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**Review Article**

# Emerging Oxidative Stress Biomarkers and Mitochondrial Dysfunction in Preeclampsia from Pathogenesis to Precision Medicine: A Narrative Review

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**Abstract**

Preeclampsia continues to be a major cause of maternal and neonatal morbidity worldwide. Current diagnostic criteria are based on clinical signs that appear relatively late. Target organ damage is already in progress, and early disease progress often goes undetected at this time. Recent research has altered our perception of this condition and has confirmed that trophoblast mitochondria are actively involved in the etiology of hypertensive disease and not just responding to it. Mitochondrial dysfunction in the placenta results in increased production of free radicals, breakdown of the membrane, disruption in cellular iron balance, and poor organelle clearance, all of which affect the function of the placenta negatively. This review focuses on five important mitochondrial biomarkers that characterize this destructive process: 8-hydroxy-2'-deoxyguanosine indicates direct oxidative damage to mitochondrial DNA, and changes in copy numbers and cell-free DNA fragments in plasma indicate increased cell damage and systemic inflammation. Oxidized cardiolipin and malondialdehyde indicate membrane lipid degradation. Changes in levels of GPX4, mitochondrial ferritin, and the transferrin receptor 1 indicate initiation of iron-dependent ferroptosis. Finally, reduced PINK1/Parkin signaling is a sign of the cell's cleanup system failing, allowing damaged mitochondria to accumulate and pushing trophoblasts into premature aging. These markers together depict the convergence of redox imbalance, structural membrane damage, iron dysregulation, and clearance defects driving placental breakdown and maternal disease.

***Keywords***: Biomarker; Mitochondrial dysfunction; Oxidative stress; Pre-eclampsia; Reactive oxygen species.

**مؤشرات الأجهاد التأكسدي الناشئة وخلل الميتوكوندريا في تسمم الحمل من المرض الى الطب الدقيق: مرجعة سردية**

**الخلاصة**

ما يزال ما قبل الإرجاع (معدّية الحمل) يشكّل أحد الأسباب الرئيسة للاعتلالات الصحية لدى الأمهات وحديثي الولادة على مستوى العالم، إذ تعتمد المعايير التشخيصية الحالية على علامات سريرية تظهر في مراحل متأخرة نسبياً، وذلك في وقت يكون فيه تلف الأعضاء المستهدفة قد بدأ بالفعل، وغالباً ما تمر التطورات المبكرة للمرض دون أن تُكتشف. غير أن البحوث الحديثة غيّرت مفهومنا لهذه الحالة، وأكّدت أن الميتوكندريا في الخلايا المغذية تسهم إسهاماً فاعلاً في الإمراضية المسببة لارتفاع ضغط الدم، بدلاً من كونها مجرد مستجيب لها. حيث يؤدي الخلل الوظيفي للميتوكندريا في المشيمة إلى زيادة إنتاج الشوارد الحرة، وتفكك الغشاء الخلوي، واضطراب التوازن الحديدي داخل الخلايا، وقصور عملية التخلص من العضيات التالفة؛ وهو ما ينعكس سلباً على وظيفة المشيمة ككل. تركز هذه المراجعة العلمية على خمسة مؤشرات حيوية ميتوكندرية رئيسة تُجسّد هذه العملية التدميرية: حيث يشير 8-hydroxy-2'-deoxyguanosine إلى الضرر التأكسدي المباشر الذي يصيب الحمض النووي للميتوكندريا، وتؤشر تغيرات أعداد النسخ والحمض النووي الطليق في البلازما إلى تفاقم التلف الخلوي والالتهاب الجهازي، بينما يدل الكارديوليبين المؤكسَد والمالونيألدهيد على تحلل الليبيدات المكونة للغشاء الخلوي. كما تعكس تغيرات مستويات GPX4 والفيريتين الميتوكندري ومستقبل الترانسفيرين 1 بدء عملية الموت الخلوي الحديدي، وأخيراً يمثّل تراجع إشارات PINK1/Parkin دليلاً على إخفاق نظام التنظيف الخلوي، مما يسمح بتراكم الميتوكندريا التالفة ويدفع الخلايا المغذية نحو الشيخوخة المبكرة. تُظهر هذه المؤشرات مجتمعةً التقاء الاختلال التأكسدي، والتلف الهيكلي للغشاء، واضطراب تنظيم الحديد، وقصور التخلص من العضيات التالفة، وهي العوامل التي تُحرّك بمجموعها الانهيار الوظيفي للمشيمة وتطور المرض لدى الأم.

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## INTRODUCTION

Pregnancy is a unique physiological condition with complex metabolic, endocrine, biochemical, and cellular changes to ensure the survival and growth of the developing fetus [1] [2]. A key part of this process is the placenta, which acts as a vital interface for the transfer of nutrients and gases, the production of hormones, and the regulation of immunity [2]. These systemic adaptations are either tolerated smoothly or impose a considerable physiological burden that contributes to the development of pregnancy-related illnesses depending on the health of the mother [1]. Preeclampsia [PE] is one of the leading causes of fetomaternal morbidity and mortality, among these, affecting an estimated 2% to 10% of all pregnancies worldwide [3]. Clinically, preeclampsia is characterized by the new onset of hypertension (>20 weeks of gestation) with significant proteinuria or evidence of maternal end-organ dysfunction [4]. The clinical presentation is highly variable, from mild tracking to severe, life-threatening multi-system crises [5]. The syndrome usually involves multiple system dysfunction, including the kidneys (renal insufficiency), liver, brain, and placenta [6]. The long-term sequelae of PE extend far beyond delivery for both mother and child: The long-term sequelae of PE extends beyond delivery. Mothers with a history of PE face an elevated lifetime risk of developing chronic hypertension, coronary artery disease, ischemic stroke,

metabolic syndrome, and end-stage renal disease [7]. Simultaneously, infants born from preeclamptic pregnancies face an increased risk of short-term complications due to induced preterm birth and impaired growth, as well as long-term vulnerabilities to neurodevelopmental delays, Type 2 diabetes mellitus, and early-onset cardiovascular disease [8]. Despite extensive clinical research, the absolute primary drivers remain partially elusive due to the uniquely human nature of deep hemochorial emerging oxidative stress biomarkers and mitochondrial dysfunction in PE, which creates an ongoing barrier to translating animal models into therapeutic solutions. At the core of the progression from placental ischemia to maternal systemic endothelial dysfunction is a profound imbalance between the generation of reactive oxygen and nitrogen species (ROS/RNS) and the neutralizing capacity of maternal-placental antioxidant defenses [9]. In preeclampsia, restricted placental perfusion triggers chronic oxidative stress, lipid peroxidation, and an exaggerated systemic inflammatory response [10,11]. ROS drives the oxidation of low-density lipoproteins [LDL] within vascular walls, leading to foam cell formation and structural endothelial cell death [12]. This condition is also associated with significant alterations in the maternal lipid profile, with a marked increase in triglycerides, total cholesterol, and LDL-cholesterol compared to normal pregnancies [13]. At the same time, the accumulation of reactive oxygen species/reactive nitrogen species inhibits cell survival pathways, leading to dysregulation of apoptosis and autophagy in the placenta [14]. Apart from lipids, homeostatic electrolyte gradients are critical to the regulation of systemic blood pressure. Alterations in the metabolism of sodium, potassium, calcium, and magnesium cause changes in vascular reactivity that make vessels hyper-responsive to endogenous vasoconstrictors (e.g., vasopressin) and accelerate the clinical presentation of hypertension [15]. Early detection of preeclampsia is essential to mitigate its complications so that it is of utmost importance to identify reliable and available biochemical markers. This review discusses the clinical utility of oxidative stress markers as important biomarkers of mitochondrial dysfunction. The evaluation of these specific biochemical parameters is expected to enhance current diagnostic frameworks and identify new targeted interventions that leverage these molecular pathways to restore oxidative homeostasis and improve maternal and fetal outcomes.

