Reactive oxygen species in fetal growth restriction mechanisms and therapeutic directions (Review)

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Received October 20, 2025; Accepted January 20, 2026

DOI: 10.3892/ijmm.2026.5792

Abstract. Fetal growth restriction (FGR) is strongly associated with adverse perinatal outcomes, and placental oxidative stress has been identified as a central pathological mechanism. In maternal plasma, cord blood and placental tissues from FGR pregnancies, the levels of malondialdehyde, 4-hydroxynonenal, reactive oxygen metabolites and 8-hydroxy-2'-deoxyguanosine are consistently elevated. In parallel, superoxide dismutase and glutathione peroxidase show compensatory upregulation, while catalase activity declines, reflecting increased oxidative burden coupled with impaired antioxidant defense. Major sources of reactive oxygen species include NADPH oxidase and xanthine oxidase, mitochondrial electron transport and ischemia-reperfusion events. Mechanistic evidence further indicates that oxidative stress interacts with endoplasmic reticulum stress, metabolic reprogramming and epigenetic alterations, thereby aggravating trophoblast dysfunction and placental vascular injury. Aberrant DNA hypomethylation, histone modifications and dysregulation of noncoding RNAs, such as microRNA (miR)-199a, miR-210-3p and miR-21, contribute to persistent remodeling of trophoblast behavior and vascular networks. Early clinical studies have suggested that melatonin and pentoxifylline may alleviate placental oxidative injury and improve selected perinatal outcomes, whereas vitamin C and E supplementation shows no clear benefit. Preclinical investigations have highlighted the potential of mitochondria-targeted and classical antioxidants, including mitoquinone mesylate, N-acetylcysteine, tempol and resveratrol; however, their efficacy and safety appear to be dependent on gestational timing and dosage. Further well-designed clinical trials are warranted to establish effective antioxidant-based strategies for FGR.

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Key words: fetal growth restriction, placenta, oxidative stress, antioxidant therapy, epigenetics

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1. Introduction

Fetal growth restriction (FGR) refers to a condition in which the birth weight of a fetus is below two standard deviations of the mean weight for the same gestational age, or below the 10th percentile of the normal weight for that gestational age (1). FGR is one of the major complications in perinatal medicine, with a mortality rate four to six times higher than that of normal neonates (2). The etiology of FGR is multifactorial and complex, and it remains incompletely elucidated. Current evidence suggests that key contributing factors include maternal malnutrition or selective eating habits (3), gestational hypertension (4), intrauterine infections (5), fetal chromosomal abnormalities (6), reduced levels of certain hormones (7), umbilical cord torsion (8) and diverse placental pathologies, including preeclampsia, FGR, maternal and fetal vascular malperfusion, and chronic villitis (9). Collectively, these factors result in reduced placental blood flow and diminished perfusion, which ultimately compromise the nutrient supply to the fetus (1). FGR not only hampers fetal development, leading to outcomes such as stillbirth and neonatal asphyxia, but also exerts long-term effects on physical and cognitive development during childhood and adolescence (7). Furthermore, individuals who experienced FGR in utero are at a higher

risk of cardiovascular, neurological and metabolic disorders in adulthood compared with their peers (2). Consequently, the prevention and management of FGR are of considerable clinical importance, with implications for maternal and child health as well as the promotion of favorable perinatal outcomes.

Oxidative stress arises from an imbalance between the generation of reactive oxygen species (ROS) and the biological system's capacity to neutralize or repair their effects (10). ROS, also referred to as free radicals, are highly reactive oxygen-containing molecules with unpaired electrons. They readily trigger chain oxidation reactions that damage DNA, RNA, lipids and proteins, which in turn leads to cellular dysfunction and, in severe cases, organ failure. Antioxidants exert a protective role by scavenging ROS or reducing free radicals (10). During pregnancy, the placenta, due to its high metabolic rate and mitochondrial activity, constitutes a major source of ROS (11). While moderate oxidative stress is essential for placental function, particularly during early gestation when it facilitates trophoblast invasion, placental remodeling and angiogenesis, as well as in late pregnancy when it participates in the initiation of parturition (12), excessive oxidative stress can disrupt placental formation. This imbalance may trigger immune dysregulation and functional impairment, which are closely associated with pregnancy complications, including FGR (13).

The present review outlines the role of redox imbalance in FGR, highlighting the principal sources of oxidative stress and discussing its regulatory and promoting effects on the pathogenesis of FGR from three perspectives: Endoplasmic reticulum (ER) stress, metabolic reprogramming and epigenetic regulation (Fig. 1). Finally, based on current evidence, the present review summarizes advances in preclinical and clinical research on antioxidant interventions for FGR, with the aim of providing insights for translational applications and future therapeutic strategies.

2. Origins and mechanisms of oxidative stress

Placental redox imbalance and oxidative stress markers. Placental oxidative stress is a central pathogenic mechanism underlying placental dysfunction in pregnancies complicated by FGR (14). During early gestation, a mild degree of oxidative stress occurs naturally in the placenta. This physiological phenomenon is critical for vascular formation and angiogenesis within the placenta. Evidence indicates that excessive use of potent antioxidants during this stage, which reduces ROS levels, can suppress angiogenesis and increase the risk of FGR (14). However, when oxidative stress exceeds the physiological range, the remodeling of spiral arteries becomes impaired, thereby limiting trophoblast invasion. Failure of spiral artery remodeling leads to local ischemia, followed by reperfusion and reoxygenation, which together create a cyclic hypoxia-reoxygenation process. This process is considered a major trigger of enhanced local oxidative stress and can activate the mitochondrial respiratory chain as well as ROS-generating enzymes such as NADPH oxidase (NOX) and xanthine oxidase (XO) (15). The major enzymatic, mitochondrial and ischemia-reperfusion-related sources of ROS and their downstream effects on ER stress, cellular metabolism and epigenetic regulation in FGR are summarized in Fig. 1. Increased activity of these enzymes promotes excessive ROS production, disrupting the redox balance of the placenta and ultimately inducing damage to DNA, proteins and lipids (16). Furthermore, oxidative metabolites released by the placenta, particularly lipid peroxidation products, may enter the maternal circulation. This process enhances oxidation of maternal low-density lipoprotein, sustaining lipid peroxidation cascades and resulting in maternal vascular dysfunction (17,18). To provide a more direct representation of the pathological trends, previous studies (19-23) have summarized key oxidative stress biomarkers in FGR, as shown in Table I.

Compared with normal pregnancies, higher levels of malondialdehyde (MDA) have been detected in maternal blood, cord blood and placental tissue from FGR-related pregnancies (19). A recent meta-analysis including 48 studies and 4,684 newborns reported a moderate pooled effect size for cord blood MDA levels in FGR neonates compared with controls, supporting a robust association between elevated MDA and FGR at the population level; however, because nearly all included studies used cross-sectional or case-control designs, these data cannot demonstrate from an epidemiological standpoint that increased MDA levels are a direct causal driver of FGR (24). The same meta-analysis further demonstrated that the direction and magnitude of MDA differences varied substantially across studies according to the diagnostic criteria for FGR, the presence or absence of concomitant preeclampsia, and the gestational age at sampling, resulting in considerable heterogeneity in the sensitivity and specificity of MDA when used as a stand-alone screening marker. Therefore, MDA appears more suitable as a biomarker for risk stratification of fetal exposure to an oxidative lipid milieu rather than as an independent diagnostic or predictive tool (24). In a human FGR cohort, XO activity was increased, whereas total antioxidant capacity was decreased in maternal plasma, cord blood and placental tissue, further indicating a systemic shift toward a pro-oxidant state (19). In preeclampsia, the concentrations of MDA and 4-hydroxynonenal (4HNE) in both placenta and plasma are also markedly elevated (25). 4HNE can form adducts with proteins, including sirtuin 1 (SIRT1), thereby mediating protein modification under oxidative stress (20). Interactions between SIRT1 and 4HNE have also been observed in placental tissue from mouse models of FGR (20). An *in vitro* study has further demonstrated that 4HNE induces increased senescence-associated-β-galactosi dase activity and acetylated protein accumulation in human trophoblast cells (HTR-8/SVneo), consistent with the formation of 4HNE-SIRT1 adducts (20). Collectively, these findings indicate that the accumulation of 4HNE protein adducts, including 4HNE-SIRT1 conjugates, is a characteristic feature of placental oxidative injury in FGR and related disorders (20).

Derivatives of reactive oxygen metabolites (d-ROMs) represent another oxidative stress indicator and are elevated in preeclamptic pregnancies regardless of the presence of FGR (21,22). In cord blood, increased d-ROM levels have been detected only in preeclamptic cases complicated by FGR, but not in isolated preeclampsia (21). In the same placental specimens, expression of redox factor-1, a redox-sensitive DNA repair protein, was increased in preeclampsia without FGR but not in preeclampsia complicated by FGR, suggesting

