Received: 2 November 2016 | Accepted: 20 January 2017

DOI: 10.1111/aji.12653

REVIEW ARTICLE

WILEY AJRI American Journal of Reproductive Immunology

Oxidative stress, placental ageing-related pathologies and adverse pregnancy outcomes

Zakia Sultana[1,2,3] | Kaushik Maiti[1,2,3] | John Aitken[3] | Jonathan Morris[4] | Lee Dedman[5] | Roger Smith[1,2,3]

[1]Mothers and Babies Research Centre, Hunter Medical Research Institute, Newcastle, NSW, Australia

[2]Faculty of Health and Medicine, School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, Australia

[3]Priority Research Centre for Reproductive Science, University of Newcastle, Newcastle, NSW, Australia

[4]Kolling Institute, Royal North Shore Hospital, University of Sydney, Sydney, NSW, Australia

[5]Faculty of Science and Information Technology, School of Design, Communication and Information Technology, University of Newcastle, Newcastle, NSW, Australia

Correspondence
Roger Smith, Mothers and Babies Research Centre Hunter, Hunter Medical Research Institute, Newcastle, NSW, Australia.
Email: Roger.Smith@newcastle.edu.au

Oxidative stress (OS), an imbalance between free radical generation and antioxidant defence, is recognized as a key factor in the pathogenesis of adverse pregnancy outcomes. Although OS is a common future of normal pregnancy, persistent, overwhelming OS leads to consumption and decline of antioxidants, affecting placental antioxidant capacity and reducing systems. The accumulation of OS causes damage to lipids, proteins and DNA in the placental tissue that induces a form of accelerated ageing. Premature ageing of the placenta is associated with placental insufficiency that prevents the organ meeting the needs of the foetus, and as a consequence, the viability of the foetus is compromised. This review summarizes the literature regarding the role of OS and premature placental ageing in the pathophysiology of pregnancy complications.

KEYWORDS
intrauterine growth restriction, oxidative stress, placental ageing, pre-eclampsia, preterm birth, senescence, stillbirth

1 | INTRODUCTION

All living organisms have limited life cycles, and ageing is part of that life cycle. Each organ within an organism also exhibits ageing-related changes; the placenta is no exception. The placenta, a specialized organ formed during pregnancy, grows throughout gestation, performs multiple functions, including endocrine regulation and nourishment of the foetus,[1] but also ages and is discarded at the end of pregnancy, while the foetus may live for another hundred years. So placental ageing is a normal physiologic phenomenon.[2] However, there are likely to be some placentas which show signs of ageing earlier than others, in the same way as some individuals age more quickly than others. Premature ageing and degenerative changes in the placenta may reduce the functional capacity of the placenta and lead to abnormal pregnancy outcomes. The placenta is the primary organ for transferring nutrients from the mother to the foetus, so growth and function of the placenta are precisely regulated and coordinated to ensure the optimal growth and development of the foetus. The placenta exchanges nutrients, for example oxygen, amino acids, carbohydrates, minerals and waste products, for example carbon dioxide between the maternal and foetal circulatory systems.[3] It releases hormones into both the maternal and foetal circulations to affect uterine function, maternal metabolism, foetal growth and development. Moreover, it metabolizes some substances and can release metabolic products into both foetal and maternal circulations. The placenta can help to protect the foetus against certain xenobiotic molecules, infections and maternal diseases. Therefore, the adequate function of this organ is crucial for a normal physiologic gestational process and a healthy baby as a final outcome.

In this review, we focus on the role of OS in the pathophysiology of pregnancy complications, beginning with a brief overview of placental development at different stages of gestation. We then discuss the biochemical markers of ageing and OS-induced placental ageing. Finally, we discuss the studies indicating that OS and placental ageing play a role in the pathophysiology of abnormal pregnancies, with a particular emphasis on pregnancy complicated by spontaneous preterm birth, intrauterine growth restriction, pre-eclampsia, pregnancy loss and stillbirth.