## Pathogenetic Model and Mitochondrial Interface

Preeclampsia is classically discussed in terms of a two-stage sequential mechanism in which placental mitochondrial dysfunction connects local vascular defects with systemic maternal disease; see Figure 1 [16]. The first stage is related to the defect of placental formation at early stages of pregnancy. Extravulsive trophoblasts (EVTs) normally participate in the remodeling of the high resistance maternal spiral arteries into dilated, low-resistance channels to ensure a steady blood flow to the fetus [17].

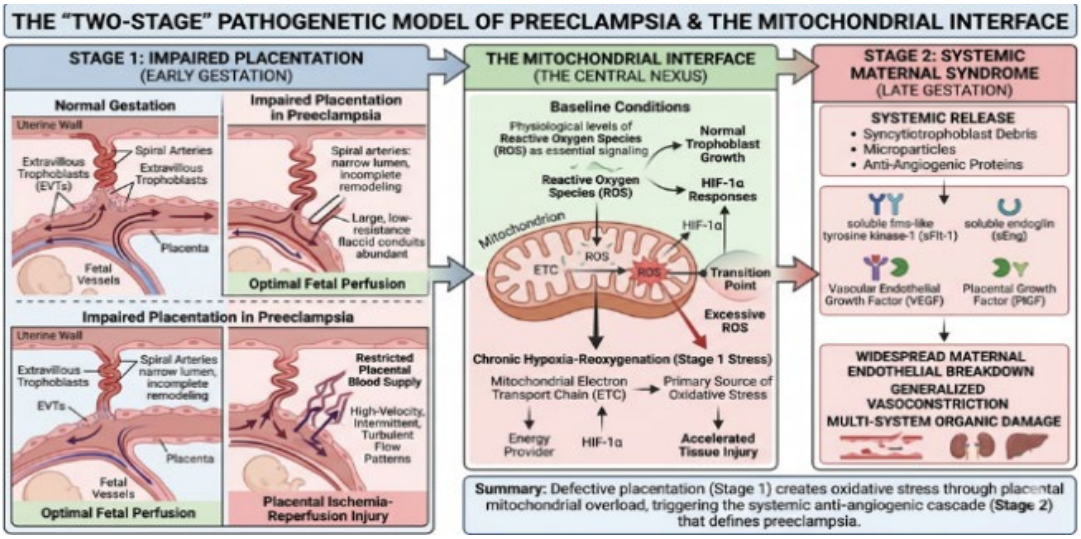



**Figure 1**: Pathogenetic model of preeclampsia [16].

Preeclampsia is characterized by inadequate extravuloblast invasion leading to vasoconstriction, and consequently the placenta is exposed to turbulent and intermittent blood flow. This ongoing ischemia and reperfusion stress accelerates phase II: release of polynuclear trophoblast debris and anti-angiogenic factors, particularly soluble FMS-like tyrosine kinase-1 (sFlt-1) and soluble endoglin [sEng], into maternal circulation. These anti-angiogenic factors induce systemic vasoconstriction, widespread endothelial breakdown, and multiorgan damage by neutralizing vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) in the circulation [18,19]. Placental mitochondria are central to this pathological cascade. Although physiological levels of reactive oxygen species are essential for stimulating trophoblast growth in the early stages and modulating hypoxia-1α (HIF-1α) pathways, chronic hypoxia and excessive reoxygenation to the point of depleting the mitochondrial electron transport chain cause a critical metabolic shift. Consequently, mitochondria cease to function primarily as energy generators and become

highly oxidative stressors, accelerating tissue damage and contributing to the development of systemic maternal syndrome [9].

## Structural Basis of Placental Mitochondrial Dysfunction

In preeclampsia placenta, profound morphological and functional abnormalities in the mitochondria severely impair cellular energy and viability. Persistent tissue ischemia disrupts the activities of electron transport chain (ETC) complexes I, II, and III, thereby weakening the proton-driven force across the mitochondrial inner membrane [20]. This loss of membrane potential not only stalls adenosine triphosphate (ATP) generation but also promotes premature electron transfer to molecular oxygen. This leakage leads to the synthesis of enormous quantities of oxygen-free radicals and the subsequent accumulation of hydrogen peroxide ($H_2O_2$) [21]. This local oxidative environment creates a damaging feedback loop that directly targets mitochondrial DNA (mtDNA). Mitochondrial DNA is particularly susceptible to oxidative degradation because it lacks protective histone proteins and has rudimentary base excision repair pathways. This accumulation of genetic mutations leads to the erroneous translation of essential subunits of the electron transport chain, creating a vicious cycle of increased electron leakage and rapid generation of reactive oxygen species (ROS). These energy imbalances drive placental cells toward programmed cell death. First, cells respond to stress by upregulating mitochondrial autophagy in order to remove defective mitochondria that produce reactive oxygen species. However, with continued metabolic stress, this protective cleanup system is spent, and the cell switches from survival-oriented recycling to destructive autophagy and subsequent cell death [22]. Simultaneously, increasing oxidative damage weakens the mitochondrial structure and makes its outer membrane permeable, allowing cytochrome c to leak into the cytosol, where it binds to Apaf-1 to activate the caspase-9 and caspase-3 enzyme pathways. This ultimately leads to the rapid death of multinucleated nutritive cells and the release of cellular debris into the maternal circulation [23]. In addition to depleting the energy reserves necessary for the active transport of nutrients across the placenta, the dissociation of oxidative phosphorylation in mitochondria accelerates aging and structural deterioration within them. This cellular deterioration forms a crucial link, directly connecting early placental ischemia with the cascade of widespread inflammatory reactions in the mother that characterize late-stage preeclampsia [24].

## Novel Pathological Mechanistic Axes

Recent investigations have revealed a triad of interrelated molecular pathways—specifically, iron-induced cell death, accelerated cellular senescence, and neutrophil extracellular trapping that together intensify tissue degradation caused by placental mitochondrial dysfunction and oxidative stress in preeclampsia [25].

