 2021 Feb 11;35(2). doi: 10.1096/fj.202002193R

[259] Ganguly E, Aljunaidy MM, Kirschenman R, et al. Sex-specific effects of nanoparticle-encapsulated MitoQ (nMitoQ) delivery to the placenta in a rat model of fetal hypoxia. Front Physiol. 2019 May 24;10. doi: 10.3389/fphys.2019.00562

[260] Vaka VR, McMaster KM, Cunningham MW, et al. Role of mitochondrial dysfunction and reactive oxygen species in mediating hypertension in the reduced uterine perfusion pressure rat model of preeclampsia. Hypertension. 2018 Sep;72(3):703–711. doi: 10.1161/HYPERTENSIONAHA.118.11290

[261] Long J, Huang Y, Tang Z, et al. Mitochondria targeted antioxidant significantly alleviates preeclampsia caused by 11β-HSD2 dysfunction via OPA1 and MtDNA maintenance. Antioxidants. 2022 Jul 31;11(8):1505. doi: 10.3390/antiox11081505

[262] Gane EJ, Weilert F, Orr DW, et al. The mitochondria-targeted anti-oxidant mitoquinone decreases liver damage in a phase II study of hepatitis C patients. Liver Int. 2010 May 18;30(7):1019–1026. doi: 10.1111/j.1478-3231.2010.02250.x

[263] Kirkman DL, Muth BJ, Ramick MG, et al. Role of mitochondria-derived reactive oxygen species in microvascular dysfunction in chronic kidney disease. Am J Physiol Physiol. 2018 Mar 1;314(3):F423–9. doi: 10.1152/ajprenal.00321.2017

[264] Mason SA, Wadley GD, Keske MA, et al. Effect of mitochondrial-targeted antioxidants on glycaemic control, cardiovascular health, and oxidative stress in humans: a systematic review and meta-analysis of randomized controlled trials. Diabetes, Obes Metab. 2022 Jun 3;24(6):1047–1060. doi: 10.1111/dom.14669

[265] Borodina I, Kenny LC, McCarthy CM, et al. The biology of ergothioneine, an antioxidant nutraceutical. Nutr Res Rev. 2020 Dec 13;33(2):190–217. doi: 10.1017/S0954422419000301

[266] Cheah IK, Feng L, Tang RMY, et al. Ergothioneine levels in an elderly population decrease with age and incidence of cognitive decline; a risk factor for neurodegeneration? Biochem Biophys Res Commun. 2016 Sep;478(1):162–167. doi: 10.1016/j.bbrc.2016.07.074

[267] Cheah IK, Tang R, Ye P, et al. Liver ergothioneine accumulation in a guinea pig model of non-alcoholic fatty liver disease. A possible mechanism of defence? Free Radic Res. 2016 Jan 2;50(1):14–25. doi: 10.3109/10715762.2015.1099642

[268] Cheah IK, Tang RMY, Yew TSZ, et al. Administration of pure ergothioneine to healthy human subjects: uptake, metabolism, and effects on biomarkers of oxidative damage and inflammation. Antioxid Redox Signal. 2017 Feb 10;26(5):193–206. doi: 10.1089/ars.2016.6778

[269] Halliwell B, Cheah IK, Drum CL. Ergothioneine, an adaptive antioxidant for the protection of injured tissues? A hypothesis. Biochem Biophys Res Commun. 2016 Feb;470(2):245–250. doi: 10.1016/j.bbrc.2015.12.124

[270] Paul BD, Snyder SH. The unusual amino acid L-ergothioneine is a physiologic cytoprotectant. Cell Death Differ. 2010 Jul 13;17(7):1134–1140. doi: 10.1038/cdd.2009.163

[271] Ames BN. Prolonging healthy aging: longevity vitamins and proteins. Proc Natl Acad Sci USA. 2018 Oct 23;115(43):10836–10844. doi: 10.1073/pnas.1809045115

[272] Cheah IK, Ng L, Ng L, et al. Inhibition of amyloid-induced toxicity by ergothioneine in a transgenic *Caenorhabditis elegans* model. FEBS Lett. 2019 Aug 30;593(16):2139–2150. doi: 10.1002/1873-3468.13497