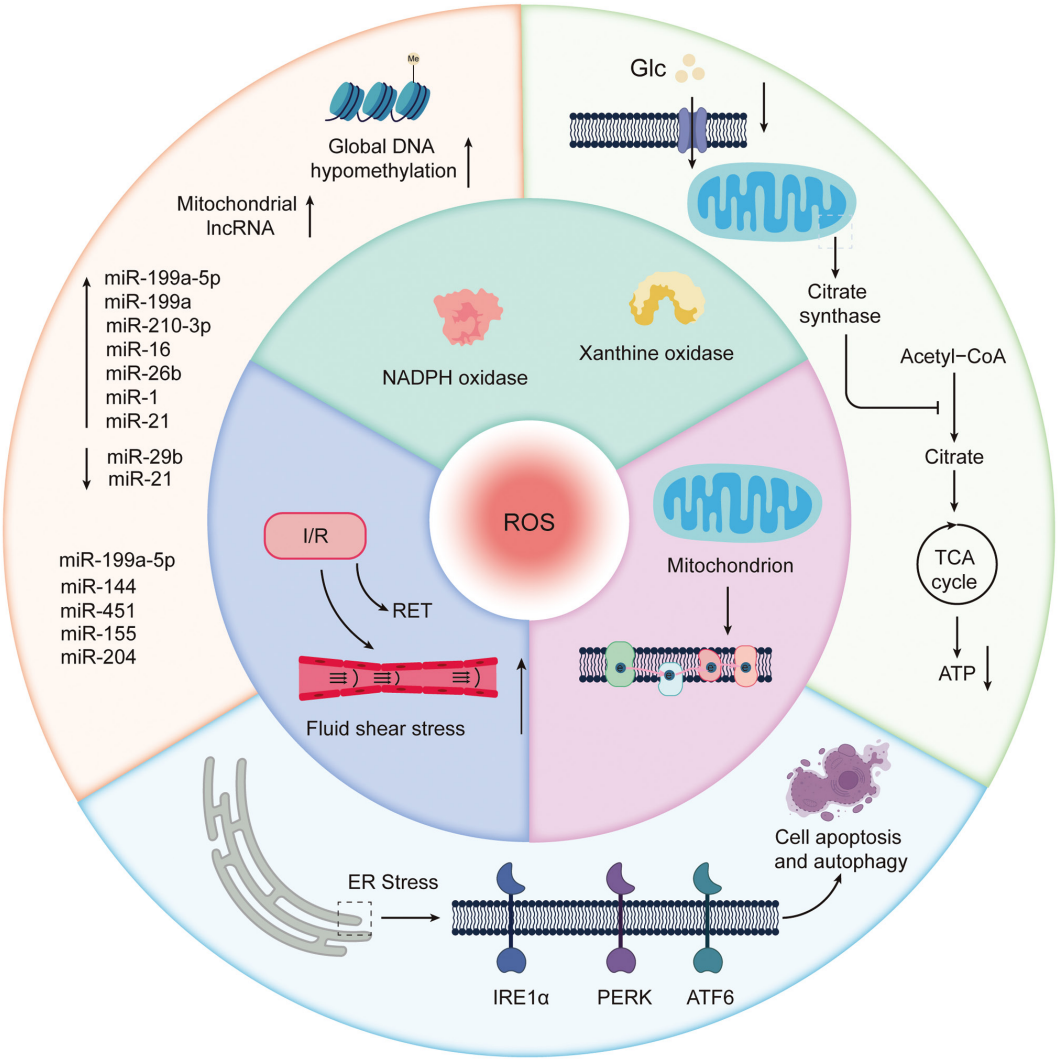

Figure 1. Major sources of ROS and their molecular roles in the pathogenesis of FGR. ROS are mainly generated from three sources: Enzyme-derived ROS, mitochondrial ROS and I/R-induced ROS. Enzyme-derived ROS are mainly produced by NOX and xanthine oxidase, while mitochondrial ROS mainly result from electron leakage at complexes I and III of the electron transport chain. During I/R, RET occurs at complex I. ER stress regulates cell apoptosis and autophagy via the IRE1α, PERK and ATF6 signaling pathways, thereby contributing to the progression of FGR. In FGR, glucose uptake is reduced, the mitochondrial structure is disrupted, and the TCA cycle is impaired, ultimately resulting in decreased ATP production. Furthermore, epigenetic regulation also serves a key role in FGR. The placenta of growth-restricted fetuses exhibits global hypomethylation in hypoxia-related pathways, accompanied by marked upregulation of mitochondrial lncRNAs. Several miRNAs, including miR-199a-5p, miR-155, miR-16, miR-29b, miR-204, miR-1 and miR-21, are also implicated in placental development and are dynamically regulated by oxidative stress. ROS, reactive oxygen species; I/R, ischemia-reperfusion; NOX, NADPH oxidase; RET, reverse electron transport; ER, endoplasmic reticulum; FGR, fetal growth restriction; TCA, tricarboxylic acid; lncRNA/lnc, long noncoding RNA; miRNA/miR, microRNA; PERK, protein kinase RNA-like endoplasmic reticulum kinase; ATF6, activating transcription factor 6; IRE1α, inositol-requiring enzyme 1α; Glc, glucose.

a relatively limited activation of redox-regulated repair pathways when FGR coexists (21). DNA oxidative damage markers such as 8-hydroxy-2'-deoxyguanosine (8-OHdG) are also upregulated in placentas from patients with preeclampsia, with or without FGR (21,22). In addition, elevated levels of histone H2A.X phosphorylated at serine 139, a marker of DNA double-strand breaks, have been reported in placental tissue from mouse models of FGR (20). A recent scoping review of multiple cord blood oxidative stress markers found that reports linking d-ROMs to FGR are few in number and based on relatively small sample sizes, suggesting that its stand-alone diagnostic and predictive utility in clinical practice may be limited (26).

The occurrence of FGR is also closely linked to dysregulation of the placental antioxidant defense system (19). In FGR pregnancies, increased activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx) has been observed in maternal blood, cord blood and placental tissue, whereas catalase (CAT) levels are reduced (19). A recent meta-analysis demonstrated that SOD and CAT activities in FGR neonates are overall lower than in controls, with effect sizes even exceeding those observed for MDA, suggesting that under conditions of more severe disease or prolonged exposure, antioxidant enzyme activity may shift from an early compensatory upregulation to a later-stage depletion, thereby amplifying lipid peroxidation and DNA damage (24). The pathogenic role of oxidative stress in FGR and preeclampsia has also been validated in animal models. For example, microcystin-LR (MC-LR), a cyanobacterial toxin, reduced fetal and placental weights in mice (23). Histopathological findings revealed decreased vascular density

Table I. Alterations in oxidative stress biomarkers in FGR.

Authors, year	Biomarker	Sample	Model	Observed change	(Refs.)
Biri *et al*, 2007	MDA	Maternal plasma, cord blood, placenta	Human FGR	Higher in maternal plasma, cord plasma and placenta compared with controls	(19)
Zhao *et al*, 2020	MDA	Placenta	FGR mouse model	Placental MDA increased; fetal and placental weights reduced; placental function impaired	(23)
Biri *et al*, 2007	Xanthine oxidase	Maternal plasma, cord blood, placenta	Human FGR all three samples	XO activity was increased in	(19)
Biri *et al*, 2007	Total antioxidant capacity	Maternal plasma, cord blood, placenta	Human FGR	Total antioxidant capacity was decreased in all three samples	(19)
Biri *et al*, 2007	Superoxide dismutase	Maternal plasma, cord blood	Human FGR	SOD activity was increased in maternal and cord blood	(19)
Biri *et al*, 2007	Glutathione peroxidase	Maternal blood, placenta	Human FGR	Enzyme activity increased	(19)
Biri *et al*, 2007	Catalase	Cord blood, placenta	Human FGR	Enzyme activity reduced	(19)
Kimura *et al*, 2013	d-ROMs	Maternal blood	Preeclampsia with or without FGR, human	Elevated in PE with or without FGR	(22)
Fujimaki *et al*, 2011	d-ROMs	Umbilical cord blood	Preeclampsia with FGR, human	Increased only when FGR coexisted with PE	(21)
Fujimaki *et al*, 2011; Kimura *et al*, 2013	8-OHdG	Placenta	Preeclampsia with or without FGR, human	Oxidative DNA damage marker elevated	(21,22)
Fujimaki *et al*, 2011	Ref-1	Placenta	Preeclampsia with or without FGR, human	Increased in preeclampsia without FGR; not increased in preeclampsia with FGR, suggesting limited repair response	(21)
Tasta *et al*, 2021	γH2AX	Placenta	FGR mouse model	Elevated in FGR mouse	(20)
Tasta *et al*, 2021	4HNE protein adducts	Placenta	FGR mouse model; human trophoblasts *in vitro*	SIRT1-4HNE adducts detected in FGR mouse placentas; 4HNE induced SA-β-gal activity in HTR-8/SVneo cells	(20)
Kimura *et al*, 2013	GSH	Placenta	FGR mouse model	Decreased	(22)

γH2AX, phosphorylated H2A histone family member X; 4HNE, 4-hydroxy-2-nonenal; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; d-ROMs, derivatives of reactive oxygen metabolites; FGR, fetal growth restriction; GSH, glutathione; MDA, malondialdehyde; PE, preeclampsia; Ref-1, redox factor-1; SA-β-gal, senescence-associated β-galactosidase; SIRT1, sirtuin 1; SOD, superoxide dismutase; XO, xanthine oxidase.

in the placental labyrinth layer of MC-LR-treated mice, accompanied by reduced expression of key placental factors such as VEGFA and placental growth factor (PlGF), as well as nutrient transporters, including glucose transporter 1 and proton-coupled folate transporter. These changes were associated with increased MDA levels and diminished antioxidant capacity, including reduced glutathione (GSH) levels, total antioxidant capacity and enzymatic activity, which are indicative of oxidative stress-mediated injury (23). Furthermore, ER stress signaling was activated in placentas, further impairing placental development and reducing fetal weight (23). Similarly, Toblli *et al* (27) demonstrated that iron-deficiency anemia in rat models increased placental MDA and SOD1 activity, while reducing GSH, CAT and GPx activity, leading to FGR and smaller litter sizes. In another study, Huang *et al* (28) showed that mangiferin, a natural antioxidant, effectively alleviated hypertension and proteinuria, improved fetal weight, and reduced placental and maternal oxidative stress in a preeclampsia mouse model complicated by FGR. These effects, reflected by decreased MDA levels and increased SOD, GPx and GSH levels, may involve activation of the mTOR signaling pathway, which helps regulate oxidative stress responses (28). A prospective clinical study demonstrated that, in women with severe FGR complicated by preeclampsia, systemic free