### *Ferroptosis and altered iron metabolism*

Ferroptosis represents a regulated, iron-mediated form of non-apoptotic cell death driven by catastrophic lipid peroxidation [26]. Within the preeclamptic placenta, divergence in maternal-fetal iron homeostasis causes a pathological accumulation of labile ferrous iron ($Fe^{2+}$) within localized placental micro-environments. This excess pool of $Fe^{2+}$ drives the Fenton reaction, interacting with hydrogen peroxide to yield highly destructive hydroxyl radicals [•OH] [27].

$$Fe2+ H2O2 \rightarrow Fe3+ \bullet OH + OH-$$

These hydroxyl radicals directly attack membrane-bound polyunsaturated fatty acids (PUFAs), triggering an autocatalytic lipid peroxidation cascade that systematically dismantles structural membrane integrity [28].

### *Premature placental senescence*

Chronic oxidative stress and lipid damage cause the placenta to age prematurely. In the early stage of pregnancy, preeclamptic placentas show clear signs of advanced cellular aging, such as telomere shortening, increased beta-galactosidase activity, and higher levels of cell-cycle inhibitors. These aging cells change their behavior and develop a senescence-associated secretory phenotype. Rather than shut down, they actively secrete high amounts of inflammatory cytokines and chemokines. This localized inflammation damages surrounding placental tissues and exacerbates endothelial injury throughout the maternal vascular system [29,30].

### *Netosis and systemic inflammation*

Neutrophil extracellular traps (NETosis) further drive the prevalent inflammation seen in preeclampsia. This is a specialized process where maternal neutrophils release neutrophil extracellular traps (NETs), which are extracellular DNA networks packed with oxidative enzymes and antimicrobial proteins [31,32]. This process is activated when circulating placental debris, inflammatory cytokines, and free fetal DNA stimulate maternal neutrophils. Once released into the bloodstream, these NETs block small blood vessels, trap platelets, and produce additional reactive oxygen species (ROS). This prevalent microvascular obstruction directly causes severe vasoconstriction and multi-organ damage that characterize severe preeclampsia [31,33]. Hypoxia is a common and severe stress to an organism's homeostatic mechanisms and is associated with increased incidence of maternal complications of preeclampsia [34,35].

## Mitochondrial Oxidative Stress Markers

Because mitochondria serve as the primary source of intracellular ROS, their functional failure triggers targeted molecular damage cascades. The biomarkers

detailed below (Table 1) provide a direct read-out of mitochondrial redox imbalance, organellar damage, and disrupted cell survival pathways in the preeclamptic placenta.

**Table 1**: Summary of mitochondrial biomarkers in preeclampsia

| Biomarker | Primary Matrix / Location | Pathological Relevance in Preeclampsia |
|---|---|---|
| 8-OHdG | Placental Tissue, Urine, Plasma | Direct marker of oxidative damage to mtDNA. |
| mtDNA-CN/ccf-mtDNA | Maternal Plasma, Whole Blood, Placenta | Indicator of organellar turnover, cellular stress, and systemic DAMP release. |
| Oxidized Cardiolipin/MDA | Placental Mitochondria | Measures membrane damage and pro-apoptotic signaling. |
| GPX4/FtMt/TfR1 | Trophoblast Cells | Identifies iron overload and ferroptotic pathways. |
| PINK1/Parkin | Syncytiotrophoblast | Tracks mitophagy failure and accelerated tissue aging. |

### *Mitochondrial DNA and integrity markers*

Dissimilar nuclear DNA and mitochondrial DNA (mtDNA) are maternally inherited and form a compact genome essential for mitochondrial function, particularly energy production [36, 37]. This genome encodes many of the proteins vital to the electron transport chain and oxidative phosphorylation processes critical for adenosine triphosphate synthesis [38]. The regulation of mtDNA copy number is adaptive, fluctuating in response to cellular energy demands and stress responses, thereby highlighting its role in cellular metabolism and adaptability [39]. In preeclampsia, oxidative modification of histone-free mitochondrial DNA by ROS forms 8-hydroxy-2'-deoxyguanosine (8-OHdG) lesions, which directly regulate mitochondrial DNA copy number (mtDNA-CN) through a dynamic, stage-dependent mechanism [40][41]. During primary chorionic ischemia, increased levels of 8-OHdG stimulate compensatory mitochondrial biogenesis via PGC-1alpha and TFAM pathways, temporarily boosting the number of mitochondrial DNA copies in tissues to maintain vital energy production despite transcriptional damage [21,42]. Once this pathway is activated, it upregulates the transcription factor TFAM and accelerates gamma polymerase activity, leading to the synthesis of additional mitochondrial DNA copies to replace damaged ones [43,44]. This compensatory increase expands the mitochondrial DNA stock to compensate for damaged templates and maintain electron transport chain function. Conversely, under severe or prolonged oxidative stress, extensive 8-OHdG lesions overwhelm the scrutiny capacity of gamma polymerase, resulting in replication fork arrest and dissipation of mitochondrial membrane potential. This metabolic failure triggers widespread organellar breakdown and a sharp decline in the mtDNA-CN [41]. Therefore, the rupture of the membrane of multinucleated nutritive cells leads to the release of these damaged genomic fragments into the maternal plasma in the form of cell-free mitochondrial DNA (ccf-mtDNA), where they act as damage-associated molecular patterns (DAMPs) that initiate systemic immune activation and damage to the maternal endothelium [45,46].

### *Lipid peroxidation-targeted mitochondrial membranes*

Cardiolipin is a unique polyunsaturated phospholipid abundant in the inner mitochondrial membrane and crucial for the structural integrity and anchoring of the electron transport chain (ETC) complexes [47,48]. Cardiolipin oxidation occurs when reactive oxygen species [ROS] directly attack the polyunsaturated fatty acid chains, resulting in the loss of its ability to bind cytochrome c [49]. The quantification of this oxidized cardiolipin provides a definitive tissue biomarker for the initiation of mitochondrial outer membrane permeabilization, an event critical for the systemic release of toxic syncytiotrophoblast microparticles into maternal circulation [24,50]. Moreover, systemic lipid damage and the evaluation of isolated mitochondrial malondialdehyde (MDA) levels quantify this localized free radical-induced damage to the organelle double-membrane system, highlighting severe mitochondrial decay [51,52].

### *Enzyme-regulated ferroptosis and mitochondrial iron load*

Ferroptosis is an iron-dependent regulated cell death driven by lipid peroxidation, which is closely related to mitochondrial metabolic activity in preeclampsia [53,54]. This pathway is mainly driven by a substantial decrease in the antioxidant enzyme glutathione peroxidase 4 (GPX4), which neutralizes neutralizing lipid peroxides in cellular and mitochondrial membranes [53,55]. Placental GPX4 expression is profoundly downregulated in late-onset preeclampsia, representing a hallmark biomarker, with mitochondrial membranes being completely unshielded from destructive, iron-catalyzed Fenton reactions [10]. This vulnerability is worsened by impaired function of iron transport proteins, particularly mitochondrial ferritin [FtMt] and the transferrin receptor 1 [TfR1]. Dysregulated expression of these proteins leads to an abnormal accumulation of unstable, labile iron directly inside the mitochondria, which accelerates the production of highly reactive hydroxyl radicals [56,57]. Eventually, measuring these altered ratios of iron transport proteins within placental tissue provides a clear molecular image of the intracellular iron overload that precipitates mitochondrial ferroptosis [58,59].

