Placenta and Reproductive Medicine

REVIEW ARTICLE

Mitochondrial dysfunction in placental ischemic diseases: Mechanisms and therapeutic implications

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ABSTRACT

Placental ischemic diseases, including preeclampsia (PE) and intrauterine growth restriction (IUGR), are leading causes of maternal and neonatal morbidity and mortality worldwide. These conditions originate from defective spiral artery remodeling, leading to reduced uteroplacental perfusion and chronic placental ischemia. The resultant hypoxia/reoxygenation injury creates a hostile environment that profoundly impacts placental cellular function. Central to this dysfunction is the mitochondrion, an organelle critical for energy production, calcium homeostasis, and the regulation of apoptosis. Emerging evidence positions mitochondrial dysfunction as a key nexus in the pathophysiology of placental ischemia. This review synthesizes current knowledge on the mechanisms driving mitochondrial impairment in the ischemic placenta. We explore the role of oxidative stress, the opening of the mitochondrial permeability transition pore (mPTP), disrupted mitochondrial dynamics (fusion/fission), and subsequent activation of apoptotic and inflammatory cascades. Furthermore, we discuss the potential of mitochondrial-targeted therapeutics, such as specific antioxidants and inhibitors of the mPTP, as novel strategies to alleviate placental damage and improve pregnancy outcomes. A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science to identify relevant preclinical studies and mechanistic insights, which were synthesized narratively. Understanding these intricate mitochondrial pathways is crucial for developing effective interventions for these devastating disorders.

Keywords: mitochondria, placenta, ischemia, preeclampsia, intrauterine growth restriction, oxidative stress, mitophagy, apoptosis, therapeutics

INTRODUCTION

Placental ischemic diseases, principally preeclampsia (PE) and intrauterine growth restriction (IUGR), represent a spectrum of disorders that originate from a poorly perfused placenta, largely due to deficient spiral artery remodeling and malplacentation that impair uteroplacental blood flow.[1,2] These conditions affect 5%–10% of all pregnancies and are a global health concern, contributing substantially to preterm birth and maternal cardiovascular morbidity, with long-term cardiovascular and metabolic risks documented in offspring.[3,4] Estimates for IUGR range from 5%–15% in high-income regions and are higher in developing countries, with lifelong risks that include hypertension and vascular/endothelial dysfunction in exposed offspring.[5] Epidemiologic and mechanistic studies link IUGR to increased blood pressure and vascular stiffness from childhood into adulthood, supporting these long-term cardiovascular risks.[6]

The accepted two-stage model of PE holds that

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inadequate trophoblast invasion and failure to remodel maternal spiral arteries in early pregnancy (placental stage) lead to reduced and intermittent uteroplacental blood flow, which then triggers release of anti-angiogenic and inflammatory factors causing the maternal clinical syndrome (maternal stage).[7] Histopathology shows persistence of smooth muscle and endothelial cells in spiral arteries and features like acute atherosis, consistent with impaired remodeling and altered flow in PE.[8] This ischemia–reperfusion injury in the placenta provokes oxidative stress and release of placental factors, priming the maternal systemic syndrome with endothelial activation and dysfunction.[9] The resulting exaggerated inflammatory response driven by cytokines and immune activation amplifies vascular injury and the clinical features of PE.[10]

The placental trophoblast, with its high energy needs, is particularly vulnerable to fluctuations in oxygen tension; resulting ischemia drives cellular stress with nutrient limitation, adenosine triphosphate (ATP) depletion, and excessive reactive oxygen species generation in trophoblast mitochondria.[11] While once viewed as a passive bystander to ischemia, the mitochondrion is now recognized as a central orchestrator of cellular stress responses integrating redox signaling, dynamics (fission/fusion), mitophagy, and bioenergetics to determine trophoblast fate under hypoxia–reoxygenation.[12] In PE models and placental tissue, mitochondrial reactive oxygen species (ROS), altered respiration, and fragmented networks actively drive downstream inflammatory and antiangiogenic pathways, underscoring mitochondria as primary regulators rather than mere victims of injury.[13]

Beyond ATP synthesis *via* oxidative phosphorylation, mitochondria regulate intracellular Ca^{2+} by buffering cytosolic calcium and shaping Ca^{2+} signaling microdomains, which in turn modulate trophoblast function and fate.[14] They also maintain redox homeostasis as both major sources and sensors of reactive oxygen species, integrating antioxidant systems to balance signaling versus oxidative damage.[11] Mitochondria further govern programmed cell death by coordinating mitochondrial outer membrane permeabilization, release of cytochrome c, and downstream caspase activation in apoptosis, while also intersecting with necroptosis, autophagy/mitophagy, and ferroptosis pathways at the maternal–fetal interface.[15] At this interface, balanced engagement of these pathways shapes trophoblast behavior and placental homeostasis; dysregulation links to pregnancy complications, highlighting mitochondria as central integrators of apoptotic and non-apoptotic death signaling in placental tissues.[16] In placental tissue, dysregulated mitochondrial signaling shifts the balance toward apoptosis and other regulated cell death modalities, contributing to disorders such as PE and fetal growth restriction.[17] Elevated necroptotic and ferroptotic signatures, disrupted mitochondrial quality control, and oxidative stress correlate with placental dysfunction in these conditions, linking mitochondrial imbalance to adverse maternal–fetal outcomes.[18]

In the context of placental ischemia, mitochondrial dysfunction creates a vicious cycle. Ischemia-induced oxidative damage impairs the electron transport chain (ETC), increasing mitochondrial reactive oxygen species and propagating further ROS production—a process termed "ROS-induced ROS release" that amplifies oxidative stress and placental injury.[19] In PE models with reduced uterine perfusion, placental complex activities and respiration decline while mitochondrial ROS (mtROS) rise, and targeting mitochondrial ROS lowers maternal blood pressure, underscoring this feed-forward mechanism.[13] Together, human and experimental data show that hypoxia/ischemia-driven electron transport chain dysfunction and excess mitochondrial ROS sustain each other, worsening trophoblast damage and contributing to PE and fetal growth restriction.[19] Reduced uteroplacental perfusion models demonstrate decreased placental mitochondrial complex activity and respiration with increased mitochondrial ROS, linking this vicious cycle to hypertension and impaired fetal growth *in vivo*.[13]

This triggers the opening of the mitochondrial permeability transition pore (mPTP), dissipating the mitochondrial membrane potential and leading to the release of pro-apoptotic factors such as cytochrome c.[20] In human placental tissues, hypoxia–reoxygenation increases mitochondrial cytochrome c release and activates caspase-3, confirming apoptosis downstream of mitochondrial membrane potential ($\Delta\Psi m$) collapse and mPTP opening.[21] Furthermore, the dynamic processes of mitochondrial fusion, fission, and mitophagy (collectively known as mitochondrial quality control) are disrupted, leading to an accumulation of damaged, dysfunctional organelles, as shown in PE placentas with increased DRP1-mediated fission, altered OPA1/MFN balance, and maladaptive activation of PINK1/Parkin pathways that correlate with reduced mitochondrial content and heightened oxidative stress.[22] Reviews of placental mitochondrial biology in PE consistently describe disturbed fusion–fission dynamics and impaired mitophagy as central to placental dysfunction and trophoblast injury, supporting the link between defective mitochondrial quality control and buildup of dysfunctional mitochondria.[23]

This review aims to provide a comprehensive overview of the molecular mechanisms linking placental ischemia to mitochondrial dysfunction. We will dissect the key pathways involved, including the role of oxidative stress, mPTP opening, and altered mitochondrial dynamics. Finally, we will explore the therapeutic landscape,

focusing on emerging strategies to target these mitochondrial defects as a means to mitigate placental injury and improve clinical outcomes in pregnancies complicated by PE and IUGR.