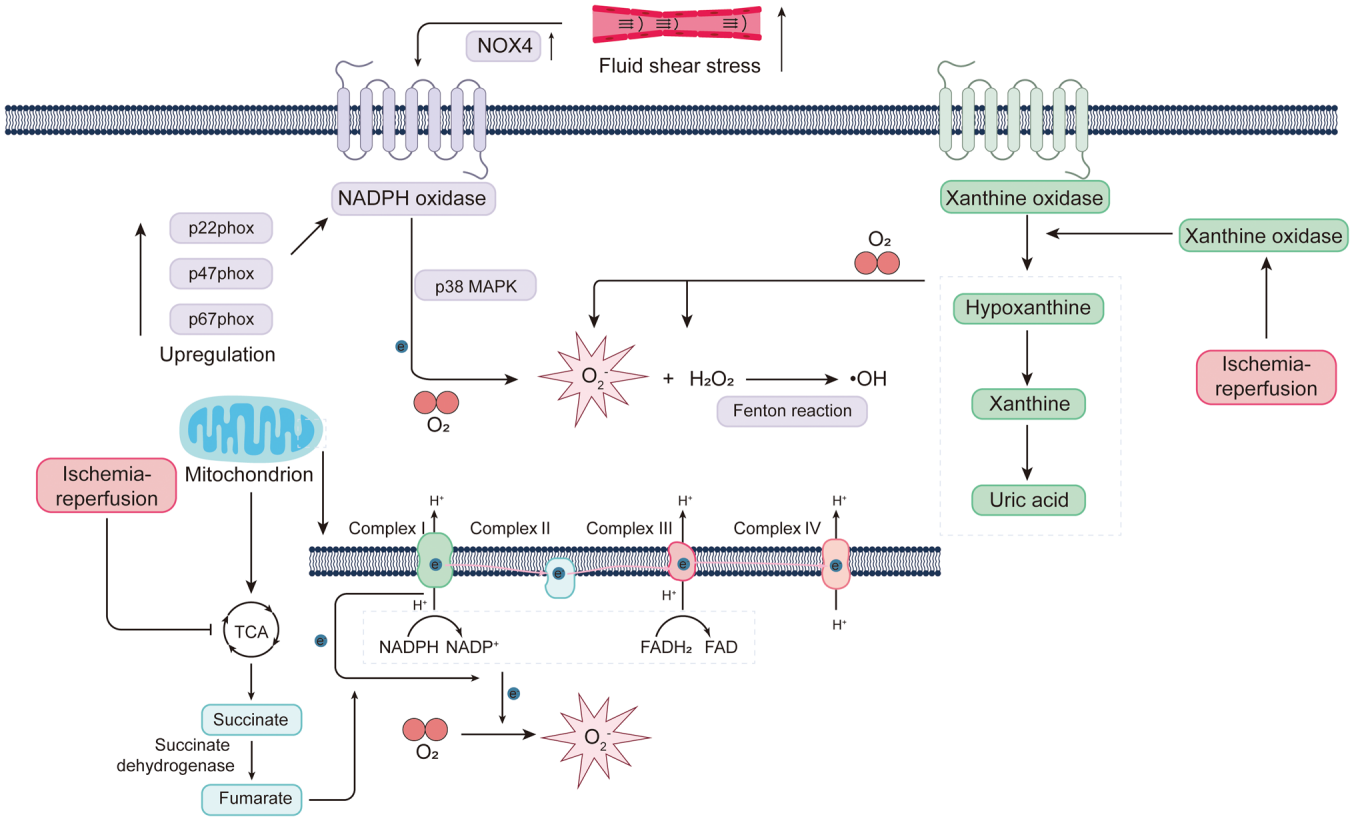

Figure 2. Major sources and molecular mechanisms of ROS generation. NOX is a major source of O_2•$^-$, and elevated O_2•$^-$ levels are associated with activation of the p38 MAPK pathway. The NOX subunits p22^{phox}, p47^{phox} and p67^{phox} are highly expressed in the placenta. Excess H_2O_2 can be further converted into •OH via the Fenton reaction. XO catalyzes the stepwise oxidation of hypoxanthine to xanthine and uric acid, accompanied by the generation of H_2O_2 and O_2^-. The electron transport chain, consisting of five multi-subunit protein complexes (I-V), resides in the mitochondrial inner membrane. Complexes I, III and IV pump protons (H^+) from the mitochondrial matrix into the intermembrane space. During oxidative phosphorylation, O_2 undergoes partial reduction by electrons leaking from complexes I and III, giving rise to O_2•$^-$. In the matrix, O_2•$^-$ is dismutated to H_2O_2. H_2O_2 may subsequently undergo the Fenton reaction with Fe^{2+}/Cu^+ to produce •OH. During reperfusion, the TCA cycle intermediate succinate selectively accumulates. The accumulated succinate is rapidly re-oxidized by succinate dehydrogenase, driving reverse electron transport at complex I and triggering a burst of ROS. Ischemia-reperfusion also facilitates the conversion of xanthine dehydrogenase to XO, which in its oxidase form uses O_2 as an electron acceptor to continuously generate oxygen radicals. Increased FSS further induces NOX4 expression, thereby enhancing H_2O_2 production. NOX, NADPH oxidase; XO, xanthine oxidase; TCA, tricarboxylic acid cycle; ROS, reactive oxygen species; FSS, fluid shear stress; phox, phagocyte oxidase; FAD, flavin adenine dinucleotide.

thiol levels were markedly reduced, whereas plasma ischemia modified albumin (IMA) concentrations were increased and associated with blood pressure and the extent of placental histopathological damage, suggesting that systemic oxidative markers measured in maternal blood may provide incremental information on disease severity and complement placenta- or fetus-derived indices, although their predictive performance still requires validation in larger cohorts (29). A recent scoping review of cord blood oxidative stress biomarkers further indicated that indices of overall oxidative status, CAT, GSH and IMA showed relatively consistent associations with FGR across multiple studies, whereas results for individual ROS or single antioxidant enzymes were often highly variable, supporting the notion that the integrated status of the antioxidant network is more clinically interpretable than any single marker alone (25).

Overall, extensive evidence from human studies and animal models consistently indicates that enhanced oxidative stress combined with impaired antioxidant defense serves a pivotal role in the pathogenesis and progression of FGR.

Major sources of oxidative stress in the placenta

Enzymatic drivers of ROS generation: NOXs and XO. i) NOXs. The NOX family comprises transmembrane proteins that transfer electrons to O_2, thereby generating superoxide anions (O_2•-) (Fig. 2) (30). This family includes seven members, namely NOX1-5 and dual oxidase 1-2 (30). Matsubara and Sato (31) have detected NOX enzymatic activity in the microvillous membrane of human syncytiotrophoblasts, with activity most evident at 25 weeks of gestation but undetectable before 12 weeks. The absence of activity in early pregnancy may reflect the low-oxygen environment of the placenta at that stage (31). Their study also compared NOX activity between FGR placentas and normal placentas, and found no significant differences. Nevertheless, subtle or qualitative changes cannot be excluded because enzyme histochemistry may lack sensitivity to detect minor alterations (31). Experimental evidence has demonstrated that NOX1, NOX2 and NOX5 are present in the chorionic villi, mainly localized in trophoblast cells (32). In early villi, NOX enzymes are the predominant source of O_2•- before 10 weeks of gestation, with p47-phagocyte oxidase (phox) localized at the apical membrane of syncytiotrophoblasts (33). Increased superoxide levels are associated with activation of the p38MAPK pathway, suggesting that NOX may contribute to early placental development through MAPK signaling (33). Clinical and experimental data have indicated that NOX1 expression is elevated in preeclampsia during early

pregnancy, resulting in excessive superoxide production, which promotes disease progression (34). In addition, NOX subunits, including p22phox, p47phox and p67phox, are upregulated in preeclamptic placentas (35). Poinsignon *et al* (36) reported that NOX4 expression was also increased in preeclampsia. Unlike NOX1 and NOX2, NOX4 predominantly produces hydrogen peroxide (H_2O_2), which may function as a redox signaling mediator (36). In control placentas, NOX4 in syncytiotrophoblasts is predominantly localized to the nucleus, whereas in early-onset preeclampsia it shows stronger cytoplasmic and membrane staining (36). This pattern may reflect an adaptive mechanism by which trophoblasts respond to maternal hypertension by releasing H_2O_2 into the intervillous space to activate antioxidant and vasodilatory pathways (36). However, excess H_2O_2 can be converted to hydroxyl radicals (•OH) through the Fenton reaction, which induces lipid peroxidation and cellular damage (36).

ii) XO. XO, an enzymatic form of xanthine oxidoreductase (XOR), serves a central role in purine metabolism by catalyzing the sequential oxidation of hypoxanthine to xanthine and xanthine to uric acid. These reactions are accompanied by the generation of ROS such as H_2O_2 and O_2•-, positioning XO as a key regulator of redox homeostasis and oxidative stress (37). Evidence has highlighted the critical role of XO in pregnancy-related disorders. This enzyme is not only the major source of uric acid but also an important mediator of oxidative stress responses during gestation. Under ischemic conditions, the dehydrogenase form of xanthine oxidoreductase is converted into XO through sulfhydryl oxidation or limited proteolysis. Upon reperfusion, when oxygen supply is restored and hypoxanthine/xanthine have accumulated, XO uses O_2 as an electron acceptor and generates large amounts of superoxide and H_2O_2, thereby producing a burst of ROS characteristic of ischemia-reperfusion injury (Fig. 2) (37).

An animal study has indicated that exposure to electronic cigarettes during pregnancy reduces fetal and placental weights while markedly increasing placental XO activity, suggesting that environmental exposures may impair placental function through XO upregulation (38). Similarly, maternal inhalation of titanium dioxide nanoparticles has been shown to elevate XOR activity in the placental labyrinth of fetal mice. This was accompanied by decreased antioxidant defenses, such as reduced CAT activity, along with increased prostaglandin and thromboxane synthesis, favoring H_2O_2 accumulation and a more pro-oxidant, inflammatory milieu in the labyrinth zone, and thus, aggravating placental oxidative stress (39,40). In addition, high fructose intake, serving as a model of metabolic stress, has been found to enhance XO activity and uric acid production in the placenta, leading to functional impairment and FGR (41). These findings collectively suggest that excessive XO activation represents a convergent pathway through which diverse exogenous stressors compromise placental function.

In human pregnancy, XO activity is also markedly elevated under pathological conditions. In preeclampsia, maternal serum XO activity and uric acid levels are increased even when renal function remains normal, indicating that hyperuricemia is not solely attributable to impaired renal clearance but is closely linked to XO-mediated uric acid overproduction (42). XO levels are simultaneously elevated in the fetal circulation, further underscoring the active role of the placenta-fetal unit in pathological hyperuricemia (42). An experimental study has demonstrated that the XO inhibitor allopurinol effectively lowered placental uric acid levels and improved placental function, supporting the causal involvement of XO in gestational oxidative injury (43).

Clinical evidence provides further support. In FGR pregnancies, maternal plasma, cord plasma and placental tissues exhibit higher XO activity, accompanied by increased lipid peroxidation products, such as MDA, and decreased antioxidant capacity, which together implicate XO activation as a major contributor to placental oxidative injury (19). A large cohort study involving 665 women with suspected or confirmed placental insufficiency demonstrated that maternal uric acid levels were inversely associated with neonatal birth weight, with the association being particularly pronounced in infants whose weight fell below the third percentile (44). These findings not only highlight the pathogenic role of XO-derived products in FGR but also suggest their potential as early predictive biomarkers and therapeutic targets.

Mitochondrial electron transport chain (ETC) as a central source of ROS. Mitochondria are multifunctional organelles that serve essential roles in cellular metabolism, calcium (Ca^{2+}) homeostasis, redox balance and cell fate determination. They serve as the cellular powerhouses by generating ATP through oxidative phosphorylation. In addition to ATP, mitochondria also provide metabolic intermediates required for the synthesis of macromolecules such as DNA, RNA, proteins and lipids (45). They are further involved in maintaining intracellular Ca^{2+} homeostasis (46,47) and regulate cell death by releasing cytochrome c and activating apoptotic factors such as caspases (48). ROS are by-products of oxidative phosphorylation and participate in the regulation of redox homeostasis (49).