### *Mitochondrial senescence and mitophagy inhibition*

Functional cells eliminate dysfunctional mitochondria via mitophagy, a selective autophagic pathway responsible for organellar quality control [60,61]. In preeclampsia, this degradative machinery becomes

impaired or saturated [60]. Normally, a protein called PINK1 [PTEN-induced kinase 1] builds up on the outside of damaged mitochondria and recruits another protein called Parkin [E3 Ubiquitin Ligase], which acts as a molecular tag to mark the organelle for destruction [62]. In preeclamptic placental tissue, alteration or complete drop of PINK1/Parkin levels serve as new biomarkers for early placenta [63]. Monitoring these altered protein levels provides a key metric for evaluating the retention of non-functional mitochondria, which act as a continuous source of ROS leakage within preeclamptic placental tissue.

## DISCUSSION

The biomarkers discussed here suggest that mitochondrial oxidative stress is a central feature of preeclampsia pathobiology (Figure 2) [64]. Markers such as 8-OHdG and oxidized cardiolipin directly reflect oxidative damage within placental mitochondria [65,66]. While elevated mtDNA fragments in maternal circulation indicate this stress has exceeded the local repair capacity and entered the systemic compartment [67,68]. Instead of considering preeclampsia as a mere vascular disorder, these indicators suggest that mitochondrial redox imbalance in trophoblast cells could be an early and driving event [69,70]. Elevated 8-OHdG levels showed that oxidative damage to mitochondrial DNA extends beyond the placenta [71,72]. Previous studies reported an increased production of placental tissue of 8-OHdG in PE women [73,74]. Early imbalance of serum levels of oxidative stress biomarkers was observed among suboptimal health status (SHS) normotensive pregnant women, and this imbalance corresponded with abnormal histomorphological features and immunohistochemical expression of oxidative stress among women who developed PE, suggesting the potential involvement of SHS in the pathophysiology of PE [75].

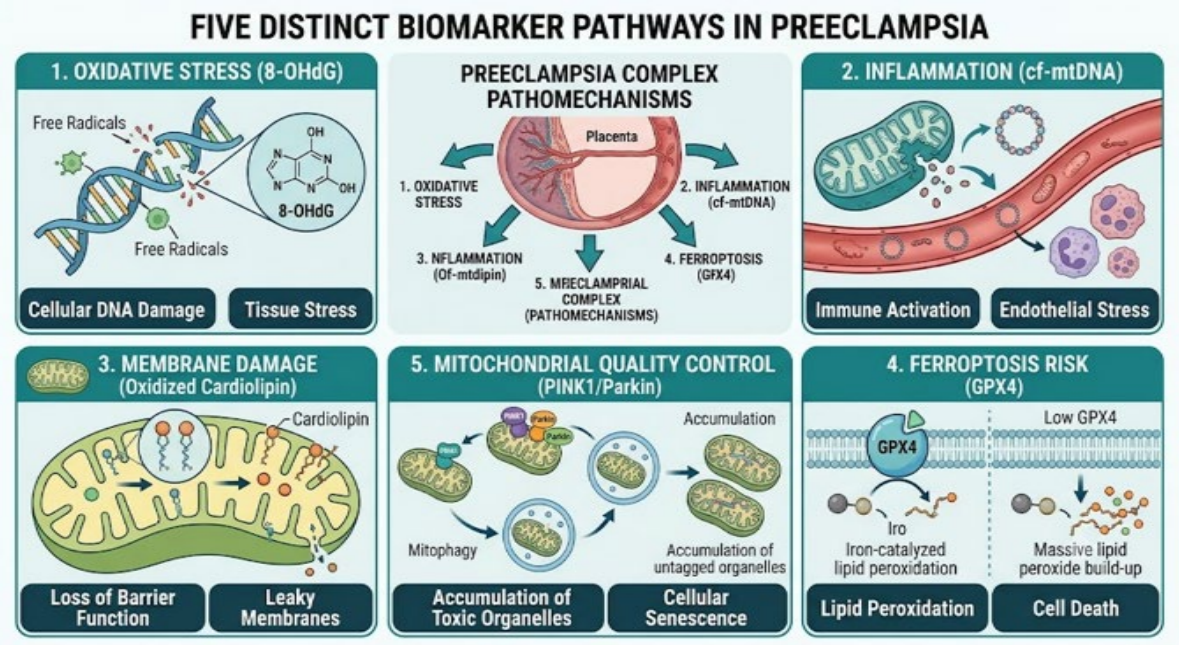



**Figure 2:** The distinctive pathways involved in preeclampsia [64].

As DNA oxidation occurs early in the subclinical phase of the disease, measuring 8-OHdG (in blood or urine) can identify pregnant women who are at risk, not optimally healthy, before they develop clinical symptoms like high blood pressure or protein in the urine [76]. Higher levels of mitochondrial DNA copies and circulating cell-free mitochondrial DNA add an immune-related layer to preeclampsia understanding. Fragments of mitochondrial DNA leak out when trophoblast cells are under stress or die, acting as an internal alarm signal [20]. Human studies show that cfDNA is elevated in PE, and circulating levels correlate with disease severity and adverse maternal-fetal outcomes [77–79]. This suggests the DNA is not simply a passive marker but could be an active driver of maternal blood vessel damage. If confirmed, these findings change our view of treatment: approaches to remove the extracellular DNA or inhibit its immune sensors could give rise to novel therapeutic approaches.

Oxidized cardiolipin and malondialdehyde highlight a less appreciated weakness, the inner mitochondrial membrane. Cardiolipin is only found in this place and is critical for holding together the protein complexes that power energy production [80]. Oxidized cardiolipin causes the mitochondrion to collapse its internal folds, release cytochrome c, and push the cell toward programmed death [81]. At the same time MDA provides a comprehensive assessment of oxidative stress by capturing damage from several types of free radicals [82]. The overlap between the membrane damage makers and regulators of GPX4, mitochondrial ferritin, and transferrin receptor 1 suggests that trophoblast loss in preeclampsia may be due to iron-driven lipid destruction rather than the traditional caspase-mediated cell death pathway [55,83]. Ferroptosis leads to a characteristic mitochondrial morphology: collapsed organelles with abnormally dense membranes. This morphology has been described in placentas from women with

preeclampsia, but it is rarely linked to ferroptosis [84]. This perspective on trophoblast death opens up new therapeutic options such as fat-soluble antioxidants and iron chelators, which are currently being investigated in cancer and neurodegenerative diseases [85,86]. The PINK1/Parkin system serves as the main quality control system employed by mammalian cells to identify and remove dysfunctional mitochondria [87]. Under normal circumstances, PINK1 builds up on defective mitochondrial membranes, attracts Parkin from the cell fluid, and leads to the packaging of the defective organelle in an autophagosome for destruction [87,88]. When this process is impaired, as indicated by studies in preeclampsia, damaged mitochondria remain in the cell, continue to release reactive oxygen species, and activate inflammatory signaling platforms [89]. No single biomarker can fully reflect the complex nature of preeclampsia. Each reveal only shows part of the underlying disease process. However, combining several markers into a single panel could substantially improve early risk prediction. For example, measuring 8-OHdG for oxidative stress, cell-free mitochondrial DNA for inflammation, oxidized cardiolipin for membrane damage, GPX4 for ferroptosis risk, and PINK1/Parkin levels for mitochondrial quality control would provide a layered risk assessment far more informative than any test used alone.