METHODS

This review was prepared in accordance with the guidelines for narrative reviews outlined by the journal. A comprehensive literature search was performed using the PubMed, Scopus, and Web of Science databases to identify relevant studies published up to March 2026. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to three core concepts: (1) placental ischemic diseases ("preeclampsia," "intrauterine growth restriction," "IUGR," "placental ischemia," "uteroplacental insufficiency"); (2) mitochondrial biology ("mitochondria," "mitochondrial dysfunction," "oxidative stress," "mitochondrial permeability transition pore," "mPTP," "mitochondrial dynamics," "fission," "fusion," "mitophagy," "DRP1," "OPA1," "PINK1," "Parkin"); and (3) therapeutics ("mitochondria-targeted antioxidants," "MitoQ," "MitoTEMPO," "SkQ1," "cyclosporine A," "NIM811," "Debio-025," "TRO40303," "Mdivi-1," "P110," "siRNA," "urolithin A," "NAD+ precursors," "nanoparticles," "liposomes").

The search was limited to articles published in English. Both original research articles and review articles were considered. Reference lists of retrieved articles were manually screened to identify additional relevant studies (snowballing method). The inclusion criteria prioritized studies that: (1) investigated mitochondrial mechanisms in the context of placental ischemia, PE, or IUGR; (2) provided mechanistic insights into oxidative stress, mPTP opening, mitochondrial dynamics, or mitophagy; (3) evaluated mitochondrial-targeted therapeutics in preclinical models of placental dysfunction or related ischemia-reperfusion injury; and (4) were published in peer-reviewed journals. Studies unrelated to placental biology or mitochondrial function were excluded.

Data extraction focused on the molecular mechanisms of mitochondrial dysfunction, the sequence of pathological events linking ischemia to organelle damage, and the efficacy, advantages, and limitations of therapeutic interventions. Key findings were synthesized narratively and organized into thematic sections addressing mechanisms, therapeutic strategies, and future directions.

MECHANISMS OF MITOCHONDRIAL DYSFUNCTION IN THE ISCHEMIC PLACENTA

The hypoxic and reperfusion environment of the ischemic placenta triggers a cascade of events that converge on the mitochondrion, compromising its integrity and function. This section examines the key mechanisms oxidative stress, electron transport chain impairment, mitochondrial permeability transition pore opening, and disrupted mitochondrial dynamics that drive trophoblast injury and contribute to the pathophysiology of PE and IUGR.

Oxidative stress and the ETC

The primary driver of mitochondrial damage in placental ischemia is oxidative stress. Intermittent reperfusion, while restoring much-needed oxygen, paradoxically triggers a burst of reactive oxygen species that overwhelms antioxidant defenses and impairs electron transport chain activity in trophoblast mitochondria, as evidenced by reduced complex activities and diminished respiration observed in both human preeclamptic placentas and experimental ischemia models.[13] Ischemia-reperfusion injury in PE elevates placental ROS from both mitochondrial sources and enzymatic sources such as xanthine oxidase, driving endothelial dysfunction and antiangiogenic signaling.[9,13] Experimental studies confirm that hypoxia or reperfusion increases trophoblast mitochondrial ROS and impairs respiratory complex activities, while treatment with mitochondrial-targeted antioxidants attenuates these effects and lowers blood pressure in ischemic animal models, directly implicating mitochondrial oxidative stress in the pathogenesis of PE.[13] Furthermore, mitigating mitochondrial ROS in trophoblast cultures reduces stabilization of hypoxia-inducible factor-1α and downstream secretion of soluble fms-like tyrosine kinase 1, providing a direct mechanistic link between ROS bursts and the release of antiangiogenic factors that characterize the maternal syndrome.[24,25]

Sources of mitochondrial ROS generation

Within mitochondria, complexes I and III of the electron transport chain serve as the predominant sites of superoxide generation.[26] Complex I releases superoxide exclusively into the mitochondrial matrix, whereas complex III generates superoxide that can be released into both the matrix and the intermembrane space, allowing it to potentially reach the cytosol.[26,27] Under normoxic conditions, the ETC efficiently transfers electrons to molecular oxygen to form water. However, during ischemia, the absence of oxygen as the final electron acceptor drives the ETC into a highly reduced state. Upon reperfusion, the sudden reintroduction of oxygen causes a massive, uncontrolled transfer of electrons, generating a burst of superoxide through reverse electron transport, predominantly at complex I, with additional contributions from complex III.[28]

Quantitative studies have elucidated the relative contri-

butions of these sites: succinate accumulation during ischemia fuels reverse electron transport upon reperfusion. Under simulated early reperfusion conditions, total mitochondrial ROS production falls to approximately 56% of succinate-alone conditions, with roughly half attributable to complex I-mediated reverse electron transport (RET), approximately 14% from complex III, and the remainder from upstream sources.[29] Complementary work confirms that ischemic succinate oxidation dominantly drives RET and superoxide formation during early reperfusion, but contributions from complex III and other ETC defects increase overall ROS capacity and output following ischemia, supporting a large, rapid ROS surge when electron supply and membrane potential recover.[29,30]

Deleterious effects of excessive ROS

This excessive ROS production has several interrelated deleterious effects that propagate mitochondrial injury.

Direct damage to mitochondrial components

Reactive oxygen species directly damage mitochondrial DNA, which lacks protective histones and has limited repair capacity.[31] Increased ROS correlates with a 44% reduction in mitochondrial DNA (mtDNA) copy number and 30%–50% decreases in mtDNA-encoded transcripts, with corresponding reductions in the activities of complexes I, III, and IV, thereby reinforcing a vicious cycle of dysfunction.[32,33] ROS also induce lipid peroxidation of cardiolipin, a phospholipid uniquely abundant in the inner mitochondrial membrane that is essential for maintaining ETC supercomplex stability and optimal function.[32] Cardiolipin peroxidation adjacent to ETC complexes destabilizes these supercomplexes and impairs electron transfer, facilitating further ROS output.[32] Additionally, ROS directly oxidize protein subunits of the ETC, notably the iron–sulfur centers in complexes I and III. Complex I's N2 iron–sulfur cluster is a probable one-electron donor to oxygen; oxidative insults to these centers increase superoxide release into the matrix and intermembrane space, respectively.[34,35] Oxidative modification of susceptible amino acid "hot spots" within ETC proteins further inhibits complexes I, III, and IV, promoting electron leak and amplifying superoxide formation.[32]

Inactivation of antioxidant enzymes

The high concentration of ROS can inactivate key antioxidant enzymes localized within mitochondria. Manganese superoxide dismutase, which resides in the mitochondrial matrix and serves as the primary defense against matrix superoxide, is particularly susceptible to oxidative inactivation.[36,37] Compromising this intrinsic defense system leaves mitochondria increasingly vulnerable to subsequent oxidative insults.