2 | HUMAN PLACENTAL DEVELOPMENT

In human embryonic development, the blastocyst is formed by 5-6 days after fertilization and is composed of the outer trophectoderm layer and the inner cell mass.[4] The blastocyst makes contact with the endometrium and invades into the decidua of the endometrium at approximately 6-7 days after fertilization.[5] Immediately after attachment to the endometrium, the trophectoderm layer proliferates rapidly and differentiates into an inner layer of mononuclear cytotrophoblasts and a multinucleated outer epithelial layer known as the syncytiotrophoblast.[3] The syncytiotrophoblast is a terminally differentiated cell layer which is formed by the fusion of multiple cytotrophoblasts, a process called syncytialization. The combination of inner cytotrophoblasts and outer syncytiotrophoblast forms finger-like structures called primary chorionic villi.[3] At the initial phase of differentiation, these villi are distributed symmetrically over the chorion. As gestation progresses, the chorionic villi grow like branches of a tree (arborization) and accumulate asymmetrically towards the uterine wall where the embryo is attached.[3] After the invasion of mesenchymal cells into the centre of the primary villi forming secondary villi, foeto-placental blood vessels arise inside the villi at the 5th week of gestation to form tertiary villi.[6] The placental vasculature system is essential for transferring nutrients, gases and hormones to the growing foetus. The proper branching of placental blood vessels (angiogenesis) is part of a successful pregnancy. Inadequate placental development, trophoblast invasion and vascular remodelling, as well as abnormal placental angiogenesis, have been reported in pathological pregnancies such as intrauterine growth restriction and pre-eclampsia.[5,7,8]

In the first trimester, the chorionic villi of the placenta are large, and the blood vessels in the villi are not prominent. In addition to villous trophoblast, an additional set of mononuclear trophoblasts, termed the extravillous trophoblast, grows outside the villi and extends into the decidualized endometrium.[3,9] During the first trimester of differentiation (up to 11-12 weeks), these extravillous trophoblasts erode into and plug the uterine spiral arteries and restrict the ability of the oxygenated maternal blood to access the placenta.[10] Consequently, the early stages of human embryonic development occur in an environment of low oxygen tension.[11] The hypoxic environment is thought to be necessary for the initial differentiation of the trophoblasts; in fact, miscarriage has been reported in cases of the early arrival of oxygenated blood in the intervillous space.[12] As the placenta matures and increases in size in the second trimester, the villi become smaller and more vascular. The syncytiotrophoblast cell layer draws up into "syncytial knots" which are small clusters of nuclei, leaving a single cytotrophoblast layer. Later the extravillous trophoblasts replace the endothelial layer covering the smooth muscle of the spiral arteries and render them flaccid and non-contractile.[13] The trophoblast plugs are gradually dislodged from the spiral arteries after 11-12 weeks of gestation, and maternal blood invades from the maternal spiral arteries into the intervillous spaces.[11,14] This process is associated with a sharp rise in oxygen tension, increased free radical generation and a burst of OS within the placental tissues; however, this OS returns to baseline upon a surge of antioxidant activity, as placental cells gradually acclimate to the new oxidative surroundings.[15] The nutrients, gases and growth factors carried by maternal blood are readily taken up by the large surface of the syncytiotrophoblast allowing the foetus to grow in an oxygen- and nutrient-rich environment. A mature placenta in the third trimester has small and highly vascularized chorionic villi to support the blood gas and nutrient exchange of the maternal-foetal circulation required by the growing foetus approaching term gestation. Syncytial knots are prominent in the third-trimester chorionic villi. Figure 1 illustrates the development of human placental chorionic villi at different stages of gestation.