## Limitations and Prospects

The biomarkers discussed here were selected based on their mitochondrial specificity, yet preeclampsia is undoubtedly a multifactorial disorder involving angiogenic imbalance, immune maladaptation, and genetic susceptibility. Mitochondrial biomarkers should therefore be viewed as complementary to, rather than a replacement for, established indicators such as soluble fms-like tyrosine kinase-1 and placental growth factor [63,90]. Future research should be directed towards several objectives. Mechanistic studies using trophoblast-specific genetic or pharmacological manipulations in animal models are required to establish a causal link between mitochondrial dysfunction and the preeclampsia phenotype. Multibiomarker panels require validation in large ethnically diverse cohorts with stringent pre-analytical standardization. Finally, the urgent requirement for interventional trials of mitochondrial pathways, such as antioxidants, mitophagy enhancers, or ferroptosis inhibitors to determine whether the associations described here are therapeutically modifiable. If such trials are successful, the mitochondrion may pass from a diagnostic curiosity to a true therapeutic target in obstetric medicine.

## Conclusion

Mitochondrial dysfunction has emerged as a central mechanistic hub linking placental pathology to the systemic manifestations of preeclampsia. The biomarkers discussed here, representing oxidative DNA damage, mitochondrial turnover, membrane lipid peroxidation, iron-dependent cell death, and defective organellar clearance, collectively indicate that preeclampsia is not merely a disorder of vascular maladaptation but a syndrome arising from bioenergetic failure and cellular stress at the maternal-fetal interface. An 8-OHdG represents direct molecular evidence of reactive oxygen species-induced damage on mtDNA placental tissues and biofluids, thus defining oxidative mtDNA damage as an initiating event and a measurable marker of disease severity. The increase in circulating mtDNA copy numbers and cell-free mitochondrial DNA fragments further extends this narrative, suggesting that preeclampsia involves not only local placental injury but also a systemic inflammatory response driven by the release of damage-associated molecular patterns into maternal circulation. Meanwhile, markers of oxidized cardiolipin and malondialdehyde underscore the susceptibility of the inner mitochondrial membrane, an event that destroys the integrity of the respiratory chain and propagates pro-apoptotic signaling across the trophoblast layer. The mitochondrial perspective on preeclampsia offers both explanatory depth and translational opportunity. As our capacity to detect and quantify organellar stress in maternal biofluids improves, the use of mitochondrial biomarkers in routine risk stratification may offer additional insight into the long-standing goal of preventing, rather than managing, this life-threatening pregnancy complication.

### Conflict of interests

The authors declared no conflict of interest.

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### Data sharing statement

The data that supports the findings of this study are available from the corresponding author upon a reasonable request.

## REFERENCES

1. Parrettini S, Caroli A, Torlone E. Nutrition and metabolic adaptations in physiological and complicated pregnancy: Focus on obesity and gestational diabetes. *Front Endocrinol (Lausanne)*. 2020;11. doi: 10.3389/fendo.2020.611929.
2. Chiang YT, Chen JH, Chen KH. The molecular and cellular basis of physiological changes in pregnancy and its implications in neurologic and ophthalmic pathologies. *Int J Mol Sci*. 2025;26(11):5220. doi: 10.3390/ijms26115220.
3. Chakulya M, Mulambo P, Chama GC, Nalavwe L, Pulukuta IM, Simwaba P, et al. Preeclampsia, prevalence and associated factors. *PLoS One*. 2025;20(12):e0337190. doi: 10.1371/journal.pone.0337190.
4. Kutllovci Hasani K, Ajeti N, Goswami N. Understanding preeclampsia: Cardiovascular pathophysiology, histopathological insights and molecular biomarkers. *Med Sci*. 2025;13(3):154. doi: 10.3390/medsci13030154.
5. Vigil-De Gracia P, Vargas C, Sánchez J, Collantes-Cubas J. Preeclampsia: Narrative review for clinical use. *Heliyon*. 2023;9(3):e14187. doi: 10.1016/j.heliyon.2023.e14187.
6. Witkowski P, Dzieński B, Stefańska K, Tomaszewicz M, Zabielska-Kaczorowska M, Wydra D. Preeclampsia:

Contemporary concepts in pathophysiology, risk stratification, prevention and monitoring. *J Clin Med*. 2026;15(5):1944. doi: 10.3390/jcm15051944.
7. Turbeville HR, Sasser JM. Preeclampsia beyond pregnancy: long-term consequences for mother and child. *Am J Physiol-Renal Physiol*. 2020;318(6):F1315–1326. doi: 10.1152/ajprenal.00071.2020.
8. Koulouraki S, Paschos V, Pervanidou P, Christopoulos P, Gerede A, Eleftheriades M. Short- and long-term outcomes of preeclampsia in offspring: Review of the literature. *Children*. 2023;10(5):826. doi: 10.3390/children10050826.
9. Vornic I, Buciu V, Furau CG, Gaje PN, Ceausu RA, Dumitru CS, et al. Oxidative stress and placental pathogenesis: A contemporary overview of potential biomarkers and emerging therapeutics. *Int J Mol Sci*. 2024;25(22):12195. doi: 10.3390/ijms252212195.
10. Parapob N, Luewan S, Kamlungkuea T, Tongsong T. Oxidative stress in pathogenesis of preeclampsia: Mechanistic and clinical insights. *Antioxidants*. 2026;15(3):387. doi: 10.3390/antiox15030387.
11. Chiarello DI, Abad C, Rojas D, Toledo F, Vázquez CM, Mate A, et al. Oxidative stress: Normal pregnancy versus preeclampsia. *Biochim Biophys Acta*. 2020;1866(2):165354. doi: 10.1016/j.bbadis.2018.12.005.
12. Backston K, Morgan J, Patel S, Koka R, Hu J, Raina R. Oxidative stress and endothelial dysfunction: The pathogenesis of pediatric hypertension. *Int J Mol Sci*. 2025;26(11):5355. doi: 10.3390/ijms26115355.
13. Abu-Awwad SA, Craina M, Boscu L, Bernad E, Ciordas PD, Marian C, et al. Lipid profile variations in pregnancies with and without cardiovascular risk: Consequences for both mother and newborn. *Children*. 2023;10(9):1521. doi: 10.3390/children10091521.
14. Chen YS, Tian HX, Rong DC, Wang L, Chen S, Zeng J, et al. ROS homeostasis in cell fate, pathophysiology, and therapeutic interventions. *Mol Biomed*. 2025;6(1):89. doi: 10.1186/s43556-025-00338-8.
15. Meena P, Batool A. Electrolyte homeostasis in pregnancy: from physiological adaptations to clinical disturbances—A nephrologist's perspective. *Front Nephrol*. 2026;6. doi: 10.3389/fneph.2026.1773415.
16. Kornacki J, Olejniczak O, Sibiak R, Gutaj P, Wender-Ożegowska E. Pathophysiology of pre-eclampsia—Two theories of the development of the disease. *Int J Mol Sci*. 2023;25(1):307. doi: 10.3390/ijms25010307.
17. Greenbaum S, Averbukh I, Soon E, Rizzuto G, Baranski A, Greenwald NF, et al. A spatially resolved timeline of the human maternal–fetal interface. *Nature*. 2023;619(7970):595–605. doi: 10.1038/s41586-023-06298-9.
18. Gusella A, Martignoni G, Giacometti C. Behind the curtain of abnormal placentation in pre-eclampsia: From molecular mechanisms to histological hallmarks. *Int J Mol Sci*. 2024;25(14):7886. doi: 10.3390/ijms25147886.
19. Rana S, Burke SD, Karumanchi SA. Imbalances in circulating angiogenic factors in the pathophysiology of preeclampsia and related disorders. *Am J Obstet Gynecol*. 2022;226(2):S1019–1034. doi: 10.1016/j.ajog.2020.10.022.
20. Smith AN, Wang X, Thomas DG, Tatum RE, Booz GW, Cunningham MW. The role of mitochondrial dysfunction in preeclampsia: Causative factor or collateral damage? *Am J Hypertens*. 2021;34(5):442–452. doi: 10.1093/ajh/hpab003.
21. Hu XQ, Zhang L. Mitochondrial dysfunction in the pathogenesis of preeclampsia. *Curr Hypertens Rep*. 2022;24(6):157–172. doi: 10.1007/s11906-022-01184-7.
22. Zhou X, Zhao X, Zhou W, Qi H, Zhang H, Han TL, et al. Impaired placental mitophagy and oxidative stress are associated with dysregulated BNIP3 in preeclampsia. *Sci Rep*. 2021;11(1):20469. doi: 10.1038/s41598-021-99837-1.
23. Green DR. The mitochondrial pathway of apoptosis. *Cold Spring Harb Perspect Biol*. 2022;14(5):a041038. doi: 10.1101/cshperspect.a041038.
24. Vasilaki I, Potiris A, Moustakli E, Mavrogianni D, Daponte N, Karampitsakos T, et al. Linking oxidative stress to placental dysfunction: The key role of mitochondria in trophoblast function. *Med Sci*. 2026;14(1):53. doi: 10.3390/medsci14010053
25. Kajdy A, Modzelewski J, Cymbaluk-Płoska A, Kwiatkowska E, Bednarek-Jędrzejek M, Borowski D, et al. Molecular pathways of cellular senescence and placental aging in late fetal growth restriction and stillbirth. *Int J Mol Sci*. 2021;22(8):4186. doi: 10.3390/ijms22084186.
26. Čepelak I, Dodig S, Dodig DČ. Ferroptosis: regulated cell death. *Arch Indust Hyg Toxicol*. 2020;71(2):99–109. doi: 10.2478/aiht-2020-71-3366.
27. Sangkhae V, Fisher AL, Ganz T, Nemeth E. Iron homeostasis during pregnancy: Maternal, placental, and fetal regulatory mechanisms. *Annu Rev Nutr*. 2023;43(1):279–300. doi: 10.1146/annurev-nutr-061021-030404.
28. Zheng Y, Sun J, Luo Z, Li Y, Huang Y. Emerging mechanisms of lipid peroxidation in regulated cell death and its physiological implications. *Cell Death Dis*. 2024;15(11):859. doi: 10.1038/s41419-024-07244-x.
29. Barbouti A, Varvarousis DN, Kanavaros P. The role of oxidative stress-induced senescence in the pathogenesis of preeclampsia. *Antioxidants*. 2025;14(5):529. doi: 10.3390/antiox14050529.
30. Sultana Z, Maiti K, Dedman L, Smith R. Is there a role for placental senescence in the genesis of obstetric complications and fetal growth restriction? *Am J Obstet Gynecol*. 2018;218(2):S762–773. doi: 10.1016/j.ajog.2017.11.567.
31. Wang C, Zhang M. Neutrophil extracellular traps in pregnancy complications. *Front Immunol*. 2026;17. doi: 10.3389/fimmu.2026.1798749.
32. Hernández González LL, Pérez-Campos Mayoral L, Hernández-Huerta MT, Mayoral Andrade G, Martínez Cruz M, Ramos-Martínez E, et al. Targeting neutrophil extracellular trap formation: Exploring promising pharmacological strategies for the treatment of preeclampsia. *Pharmaceuticals*. 2024;17(5):605. doi: 10.3390/ph17050605.
33. Chen WA, Boskovic DS. Neutrophil extracellular DNA traps in response to infection or inflammation, and the roles of platelet interactions. *Int J Mol Sci*. 2024;25(5):3025. doi: 10.3390/ijms25053025.
34. Hu XQ, Zhang L. Hypoxia and mitochondrial dysfunction in pregnancy complications. *Antioxidants*. 2021;10(3):405. doi: 10.3390/antiox10030405.
35. Hu XQ, Zhang L. Hypoxia and the integrated stress response promote pulmonary hypertension and preeclampsia: Implications in drug development. *Drug Discov Today*. 2021;26(11):2754–2773. doi: 10.1016/j.drudis.2021.07.011.
36. Al-Ogaidi SO, Abdulsattar SA, Al-Dulaimi HM. FTO rs17817449 gene polymorphism as a predictor for maternal obesity in Iraqi pregnant women. *Indian J Public Health Res Dev*. 2019;10(4):678. doi: 10.5958/0976-5506.2019.00780.0.
37. Zhang H, Burr SP, Chinnery PF. The mitochondrial DNA genetic bottleneck: inheritance and beyond. *Essays Biochem*. 2018;62(3):225–234. doi: 10.1042/EBC20170096.
38. Gustafsson CM, Falkenberg M, Larsson NG. Maintenance and expression of mammalian mitochondrial DNA. *Annu Rev Biochem*. 2016;85(1):133–160. doi: 10.1146/annurev-biochem-060815-014402.
39. Liu L, Wang A, Yi K. Causal relationships between mitochondrial DNA copy number and hypertensive disorders in pregnancy: A Mendelian randomization study. *Eurasian J Med Oncol*. 2025;10(1):100. doi: 10.36922/EJMO025140077.
40. Abdulsattar SA, Nori W, Mohammed EA. Biomarker-guided prediction of pregnancy viability, current evidence and emerging insights: a narrative review. *Al-Rafidain J Med Sci*. 2025;9(1):246-254. doi: 10.54133/ajms.v9i1.2300.
41. Pandey D, Yevale A, Naha R, Kuthethur R, Chakrabarty S, Satyamoorthy K. Mitochondrial DNA copy number variation – A potential biomarker for early onset preeclampsia. *Pregnancy Hypertens*. 2021;23:1–4. doi: 10.1016/j.preghy.2020.10.002.
42. Toledano JM, Puche-Juarez M, Galvez-Navas JM, Moreno-Fernandez J, Diaz-Castro J, Ochoa JJ. Pregnancy disorders: A potential role for mitochondrial altered homeostasis. *Antioxidants*. 2024;13(8):979. doi: 10.3390/antiox13080979.
43. Kamar Bashah NA, Hamid AA, Adam SH, Jaffar FHF, Abd Rahman IZ, Mokhtar MH. Role of AMP-activated protein kinase (AMPK) in female reproduction: A review. *Int J Mol Sci*. 2025;26(14):6833. doi: 10.3390/ijms26146833.

