INTRODUCTION

Mitochondria are central to regulating cellular metabolism, redox state, and determining cell fate. Pregnant is a time of large physiological changes, many of which are driven by the placenta, and placental mitochondria are critical both to a healthy pregnancy, and also in pregnancy complications.

The placenta forms the interface between maternal and fetal physiological systems, performing functions including metabolic and hormonal regulation as well as transport of oxygen from maternal to fetal circulations. The placenta is capable of responding to the signals from both mother and fetus, optimising fetal growth by modifying the maternal supply of nutrients and oxygen. As with most tissues, the primary use of oxygen in the placenta is to release energy through oxidative phosphorylation. This process also generates reactive oxygen species (ROS). ROS production is a normal part of cell biology, with intracellular levels balanced by antioxidants, and ROS important for intracellular signalling and tissue adaptations (Figure 1). However, excessive ROS are damaging, and increased ROS levels are associated with pregnancy complications, including the important disorders preeclampsia and gestational diabetes mellitus. Here we review the function of placental mitochondria in healthy pregnancy, and also in pregnancy complications. Placental mitochondria are critical to cell function, and mitochondrial damage is a feature of pregnancy complications. However, the responsiveness of mitochondria to ROS signalling may be central to placental adaptations that mitigate damage, and placental mitochondria are an attractive target for the development of therapeutics to improve pregnancy outcomes.

KEYWORDS
mitochondria, oxidative stress, placenta, reactive oxygen species, trophoblast
in a healthy pregnancy, and implicated in the pathogenesis of these conditions.

2 | PLACENTAL MITOCHONDRIA IN CYTOTROPHOBLASTS AND THE SYNCTIOTROPHOBLAST

The human placenta is composed of several cell types. We focus on the villous trophoblast cell lineage, which consist predominantly of two cell types, cytotrophoblasts and the syncytiotrophoblast, as these cells are central to important placental functions and have distinct mitochondrial populations with varying susceptibility to dysfunction. Cytotrophoblasts have typical organelle organisation, whereas the syncytiotrophoblast is a poorly organised extended cytoplasm with many thousands of nuclei and specific organelle morphology/function. Cytotrophoblast mitochondria are relatively larger (0.2–0.8 μm) and have a stereotypical shape with lamellar cristae, whereas syncytiotrophoblast mitochondria are small (≤0.1 μm), more spherical, have tubular cristae and a less dense matrix (Figure 2). The small size of syncytiotrophoblast mitochondria has been suggested to aid in their steroidogenic function, as the most common sterol carrier protein family member responsible for mitochondrial cholesterol transport in other cells — steroidogenic acute regulatory protein — is not expressed in the placenta, and cholesterol may be transported more efficiently across membranes of smaller mitochondria. Further, the atypical morphology of syncytiotrophoblast mitochondria has been attributed to reduced F_1F_0 ATP synthase supercomplex dimerization, the structural component of ATP synthase, which alters inner membrane curvature and affects formation of mitochondria cristae. ATP synthase is also critical in maintaining membrane potential (ΔΨ_m), and uses the proton motive force for ATP biosynthesis. Therefore, lower dimeric ATP synthase levels may explain decreased ATP production in the syncytiotrophoblast compared to cytotrophoblasts. In the syncytiotrophoblast, most

FIGURE 1  Reactive oxygen species signalling and damage. Reactive oxygen species (ROS) are important in cellular signalling, and can lead to cellular adaptations to counter stressful environments. However, when ROS production is greater than antioxidant and other adaptive responses, ROS-mediated damage can lead to cell death. Placental mitochondria are critical to cell function, and mitochondrial damage is a feature of pregnancy complications.
ΔΨm regulates ATP-diphosphohydrolase (an enzyme involved in cholesterol transport), and the majority of ATP produced is utilized for cholesterol transport and steroidogenesis. 18

As the syncytiotrophoblast is formed via the fusion of cytotrophoblasts, these mitochondrial differences represent an important shift in cellular function. Cytotrophoblast differentiation into the syncytiotrophoblast leads to decreased mitochondrial respiration and altered metabolism, including an increase in lactate production. 19 The syncytiotrophoblast forms the outer layer of the placenta in direct contact with maternal systems, and appears to be the placental region most responsive to changes in oxygen levels; this responsiveness is likely partly due to the unique mitochondria of the syncytiotrophoblast, and may help the placental/fetal unit adapt to maternal conditions. 20 Further, relative to cytotrophoblasts, the syncytiotrophoblast has lower antioxidant function, 20,21 which would otherwise dampen ROS levels that may be critical to signalling within this cell layer. Additionally, mitochondrial response to oxygen levels has a role in the endovascular phenotype of extravillous cytotrophoblasts 22 (critical for early placental uterine attachment and ongoing placental function), and in murine trophoblast differentiation, 23 demonstrating the importance of mitochondrial oxygen responses to a range of placental behaviours.