Establishment of a self-perpetuating cycle

Damaged ETC complexes become inherently "leaky," diverting a greater proportion of electrons to oxygen rather than to their intended acceptors. This perpetuates and amplifies ROS generation through a phenomenon termed "ROS-induced ROS release" [38,39] This feed-forward mechanism ensures that initial oxidative injury begets further oxidative injury, transforming what might have been a transient, reversible insult into sustained, progressive mitochondrial dysfunction.

The vicious cycle of oxidative stress and mitochondrial damage

The interconnected nature of these mechanisms creates a self-amplifying feed-forward loop that lies at the heart of placental ischemic injury. As illustrated in Figure 1, the initial ischemia-reperfusion event triggers a surge in ROS primarily generated by the ETC. These ROS induce oxidative damage to mtDNA, essential ETC proteins, and membrane lipids, which in turn exacerbates ETC impairment and dysfunction. This results in a secondary, more intense burst of ROS production, creating a vicious cycle that progressively worsens mitochondrial integrity. This cycle ultimately culminates in the pathological opening of the mitochondrial permeability transition pore, a critical event that commits the cell to injury or death pathways and will be discussed in detail in the following section.

The mPTP

The mitochondrial permeability transition pore is a non-specific channel of the inner mitochondrial membrane whose opening represents a critical juncture in the transition from cellular stress to cell death.[40,41] Under physiological conditions, the inner membrane maintains tight impermeability, preserving the proton electrochemical gradient essential for oxidative phosphorylation and ATP synthesis.[42,43] However, sustained opening of the mPTP is triggered by pathological stimuli characteristic of the ischemic placenta, including mitochondrial matrix calcium overload, elevated inorganic phosphate levels, and most potently, oxidative stress.[44,45]

Opening of the mPTP has catastrophic consequences for mitochondrial and cellular integrity, as illustrated in Figure 2. (1)$\Delta\Psi$m Collapse. The permeability transition dissipates the proton gradient across the inner membrane, immediately uncoupling oxidative phosphorylation and halting ATP synthesis.[46,47] This bioenergetic failure compromises energy-dependent processes critical for trophoblast function, including active nutrient transport, hormone synthesis, and maintenance of ionic homeostasis. (2) Mitochondrial swelling. The influx of solutes and water into the hyperosmotic matrix increases osmotic pressure, driving large-amplitude swelling that can mechanically distend and

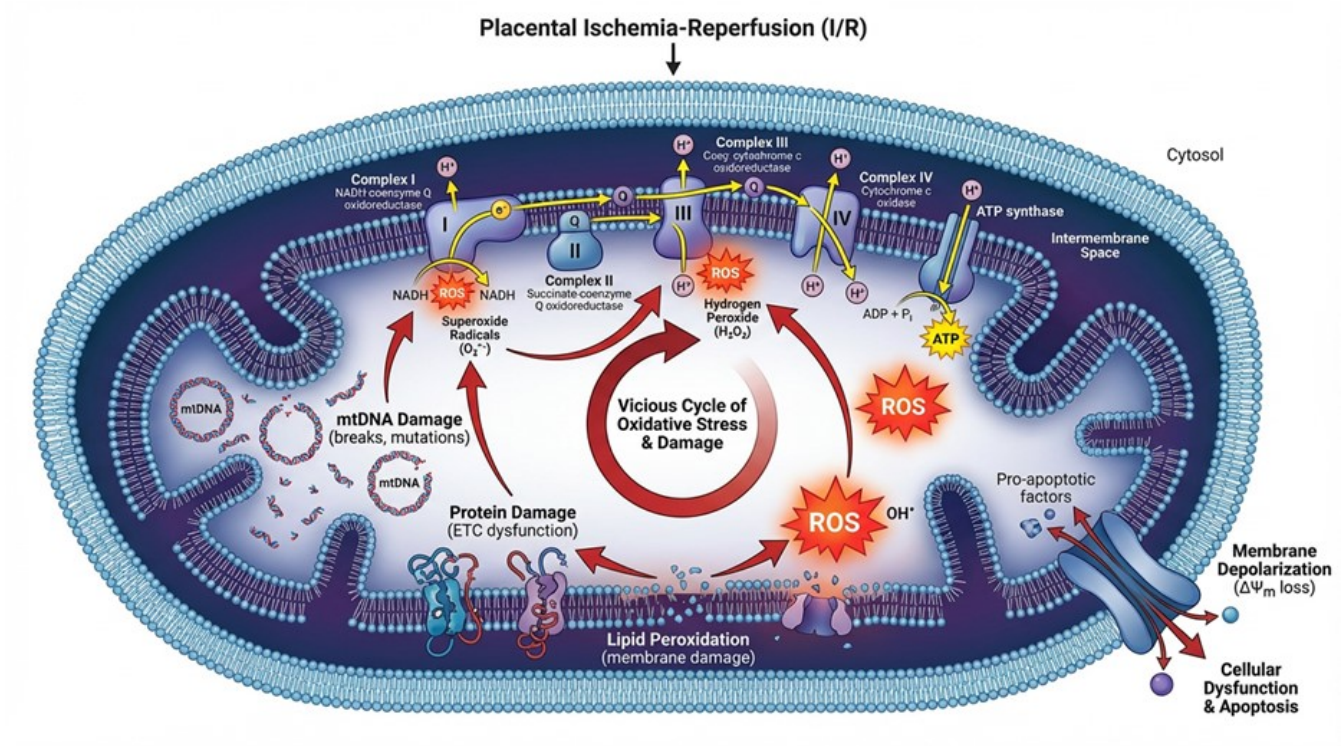

Figure 1. The vicious cycle of oxidative stress and mitochondrial damage in placental ischemia. This schematic illustrates the self-amplifying feed-forward loop of mitochondrial dysfunction during placental ischemia-reperfusion injury. The initial ischemia-reperfusion event triggers a surge in reactive oxygen species primarily generated by the electron transport chain. These ROS induce oxidative damage to mitochondrial DNA, essential proteins, and membrane lipids, which in turn exacerbates ETC impairment. This results in a secondary, more intense burst of ROS production, creating a vicious cycle that culminates in the pathological opening of the mitochondrial permeability transition pore and subsequent cellular compromise. ADP, adenosine diphosphate; ATP, adenosine triphosphate; ATP synthase, ATP synthase; Complex I, NADH: ubiquinone oxidoreductase; Complex II, succinate dehydrogenase; Complex III, cytochrome bc1 complex; Complex IV, cytochrome c oxidase; CoQ, coenzyme Q; Cyt c, cytochrome c; ETC, electron transport chain; H_2O_2, hydrogen peroxide; I/R, ischemia/reperfusion; mtDNA, mitochondrial DNA; NADH, nicotinamide adenine dinucleotide; O_2-, superoxide anion; OH•, hydroxyl radical; Pi, inorganic phosphate; ROS, reactive oxygen species; ΔΨm, mitochondrial membrane potential.