3 | APOPTOSIS AND ITS ROLE IN THE TROPHOBLAST FUNCTION

Apoptosis, or programmed cell death, is crucial to the development and homoeostasis of all multicellular organisms and for many organs including the placenta. Apoptosis is known to occur in a number of biological processes, both physiologic and pathologic. Trophoblast apoptosis is a physiologic event in normal pregnancy, increases with advancing gestational age and is higher in post-term pregnancies and therefore is considered as a normal process in the development and ageing of the placenta.[16,17] Apoptosis is proposed to occur as a normal event during the formation of the villous trophoblast bilayer and syncytiotrophoblast formation from cytotrophoblasts (trophoblast differentiation).[18] However, it is likely that placental insults can alter the regulation of apoptosis in the trophoblasts, possibly by modulating trophoblast cell turnover.[18] Cultured trophoblasts exposed to hypoxia show marked upregulation of activity of tumour suppressor protein p53, enhanced expression of the pro-apoptotic Mtd-1 and decreased expression of the anti-apoptotic Bcl-2, all of which promote apoptosis,[19–21] and the apoptosis is more marked in hypoxia/re-oxygenation.[22] Additionally, an upregulated p53 and decreased Bcl-2-mediated increased apoptosis in placental syncytiotrophoblast are associated with some pregnancy pathologies, including intrauterine growth restriction (IUGR) and pre-eclampsia.[23,24] Syncytial knots, a characteristic feature of syncytiotrophoblast apoptosis, increase in placentas associated with pre-eclampsia and IUGR.[24,25] In contrast, apoptosis decreases in extravillous trophoblasts in pregnancies complicated by pre-eclampsia and is associated with reduced trophoblast invasion.[26] Thus, apoptosis is differently regulated in villous and extravillous trophoblasts in normal placental development.

4 | AGEING, OS AND PLACENTAL AGEING

4.1 | Cellular senescence and ageing

Ageing can be defined as an age-dependent decline and deterioration of functional properties at the cellular, tissue and organ level, leading to a decreased adaptability to internal and external stress and an increased vulnerability to disease and mortality.[27] Age-related diseases and premature ageing syndromes are often characterized by