The syncytiotrophoblast also appears to be sensitive to damage from oxygen, which may be a consequence of high oxygen sensitivity through mechanisms such as low antioxidant function. 20,21 The production of steroids by the syncytiotrophoblast may also be linked to syncytiotrophoblast susceptibility to ROS-mediated damage, through increased production of superoxide (O2−•) and hydrogen peroxide (H2O2). Syncytiotrophoblast mitochondria are central to placental steroidogenesis, in particular progesterone production. 13 Increased expression of cytochrome P450scc (an enzyme that converts cholesterol to pregnenolone) in syncytiotrophoblast compared to cytotrophoblast mitochondria is associated with changes in mitochondrial morphology, 11,24 and also increased production of ROS. 25

3 | PLACENTAL MITOCHONDRIAL ADAPTATIONS

3.1 | Placental mitochondrial dynamics and apoptosis in preeclampsia

Mitochondria are constantly changing in a dynamic cycle 26; fission segregates damaged mitochondria for disposal by autophagy, whereas fusion allows dysfunctional/damaged mitochondria to be rescued by amalgamation with more functional parts of the mitochondrial network 27 (Figure 3). In the placenta, mitochondrial fission/fusion appears to be impaired in cases of preeclampsia, but this relationship is complex and not well understood. Changes in molecular mechanisms of placental mitochondrial fission/fusion may relate to preeclampsia severity and gestational length. In severe preeclampsia, increases in pro-fission regulator Optic atrophy protein 1 (OPA-1) and decreases in pro-fission regulator Dynamin-related protein 1 (DRP1) have been reported, 28,29 but no apparent changes were found in other fission/fusion regulators including Mitochondrial fission factor 29 and Mitofusins (MFN1 and MFN2). 28 In contrast, other research has found decreases in MFN1 and MFN2 associated with preeclampsia, indicating a pro-fission status. 30,31 Placental mitochondrial dynamics is also affected in GDM, with hyperglycemia inducing mitochondrial fragmentation through a proposed mechanism involving DRP1, 32,33 and this may be a reason GDM is a risk factor for preeclampsia. Damaged mitochondria are removed by autophagy (Figure 3), and in both severe preeclampsia and GDM increased placental autophagy markers have been observed. 34 Placental autophagy markers are altered in association with excessive ROS generation, decreased antioxidant capacity and enhanced mitochondrial turnover, 34 directly linking changes in mitochondrial dynamics to complications of pregnancy.

Our laboratory and others have shown that in more severe forms of preeclampsia, markers of mitochondrial fission are increased, whereas in less severe disease fusion markers predominate. 28,35
Therefore, in less severe preeclampsia, salvage mechanisms may be operating to rescue damaged placental mitochondria and protect trophoblasts from apoptosis, thereby preventing excessive generation of placental cell debris that enters the maternal circulation and is a hallmark of preeclampsia. Whether this mitochondrial salvage is a positive adaptation allowing pregnancies to reach greater gestational age, and what drives fission versus fusion in normal versus diseased placentae, remains uncertain.

Mitochondria regulate apoptosis through intrinsic activation with cytochrome C release. Increases in apoptotic markers are associated with the development of preeclampsia and GDM; however, we have also shown that anti-apoptotic B-cell lymphoma 2 (BCL2) is increased in placentae from preeclamptic pregnancies that reach term delivery and that this protective effect is not seen in preeclamptic pregnancies that are delivered preterm. Further, decreased pro-apoptotic FAS receptor, FAS ligand and Caspase-3, in addition to increased BCL2 have been observed in GDM placentae. Therefore, differences in apoptotic signalling in GDM and preeclampsia may relate to disease severity, with a mitochondrial-linked suppression of apoptosis in less severe cases of both.