ultimately rupture the outer mitochondrial membrane.[48,49] This physical disruption facilitates release of intermembrane space proteins into the cytosol and represents an irreversible structural injury. (3) Release of pro-apoptotic factors**:** Rupture of the outer membrane releases proteins normally sequestered in the intermembrane space, most notably cytochrome c.[50,51] Once in the cytosol, cytochrome c binds to apoptotic protease activating factor-1, forming the apoptosome complex which recruits and activates procaspase-9. This initiates a caspase cascade, with executioner caspases-3 and-7 cleaving cellular substrates and committing the cell to apoptotic death.[51]

Studies using placental tissues from preeclamptic pregnancies have demonstrated increased markers of mPTP opening and heightened susceptibility of isolated mitochondria to calcium-induced permeability transition compared to healthy controls, confirming this pathway's relevance in PE pathophysiology.[52,53]

Disrupted mitochondrial dynamics: fission, fusion, and mitophagy

Mitochondria are not static organelles but exist as a dynamic network, constantly undergoing fusion and fission. These processes, along with mitophagy (the selective autophagic clearance of damaged mitochondria), are essential for maintaining a healthy mitochondrial population.[54] Mitophagy works in concert with fusion–fission cycles to eliminate dysfunctional mitochondria and preserve overall cellular function.[55]

Physiological Roles of Mitochondrial Dynamics

Fusion allows for the mixing of contents and the dilution of damaged components, preserving overall function.[56] By redistributing mitochondrial DNA, proteins, and metabolites, fusion complements defects and helps maintain membrane potential and bioenergetics under conditions of cellular stress.[57] This process is mediated by mitofusin 1 and 2 (Mfn1/2) on the outer mitochondrial membrane and optic atrophy protein 1 (Opa1) on the inner membrane, which coordinate tethering and membrane merging between adjacent mitochondria.[54]

Fission is crucial for creating new mitochondria and for isolating severely damaged segments for removal by

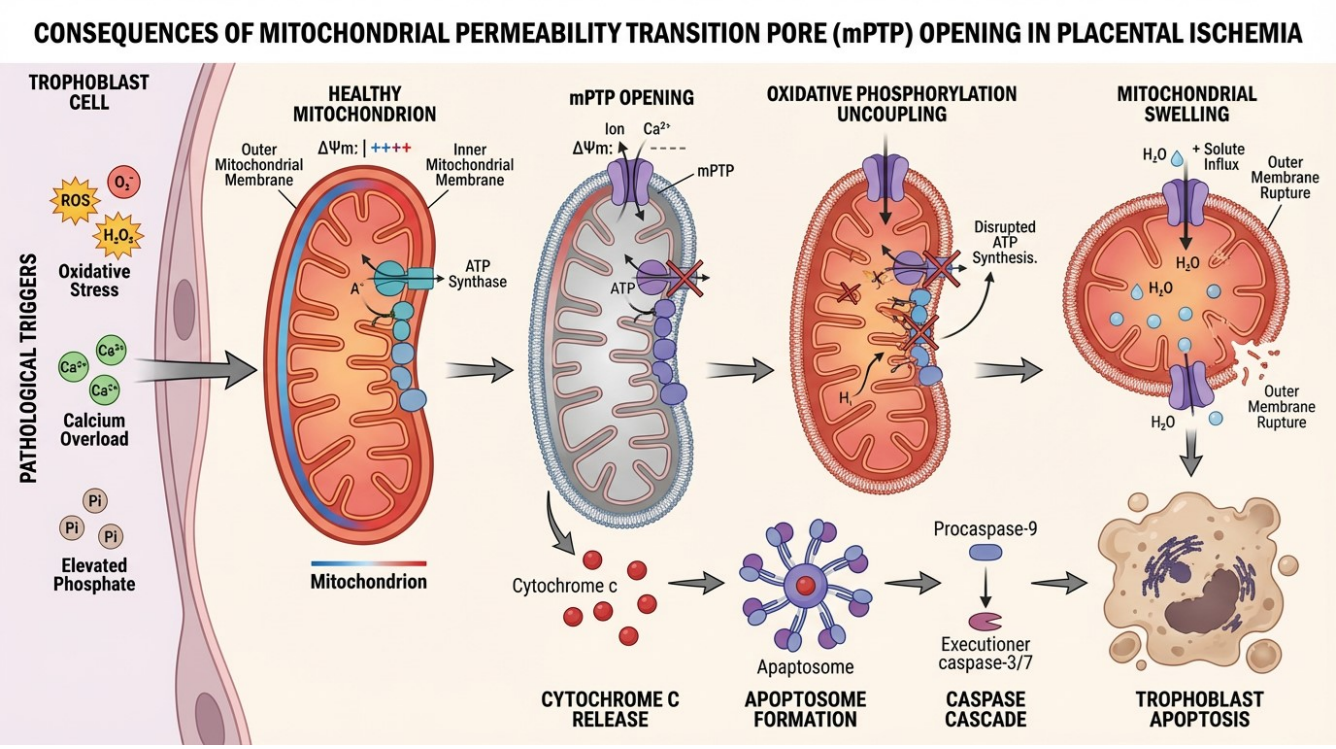

Figure 2. Consequences of mitochondrial permeability transition pore opening in placental ischemia. This schematic depicts the sequence of events following sustained mPTP opening in trophoblast mitochondria. Pathological triggers present in the ischemic placenta oxidative stress, calcium overload, and elevated phosphate induce pore opening, leading to dissipation of the mitochondrial membrane potential (ΔΨm) and uncoupling of oxidative phosphorylation. Subsequent influx of solutes and water causes mitochondrial swelling and rupture of the outer mitochondrial membrane, releasing pro-apoptotic factors including cytochrome c into the cytosol. Cytochrome c initiates apoptosome formation and caspase activation, committing the trophoblast to apoptotic cell death and contributing to placental dysfunction. ATP, adenosine triphosphate; H_2O_2, hydrogen peroxide; mPTP, mitochondrial permeability transition Pore; O_2-, superoxide anion; Pi, inorganic phosphate; ROS, reactive oxygen species; ΔΨm, mitochondrial membrane potential.