The mitochondrial ETC is composed of five multi-subunit protein complexes (complexes I-V) located in the inner mitochondrial membrane. Enzymatic reactions of the tricarboxylic acid (TCA) cycle produce reducing equivalents in the form of NADH and reduced flavin adenine dinucleotide ($FADH_2$), which transfer electrons to the ETC through complexes I and III, respectively. During electron transfer from NADH or $FADH_2$ to O_2, complexes I, III and IV pump protons (H^+) from the mitochondrial matrix into the intermembrane space (50). Molecular oxygen is reduced to water at complex IV, serving as the terminal electron acceptor (51). The proton gradient created across the inner membrane drives protons back into the matrix through complex V (ATP synthase), coupling this energy to the synthesis of ATP from ADP and inorganic phosphate (52). ROS generation is an intrinsic consequence of mitochondrial oxidative metabolism. Approximately 1-2% of O_2 consumed during oxidative phosphorylation undergoes partial reduction by electrons leaking from complexes I and III, producing O_2•$^-$ (50-52). Given the high level of O_2 consumption by mitochondria, a substantial proportion of O_2•$^-$ arises during this process. Superoxide generated at complex I is released exclusively into the mitochondrial matrix, whereas complex III produces superoxide released into both the matrix and intermembrane space (50). In the matrix, O_2•$^-$ is dismutated by SOD2 (Mn-SOD) to H_2O_2, while in the intermembrane space SOD1 (Cu,Zn-SOD) performs the same reaction (51,53). H_2O_2

may further react with Fe^{2+} or Cu^{+} via the Fenton reaction to generate OH• (54), and $O_2^{\bullet-}$ can react with nitric oxide (NO) to form peroxynitrite ($ONOO^-$) (55). Both OH• and $ONOO^-$ are highly reactive oxidants. To counterbalance these species, mitochondria possess intrinsic antioxidant systems, in which H_2O_2 is detoxified primarily by GPX1/4 and the mitochondrial peroxiredoxins peroxiredoxin 3 and peroxiredoxin 5 (53,56).

In the context of gestational hypoxia, placental mitochondria undergo metabolic reprogramming to maintain energy homeostasis. This involves structural and functional adjustments of ETC complexes, a predominance of mitochondrial fission and activation of the non-canonical unfolded protein response (UPR), highlighting the close relationship between oxidative stress adaptation and placental function (57). A clinical study in monochorionic twin pregnancies complicated by selective FGR (sFGR) has revealed placental ultrastructural abnormalities, elevated ROS levels, reduced energy reserves, and mitochondrial genomic and epigenetic alterations, supporting the coexistence of mitochondrial dysfunction and oxidative stress (57). A functional study has further demonstrated that impaired zinc finger protein 554 activity in the placenta and trophoblasts reduced the antioxidant capacity and triggered mitochondria-derived ROS-mediated apoptosis and autophagy. Administration of N-acetylcysteine (NAC) partially reversed these phenotypes, underscoring a causal link between mitochondrial ROS, cell death and placental dysfunction (58). Advanced maternal age is also associated with higher placental lipid peroxidation and apoptosis, with more pronounced effects in male fetuses, suggesting that maternal age may increase the risk of FGR through mitochondrial and oxidative stress pathways (59). A study at high altitude has demonstrated that placental mitochondrial oxidative capacity was closely related to fetal oxygen delivery, while in preeclampsia this capacity was suppressed, indicating the pathophysiological significance of placental mitochondrial metabolism under hypoxic conditions (60). Animal experiments provide mechanistic and therapeutic insights. In rodent models of hypoxic pregnancy, the mitochondria-targeted antioxidant mitoquinone mesylate (MitoQ) improved uterine artery reactivity and vascular remodeling, suggesting that attenuation of oxidative damage may enhance placental perfusion, although direct benefits to fetal growth remain to be established (61). Environmental pollutants, such as 1-nitropyrene, can inhibit progesterone synthesis and induce intrauterine growth restriction through mitochondrial ROS-driven signaling, whereas treatment with MitoQ or general control nonderepressible 2 inhibitors partially alleviates these effects (62). A human trophoblast study has shown that hydrogen sulfide regulated mitochondrial dynamics via sulfhydration of Miro2, thereby promoting cell migration and invasion, which links mitochondrial plasticity to deep placental invasion and adverse pregnancy outcomes (63). Furthermore, 25-hydroxycholesterol induces mitochondrial ROS accumulation, loss of membrane potential and lipid peroxidation, and triggers apoptosis, ferroptosis and autophagy, further establishing a connection between oxysterol-mediated mitochondrial oxidative stress and placental dysfunction (64). The impact of mitochondrial dysfunction on fetal organs also deserves attention. In an ovine FGR model, the mitochondrial oxidative phosphorylation capacity was reduced compared with that in appropriately grown control fetuses, accompanied by decreased expression of genes related to lipid metabolism, with differences observed between cardiac ventricles. These findings suggest a link between intrauterine growth restriction, cardiac maturation and abnormal energy metabolism (65). Another study demonstrated that limited substrate supply in utero reduced the number of fetal cardiac mitochondria and the content of ETC complexes, while reshaping metabolic pathways. This provides a mechanistic basis for the association between intrauterine growth restriction and increased long-term cardiovascular risk (66).

Impaired perfusion and ischemia-reperfusion-induced ROS bursts. During normal pregnancy, maternal spiral arteries undergo extensive physiological remodeling. This process involves the progressive loss of vascular smooth muscle cells and elastic membranes, which allows the vessels to dilate and relax, thereby ensuring a steady, low-resistance and continuous blood supply to the placenta. When this remodeling process is impaired and smooth muscle cells are retained, the affected tissue becomes highly susceptible to ischemia-reperfusion injury, a condition that is closely associated with excessive generation of ROS (67). Metabolomic studies have shown that succinate, an intermediate of the TCA cycle, selectively accumulates during the reperfusion phase. The rapid re-oxidation of accumulated succinate by succinate dehydrogenase drives a burst of ROS production through reverse electron transfer at mitochondrial complex I (68,69). Ischaemic succinate accumulation can, in part, be fueled by fumarate generated via the purine nucleotide cycle and the malate-aspartate shuttle, thereby linking fumarate to this ROS-generating pathway (68). At the same time, ischemia-reperfusion promotes the conversion of xanthine dehydrogenase into XO. In this oxidase state, XO utilizes oxygen as an electron acceptor, leading to sustained generation of oxygen radicals (70). From a hemodynamic perspective, failure of spiral artery remodeling causes maternal blood to enter the intervillous space in turbulent jets at abnormally high velocities of 1-2 m/sec (67). This abnormal increase in fluid shear stress (FSS) has been demonstrated to markedly upregulate PlGF in both coculture systems and intact vascular models (67). Elevated FSS also induces an increase in Nox4 mRNA expression in endothelial and smooth muscle cells, which in turn elevates H_2O_2 levels (71). Notably, knockdown of Nox4 in endothelial cells abrogates the effects of FSS on both H_2O_2 production and PlGF expression (71). Soluble fms-like tyrosine kinase 1 (sFlt-1) secretion is also regulated by NOX. The use of the Nox inhibitor diphenyleneiodonium reduces sFlt-1 release (72). A study has revealed that the p38 MAPK signaling pathway is not only involved in sFlt-1 secretion but also mediates Nox activation. Inhibition of p38 MAPK phosphorylation decreases both sFlt-1 secretion and superoxide production (72). p38 MAPK has been reported to be activated under hypoxia-reoxygenation conditions (73), suggesting that it may serve as a key regulator of ROS production and angiogenic factor expression in the context of ischemia-reperfusion injury.

3. Oxidative stress, ER stress and FGR

ER stress and the dual role of the UPR. The ER is a critical intracellular organelle responsible for the synthesis of transmembrane and secretory proteins, as well as for Ca^{2+}