### 3.2 Placental mitochondrial content

Mitochondria can alter in response to a variety of stimuli, allowing tissue adaption via changes in metabolism. Exercise promotes mitochondrial biogenesis in skeletal muscle that increases aerobic capacity, whereas various pathologies either increase or decrease placental mitochondrial content. Placentae of rats exposed to maternal undernutrition increase content and alter expression of biogenesis/bioenergetic pathways, suggesting alterations in mitochondrial content may help increase bioenergetic efficiency under adverse conditions. Placental mitochondrial content is also altered in overweight/obese women and those with hypercholesterolemia, therefore these changes in mitochondrial content may represent a similar placental response in humans.

Changes in placental mitochondrial content may be a consequence of pathology-induced damage, or an active cellular adaptation to better align organ function with the altered external environment. There appears to be no consistent pattern of either increase or decrease in placental mitochondrial content associated with specific pregnancy pathologies, suggesting that both damage and adaptive changes may be occurring. It is also likely that the distinct mitochondrial subpopulations in cytotrophoblasts and the syncytiotrophoblast respond differently to stimuli, and that these subpopulations will need to be investigated separately to understand placental responses.

Oxygen pressure and possible signalling through ROS likely influence placental mitochondrial content. Oxygen-related mechanisms operate in other tissues; in cardiac and neurological pathologies, hypoxia and mtDNA damage can trigger increased mitochondrial content. Placental mitochondrial content/respiration have been linked to oxygen fluctuations over gestation, and mitochondrial responses are correlated with changes in placental antioxidant status, demonstrating the ability of placental mitochondria to adapt to oxygen stimuli. Additionally, insulin resistance may drive mitochondrial content changes in multiple tissues, and could be a mechanism that affects placental mitochondrial biogenesis regulation in GDM.

### 4 ENDOPLASMATIC RETICULUM AND MITOCHONDRIA IN THE PLACENTA

Mitochondria and endoplasmatic reticulum (ER) form close functional units, and the role of placental mitochondria and ER has been extensively reviewed. Contact between mitochondria and ER occur through mitochondrial associated ER membranes (MAM) that enable Ca\(^{2+}\) and phospholipid trafficking, and act as mitochondrial fission/fusion sites. Ca\(^{2+}\) release must be regulated to prevent mitochondrial dysfunction and apoptotic activation, and ER control over mitochondrial Ca\(^{2+}\) release/up-take regulates mitochondrial bioenergetics. Additionally, MAM help coordinate mitochondrial fission, and may have roles in transitioning mitochondria from cytotrophoblasts into the syncytiotrophoblast through the generation of smaller mitochondria.
In pregnancy pathologies, placental mitochondrial dynamics and content can be variable.5 This variability in MAM-based responses may indicate that stimuli are at a level to induce positive adaptations, or are high enough to cause damage. Low levels or early phases of ER stress are associated with increased mitochondrial metabolism, mediated by organelle linkage through MAM formation and Ca\textsuperscript{2+} transfer.61 However, high levels of ER stress/dysfunction can lead to high levels of Ca\textsuperscript{2+} release, enhancing leakage of electrons from complex I and III of the electron transport system (ETS). Electron leakage from the ETS may be facilitated through Ca\textsuperscript{2+} activating isocitrate dehydrogenase and α-ketoglutarate, and in turn stimulation NADPH.62 This turnover has been suggested to contribute to ROS generation and mitochondrial damage, with excessive ROS shown to drive mitochondrial swelling through mitochondrial permeability transition pore.64

Placental ER stress occurs in pregnancies affected by GDM and preeclampsia.65,66 Preeclamptic placentae have decreases in intracellular Ca\textsuperscript{2+} and decreased expression of ETS enzymes,35,67,68 which are associated with ER dysfunction. Further, ER stress markers GRP78, phospho-PERK, X-box binding protein 1 (XBP1) and eukaryotic initiation factor 2α (eIF2α) increase in response to inducible nitric oxide synthase (iNOS) in preeclampsia.69 Similarly, low-grade ER stress has been observed in GDM, with increased XBP1 and phosphorylated-eIF2α.70 Additionally, MFN2 acts as a tethering antagonist preventing over accumulation of ER-mitochondrial association,71 therefore, ER dysregulation may affect mitochondrial biogenesis and content in gestational disorders through changes to mitochondrial fission/fusion.