44. Abu Shelbayeh O, Arroum T, Morris S, Busch KB. PGC-1α is a master regulator of mitochondrial lifecycle and ROS stress response. *Antioxidants*. 2023;12(5):1075. doi: 10.3390/antiox12051075.
45. Cushen SC, Ricci CA, Bradshaw JL, Silzer T, Blessing A, Sun J, et al. Reduced maternal circulating cell-free mitochondrial DNA is associated with the development of preeclampsia. *J Am Heart Assoc*. 2022;11(2). doi: 10.1161/JAHA.121.021726.
46. Vasilaki I, Potiris A, Moustakli E, Mavrogianni D, Daponte N, Karampitsakos T, et al. Linking oxidative stress to placental dysfunction: The key role of mitochondria in trophoblast function. *Med Sci*. 2026;14(1):53. doi: 10.3390/medsci14010053.
47. Paradies G, Paradies V, Ruggiero FM, Petrosillo G. Role of cardiolipin in mitochondrial function and dynamics in health and disease: Molecular and pharmacological sspects. *Cells*. 2019;8(7):728. doi: 10.3390/cells8070728.
48. Venkatraman K, Budin I. Cardiolipin remodeling maintains the inner mitochondrial membrane in cells with saturated lipidomes. *J Lipid Res*. 2024;65(8):100601. doi: 10.1016/j.jlr.2024.100601.
49. Petrosillo G, Ruggiero FM, Paradies G. Role of reactive oxygen species and cardiolipin in the release of cytochrome c from mitochondria. *FASEB J*. 2003;17(15):2202–2208. doi: 10.1096/fj.03-0012com.
50. Goswami D, Tannetta DS, Magee LA, Fuchisawa A, Redman CWG, Sargent IL, et al. Excess syncytiotrophoblast microparticle shedding is a feature of early-onset pre-eclampsia, but not normotensive intrauterine growth restriction. *Placenta*. 2006;27(1):56–61. doi: 10.1016/j.placenta.2004.11.007.
51. Afrose D, Chen H, Ranashinghe A, Liu C, Henessy A, Hansbro PM, et al. The diagnostic potential of oxidative stress biomarkers for preeclampsia: systematic review and meta-analysis. *Biol Sex Differ*. 2022;13(1):26. doi: 10.1186/s13293-022-00436-0.
52. Khoubnasabjafari M, Ansarin K, Jouyban A. Variations of malondialdehyde in pre-eclampsia. *Hypertens Pregnancy*. 2016;35(3):346–349. doi: 10.3109/10641955.2016.1148163.
53. Chen Z, Gan J, Zhang M, Du Y, Zhao H. Ferroptosis and its emerging role in pre-eclampsia. *Antioxidants*. 2022;11(7):1282. doi: 10.3390/antiox11071282.
54. Chen Y, Fang ZM, Yi X, Wei X, Jiang DS. The interaction between ferroptosis and inflammatory signaling pathways. *Cell Death Dis*. 2023;14(3):205. doi: 10.1038/s41419-023-05716-0.
55. Peng X, Lin Y, Li J, Liu M, Wang J, Li X, et al. Evaluation of glutathione peroxidase 4 role in preeclampsia. *Sci Rep*. 2016;6(1):33300. doi: 10.1038/srep33300.
56. Bucarey JL, Casas M, Espinosa A. Mitochondrial iron handling and lipid peroxidation as drivers of ferroptosis. *Int J Mol Sci*. 2026;27(5):2232. doi: 10.3390/ijms27052232.
57. Jin J, Xu Z, Liu Z, Huang L, Liu F, Liu M, et al. Association between maternal iron status and the risk of pre-eclampsia: a case-control study. *Asia Pac J Clin Nutr*. 2024;33(2):184–193. doi: 10.6133/apjcn.202406_33(2).0005.
58. Yang Y, Zuo H, Ma X, Chen W, Sun M, Xiang Q, et al. Iron overload-induced ferroptosis drives placental dysfunction in preeclampsia. *Hypertension*. 2026;83(7). doi: 10.1161/HYPERTENSIONAHA.125.26344.
59. Zhong J, Jiang R, Liu N, Cai Q, Cao Q, Du Y, et al. Iron–immune crosstalk at the maternal–fetal interface: Emerging mechanisms in the pathogenesis of preeclampsia. *Antioxidants*. 2025;14(7):890. doi: 10.3390/antiox14070890.
60. Yildirim RM, Ergun Y, Basar M. Mitochondrial dysfunction, mitophagy and their correlation with perinatal complications: Preeclampsia and low birth weight. *Biomedicines*. 2022;10(10):2539. doi: 10.3390/biomedicines10102539.
61. Zhang Z, Zhang M, Jin H, Lv S, Li Y, Li Y. Mitochondrial quality control and cell death. *Int J Mol Sci*. 2025;26(22):11084. doi: 10.3390/ijms262211084.
62. Sauvé V, Stefan E, Croteau N, Goiran T, Fakih R, Bansal N, et al. Activation of parkin by a molecular glue. *Nat Commun*. 2024;15(1):7707. doi: 10.1038/s41467-024-51889-3.
63. Sun Y, Lv D, Xie Y, Xu H, Li X, Li F, et al. PINK1-mediated mitophagy induction protects against preeclampsia by decreasing ROS and trophoblast pyroptosis. *Placenta*. 2023;143:1–11. doi: 10.1016/j.placenta.2023.09.010.
64. Vaka R, Deer E, LaMarca B. Is mitochondrial oxidative stress a viable therapeutic target in preeclampsia? *Antioxidants*. 2022;11(2):210. doi: 10.3390/antiox11020210.
65. Voros C, Stavros S, Sapantzoglou I, Mavrogianni D, Daskalaki MA, Theodora M, et al. The role of placental mitochondrial dysfunction in adverse perinatal outcomes: A systematic review. *J Clin Med*. 2025;14(11):3838. doi: 10.3390/jcm14113838.
66. Nori W, Helmi ZR. Can follicular fluid 8-oxo-2′-deoxyguanosine predict the clinical outcomes in ICSI cycle among couples with normospermia male? *Obstet Gynecol Sci*. 2023;66(5):430-440. doi: 10.5468/ogs.22170.
67. Brunst KJ, Zhang L, Zhang X, Baccarelli AA, Bloomquist T, Wright RJ. Associations between maternal lifetime stress and placental mitochondrial DNA mutations in an urban multiethnic cohort. *Biol Psychiatry*. 2021;89(6):570–578. doi: 10.1016/j.biopsych.2020.09.013.
68. Cushen SC, Sprouse ML, Blessing A, Sun J, Jarvis SS, Okada Y, et al. Cell-free mitochondrial DNA increases in maternal circulation during healthy pregnancy: a prospective, longitudinal study. *Am J Physiol-Regul Integrative Comparative Physiol*. 2020;318(2):R445–452. doi: 10.1152/ajpregu.00324.2019.
69. Afrose D, Alfonso-Sánchez S, McClements L. Targeting oxidative stress in preeclampsia. *Hypertens Pregnancy*. 2025;44(1). doi: 10.1080/10641955.2024.2445556.
70. Anto EO, Roberts P, Turpin CA, Wang W. Oxidative stress as a key signaling pathway in placental angiogenesis changes in preeclampsia: Updates in pathogenesis, novel biomarkers and therapeutics. *Curr Pharmacogenomics Person Med*. 2019;16(3):167–181. doi: 10.2174/1875692117666181207120011.
71. Ibrahim A, Khoo MI, Ismail EHE, Hussain NHN, Zin AAM, Noordin L, et al. Oxidative stress biomarkers in pregnancy: a systematic review. *Reprod Biol Endocrinol*. 2024;22(1):93. doi: 10.1186/s12958-024-01259-x.
72. Zhou X, Zhang H, Wei L, Wang Z, Zhu S, Yu J, et al. Oxidative stress, mitochondrial dysfunction, and ferroptosis in the placenta of gestational diabetes mellitus. *J Mol Med*. 2026;104(1):8. doi: 10.1007/s00109-025-02629-7.
73. Fukushima K, Murata M, Tsukimori K, Eisuke K, Wake N. 8-Hydroxy-2-deoxyguanosine staining in placenta is associated with maternal serum uric acid levels and gestational age at diagnosis in pre-eclampsia. *Am J Hypertens*. 2011;24(7):829–834. doi: 10.1038/ajh.2011.40.
74. Takagi Y, Nikaido T, Toki T, Kita N, Kanai M, Ashida T, et al. Levels of oxidative stress and redox-related molecules in the placenta in preeclampsia and fetal growth restriction. *Virchows Arch*. 2004;444(1):49–55. doi: 10.1007/s00428-003-0903-2.
75. Anto EO, Coall DA, Asiamah EA, Afriyie OO, Addai-Mensah O, Wiafe YA, et al. Placental lesions and differential expression of pro-and anti-angiogenic growth mediators and oxidative DNA damage marker in placentae of Ghanaian suboptimal and optimal health status pregnant women who later developed preeclampsia. *PLoS One*. 2022;17(3):e0265717. doi: 10.1371/journal.pone.0265717.
76. Qiu C, Hevner K, Abetew D, Enquobahrie DA, Williams MA. Oxidative DNA damage in early pregnancy and risk of gestational diabetes mellitus: A pilot study. *Clin Biochem*. 2011;44(10–11):804–808. doi: 10.1016/j.clinbiochem.2011.04.023.
77. Palei AC. Cell-free DNA as a potential biomarker for preeclampsia. *Expert Rev Mol Diagn*. 2021;21(12):1253–1256. doi: 10.1080/14737159.2021.1997593.
78. Amaral LM, Sandrim VC, Kutcher ME, Spradley FT, Cavalli RC, Tanus-Santos JE, et al. Circulating total cell-free DNA levels are increased in hypertensive disorders of pregnancy and associated with prohypertensive factors and adverse clinical outcomes. *Int J Mol Sci*. 2021;22(2):564. doi: 10.3390/ijms22020564.
79. Rafaeli-Yehudai T, Imterat M, Douvdevani A, Tirosh D, Benshalom-Tirosh N, Mastrolia SA, et al. Maternal total cell-free DNA in preeclampsia and fetal growth restriction: Evidence of differences in maternal response to abnormal