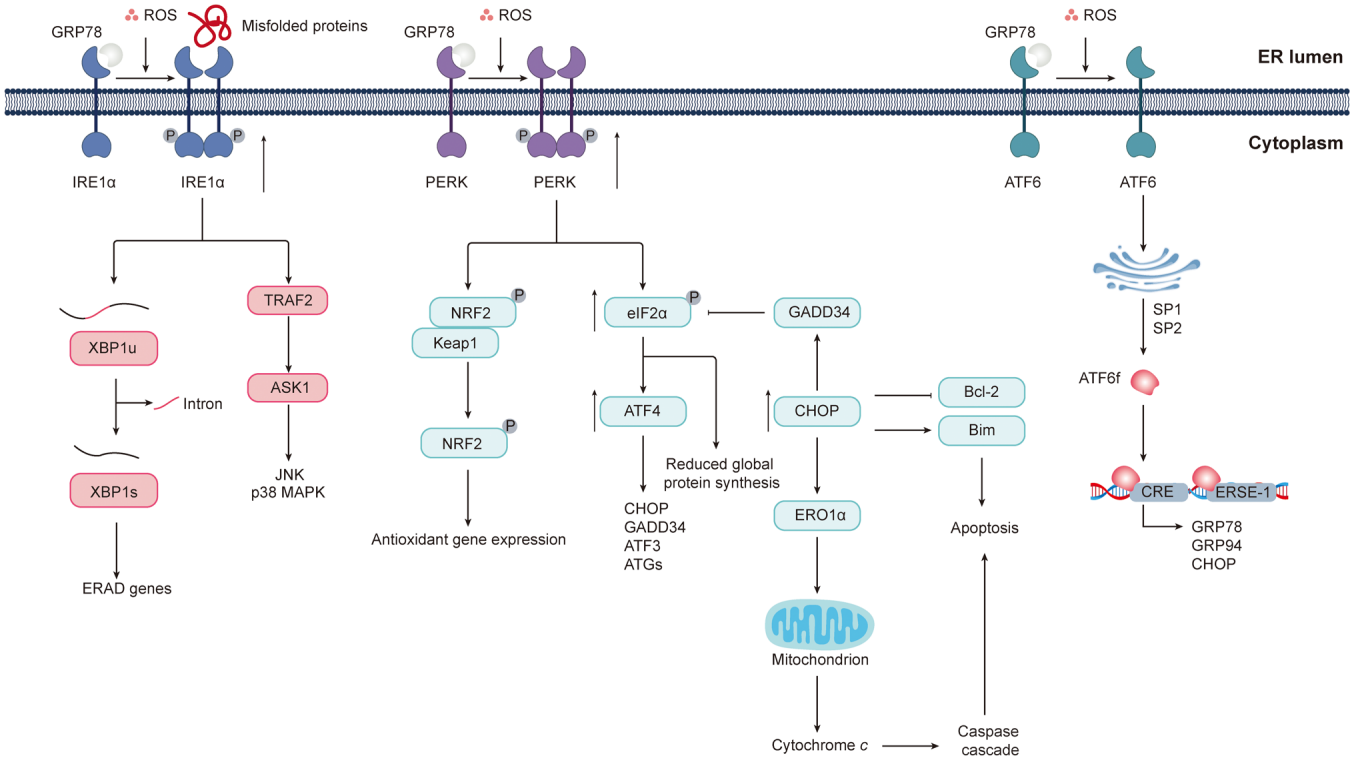

Figure 3. Oxidative stress and ROS signaling in ER stress and the UPR. The ER is highly sensitive to oxidative stress. When redox imbalance leads to the accumulation of misfolded proteins within the ER lumen, it triggers ER stress and activates the UPR. Under homeostatic conditions, the three major signaling branches of the UPR (PERK, ATF6 and IRE1α) remain inactive through their interaction with the molecular chaperone GRP78 at their luminal domains. Upon stress induction, GRP78 dissociates from these sensors, facilitating the oligomerization and autophosphorylation of PERK, the translocation and cleavage of ATF6, and the activation of IRE1α. Activated PERK phosphorylates the transcription factor NRF2, leading to its release from the Keap1 complex and the subsequent induction of antioxidant gene expression. PERK also phosphorylates the translation initiation factor eIF2α, thereby globally inhibiting protein synthesis while selectively enhancing the translation of ATF4. ATF4 regulates a series of cell fate-related genes, including CHOP, GADD34, ATF3 and ATGs. Upon CHOP upregulation, GADD34-mediated dephosphorylation of eIF2α restores translation initiation. CHOP also induces the expression of the ER oxidoreductase ERO1α, which triggers the release of cytochrome *c* and activates the caspase-dependent apoptotic signaling pathway. In addition, CHOP can transcriptionally downregulate Bcl-2 and upregulate Bim, further promoting apoptosis through multiple mechanisms. ATF6 is transported to the Golgi apparatus, where it is cleaved by SP1 and SP2 proteases to release its N-terminal transcriptionally active fragment. This fragment enters the nucleus and binds to cis-regulatory elements such as CRE and ERSE, inducing the transcription of chaperone proteins, including GRP78 and GRP94, as well as cell fate regulators such as CHOP. The activation of IRE1α also depends on oligomerization and autophosphorylation. Its ribonuclease activity then mediates the splicing of XBP1 mRNA, generating the active XBP1s protein, which enhances the expression of ERAD components and molecular chaperones. However, under prolonged stress conditions, IRE1α recruits TRAF2, leading to the activation of ASK1 and subsequent stimulation of the p38 MAPK and JNK signaling cascades. ROS, reactive oxygen species; ER, endoplasmic reticulum; UPR, unfolded protein response; PERK, PKR-like endoplasmic reticulum kinase; ATF, activating transcription factor; IRE1α, inositol-requiring enzyme 1α; GRP78, glucose-regulated protein 78; NRF2, nuclear factor erythroid 2–related factor 2; Keap1, Kelch-like ECH-associated protein 1; eIF2α, eukaryotic initiation factor 2α; CHOP, C/EBP homologous protein; GADD34, growth arrest and DNA damage-inducible protein 34; ATGs, autophagy-related genes; ERO1α, endoplasmic reticulum oxidoreductin 1α; SP1, site-1 protease; SP2, site-2 protease; CRE, cAMP response element; ERSE, ER stress response element; GRP94, glucose-regulated protein 94; XBP1, X-box binding protein 1; XBP1s, spliced X-box binding protein 1; ERAD, endoplasmic reticulum-associated degradation; TRAF2, TNF receptor-associated factor 2; ASK1, apoptosis signal-regulating kinase 1; P, phosphate group; ATF6f, activating transcription factor 6 fragment; XBP1u, X-box binding protein 1 (unspliced); Bim, Bcl-2 interacting mediator of cell death.

storage and lipid production (74). Under normal physiological conditions, the ER ensures correct protein folding and the maturation of nascent proteins into their native conformations, which are subsequently transported to the extracellular space or other cellular compartments (75). However, the ER is highly sensitive to oxidative stress. When oxidative stress occurs, misfolded proteins accumulate in the ER lumen, triggering ER stress and activating the UPR (75). The UPR leads to a general reduction in protein synthesis, the upregulation of molecular chaperones and enhanced expression of components associated with ER-associated protein degradation (ERAD) (76).

In homeostasis, the major UPR sensors, protein kinase RNA-like ER kinase (PERK), activating transcription factor 6 (ATF6) and inositol-requiring enzyme 1α (IRE1α), remain inactive through binding of their luminal domains to glucose-regulated protein 78 (GRP78) (Fig. 3) (75). GRP78 itself functions as an important chaperone protein that assists in protein folding. Under stress conditions, such as hypoxia, GRP78 dissociates from these complexes to support protein folding, while indirectly or directly enabling activation of PERK, ATF6 and IRE1α, thereby initiating the UPR (75). PERK is a transmembrane kinase that associates with GRP78 under resting conditions. Under stress conditions, dissociation allows PERK to oligomerize and undergo autophosphorylation, thereby activating its kinase activity (76). Activated PERK phosphorylates the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2), releasing it from the Keap1 complex and promoting the transcription of antioxidant genes. PERK also phosphorylates the translation initiation factor eukaryotic initiation factor 2α (eIF2α), which reduces global protein synthesis (77). Paradoxically, phosphorylation of eIF2α enhances the translation of ATF4. ATF4 in turn

regulates the transcription of genes involved in cell fate, including C/EBP homologous protein (CHOP), growth arrest and DNA damage-inducible protein 34 (GADD34), ATF3 and autophagy-related genes (78). ATF6 also remains bound to GRP78 in homeostasis. Following stress-induced dissociation, ATF6 is transported to the Golgi apparatus, where it undergoes sequential cleavage by site-1 protease and site-2 protease, generating an N-terminal fragment with transcriptional activity. This fragment translocates into the nucleus and binds to cis-regulatory elements such as cAMP response element and ER stress response element-1, thereby activating the transcription of chaperone proteins, including GRP78 and glucose-regulated protein 94, as well as cell fate regulators such as CHOP (79). IRE1α is a transmembrane protein with both kinase and endoribonuclease activities. At rest, it is bound to GRP78 in an inactive state. Upon accumulation of ROS in the ER lumen, GRP78 dissociates and facilitates folding, while IRE1α directly interacts with misfolded proteins, triggering its activation (75). Activation requires oligomerization and autophosphorylation (80). Active IRE1α exerts multiple RNA processing functions, including regulation of its own mRNA stability (81), cleavage of specific microRNAs (82), and most prominently, splicing of X-box binding protein 1 (XBP1) mRNA. The spliced XBP1 protein enhances the expression of ERAD-related genes and chaperones, thereby restoring protein homeostasis (83). In addition, IRE1α can promote autophagy via the JNK pathway (84). Notably, under prolonged stress, IRE1α shifts toward pro-apoptotic functions. Persistent activation recruits TNF receptor-associated factor 2, which subsequently activates apoptosis signal-regulating kinase 1 and initiates downstream p38 MAPK and JNK cascades, two major pro-apoptotic signaling pathways (85). In parallel, increased CHOP expression exerts multiple pro-apoptotic effects. These include activation of GADD34, which mediates eIF2α dephosphorylation, restoring translation initiation and promoting synthesis of pro-apoptotic proteins, thereby exacerbating ER stress (86). CHOP also induces ER oxidase 1α, which enhances Ca^{2+} transfer and triggers mitochondrial cytochrome *c* release, leading to caspase activation and ultimately apoptosis (87). Furthermore, CHOP modulates nuclear transcription by downregulating the anti-apoptotic protein Bcl-2 and upregulating the pro-apoptotic protein Bim, further promoting apoptosis (88).

ER stress signaling pathways in placental pathophysiology

IRE1-XBP1 axis in placental stress responses. Aberrant ER stress and excessive activation of the IRE1 signaling pathway are closely linked to abnormal placental development and adverse pregnancy outcomes. These alterations are most evident in preeclampsia and in pregnancies complicated by FGR (89). Compared with placentas from normotensive pregnancies, placental tissues from patients with preeclampsia, particularly in early-onset cases, exhibit increased IRE1 phosphorylation, enhanced XBP1 splicing and dilation of the ER lumen (89). Similarly, decidual tissues from patients with preeclampsia, with or without FGR, show higher XBP1 expression than those from normotensive patients with uncomplicated pregnancies (90). Endometrial biopsies from patients with recurrent miscarriage or implantation failure also exhibit elevated IRE1 expression compared with controls, whereas spliced X-box binding protein 1 (XBP1s) expression is lower, suggesting that dysregulated IRE1 activation may contribute to these complications (91). Phosphorylated IRE1 was not examined in decidual tissue samples from women with preeclampsia (with or without FGR) and normotensive controls, and additional studies are needed to determine whether IRE1 activity itself is altered. *In vitro* work has demonstrated that exposing trophoblast cells to hypoxia followed by reoxygenation, which models conditions in early-onset preeclampsia, markedly increased IRE1 phosphorylation together with other ER stress and apoptotic markers (92,93). These results support a role for IRE1 signaling in stress responses under pathological conditions. Other pregnancy complications associated with ER stress and IRE1 activation include intrahepatic cholestasis of pregnancy, characterized by accumulation of bile acids in the liver and systemic circulation. In a mouse model of intrahepatic cholestasis, heightened IRE1 activation in placental tissue coincided with apoptosis and FGR. Treatment with the IRE1 inhibitor 4 μ8c prevented trophoblast apoptosis and improved fetal growth (94). Similarly, in HTR 8/SVneo cells, inhibition of IRE1 signaling prevented deoxycholic acid-induced cell death (94). Physiological and environmental stressors can also trigger ER stress and activate IRE1 signaling, thereby increasing the risk of pregnancy complications. Maternal obesity is a well-known risk factor, and placental tissues from obese pregnancies exhibit higher levels of phosphorylated IRE1 and XBP1s than those from women with normal weight (95,96). Palmitic acid, which is the most abundant saturated fatty acid in circulation and commonly elevated in obesity, disrupts ER morphology, reduces trophoblast invasiveness, and induces ER stress and apoptotic signaling (97,98). Additional stressors that contribute to trophoblast ER stress and IRE1 overactivation include viral infections, such as Zika virus, and exposure to toxins, such as nicotine and ethanol (99,100). In these clinical and experimental settings, IRE1 signaling has been evaluated mainly in endpoint samples (for example, term placental tissues from complicated pregnancies or trophoblast cultures harvested hours after exposure), and usually using static measurements of protein abundance rather than dynamic readouts of IRE1 phosphorylation or XBP1 mRNA splicing. As a result, it remains uncertain whether sustained activation of the IRE1-XBP1s signaling axis is a primary driver of placental dysfunction or a downstream consequence of these stressors.