[273] Smith E, Ottosson F, Hellstrand S, et al. Ergothioneine is associated with reduced mortality and decreased risk of cardiovascular disease. Heart. 2020 May;106(9):691–697. doi: 10.1136/heartjnl-2019-315485

[274] Cheah IK, Halliwell B. Ergothioneine, recent developments. Redox Biol. 2021 Jun;42:101868. doi: 10.1016/j.redox.2021.101868

[275] Morillon AC, Williamson RD, Baker PN, et al. Effect of L-Ergothioneine on the metabolic plasma profile of the RUPP rat model of pre-eclampsia. PLoS One. 2020 Mar 31;15(3):e0230977. doi: 10.1371/journal.pone.0230977

[276] Williamson RD, McCarthy FP, Manna S, et al. L-(+)-ergothioneine significantly improves the clinical characteristics of preeclampsia in the reduced uterine perfusion pressure rat model. Hypertension. 2020 Feb;75(2):561–568. doi: 10.1161/HYPERTENSIONAHA.119.13929

[277] Covarrubias AE, Lecarpentier E, Lo A, et al. AP39, a modulator of mitochondrial bioenergetics, reduces antiangiogenic response and oxidative stress in hypoxia-exposed trophoblasts. Am J Pathol. 2019 Jan;189(1):104–114. doi: 10.1016/j.ajpath.2018.09.007

[278] Sanchez-Aranguren LC, Ahmad S, Dias IHK, et al. Bioenergetic effects of hydrogen sulfide suppress soluble flt-1 and soluble endoglin in cystathionine gamma-lyase compromised endothelial cells. Sci Rep. 2020 Sep 25;10(1):15810. doi: 10.1038/s41598-020-72371-2

[279] Blumfield ML, Hure AJ, Macdonald-Wicks L, et al. A systematic review and meta-analysis of micronutrient intakes during pregnancy in developed countries. Nutr Rev. 2013 Feb;71(2):118–132. doi: 10.1111/nure.12003

[280] Xu H, Shatenstein B, Luo ZC, et al. Role of nutrition in the risk of preeclampsia. Nutr Rev. 2009 Nov;67(11):639–657. doi: 10.1111/j.1753-4887.2009.00249.x

[281] Ramakrishnan U, Grant F, Goldenberg T, et al. Effect of women's nutrition before and during early pregnancy on maternal and infant outcomes: a systematic review. Paediatric Perinatal Epid. 2012 Jul 28;26(s1):285–301. doi: 10.1111/j.1365-3016.2012.01281.x

[282] Roberts JM, Balk JL, Bodnar LM, et al. Nutrient involvement in preeclampsia. J Nutr. 2003 May;133(5):1684S–1692S. doi: 10.1093/jn/133.5.1684S

[283] Gerald G Briggs, Roger K, Freeman. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 10th Edition. American Journal of Health-System Pharmacy. July 2015;72(14):1239–1240.

[284] Haugen M, Brantsæter AL, Trogstad L, et al. Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. Epidemiology. 2009 Sep;20 (5):720–726. doi: 10.1097/EDE.0b013e3181a70f08

[285] Ray J, Laskin C. Folic acid and homocyst(e)ine metabolic defects and the risk of placental abruption, pre-eclampsia and spontaneous pregnancy loss: a systematic review. Placenta. 1999 Sep;20(7):519–529. doi: 10.1053/plac.1999.0417

[286] Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol. 2014 Mar;21 (3):319–329. doi: 10.1016/j.chembiol.2013.12.016

[287] Chappell LC, Seed PT, Briley AL, et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. Lancet. 1999 Sep;354(9181):810–816. doi: 10.1016/S0140-6736(99)80010-5

[288] Rumbold AR, Crowther CA and Haslam RR, et al. Vitamins C and E and the risks of preeclampsia and perinatal complications. N Engl J Med. 2006;354(17). doi: 10.1056/NEJMoa054186), 1796–1806.