5 | OXYGEN AND REACTIVE OXYGEN SPECIES IN CELLULAR SIGNALLING

Reactive oxygen species are important to physiological homeostasis through mitochondrial-centred cellular signalling that allows response to external and internal stimuli. At every stage of implantation and the establishment of the placenta, ROS are critical cell function mediators. ROS may be important in preimplantation embryonic development through a shift in metabolic substrate preference with blastulation, and effects on redox-sensitive transcription factors such as hypoxia inducible factors and nuclear factor kappa B that have a range of downstream actions.72 In rabbit blastocysts, ROS are produced throughout implantation,72 and inhibiting murine embryo ROS in vivo altered production of the important second messenger cyclic guanosine monophosphate,73 suggesting ROS function in ongoing embryonic cellular messaging. In early pregnancy, ROS can trigger activation of vascular endothelial growth factor (VEGF) and glucose transporters that promote angiogenesis, and therefore the oxygen delivery critical to placental mitochondrial function continuing development.74

Differing oxygen levels across pregnancy also shape placental function. Maternal blood flow to the human placenta is not fully established until approximately 12 gestational weeks, and before this the fetal-placental unit exists in relatively low oxygen (~2%).52 Extravillous cytotrophoblasts adapt to this environment — proliferating more rapidly and being resistant to apoptosis in low oxygen75 and therefore functioning in placental implantation, as the most distal trophoblasts are exposed to higher oxygen concentrations that promote an invasive phenotype and lead to the remodelling of maternal spiral arteries that is critical to pregnancy success.76 The redox-sensitive hypoxia inducible factor 1α (HIF-1α) is also important for placenta, influencing trophoblast and uterine cell behaviour based on oxygen concentration.77 Additionally, inhibiting HIF-1α in human first trimester placental explants causes inhibition of TGFβ3 and arrest cell proliferation, suggesting that trophoblast differentiation may be partially mediated by TGFβ3 through HIF-1α transcription factors.78

Reactive oxygen species are also important in later pregnancy. Towards the end of the first trimester, maternal intraplacental circulation is established.79 The sudden increase in oxygen in and around an ETS saturated with electrons may cause reverse electron flow,80 leading to increased ROS generation.52 The syncytiotrophoblast is central to placent/fetal endocrine function and nutrient transport, and renewal of this terminally differentiated cell has also been linked to oxygen concentration, with secretion of human chorionic gonadotrophin modulated by ROS-responsive potassium channels.81 The final phase in placental vascular development occurs in the third trimester,82 and ROS are also important at this point in gestation, with ROS-responsive transcription factors regulating angiogenesis and tissue remodelling.83

5.1 | Reactive oxygen species in gestational pathologies

Reactive oxygen species are important in cellular signalling during placental-fetal development, but excessive levels can cause tissue damage, and high levels of ROS are found in several pregnancy complications, including preeclampsia and GDM. Oxidative stress caused by excessive ROS generation and/or diminished antioxidant function is associated with hypoxia, inflammation and immune responses, all characteristics of gestational disorders.84 ROS are central to preeclampsia aetiology, with inadequate placental perfusion due to poor trophoblast invasion of maternal spiral arteries85 leading to ischemic-reperfusion injury resulting in ROS generation and oxidative stress.86 This increased ROS production is associated with anti-angiogenic pathways central to preeclampsia pathogenesis,86 as well as placental damage and release of factors including soluble fms-like tyrosine kinase (sFlt-1) into the maternal periphery that are thought to lead to the classic maternal symptoms of endothelial dysfunction and hypertension.3,5 GDM pathophysiology has also been linked to ROS and placental mitochondrial dysfunction, with insulin resistance potentially a response to varying hormones levels — e.g progesterone and human placental lactogen (hPL) — synthesised by placental mitochondria.87 Oxidative stress is observed in GDM88,89 and excessive ROS is also associated with hypertension, insulin resistance and hyperglycemia, all characteristics of GDM.5,32 Indeed,
placental mitochondrial damage and ROS production may be one reason GDM predisposes women to develop preeclampsia.