PERK-eIF2α/ATF4 pathway and regulation of cell fate. The PERK pathway likely serves a key role in shaping trophoblast function and cell fate under pathological placental conditions (101). In preeclamptic placentas, higher levels of phosphorylated PERK, phosphorylated eIF2α, ATF4 and CHOP have been reported, with signals mainly confined to the syncytiotrophoblast layer (101,102). Elevated phosphorylated PERK levels have also been detected in decidual tissues (103). In decidua collected at delivery from pregnancies complicated by FGR, the levels of phosphorylated eIF2α and ATF4 were increased compared with those in decidua from gestational age-matched uncomplicated pregnancies (104). These observations indicate that altered PERK signaling in the decidua may hinder decidualization and promote pregnancy complications. Maternal serum from women with preeclampsia activates the PERK pathway in placental explants and HTR-8/SVneo cells, causing increased phosphorylation of

eIF2α and induction of CHOP. Cell death follows serum exposure, although the extent to which PERK drives this cytotoxicity has not been fully determined (105). PERK-dependent trophoblast death in preeclampsia may be tied to deficiencies in histone deacetylases (HDACs), which are essential for trophoblast differentiation and are frequently downregulated in preeclamptic placentas (106,107). Silencing of HDAC2 in HTR-8/SVneo cells augments pyroptosis, and this effect is reduced when PERK is knocked down (106). These data suggest that PERK activation contributes to heightened trophoblast cell death in placental disease. Multiple *in vitro* systems model ER stress conditions that activate PERK signaling and influence trophoblast survival. In BeWo cells, alternating hypoxia and reoxygenation at 1% O_2 and ambient air increases phosphorylated eIF2α levels and lowers cell numbers (108). Interleukin 1β, a pro-inflammatory cytokine elevated in preeclampsia, promotes apoptosis in BeWo cells via PERK signaling, whereas progesterone counteracts this effect (101). Inhibition of PERK similarly diminishes apoptosis in BeWo cells exposed to the endocannabinoid 2 arachidonoylglycerol (109). Cadmium, an environmental pollutant and carcinogen, suppresses 11β-hydroxysteroid dehydrogenase type 2 expression in JEG-3 cells, while PERK silencing or antioxidant treatment with melatonin or N-acetylcysteine restores its expression (110,111). Collectively, these findings indicate that PERK signaling governs trophoblast survival across diverse ER stress contexts.

ATF6 signaling and dysregulation of angiogenic factors. In early-onset preeclampsia with FGR, placental tissues show higher ATF6α protein levels than those in healthy controls (90,108). Whether ATF6α activation is also increased remains unresolved, since neither the active form nor nuclear localization has been assessed. A defining feature of preeclampsia is reduced secretion of PlGF, a proangiogenic factor essential for endothelial integrity. In preeclamptic placentas, lower PlGF expression is associated with nuclear localization of ATF4 and ATF6β, but not with nuclear localization of ATF6α or XBP1, and nuclear ATF4 and ATF6β directly repress PlGF transcription (112,113). In BeWo cells exposed to ER stressors, such as thapsigargin or hypoxia followed by reoxygenation, simultaneous silencing of ATF4 and ATF6β raises PlGF expression (113). These results suggest that ATF4 and ATF6β act as negative regulators of PlGF, and that modulating ATF4/ATF6β signaling may help restore the angiogenic balance in pregnancies with placental dysfunction.

4. ROS, mitochondrial dysfunction and metabolic reprogramming

During pregnancy and the neonatal period, energy requirements for both the mother and fetus rise markedly. Because mitochondria drive cellular energy metabolism, FGR is often accompanied by intensified mitochondrial stress (114). Mitochondria use oxygen as the final electron acceptor during aerobic respiration, a process that inevitably generates ROS (114). Excess ROS damage biomolecules, and since the ETC is both a principal source and a target of ROS, mitochondrial dysfunction commonly coexists with persistent oxidative stress (114). Evidence shows that FGR offspring present with elevated ROS, abnormal antioxidant enzyme activity, increased lipid peroxidation and impaired ATP synthesis (115), underscoring oxidative stress as a central driver of metabolic disturbance.

The liver is densely populated with mitochondria and is pivotal for systemic metabolism, which makes it particularly susceptible to oxidative injury (Fig. 4) (116). Previous research has demonstrated pronounced hepatic oxidative and mitochondrial stress in FGR (116). In a spontaneous FGR pig model, neonatal livers showed higher α1-acid glycoprotein levels, indicating systemic oxidative stress, together with increased ETC complex IV expression, compared with those in normal birth weight littermates, consistent with ATP depletion from excessive hydrolysis (116). In a maternal caloric restriction rat model, cutting maternal energy intake by 50% raised the levels of the lipid peroxidation marker 4HNE and lowered GSH levels in offspring at 3 weeks of age. When offspring resumed normal diets after weaning, oxidative stress markers normalized in adulthood, suggesting that prenatal undernutrition alone can induce oxidative injury (117). Maternal protein restriction models have further been used to clarify the role of catch-up growth. Offspring exposed to a low-protein diet both in utero and throughout postnatal life, did not undergo catch-up growth, remained metabolically healthy in adulthood and generated less ROS (118). By contrast, switching to a normal diet at weaning in the LP2 group (offspring exposed to a maternal low-protein diet during gestation and lactation, switched to a normal-protein control diet at weaning) or at birth in the LP3 group (offspring exposed to a maternal low-protein diet during gestation only, with diets switched to a normal-protein control diet from birth) triggered catch-up growth (118). Among these groups, only LP2 offspring developed hypercholesterolemia, impaired glucose tolerance and altered drug metabolism at 4 months of age (119). These alterations coincided with aerobic metabolic disruption, including increased hepatic protein abundance of lactate dehydrogenase and phosphorylated pyruvate dehydrogenase, decreased protein abundance of citrate synthase and complex II, elevated levels of SOD1 and SOD2, reduced CAT, and increased 4-hydroxynonenal as a marker of lipid peroxidation, compared with those in control diet-fed offspring (119). The LP2 group also exhibited upregulation of the ROS-promoting protein p66 Src homology 2 domain-containing transforming protein C, the 66-kDa isoform of the Shc adaptor protein that promotes mitochondrial ROS production and is closely linked to ER stress (119). Consistent findings have indicated that catch-up growth after weaning raises hepatic oxygen consumption, shifts antioxidant capacity and reduces expression of mitochondrial DNA-encoded genes (120). Notably, the LP3 offspring do not exhibit these metabolic and mitochondrial abnormalities observed in LP2 offspring, suggesting that the timing of nutritional recovery is a critical determinant of oxidative stress and hepatic injury (119,120).

In the pancreas, FGR offspring exhibit impaired β-cell function and insufficient insulin secretion from birth (121), a phenotype that persists into adulthood (122). Animal studies have further demonstrated age-dependent increases in pancreatic islet ROS levels. For instance, in rats, ROS levels were already elevated at 1 week of age and exceeded twice the control levels by 15 weeks, accompanied by reduced citrate synthase activity, impaired complex I and III function, and

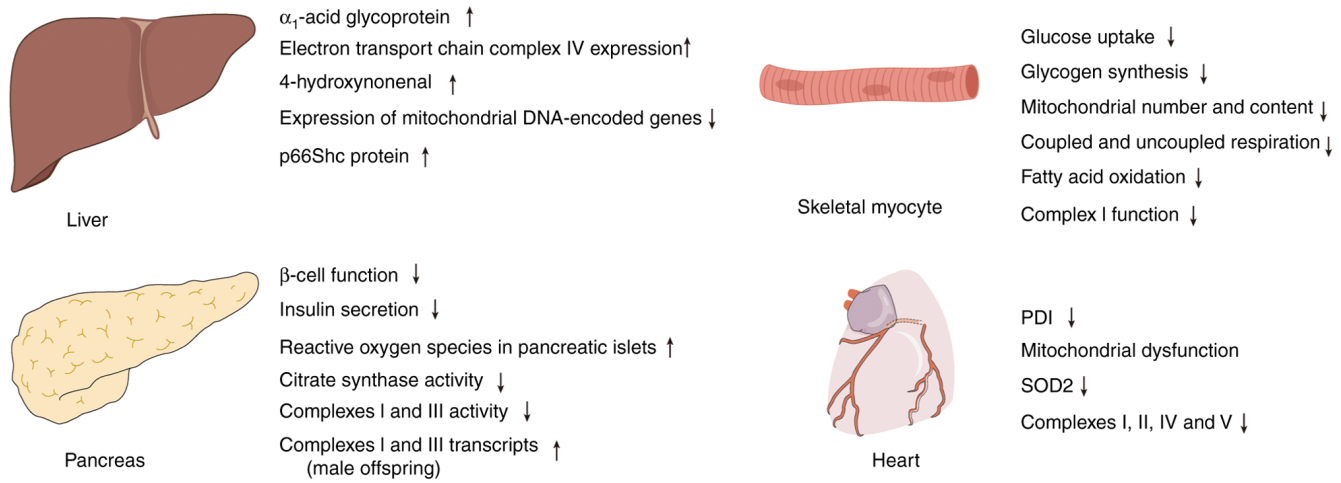

Figure 4. ROS accumulation, mitochondrial dysfunction and metabolic reprogramming in FGR and maternal nutritional models across multiple tissues. In the liver, the spontaneous FGR pig model shows that neonatal piglets exhibit elevated levels of α_1-acid glycoprotein and electron transport chain complex IV. In maternal caloric restriction experiments in rats, a reduction in maternal energy intake led to an increase in the lipid peroxidation marker 4-hydroxynonenal. Post-weaning catch-up growth reduced the expression of mitochondrial DNA-encoded genes. In the pancreas, FGR offspring exhibit impaired β-cell function and insufficient insulin secretion. Their islet ROS levels increase with age, accompanied by decreased activities of citrate synthase and complexes I and III. In skeletal muscle, early adult FGR offspring display reduced insulin-stimulated glucose uptake and glycogen synthesis. Maternal caloric restriction experiments similarly demonstrate that the mitochondrial number and content are reduced, accompanied by decreased coupled and uncoupled respiration, fatty acid oxidation, and complex I function. In the heart, prenatal nicotine exposure decreases cardiac PDI levels, and PDI deficiency further induces mitochondrial dysfunction and oxidative injury, manifested as reduced protein levels of SOD2 and mitochondrial complexes I, II, IV and V. FGR, fetal growth restriction; PDI, protein disulfide isomerase; ROS, reactive oxygen species; p66Shc, p66 Src homology 2 domain-containing transforming protein C; SOD2, superoxide dismutase 2.

insufficient ATP production (123). In maternal protein restriction models using rats, 3-month-old male offspring displayed elevated islet ROS levels and upregulation of complex I and III transcripts (124), suggesting that oxidative stress and mitochondrial dysfunction may exhibit sex-specific differences.