mitophagy.[58,59] Recruitment of the GTPase dynamin-related protein 1 (DRP1) to the mitochondrial outer membrane drives scission, enabling segregation of impaired regions that are subsequently targeted for autophagosomal degradation.[60] DRP1 oligomerizes at fission sites *via* receptors such as mitochondrial fission factor (Mff) and mitochondrial dynamics proteins MiD49/51, with lipid interactions facilitating membrane constriction.[61] Cardiolipin-rich membranes enhance DRP1 assembly and GTPase activity, reinforcing fission at damaged regions that are then routed to autophagosomes for clearance.[62]

Mitophagy serves as the terminal quality control mechanism, selectively eliminating depolarized or damaged mitochondria through autophagic degradation. The PINK1/Parkin pathway represents the best-characterized mitophagy mechanism: PTEN-induced putative kinase 1 (PINK1) accumulates on mitochondria with low membrane potential, recruiting the E3 ubiquitin ligase Parkin, which ubiquitinates outer membrane proteins and targets the organelle for autophagic engulfment.[55]

Dysregulation in the ischemic placenta

In the ischemic placenta, this carefully balanced system is profoundly perturbed. Evidence suggests a shift toward excessive mitochondrial fission, with activated DRP1 driving fragmentation under hypoxic–ischemic stress.[63] Concurrently, fusion proteins Mfn1/2 and Opa1 are reduced in diabetic and stress-related placental contexts, indicating impaired fusion capacity that compounds the fission-dominant state.[64]

Studies in preeclamptic placentae have demonstrated DRP1 upregulation and activation alongside decreased OPA1 expression, supporting a fission-dominant state linked to mitophagy impairment and trophoblast dysfunction.[65] Hypoxia-ischemia in PE perturbs mitochondrial dynamics and calcium signaling in trophoblasts, consistent with fragmentation and impaired fusion machinery.[66] Mechanistically, ischemia activates DRP1 and enhances endoplasmic reticulum-mitochondria contacts, promoting actin-mediated constriction and excessive fission.[63]

Consequences of imbalanced dynamics

Excessive fission fragments the mitochondrial network, producing numerous small, dysfunctional organelles that exhibit reduced oxidative phosphorylation capacity, diminished ATP output, and heightened reactive oxygen

species generation.[67] In models of pathological fragmentation, DRP1-driven fission increases ROS production and depolarizes mitochondria, while inhibiting aberrant fission restores membrane potential and lowers oxidative burden.[68]

This fission-dominant state is often accompanied by impaired mitophagy. Although cells attempt to clear the accumulating damaged mitochondria as evidenced by increased expression of mitophagy markers such as PINK1 and Parkin the burden of fragmented, dysfunctional organelles can exceed lysosomal degradative capacity. This results in the persistence of defective mitochondria that amplify cellular injury through continued ROS production and apoptotic priming.[22] In preeclamptic placentas and hypoxia/reoxygenation trophoblast models, disrupted PINK1-Parkin mitophagy associates with swollen and fragmented mitochondria, increased oxidative stress, and enhanced pyroptosis, supporting a model wherein quality control mechanisms become overwhelmed when damage exceeds degradative capacity.[69]

The collective impact of these dynamic disturbances excessive fission, impaired fusion, and overwhelmed mitophagy creates a self-perpetuating cycle of mitochondrial dysfunction that reinforces the oxidative and apoptotic environment established by ETC impairment and mPTP opening. This integrated model of dynamic imbalance is illustrated schematically in Figure 3.

INTEGRATION OF MITOCHONDRIAL DYSFUNCTION PATHWAYS

The four interconnected mechanisms of mitochondrial dysfunction discussed in this review oxidative stress and ETC impairment, mPTP opening, disrupted mitochondrial dynamics, and mtDNA instability with inflammation are summarized in Table 1. These pathways do not operate in isolation but rather form an integrated network of injury. Oxidative stress from ETC impairment generates ROS that damage mitochondrial components and sensitize mPTP opening. mPTP opening, in turn, releases cytochrome c and triggers apoptosis while also facilitating mtDNA escape into the cytosol. Excessive fission produces fragmented mitochondria that are both more prone to ROS generation and resistant to efficient mitophagic clearance. The accumulation of damaged mitochondria perpetuates oxidative stress, while cytosolic mtDNA activates cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS-STING) and NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammatory pathways that amplify the maternal syndrome. Together, these interconnected mechanisms create a self-sustaining cycle of mitochondrial dysfunction that propagates from the organelle to the tissue to the systemic level, driving the pathophysiology of PE and IUGR.

Therapeutic implications: targeting the mitochondrion

Targeting mitochondria aims to interrupt the feed-forward loop of hypoxia, excessive mitochondrial reactive oxygen species, and bioenergetic failure that sustains placental ischemia. In PE, placental mitochondrial dysfunction manifests as reduced oxidative phosphorylation capacity and altered electron transport chain activity, which amplifies oxidative stress and releases anti-angiogenic factors that worsen endothelial injury and perfusion defects. Conversely, mitochondria-targeted antioxidants in preclinical models reduce mitochondrial ROS and lower mean arterial pressure, supporting the concept that restoring mitochondrial redox balance can preserve cellular function and placental–maternal vascular homeostasis.[76] In a rat model of placental ischemia (reduced uterine perfusion pressure), mitochondrial respiration and complex activities fall while mitochondrial ROS rise in placenta, kidney, and endothelium; treatment with mitochondria-specific antioxidants significantly reduces hypertension and attenuates endothelial ROS, indicating that breaking the mitochondrial ROS–ischemia cycle can stabilize function and improve hemodynamics.[13]

Mitochondria-targeted antioxidants

Conventional antioxidants have shown limited efficacy in clinical trials, likely due to poor bioavailability and an inability to accumulate at the primary site of reactive oxygen species production the mitochondria.[77] To overcome this limitation, compounds specifically designed to concentrate within mitochondria have been developed. The most prominent of these are triphenylphosphonium (TPP^+)-based antioxidants, such as MitoQ and MitoTEMPO, which leverage the mitochondrial membrane potential to achieve hundreds- to thousand-fold intramitochondrial enrichment and reduce oxidative injury in preclinical models.[78]

MitoQ (Mitoquinone) is a ubiquinone derivative conjugated to a triphenylphosphonium cation. The positive charge drives uptake across the inner mitochondrial membrane, enabling several hundred-fold matrix accumulation; the ubiquinone component is reduced to ubiquinol by the electron transport chain, sustaining antioxidant protection against lipid peroxidation.[13] In PE models, mitochondria-targeted antioxidants—including MitoQ—attenuate oxidative stress and dysfunction. In the reduced uterine perfusion pressure (RUPP) rat model, mitochondrial-targeted antioxidants lowered mean arterial pressure and reduced mitochondrial ROS in placenta, kidney, and endothelium.[79] Complementary *ex vivo* data show MitoQ mitigates