Reactive oxygen species are generated by several mechanisms, and increased ROS lead to numerous downstream effects. In the preeclamptic placenta, increased NADPH oxidase isoform NOX1 is overexpressed in the syncytiotrophoblast, possibly due to increased $O_2^{•−}$ and related cytokine production, which may then contribute to maternal endothelial dysfunction.$^{90,91}$ Additionally, NOX may be activated by ROS in a positive feedback loop, inducing further oxidative stress and generating systemic maternal inflammation,$^{92}$ possibly directly linking placental ROS and maternal effects. Excessive ROS production also causes mitochondrial transition pore opening and the intrinsic activation of apoptosis, and is another mechanism of leading increased trophoblast shedding into the maternal circulation and therefore induction of maternal symptoms.$^{93}$ Further, xanthine oxidase (XO) and XO-induced damage also occurs in umbilical cord blood from GDM pregnancies,$^{89}$ further associating similar mitochondrial mechanisms of ROS overproduction in the pathogenesis of both preeclampsia and GDM. Hyperglycaemia is associated with increased NOX, and hyperglycaemia-induced ROS production has been attributed to mitochondrial morphological changes across multiple tissues including the placenta,$^{32,94}$ suggesting that hyperglycaemic-related mitochondrial damage may lead to ROS through an imbalance of metabolic function and mitochondrial bioenergetics.

Both preeclampsia and GDM range widely in severity. As the placenta and ROS are central to the pathogenesis of both disorders, the ability of the placenta to respond to ROS may be important in determining disease severity. ROS production is countered by antioxidants (Figure 1). In preeclamptic placenta there is decreased function of antioxidants Superoxide dismutase (SOD), Thioredoxin reductase (ThRed) and Glutathione peroxidase (GPx).$^{95,96}$ The severity of preeclampsia may be linked to antioxidant responses, with placentae from preeclampsia pregnancies that reached term exhibiting increased ROS, but also potentially responding via compensatory mechanisms including increased GPx activity.$^{35,97}$ Indeed, correct ROS signalling and antioxidant responses may be critical in the development of preeclampsia, with animal work showing increased activity of the antioxidant response element Nrf2 linked to repressed angiogenesis.$^{98}$ Further, modulation of trophoblast antioxidant function can affect mitochondrial performance and ultimately determine cell fate.$^{46,99}$ ROS overproduction in GDM may be a result of impaired glycaemic control, rather than due to deficiencies in antioxidants.$^{100}$ However, antioxidant function is still important in GDM; increased placental protein carbonyls (formed via protein oxidation) are associated with increased placental SOD and catalase activity. This may represent an adaptive response of antioxidant upregulation to counter damage,$^{101}$ although mitochondria may respond differently in different severities of the disorder, with less severe forms of GDM exhibit decreased maternal circulating SOD, catalase and GPx function.$^{102}$

Indeed, in animal models of pregnancies experiencing hypoxia, therapy in the form of the mitochondrial targeted MitoQ (a ubiquinone derivative) limits activation of mitochondrial and ER stress pathways in placentae and protects fetal brain development.$^{103}$ Together, these results demonstrate the importance of supporting placental mitochondrial function (eg through endogenous antioxidants) under stressful conditions, and also the utility of targeting mitochondria with exogenous therapeutics to improve pregnancy outcomes.

6 | CONCLUSIONS

Mitochondria are critical to placental function, and therefore in supporting the fetus. ROS are fundamental messaging molecules that allow cells to sense their environment and to respond through mitochondrial-centred signalling cascades. Mitochondrial response to ROS is adaptive, and can be critical to allowing tissues to cope with adverse environments; this can be observed in alterations such as increased antioxidant function in some preeclamptic placentae. Conversely, excessive ROS can lead to tissue damage, and ROS-induced mitochondrial adaptations are central to two important pregnancy complications; preeclampsia and GDM.

The effects of ROS in the placenta are complex and require further investigation, especially around the different placental mitochondrial subpopulations. The critical functions of mitochondria mean they are sensitive to damage, but the ability of mitochondria to sense and respond to stimuli also makes them attractive targets for future therapies that may improve pregnancy outcomes.

ACKNOWLEDGEMENTS

The authors acknowledge the facilities and scientific and technical assistance of Microscopy Australia, Centre for Microscopy and Microanalysis, University of Queensland.

CONFLICT OF INTERESTS

Authors declare they have no conflict of interest.