Skeletal muscle metabolism is also markedly impaired in FGR. In a rat model of uteroplacental insufficiency, FGR offspring in early adulthood showed reduced insulin-stimulated glucose uptake and glycogen synthesis in skeletal muscle, together with decreased ATP production and impaired aerobic enzyme activity (125). Pig models have revealed that FGR piglets are more susceptible to diet-induced mitochondrial damage in skeletal muscle when exposed to a high-fat diet after birth (126). Maternal caloric restriction experiments have demonstrated reduced mitochondrial number and content in offspring at 10 weeks of age, with concomitant reductions in coupled and uncoupled respiration, fatty acid oxidation, and complex I function (127).

The heart is another organ that is highly vulnerable to FGR-associated oxidative stress (128). Because mammalian hearts have limited regenerative capacity after birth, mitochondria-dependent oxidative stress may shorten the proliferative window (128). Prenatal nicotine exposure reduces the levels of protein disulfide isomerase (PDI), a protein essential for cardioprotection against ischemic injury (129). PDI deficiency exacerbates mitochondrial dysfunction and oxidative damage, leading to reduced levels of SOD2 and decreased expression of ETC complexes I, II, IV and V in cardiac tissue (129).

5. Epigenetic regulation and placental oxidative stress

Epigenetics refers to heritable modifications of chromatin that regulate gene expression without altering the underlying DNA sequence (130). A typical example is DNA methylation, which involves the addition of a methyl group to cytosine residues under the catalysis of DNA methyltransferases (131). In mammals, DNA methylation predominantly occurs at CpG sites, where cytosine is followed by guanine in the 5'-3' direction (132). Methylation of gene-regulatory regions, such as promoters, is generally associated with transcriptional silencing (132). In addition, DNA methylation serves key roles in X chromosome inactivation and genomic imprinting (133). Regulatory non-coding RNAs also contribute to transcriptional, post-transcriptional and translational regulation, and thus, are important components of epigenetic regulation (134,135).

These epigenetic mechanisms not only govern fundamental molecular processes but also have direct relevance to placental function and fetal growth (136). Current evidence indicates that epigenetic alterations serve critical roles in the regulation of fetal development. Genome-wide methylation analysis of placental samples from 12 monochorionic twin pregnancies complicated by sFGR revealed a global shift toward hypomethylation compared with normal placentas, involving 5,625 hypomethylated and 452 hypermethylated CpG sites, primarily located in CpG islands, gene bodies and promoter regions (136). Multi-omics analysis has further demonstrated activation of oxidative stress pathways in sFGR placentas. RNA sequencing identified 68 differentially expressed genes related to oxidative stress, while DNA hypomethylation was enriched in hypoxia-related pathways. Integrated analysis identified HK2 as a key upregulated node, linked to hypoxia-induced metabolic stress and oxidative injury, with strong predictive potential (area under the curve, 0.917), suggesting its pivotal role in hypoxia-driven metabolic-oxidative pathways (137). An animal study also supports this link. In a rat model of FGR induced by a high-sucrose, low-copper diet, placentas exhibited reduced size, elevated oxidative stress and global

DNA hypomethylation, while copper supplementation ameliorated oxidative stress and partially rescued placental morphology (138). Hu *et al* (139) reported mitochondrial abnormalities in placental villi from human monochorionic diamniotic twin pregnancies complicated by sFGR, accompanied by elevated mitochondrial oxidative stress and widespread hypomethylation of mitochondrial DNA. Epigenetic profiling further showed aberrant upregulation of mitochondrial long non-coding RNAs (lncRNAs/lncs), including lncND5, lncND6 and lncCyt b, along with reduced expression of cytochrome *c* oxidase I, a key component of respiratory chain complex IV, suggesting that dysregulated mitochondrial lncRNAs may contribute to respiratory dysfunction in sFGR (139). In trophoblasts isolated from the placentas of female patients with preeclampsia, mono-, di- and tri-methylation of histone H3 lysine 9, accompanied by reduced SOD expression, indicated that intrauterine oxidative stress may impair placental antioxidant defenses through H3K9 methylation and contribute to preeclampsia and fetal programming (140).

MicroRNAs (miRNAs/miRs) represent another layer of epigenetic regulation with strong implications for FGR. miR-199a-5p, previously linked to cardiovascular disease (141), inhibits VEGFA expression in endometrial mesenchymal stem cells (142), suppresses angiogenesis and induces oxidative stress in tumor models (143). In placentas from human monochorionic twin pregnancies complicated by sFGR, miR-199a-5p is upregulated, and associated with impaired angiogenesis, elevated oxidative stress and mitochondrial dysfunction (144). miR-199a also targets hypoxia-inducible factor 1-α (HIF-1α) (145) and is markedly elevated in severe preterm FGR (146). HIF-1α induces miR-210-3p, which suppresses fibroblast growth factor 1 and disrupts placental development, contributing to adverse placental outcomes in selective intrauterine growth restriction twin pregnancies (147). Other miRNAs also serve essential roles in oxidative stress regulation. miR-144 downregulates Nrf2, impairing cellular tolerance to oxidative stress (148), while miR-451 promotes antioxidant gene expression by inhibiting 14-3-3ζ, a repressor of the transcription factor FoxO3 (149). Both miRNAs are dysregulated under ischemic conditions and protect erythrocytes from oxidative damage (150). Oxidative stress induced by N-(4-hydroxyphenyl)-retinamide upregulates miR-16 and miR-26b in ARPE-19 cells (151). Chronic oxidative stress in human trabecular meshwork cells downregulates miR-29b, resulting in extracellular matrix gene upregulation (152). Similarly, primary fibroblasts exposed to H_2O_2 exhibit altered miR-155 and miR-16 expression (152). These findings are of particular relevance, as miR-155, miR-16 and miR-29b regulate normal placental development: miR-155 suppresses trophoblast proliferation and migration; miR-16 inhibits trophoblast invasion, proliferation and angiogenesis; and miR-29b reduces invasion and angiogenesis while promoting apoptosis (153-155). Other miRNAs with known links to oxidative stress include miR-204 and miR-1. miR-204 regulates oxidative stress responses in human trabecular meshwork cells by enhancing apoptosis, reducing cell viability and promoting accumulation of oxidized proteins (156). miR-1 is upregulated by ROS in ischemic myocardium (157) and has also been implicated in preeclampsia (158). Furthermore, downregulation of miR-21 is strongly associated with FGR (159). In placental cells, reduced miR-21 expression decreases trophoblast invasion of the maternal decidua, impairs migration and restricts growth, highlighting its role in trophoblast function (160). miR-21 expression itself can be induced by ROS (161).

Taken together, evidence from human studies, animal models and *in vitro* experiments demonstrates that epigenetic alterations occupy a central position in the pathogenesis of FGR and are closely intertwined with placental oxidative stress (136,138,140). Aberrations such as global DNA hypomethylation, dysregulation of non-coding RNAs and miRNA imbalances are frequently accompanied by elevated oxidative stress, mitochondrial damage and impaired angiogenesis (136,139,144). These findings suggest that oxidative stress may serve as a mechanistic bridge linking epigenetic alterations to placental dysfunction (138,140). Mapping the epigenetic landscape of FGR not only provides insights into its molecular pathology but also offers promising directions for antioxidant-based interventions aimed at improving placental function and optimizing fetal outcomes (138,159).

6. Calcium signaling in placental vascular endothelium, NO production and mechanisms of imbalance under oxidative stress

In normal pregnancies, endothelial cells on the fetal side of the placenta sense blood flow-induced shear stress and, via the mechanosensitive channel Piezo1, promote phosphorylation of endothelial NO synthase (eNOS) and enhancement of NO signaling, thereby supporting placental vasodilation and maintaining a relatively low-resistance perfusion environment (162). In placentas from pregnancies complicated by FGR, NO signaling and phosphorylation of eNOS at Ser1177 are increased, and can be further augmented by pharmacological activation of Piezo1, suggesting a compensatory endothelial response aimed at enhancing the NO pathway in the setting of altered placental blood flow (162). However, under persistent oxidative stress, NO is readily scavenged by excessive superoxide anions to form peroxynitrite, which reduces the effective bioavailability of NO and prevents this compensatory upregulation from fully restoring placental perfusion (163,164).

Abnormal intracellular calcium signaling is a key link between oxidative stress and the imbalance of NO production. In endothelial cells, persistent calcium oscillations induced by stimuli such as ATP drive sustained NO generation, whereas in human umbilical vein endothelial cells derived from preeclamptic patients, both sustained calcium signaling and sustained NO production are attenuated, indicating that disrupted calcium signaling is a direct cause of insufficient NO generation (165). In human umbilical vein endothelial cells obtained from pregnancies complicated by FGR and gestational hypertension, ATP-induced intracellular calcium responses show a prolonged time to peak and a reduced plateau during the sustained phase. After depletion of ER calcium stores, store-operated calcium entry driven by high extracellular calcium is markedly enhanced, suggesting an adaptive remodeling of calcium-buffering capacity and of the composition or functional coupling of calcium channels (166). Sustained calcium signals provide a critical temporal window for continuous release of endothelial vasodilators. Thus, when the sustained calcium plateau is blunted while compensatory

calcium influx is paradoxically enhanced, endothelial calcium homeostasis is more prone to disruption, leading to associated functional impairment (166). Consistent with this, placental endothelial cells in placentas from female patients with preeclampsia exhibit marked S-glutathionylation of eNOS, a modification associated with eNOS uncoupling, characterized by reduced NO production and increased superoxide generation, thereby providing molecular support for the concept that oxidative stress reduces effective NO bioavailability (167). In trophoblast cells and mouse models overexpressing an isoform of the transcription factor storkhead box 1, which recapitulate key features of preeclampsia, supplementation with tetrahydrobiopterin preserves NOS coupling, and alleviates nitrosative and redox imbalance, as well as excessive mitochondrial activation, suggesting that insufficient cofactor supply may amplify NO dysregulation in the context of oxidative stress (168). Furthermore, in a rat model of intrauterine growth restriction induced by maternal low-protein diet, offspring develop impaired endothelium-dependent vasodilation accompanied by increased arginase activity, reduced NO production and enhanced superoxide generation. Administration of L-arginine or pharmacological inhibition of arginase restored vasodilatory responses, indicating that upregulated arginase competes with eNOS for L-arginine and promotes eNOS uncoupling, thereby directly linking oxidative stress to NO deficiency (169).