[289] Vanderlelie J, Scott R, Shibl R, et al. First trimester multivitamin/mineral use is associated with reduced risk of pre-eclampsia among overweight and obese women. Matern Child Nutr. 2016 Apr 22;12(2):339–348. doi: 10.1111/mcn.12133

[290] Myatt L. Review: reactive oxygen and nitrogen species and functional adaptation of the placenta. Placenta. 2010 Mar;31:S66–9. doi: 10.1016/j.placenta.2009.12.021

[291] Rumbold A, Duley L, Crowther CA, et al. Antioxidants for preventing pre-eclampsia. Cochrane Database Syst Rev. 2008 Jan 23;2012(6). doi: 10.1002/14651858.CD004227.pub3

[292] Poston L, Igosheva N, Mistry HD, et al. Role of oxidative stress and antioxidant supplementation in pregnancy disorders. Am J Clin Nutr. 2011 Dec;94:S1980–5. doi: 10.3945/ajcn.110.001156

[293] Chang KJ, Seow KM, Chen KH. Preeclampsia: recent advances in predicting, preventing, and managing the maternal and fetal life-threatening condition. Int J Environ Res Public Health. 2023 Feb 8;20 (4):2994. doi: 10.3390/ijerph20042994

[294] Qi J, Wu B, Chen X, et al. Diagnostic biomolecules and combination therapy for pre-eclampsia. Reprod Biol Endocrinol. 2022 Sep 6;20(1):136. doi: 10.1186/s12958-022-01003-3

[295] Ferreira RC, Fragoso MBT, Bueno NB, et al. Oxidative stress markers in preeclamptic placentas: a systematic review with meta-analysis. Placenta. 2020 Sep;99:89–100. doi: 10.1016/j.placenta.2020.07.023

[296] Rosdah AA, Holien K, Delbridge LMD et al. Mitochondrial fission – a drug target for cytoprotection or cytodestruction? Pharmacol Res Perspect. 2016 Jun 21;4(3):e00235 doi: 10.1002/prp2.235

[297] Cassidy-Stone A, Chipuk JE, Ingerman E, et al. Chemical inhibition of the mitochondrial division dynamin reveals its role in bax/bak-dependent mitochondrial outer membrane permeabilization. Dev Cell. 2008 Feb;14(2):193–204.

[298] Ong SB, Hall AR, Hausenloy DJ. Mitochondrial dynamics in cardiovascular health and disease. Antioxid Redox Signal. 2013 Aug;19(4):400–414.

[299] Upadhyay NS, Vafadari N, Zhang RK, et al. The importance of interdisciplinary care in the management of postpartum hypertensive crisis. Cureus. 2023 Oct 21. doi: 10.7759/cureus.47423

[300] Roth H, Morcos MV, Roberts L, et al. "I think we should pull together as a team"- together on the path to the top: interdisciplinary collaboration in partnership with women on long-term health after hypertensive disorder of pregnancy. Women And Birth. 2022 Sep;35:14. doi: 10.1016/j.wombi.2022.07.039

[301] Myatt L, Clifton RG, Roberts JM, et al. The utility of uterine artery Doppler velocimetry in prediction of preeclampsia in a low-risk population. Obstet Gynecol. 2012 Oct;120(4):815–822. doi: 10.1097/AOG.0b013e31826af7fb

[302] Cottrell E, Sibley C. From pre-clinical studies to clinical trials: generation of novel therapies for pregnancy complications. Int J Mol Sci. 2015 Jun 8;16 (6):12907–12924. doi: 10.3390/ijms160612907

[303] Gatford KL, Andraweera PH, Roberts CT, et al. Animal models of preeclampsia. Hypertension. 2020 Jun;75(6):1363–1381. doi: 10.1161/HYPERTENSIONAHA.119.14598

[304] Bisson C, Dautel S, Patel E, et al. Preeclampsia pathophysiology and adverse outcomes during pregnancy and postpartum. Front Med. 2023 Mar 16;10. doi: 10.3389/fmed.2023.1144170

[305] Milano-Foster J, Schulz LC. RISING STARS: approaches to modeling placental function in preeclampsia in vitro and in vivo. J Endocrinol. 2023 Apr 4;258(1). doi: 10.1530/JOE-23-0008

[306] Shankar M, Hazfiarini A, Zahroh RI, et al. Factors influencing the participation of pregnant and lactating women in clinical trials: a mixed-methods systematic review. PLoS Med. 2024 May 30;21(5):e1004405. doi: 10.1371/journal.pmed.1004405