implantation. *PLoS One*. 2018;13(7):e0200360. doi: 10.1371/journal.pone.0200360.

80. Paradies G. Oxidative stress, cardiolipin and mitochondrial dysfunction in nonalcoholic fatty liver disease. *World J Gastroenterol*. 2014;20(39):14205. doi: 10.3748/wjg.v20.i39.14205.
81. Fiorucci L, Erba F, Santucci R, Sinibaldi F. Cytochrome c interaction with cardiolipin plays a key role in cell apoptosis: Implications for human diseases. *Symmetry (Basel)*. 2022;14(4):767. doi: 10.3390/sym14040767
82. Baş A, Dur R. The relationship between trace element imbalance, oxidative stress, and endothelial dysfunction in preeclampsia diagnosis. *BMC Pregnancy Childbirth*. 2026;26(1):766. doi: 10.1186/s12884-026-09277-w.
83. Beharier O, Kajiwara K, Sadovsky Y. Ferroptosis, trophoblast lipotoxic damage, and adverse pregnancy outcome. *Placenta*. 2021;108:32–38. doi: 10.1016/j.placenta.2021.03.007.
84. Liu M, Wu K, Wu Y. The emerging role of ferroptosis in female reproductive disorders. *Biomed Pharmacother*. 2023;166:115415. doi: 10.1016/j.biopha.2023.115415.
85. Abbasi U, Abbina S, Gill A, Takuechi LE, Kizhakkedathu JN. Role of iron in the molecular pathogenesis of diseases and therapeutic opportunities. *ACS Chem Biol*. 2021;16(6):945–972. doi: 10.1021/acschembio.1c00122.
86. Salimi Z, Afsharinasab M, Rostami M, Eshaghi Milasi Y, Mousavi Ezmareh SF, Sakhaei F, et al. Iron chelators: as therapeutic agents in diseases. *Ann Med Surg*. 2024;86(5):2759–2776. doi: 10.1097/MS9.0000000000001717.
87. Ge P, Dawson VL, Dawson TM. PINK1 and Parkin mitochondrial quality control: a source of regional vulnerability in Parkinson's disease. *Mol Neurodegener*. 2020;15(1):20. doi: 10.1186/s13024-020-00367-7.
88. Narendra DP, Jin SM, Tanaka A, Suen DF, Gautier CA, Shen J, et al. PINK1 is selectively stabilized on impaired mitochondria to activate parkin. *PLoS Biol*. 2010;8(1):e1000298. doi: 10.1371/journal.pbio.1000298
89. Sun Y, Lv D, Xie Y, Xu H, Li X, Li F, et al. PINK1-mediated mitophagy induction protects against preeclampsia by decreasing ROS and trophoblast pyroptosis. *Placenta*. 2023;143:1–11. doi: 10.1016/j.placenta.2023.09.010.
90. Papapanagiotou A, Daskalaki MA, Gargalionis AN, Margoni A, Papapanagiotou A, Daskalaki MA, et al. The role of angiogenetic factors in preeclampsia. *Int J Mol Sci*. 2025;26(21):10431. doi: 10.3390/ijms262110431.