Pregnancy-associated increases in uterine blood flow rely on localized calcium release in vascular smooth muscle that activates large-conductance calcium-activated potassium (BKCa) channels, generating spontaneous transient outward currents and membrane hyperpolarization, which in turn inhibit voltage-dependent calcium channel-mediated calcium entry, lower myogenic tone and help maintain low-resistance perfusion (170). A mechanistic study has shown that, in uterine arteries, pregnancy induces ten-eleven translocation methylcytosine dioxygenase 1-mediated active DNA demethylation of the BKCa channel β1-subunit gene, which in turn upregulates β1-subunit expression and enhances BKCa channel function, providing an epigenetic explanation for how the endocrine milieu chronically tunes the efficiency of calcium signaling-vasodilation coupling (171). When pregnancy is complicated by hypoxia, a condition commonly associated with impaired placental perfusion, gestational hypoxia blunts pregnancy-induced enhancement of calcium release and spontaneous transient outward currents, and is accompanied by activation of ER stress and oxidative stress pathways, rendering uterine arteries more prone to a high-tone state and thereby increasing the risk of preeclampsia and fetal intrauterine growth restriction (172). In the placental circulation, BKCa channel function is impaired in chorionic plate arteries from preeclamptic pregnancies and is associated with increased placental vascular resistance, indicating that dysregulation of the BKCa channel system may consolidate oxidative stress and calcium-dependent contractile dominance into a hemodynamic outcome of low perfusion (173). Furthermore, purinergic receptor-dependent pathways can form a positive feedback loop between calcium signaling and oxidative stress. For example, in human umbilical vein endothelial cells exposed to high glucose, purinergic receptor P2X 4 (P2X4) expression is upregulated, accompanied by increased intracellular calcium levels, elevated ROS levels and reduced NO production. Inhibition of P2X4 signaling attenuates inflammatory injury, suggesting that P2X4 is a key coupling molecule that links calcium influx to oxidative stress and contributes to reduced NO bioavailability (174).

7. Antioxidant-based therapeutic strategies in FGR

As aforementioned, oxidative stress is closely involved in the pathogenesis and progression of FGR. Protecting the placenta and fetus from oxidative damage has therefore emerged as a promising therapeutic strategy. Table II summarizes the application of antioxidants in the treatment of FGR.

A pilot clinical study first confirmed the feasibility and safety of maternal oral melatonin supplementation. Treatment was well tolerated, increased fetal melatonin levels and reduced oxidative stress in FGR placentas (175). Another pilot study suggested that pentoxifylline may improve endothelial function and promote vasodilation by lowering inflammation-mediated cytokine levels. In women with early-onset FGR, pentoxifylline administration was associated with increased fetal weight, enhanced serum antioxidant capacity, improved neonatal outcomes and reduced mortality (176). By contrast, a large multicenter randomized controlled trial involving 1,877 nulliparous women between 14 and 22 weeks of gestation evaluated vitamin C (1,000 mg/day) and vitamin E (400 IU/day) supplementation. The trial showed no significant difference between the intervention and placebo groups in terms of the incidence of low birth weight or in rates of infant death or severe adverse outcomes, suggesting that routine vitamin C and E supplementation during pregnancy does not improve maternal or fetal outcomes (177).

Findings from animal studies further support the potential of antioxidant interventions. In a sheep model of FGR, maternal melatonin supplementation from 0.7 gestation to term reduced cerebral lipid peroxidation, improved white matter myelination and axonal integrity in growth-restricted offspring, and ameliorated neurobehavioral deficits (178). In rats, the mitochondria-targeted antioxidant MitoQ was shown to cross the placenta, improve uterine artery reactivity and prevent hypoxia-induced vascular remodeling (61). However, in a reduced uterine perfusion pressure mouse model of preeclampsia, in which mild oxidative stress is required for trophoblast proliferation, invasion and migration, administration of MitoQ in early pregnancy may interfere with placental development and exacerbate preeclampsia-like phenotypes (179). These findings highlight the need for careful timing and dosing when considering antioxidant therapies in pregnancy (61,179).

Other antioxidants have also shown therapeutic benefits in experimental models. In a mouse model of FGR, tempol increased fetal body weight and crown-rump length, and improved uterine artery blood flow velocity (180). In guinea pigs, maternal oral administration of NAC reduced placental vascular resistance, restored fetal weight, and increased the fetal-to-placental weight ratio at term. NAC also improved eNOS-dependent relaxation in fetal aortas and umbilical arteries, normalized eNOS mRNA levels in endothelial cells, and reversed hypomethylation of the nitric oxide synthase 3 (Nos3) promoter at CpG-170, suggesting that NAC confers vascular benefits at least in part through

Table II. Clinical and preclinical studies investigating interventions targeting oxidative stress in FGR.

Authors, year	Intervention	Clinical/preclinical	Model	Key findings	(Refs.)
Alers *et al*, 2013	Melatonin	Clinical (NCT01695070)	12 women with severe early-onset FGR	Maternal melatonin therapy was well-tolerated, increased fetal melatonin levels, and reduced oxidative stress in the placenta of FGR fetuses.	(175)
Miller *et al*, 2014	Melatonin	Preclinical	Pregnant sheep with FGR	Melatonin could improve white matter and axonal injury in FGR lamb brains and was accompanied by improvements in the behavioral capacities of FGR lambs.	(178)
Asadi *et al*, 2022	Pentoxifylline	Clinical (IRCT2014031 7017034N9)	40 pregnant women with the diagnosis of severe early-onset FGR	Enhanced fetal growth and serum antioxidant capacity, thereby contributing to improved neonatal outcomes and reduced mortality.	(176)
Rumbold *et al*, 2006	Vitamins C and E	Clinical (ISRCTN00416244)	Nulliparous women between 14 and 22 weeks of gestation	Supplementation with vitamins C and E during pregnancy did not improve maternal or neonatal outcomes.	(177)
Wang *et al*, 2024	MitoQ	Preclinical	Wistar rats	Oral administration of the mitochondria-targeted antioxidant MitoQ could effectively protect against uterine artery vascular dysfunction and remodeling.	(61)
Yang *et al*, 2021	MitoQ	Preclinical	Reduced uterine perfusion pressure mice	The efficacy of mitochondria-targeted antioxidant therapy was highly gestational-stage dependent: Potentially beneficial in late pregnancy but harmful in early pregnancy; excessive suppression of trophoblastic oxidative stress during early gestation may impair placentation.	(179)
Stanley *et al*, 2012	Tempol	Preclinical	FGR mice	The antioxidant tempol increased fetal weight and crown-rump length, and enhanced uterine artery blood flow velocity.	(180)
Herrera *et al*, 2017	NAC	Preclinical	FGR guinea pigs	Lowered placental vascular resistance and restored fetal growth, while rescuing eNOS-dependent vasodilation and normalizing endothelial eNOS expression with reversal of Nos3 promoter CpG-170 hypomethylation.	(181)
Vega *et al*, 2016; Bourque *et al*, 2012	Resveratrol	Preclinical	Wistar rats	Improved oxidative stress markers in the mother, fetus and placenta, and reduced fetal mortality in a prenatal hypoxia model.	(182, 183)

eNOS, endothelial nitric oxide synthase; FGR, fetal growth restriction; MitoQ, mitoquinone mesylate; NAC, N-acetylcysteine; Nos3, nitric oxide synthase 3.

epigenetic modulation of Nos3 (181). Similarly, in Wistar rats, maternal resveratrol supplementation ameliorated oxidative stress marker levels in mothers, fetuses and placentas, and in a hypoxic pregnancy model, it reduced fetal mortality and improved intrauterine survival (182,183).

Collectively, clinical and preclinical evidence suggests that antioxidant-based therapies hold promise for mitigating FGR by alleviating oxidative stress and improving placental and fetal outcomes. Nevertheless, the results remain heterogeneous, and the safety, timing and specificity of antioxidant interventions require careful consideration before translation into clinical practice.

8. Conclusions and future perspectives

Placental oxidative stress serves a central role in the pathogenesis and progression of FGR. During early pregnancy, moderate levels of oxidative stress facilitate trophoblast invasion, spiral artery remodeling and angiogenesis. However, when perfusion abnormalities and recurrent ischemia-reperfusion occur, the oxidative burden rises sharply. ROS generated from NOX, XO and mitochondria accumulate, triggering ER stress and the UPR. This subsequently activates key signaling pathways, including the PERK-eIF2α/ATF4, IRE1α-XBP1 and ATF6 signaling pathways. In parallel, both placental and fetal tissues undergo metabolic reprogramming, with mitochondrial dysfunction as the central hallmark. Oxidative stress is further accompanied by marked epigenetic alterations, such as global DNA hypomethylation, aberrant H3K9 modifications and dysregulation of noncoding RNAs, including miR-199a-5p, miR-210-3p and miR-21. Several antioxidants, such as melatonin, pentoxifylline, NAC and tempol, show potential in alleviating FGR, although the precise choice of molecular targets and the optimal timing of intervention may be critical for successful clinical translation.

Future research should aim to establish an integrated biomarker system that combines oxidative stress markers (such as MDA, 4HNE, 8-OHdG and d-ROMs), uterine artery Doppler indices reflecting impaired uteroplacental perfusion (184), metabolic profiling and epigenetic signatures to enable early risk stratification and therapeutic monitoring. Clinically, antioxidant interventions must strike a balance between preserving physiological ROS levels required for placental development and preventing pathological oxidative injury. Promising strategies may include mitochondria-targeted therapies and selective inhibition of XO, potentially in combination with pro-angiogenic or immunomodulatory approaches. Optimizing treatment windows and dosing regimens, together with long-term maternal-fetal follow-up, will be essential to translate antioxidant-based interventions from experimental evidence to a tangible clinical benefit.

Acknowledgements

Not applicable.

Funding

The present review was funded by the Science and Technology Development Program of Jinan Municipal Health Commission (grant no. 2024203001), and The Medical Clinical and Technology Transfer Fund of China International Medical Exchange Foundation (grant no. Z-2014-08-2309-6).

Availability of data and materials

Not applicable.

Authors' contributions

DC, SY, FG and QS reviewed the literature and wrote the manuscript. CW and KF critically revised the manuscript for important intellectual content and approved the final manuscript version to be published. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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