Table 1: Summary of key mechanisms of mitochondrial dysfunction in placental ischemia

Mechanism	Key molecular players	Causes / Triggers in ischemic placenta	Specific molecular consequences	Functional/Cellular outcomes	Evidence in PE/IUGR placenta	References
Oxidative Stress & ETC Dysfunction	Complex I, Complex III, MnSOD, GPx1, Cardiolipin	Intermittent hypoxia/reperfusion; reduced O_2 during ischemia; sudden O_2 burst upon reperfusion	Oxidation of Fe-S clusters; cardiolipin peroxidation; mtDNA damage; MnSOD inactivation	↓ ATP; ↑ superoxide and H_2O_2; ROS-induced ROS release; ΔΨm instability	Increased 8-OHdG; elevated mitochondrial oxidative stress in PE models	[13,70]
mPTP Opening	VDAC, ANT, CypD, Ca^{2+}, Pi, ROS	Matrix Ca^{2+} overload; oxidative stress; high phosphate; low ΔΨm	Pore opening; ΔΨm collapse; matrix swelling; outer membrane rupture; cytochrome c release	Bioenergetic failure; apoptosis *via* caspase activation; necrosis if ATP depleted	Increased CypD expression; enhanced Ca^{2+}-induced swelling; cytosolic cytochrome c in PE	[71,72]
Imbalanced Mitochondrial Dynamics	DRP1, Fis1, Mfn1/2, Opa1, PINK1, Parkin	High ROS; elevated Ca^{2+}; hypoxia *via* HIF-1α; ceramide accumulation	Excessive DRP1-mediated fission; reduced Mfn2/OPA1 expression; network fragmentation; overwhelmed mitophagy	↓ Respiratory capacity; ↑ ROS; apoptosis priming; persistence of damaged mitochondria	Increased DRP1 activation; decreased OPA1; fragmented mitochondria on EM; ceramide-BOK signaling	[22,65,73]
mtDNA Instability & Inflammation	mtDNA, cGAS, STING, NLRP3, ASC, Caspase-1	Oxidative damage; mPTP opening; excessive fission	mtDNA mutations; altered copy number; cytosolic mtDNA escape; cGAS-STING activation; NLRP3 inflammasome activation	Impaired ETC subunit synthesis; pro-inflammatory cytokines (IL-1β, IL-6, TNF-α); endothelial dysfunction	Altered cell-free mtDNA in PE plasma; changed placental mtDNA copy number; NLRP3 activation	[74,75]

8-OHdG, 8-hydroxy-2'-deoxyguanosine; ANT, adenine nucleotide translocase; ASC, apoptosis-associated speck-like protein containing a CARD; ATP, adenosine triphosphate; Ca^{2+}, calcium ion; cGAS, cyclic GMP-AMP synthase; CypD, cyclophilin D; ΔΨm, mitochondrial membrane potential; DRP1, dynamin-related protein 1; EM, electron microscopy; ETC, electron transport chain; Fe-S, iron-sulfur; Fis1, mitochondrial fission protein 1; GPx1, glutathione peroxidase 1; H_2O_2, hydrogen peroxide; HIF-1α, hypoxia-inducible factor-1α; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IUGR, intrauterine growth restriction; Mfn1/2, mitofusin 1 and 2; MnSOD, manganese superoxide dismutase; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; NLRP3, NOD-like receptor family pyrin domain containing 3; O_2, molecular oxygen; Opa1, optic atrophy protein 1; PE, preeclampsia; Pi, inorganic phosphate; PINK1, PTEN-induced putative kinase 1; ROS, reactive oxygen species; STING, stimulator of interferon genes; TNF-α, tumor necrosis factor-alpha; VDAC, voltage-dependent anion channel.

methylglyoxal-induced vascular barrier impairment, highlighting protection of endothelial function relevant to PE pathophysiology.[13]

MitoTEMPO conjugates the superoxide dismutase mimetic TEMPO to a triphenylphosphonium cation, enabling selective accumulation in mitochondria and targeted scavenging of mitochondrial superoxide, thereby normalizing redox signaling and mitochondrial metabolism in endothelial and trophoblast cells exposed to PE-associated stressors.[80] In pregnancy complication models, MitoTEMPO reduces placental and vascular oxidative stress and improves hypertension. In the RUPP rat model, mitochondrial-targeted antioxidants including MitoTEMPO lowered mean arterial pressure and attenuated mitochondrial ROS across placenta, kidney, and endothelium; endothelial mtROS induced by RUPP serum was diminished when dams received mito-antioxidants.[13]

These and other mitochondria-targeted antioxidants, including SkQ1, are summarized in Supplementary table 1, which details their mechanisms, preclinical evidence, advantages, and pregnancy-specific limitations.

Inhibitors of the mitochondrial permeability transition pore

Preventing the opening of the mitochondrial permeability transition pore represents a logical strategy to preserve mitochondrial integrity and prevent cell death during ischemia-reperfusion, where calcium overload and oxidative stress trigger pore formation.[81,82]

Cyclosporine A (CsA) is a well-known inhibitor of the mPTP, acting by binding to cyclophilin D, a key regulatory component of the pore, which desensitizes mitochondria to calcium and limits injury.[81] While CsA has shown cardioprotective effects in myocardial ischemia-reperfusion models and reduced infarct size in preclinical meta-analyses, translation to consistent clinical benefit has been uncertain.[83,84] Its use in pregnancy is limited by potent immunosuppression and toxicity concerns, including risks of prematurity and low birthweight, and rare thrombotic microangiopathy reports, so continuation requires careful risk–benefit assessment and close monitoring.[85,86]

Non-immunosuppressive cyclosporine analogues have been developed to circumvent the limitations of CsA.