ORCID

Joshua J. Fisher https://orcid.org/0000-0002-0505-0598
Lucy A. Bartho https://orcid.org/0000-0002-9150-6052
Anthony V. Perkins https://orcid.org/0000-0002-9829-6772
Olivia J. Holland https://orcid.org/0000-0002-5798-5264

REFERENCES

1. Scheffler IE. Mitochondria. Vol 2nd ed. Hoboken, NJ: John Wiley & Sons; 2007.
2. Sferruzzi-Perri AN, Camm EJ. The programming power of the placenta. Front Physiol. 2016;7:33.
3. Chamley LW, Holland OJ, Chen Q, Viall CA, Stone PR, Abumaree M. Review: where is the maternofetal interface? Placenta. 2014;35:574-580.
65. Burton GJ, Yung HW, Cindrova-Davies T, Charnock-Jones DS. Placental endoplasmic reticulum stress and oxidative stress in the pathophysiology of unexplained intrauterine growth restriction and early onset preeclampsia. Placenta. 2009;30(Suppl A):S43-S48.

66. Yung HW, Atkinson D, Campion-Smith T, Olovsson M, Charnock-Jones DS, Burton GJ. Differential activation of placental unfolded protein response pathways implies heterogeneity in causation of early- and late-onset pre-eclampsia. J Pathol. 2014;234(2):262-276.

67. Vuorinen K, Remes A, Sormunen R, Tapanainen J, Hassinen IE. Placental mitochondrial DNA and respiratory chain enzymes in the etiology of preeclampsia. Obstet Gynecol. 1998;91(6):950-955.

68. Hache S, Takser L, LeBellegue F, et al. Alteration of calcium homeostasis in primary preeclamptic syncytiotrophoblasts: effect on calcium exchange in placenta. J Cell Mol Med. 2011;15(3):654-667.

69. Du L, He F, Kuang L, Tang W, Li Y, Chen D. eNOS/iNOS and endoplasmic reticulum stress-induced apoptosis in the placentas of patients with preeclampsia. J Hum Hypertens. 2017;31(1):49-55.

70. Yung H-W, Almaes-Katjavivi P, Jones CJP, et al. Placental endoplasmic reticulum stress in gestational diabetes: the potential for therapeutic intervention with chemical chaperones and antioxidants. Diabetologia. 2016;59(10):2240-2250.

71. Harvey AJ, Kind KL, Thompson JG. REDOX regulation of early embryonic development. Reproduction. 2002;123(4):479-486.

72. Manes C, Lai N. Nonmitochondrial oxygen utilization by rabbit blastocysts and surface production of superoxide radicals. J Reprod Fertil. 1995;104(1):69-75.

73. Chen HW, Jiang WS, Tzeng CR. Nitric oxide as a regulator in pre-implantation embryo development and apoptosis. Fertil Steril. 2001;75(6):1163-1171.

74. Al-Gubory KH, Fowler PA, Garrel C. The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes. Int J Biochem Cell Biol. 2010;42(10):1634-1650.

75. Arman DR, Kilburn BA, Petkova A, et al. Human trophoblast survival at low oxygen concentrations requires metalloproteinsase-mediated shedding of heparin-binding EGF-like growth factor. Development. 2006;133(4):751-759.

76. Seeho SKM, Park JH, Rowe J, Morris JM, Gallery EDM. Villous explant culture using early gestation tissue from ongoing pregnancies with known normal outcomes: the effect of oxygen on trophoblast outgrowth and migration. Hum Reprod. 2008;23(5):1170-1179.

77. Kenchegowda D, Natale B, Lemus MA, Natale DR, Fisher SA. Inactivation of maternal Hif-1alpha at mid-pregnancy causes placental deficits and deficits in oxygen delivery to the fetal organs under hypoxic stress. Dev Biol. 2017;422(2):171-185.

78. Canigga I, Mostachfi H, Winter J, et al. Hypoxia-inducible factor-1 mediates the biological effects of oxygen on human trophoblast differentiation through TGFbeta(3). J Clin Invest. 2000;105(5):577-587.

79. Jauiaux E, Hempstock J, Greenwood N, Burton GJ. Trophoblastic oxidative stress in relation to temporal and regional differences in maternal placental blood flow in normal and abnormal early pregnancies. Am J Pathol. 2003;162(1):115-125.

80. Hu H, Nan J, Sun Y, et al. Electron leak from NDUFA13 within mitochondrial complex I attenuates ischemia-reperfusion injury via dimerized STAT3. Proc Natl Acad Sci. 2017;114(45):11908-11913.