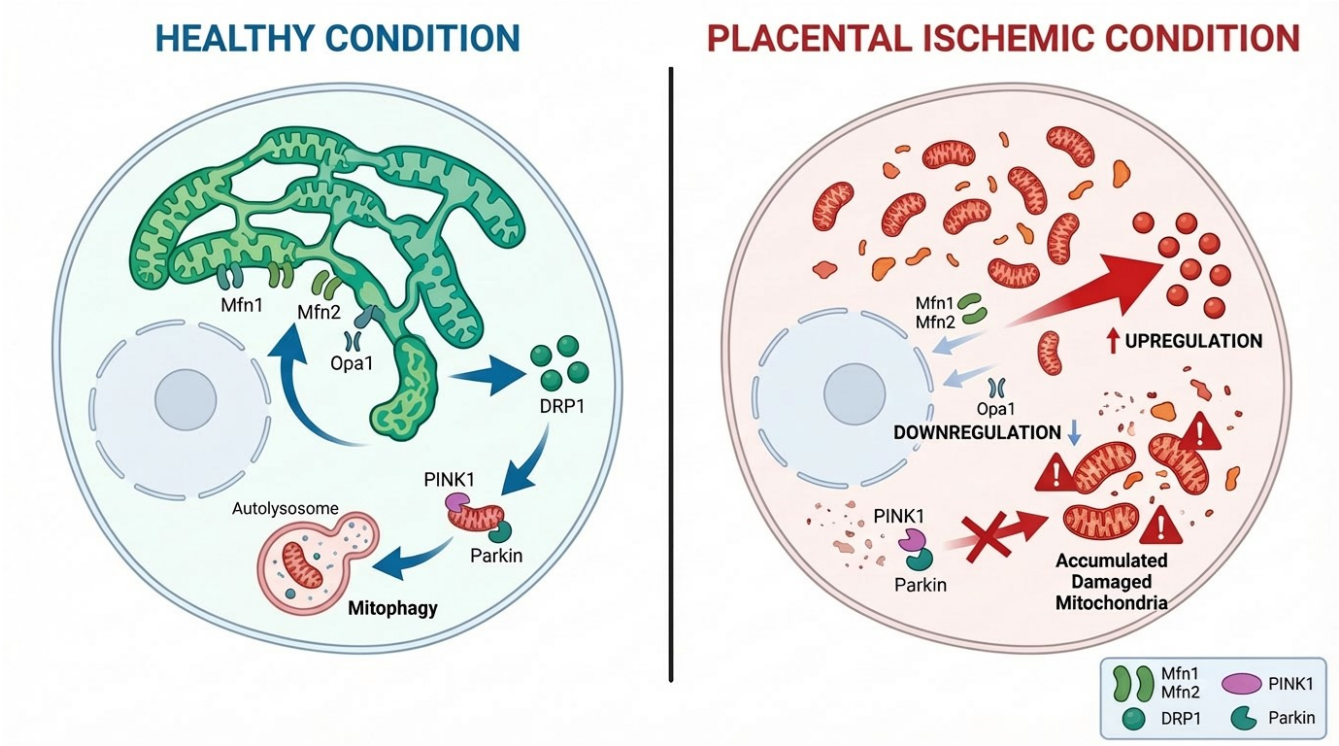

Figure 3. Imbalance in mitochondrial dynamics in placental ischemia. Under healthy physiological conditions (left panel), a homeostatic balance between mitochondrial fusion (mediated by Mfn1/2 and Opa1) and fission (mediated by DRP1) maintains a functional, interconnected mitochondrial network and efficient quality control *via* PINK1/Parkin-mediated mitophagy. In placental ischemic pathologies (right panel), this equilibrium is shifted toward excessive fission due to the upregulation and activation of DRP1 and the concurrent downregulation of fusion proteins (Mfn1/2 and Opa1), resulting in significant mitochondrial fragmentation. Furthermore, the PINK1/Parkin-mediated mitophagy pathway becomes overwhelmed by the accumulating burden of damaged, fragmented mitochondria, leading to their persistence within the trophoblast. This accumulation of dysfunctional organelles amplifies reactive oxygen species production, reduces ATP synthesis, and contributes to trophoblast dysfunction and cell death. DRP1, dynamin-related protein 1; Mfn1, mitofusin 1; Mfn2, mitofusin 2; Opa1, optic atrophy protein 1; PINK1, phosphatase and tensin homolog (PTEN)-induced putative kinase 1.

These compounds inhibit cyclophilin D to block mPTP opening without calcineurin-mediated immunosuppression, improving suitability for chronic indications like placental insufficiency.[87,88]

NIM811 is a non-immunosuppressive cyclosporine analogue that has demonstrated efficacy in multiple ischemia-reperfusion models. Preclinical and translational data show NIM811 reduces ischemia-reperfusion (I/R) injury and neuronal death in brain and spinal cord models, improving mitochondrial function and cognitive outcomes, which supports investigation in placental I/R models.[89] In myocardial I/R, NIM811 given at reperfusion reduced infarct size and apoptosis, indicating potent mPTP inhibition relevant to placental protection.[90] In hepatic I/R, NIM811 lowered liver injury markers (*e.g.*, ALT) and reduced histologic damage similarly to CsA in murine models, supporting non-immunosuppressive mitochondrial protection *in vivo*.[91] NIM811 also curtailed post-reperfusion endothelial activation, lowering chemokines (CCL2, KC) and surface molecules (VCAM-1, MHC-I, TAP1), coupling mitochondrial fitness rescue with reduced immunogenicity relevant to fetal–maternal interfaces.[92] Careful monitoring for off-target bioenergetic effects is warranted, as partial dissociation between mPTP blockade and bioenergetic recovery has been observed in transient focal cerebral ischemia NIM811 increased calcium retention capacity (~20%) and reduced cytochrome c release and reactive species, yet did not restore bioenergetics.[89] Dose–response work in traumatic brain injury shows variable functional gains, with 10 mg/kg as the most effective dose for neuroprotection and cognition, linking dosing to mitochondrial outcomes.[93]

Debio-025 (Alisporivir) is another non-immunosuppressive cyclosporin analogue that achieves nanomolar inhibition of the mPTP in brain mitochondria and matches or exceeds CsA potency, indicating mitochondrial protection without calcineurin suppression and suggesting favorable tolerability compared with CsA.[94] Its potent nanomolar inhibition of mitochondrial permeability transition without immunosuppression and favorable tolerability profiles in brain and muscle models make it an attractive candidate for placental protection.[95]

Preclinical studies are needed to assess placental

protection, define dosing, and confirm absent fetal–maternal immunologic effects.[96,97] Evaluations should focus on mitochondrial function, calcium retention capacity, and oxidative stress, leveraging evidence that NIM811 raises the calcium threshold for mPTP opening, reduces reperfusion injury[98], improves mitochondrial fitness, and lowers reactive species and cytochrome c release.[89] Cross-organ ischemia-reperfusion models further support this approach: NIM811 limits mPTP opening, preserves respiration, and reduces organ failure across heart, brain, kidney, liver, and lung, justifying parallel assessment of bioenergetics and immune activation in placental contexts.[99,100]

Modulators of mitochondrial dynamics

As our understanding of the role of DRP1-mediated fission in cell injury grows, inhibitors of this process are gaining interest. The best-characterized compound, Mdivi-1 (mitochondrial division inhibitor-1), is a small molecule that inhibits DRP1 GTPase activity. Across diverse models of cellular stress including cerebral ischemia, spinal cord injury, excitotoxicity, and sepsis Mdivi-1 consistently reduces mitochondrial fragmentation, attenuates ROS production, preserves ATP levels, and limits apoptosis. [99–104] Mechanistically, Mdivi-1 maintains $\Delta\Psi m$, prevents cytochrome c release, blocks Bax translocation to mitochondria, and inhibits downstream caspase-3/9 activation.[103,104] In murine stroke models, it reduces infarct size and improves neurological outcomes in a dose-dependent manner.[105]

In the context of placental ischemia, Mdivi-1 could theoretically restore a healthier mitochondrial network, preserving ATP production and reducing pro-apoptotic signaling by limiting excessive DRP1-mediated fission.[101,102] Supporting this, trophoblast studies demonstrate that Mdivi-1 rescues mitochondrial dysfunction under high-glucose or toxin-induced stress and mitigates ROS-DRP1-mediated PANoptosis, improving fetal growth in mouse models of gestational dysfunction.[65,106] However, direct evidence in placental ischemia models remains limited, and preclinical studies reveal context-specific risks. Mdivi-1 has off-target effects, including reversible complex I inhibition, and DRP1 suppression may impair early embryo development, where physiological fission is essential.[107,108] Reviews emphasize divergent cytoprotective versus cytotoxic actions depending on dose and context, reinforcing uncertainty about maternal-fetal safety outside controlled experimental settings.[108,109] Other dynamics modulators, including the highly specific peptide P110 and DRP1 siRNA/ASO approaches, are also under investigation. Supplementary table 1 provides a detailed comparison of these strategies, highlighting their specificity, preclinical evidence, and limitations for placental application.

Mitophagy enhancers

Enhancing the clearance of damaged mitochondria represents an alternative strategy to restore mitochondrial quality control. Rapamycin, an mechanistic target of rapamycin complex 1 (mTORC1) inhibitor, induces autophagy and mitophagy, enhancing clearance of damaged mitochondria in trophoblast cells under hypoxia, where autophagy plays a prosurvival role.[110] However, mTORC1 inhibition is critical for placental nutrient transport and fetal growth, raising concerns that rapamycin could worsen IUGR, and its immunosuppressive effects limit pregnancy applicability.[111]

Urolithin A, a natural gut-derived metabolite, induces mitophagy *via* the PINK1/Parkin pathway and improves mitochondrial quality control in aging and ischemia models, though placental data are lacking. [112–115] NAD+ precursors (nicotinamide riboside, NMN) boost NAD+ levels, activate sirtuin 1/3 (SIRT1/3), and enhance mitophagy and mitochondrial biogenesis. In lipopolysaccharide (LPS)-induced PE-like rats, nicotinamide riboside (NR) restored placental NAD+, improved mitochondrial respiration, and prevented hypertension and fetal growth restriction, representing a promising approach.[76,116] These mitophagy-enhancing strategies, along with their mechanisms and stage of development, are summarized in Supplementary table 1.

Targeted delivery systems

To minimize fetal exposure and enhance placental specificity, targeted delivery systems are under development. Poly (lactic-co-glycolic acid) (PLGA) nanoparticles encapsulating mitochondrial-targeted drugs (*e.g.*, MitoQ) accumulate in placental syncytiotrophoblast with limited maternal-to-fetal transfer in ex vivo perfusion models and improve placental mitochondrial function in rodent hypoxia models. [117–122] Liposomes surface-modified with placental-targeting ligands (*e.g.*, placental alkaline phosphatase [PLAP] antibodies or peptides) home to syncytiotrophoblast and uterine vasculature, enhancing retention and functional delivery of encapsulated agents while reducing systemic exposure. [123–126] These platforms offer potential to improve efficacy and safety of mitochondrial-targeted therapies in pregnancy and are detailed in Supplementary table 1, which outlines their formulation properties, preclinical evidence, and the regulatory challenges that remain for pregnancy-specific applications.

DISCUSSION AND FUTURE DIRECTIONS

The evidence positions mitochondrial dysfunction as a core pathological feature of placental ischemic diseases. The ischemic placenta mounts a complex stress response in which mitochondria act as both sensors and effectors. Excess reactive oxygen species drive a self-perpetuating

loop involving oxidative stress, mitochondrial permeability transition pore opening, and disrupted mitochondrial dynamics, leading to loss of membrane potential, impaired electron transport, and apoptosis that compromise trophoblast viability.[127,128] This mitochondrial stress promotes hypoxia-inducible factor 1-alpha (HIF-1α) stabilization and upregulates anti-angiogenic factors (sFlt-1, sEng), amplifying endothelial dysfunction and maternal hypertension. Targeting mitochondrial bioenergetics reduces ROS, HIF-1α, and sFlt-1 in hypoxic trophoblasts, supporting causality.[24,25] In human preeclamptic placentas, reduced cytochrome c oxidase activity and smaller trophoblast mitochondria correlate inversely with sFlt-1, linking bioenergetic failure to anti-angiogenic drive and the maternal syndrome.[129] Mitochondria-Endoplasmic Reticulum stress crosstalk and malperfusion further escalate pro-inflammatory signaling, sustaining the loop underlying placental dysfunction and systemic disease.[130,131]

Targeting these mitochondrial pathways offers a paradigm shift from managing maternal symptoms to addressing underlying placental pathology. The success of mitochondria-targeted antioxidants like MitoQ in preclinical models—reducing hypertension in the reduced uterine perfusion pressure rat model and protecting against hypoxia-induced placental oxidative stress—is encouraging.[13,132] However, critical questions remain before clinical translation. First, timing of intervention is crucial: should therapy be prophylactic from the first trimester in high-risk women, or is there a therapeutic window after disease establishment Second, fetal safety must be rigorously evaluated, as drugs targeting placental mitochondria could cross the placenta and affect fetal mitochondria with different bioenergetic profiles.[133,134] Third, disease heterogeneity suggests "one-size-fits-all" approaches may fail; identifying biomarkers of specific mitochondrial defects (*e.g.*, high *vs.* low fission) could guide personalized therapies.[135]

Advanced *in vitro* platforms placental organoids and trophoblast stem cells from PE and IUGR pregnancies integrated with placenta-on-a-chip systems will enable mechanistic dissection of hypoxia responses and provide human-relevant testbeds for therapeutic screening under dynamic flow conditions.[136,137] Complementary multi-omics (genomics, transcriptomics, metabolomics) applied to placental tissue can uncover metabolic pathway disruptions, refine disease signatures, and identify mitochondrial dysfunction biomarkers and therapeutic targets.[138,139]

In conclusion, the mitochondrion is a central hub in placental ischemia pathophysiology. Continued exploration of mechanisms governing mitochondrial health in trophoblasts holds the key to developing the first disease-modifying therapies for these devastating pregnancy conditions.

DECLARATION

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Author contributions
Conceptualization, Waseem S, Wang LY, and Hong YQ; Writing—Original Draft, Waseem S; Writing—Review & Editing, Waseem S, Zou J, Yu L, Zeng SY, Zhao H, Wang RQ, li X, Ma QZ, and Jia XY; Supervision, Wang LY and Hong YQ; Project Administration, Hong YQ. All authors have read and agreed to the published version of the manuscript.

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The authors declare no conflicts of interest.

Use of large language models, AI and machine learning tools
None declared. Only basic grammar and spell-checking software was employed.

Data availability statement
All data generated or analyzed during this study are included in this published article and its supplementary information files. This review synthesizes information from previously published studies, which are cited in the references section.

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