81. Diaz P, Sibley CP, Greenwood SL. Oxygen-sensitive K+ channels modulate human choric gonadotropin secretion from human placental trophoblasts. PLoS One. 2016;11(2):e0149021.

82. Kingdom J, Huppertz B, Seaward G, Kaufmann P. Development of the placental villous tree and its consequences for fetal growth. Eur J Obstet Gynecol Reprod Biol. 2000;92(1):35-43.

83. Pereira RD, De Long NE, Wang RC, Yazdi FT, Holloway AC, Raha S. Angiogenesis in the placenta: the role of reactive oxygen species signaling. Biomed Res Int. 2015;2015:814543.
85. Guo X, Feng L, Jia J, Chen R, Yu J. Upregulation of VEGF by small activating RNA and its implications in preeclampsia. Placenta. 2016;46:38-44.
86. Sánchez-Aranguren LC, Prada CE, Riaño-Medina CE, Lopez M. Endothelial dysfunction and preeclampsia: role of oxidative stress. Front Physiol. 2014;5:372.
87. Jameson JL, De Groot LJ, Metzger BE. Endocrinology: Adult & Pediatric 7th ed. Philadelphia, PA: Elsevier Saunders; 2016, 2015: 788-804. Chapter 45.
88. Sivitz WI, Yorek MA. Mitochondrial dysfunction in diabetes: from molecular mechanisms to functional significance and therapeutic opportunities. Antioxid Redox Signal. 2010;12(4):537-577.
89. Biri A, Onan A, Devrim E, Babacan F, Kavutcu M, Durak I. Oxidant status in maternal and cord plasma and placental tissue in gestational diabetes. Placenta. 2006;27(2-3):327-332.
90. Pantham P, Viall CA, Chen Q, Kleffmann T, Print CG, Chamley LW. Antiphospholipid antibodies bind syncytiotrophoblast mitochondria and alter the proteome of extruded syncytial nuclear aggregates. Placenta. 2015;36(12):1463-1473.
91. Mandò C, Anelli GM, Novielli C, et al. Impact of obesity and hyperglycemia on placental mitochondria. Oxid Med Cell Longev. 2018;2018:1-10.
92. Wang Y, Walsh SW. Increased superoxide generation is associated with decreased superoxide dismutase activity and mRNA expression in placental trophoblast cells in pre-eclampsia. Placenta. 2001;22(2):206-212.
93. Vanderlelie J, Venardos K, Clifton VL, Gude NM, Clarke FM, Perkins AV. Increased biological oxidation and reduced anti-oxidant enzyme activity in pre-eclamptic placentae. Placenta. 2005;26(1):53-58.
94. Cuffe JSM, Holland O, Salomon C, Rice GE, Perkins AV. Review: placental derived biomarkers of pregnancy disorders. Placenta. 2017;54:104-110.
95. Nezu M, Souma T, Yu L, et al. Nrf2 inactivation enhances placental angiogenesis in a preeclampsia mouse model and improves maternal and fetal outcomes. Sci Signal. 2017;10(479):eaam5711.
96. Khera A, Vanderlelie JJ, Holland O, Perkins AV. Overexpression of endogenous anti-oxidants with selenium supplementation protects trophoblast cells from reactive oxygen species-induced apoptosis in a Bcl-2-dependent manner. Biol Trace Elem Res. 2017;177(2):394-403.
97. West IC. Radicals and oxidative stress in diabetes. Diabet Med. 2000;17(3):171-180.
98. Lopez-Tinoco C, Roca M, Garcia-Valero A, et al. Oxidative stress and antioxidant status in patients with late-onset gestational diabetes mellitus. Acta Diabetol. 2013;50(2):201-208.
99. Nuzzo AM, Camm EJ, Sferruzzi-Perri AN, et al. Placental adaptation to early-onset hypoxic pregnancy and mitochondria-targeted antioxidant therapy in rat. Am J Pathol. 2018; 188(12):2704-2716.

How to cite this article: Fisher JJ, Bartho LA, Perkins AV. Holland OJ. Placental mitochondria and reactive oxygen species in the physiology and pathophysiology of pregnancy. Clin Exp Pharmacol Physiol. 2020;47:176-184. https://doi.org/10.1111/1440-1681.13172