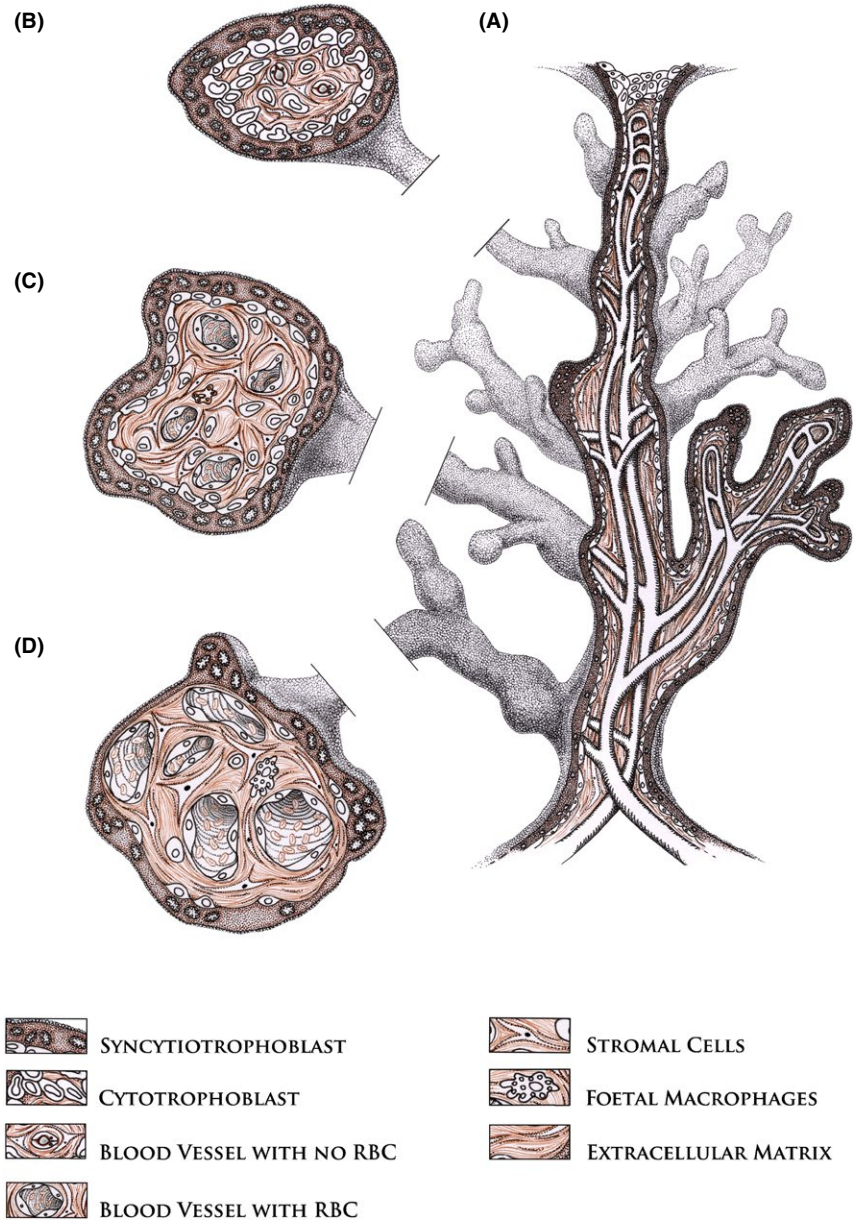

FIGURE 1 Development of human placental chorionic villi. Cross sections of (A) primary villi arborization, (B) first-trimester, (C) second-trimester and (D) third-trimester villi. The chorionic villi in the first trimester (B) are large, covered by two layers of cells, cytotrophoblasts and syncytiotrophoblasts, and the blood vessels in the villi are not prominent. Second-trimester placental villi (C) are more vascular with a single cytotrophoblast layer. The third trimester (D) has highly vascularized chorionic villi, and syncytial knots are prominent

short telomeres and reduced or complete loss of telomerase activity.[28] Telomeres are nucleoprotein structures comprised of double-stranded DNA region of TTAGGG repeats which is typically 10-15 kb long in humans, located at the termini of the chromosomes and are essential for chromosomal stability and cell survival.[29] Telomeres protect DNA ends from breaks, end-to-end fusion and degradation by forming a protective cap with a 150- to 200-nucleotide-long G-rich single-stranded telomere overhang and telomere-binding protein complexes.[28] Telomeres are progressively shortened with each cell division, and shortening is accelerated as a consequence of environmental stressors and insults, such as hyperglycaemia, hypoxia and OS.[30–33] Once a critical shortening of telomeres is attained, cells enter a state of irreversible metabolic arrest known as senescence, which leads to a process of cellular or tissue ageing.[29,34] Cell senescence is distinct from apoptotic cell death. Senescence is a biological ageing process in which cells change morphologically, in gene and protein expression, and in the activation of key signalling constituents (such as p38 and p53) that determine the fate of a tissue.[35] Cellular senescence has been associated with a gradual deterioration of functional characteristic of the cell, although there is no evidence that senescent cells undergo a cell death pathway. Senescent cells are resistant to apoptosis or programmed cell death through the overexpression of Bcl-2 protein, leading to the accumulation of these cells within tissues.[36] The accumulation of senescent cells within tissues contributes to the ageing process and generates age-related phenotypes by altering metabolic function, degrading structural components, reducing tissue renewal and repair, changing the behaviour of neighbouring cells or the extracellular environment, and reducing the pool of growth-competent mitotic cells.[37] Premature senescence can also occur, independent of telomere size, as a consequence of progressive DNA damage, telomere uncapping and telomere dysfunction caused by extrinsic or intrinsic stressors including OS, resulting in end-to-end

fusion and aggregation of telomeric DNA.[1,38,39] Telomere length is regulated by the enzyme telomerase, a specific reverse transcriptase, capable of adding telomeric repeats to the ends of the chromosome.[40] Telomerase consists of a catalytic protein component, telomerase reverse transcriptase (TERT) and an RNA template component, telomerase RNA component (TERC). TERC is widely expressed, but TERT expression is tightly regulated and is considered to be the rate-limiting factor in telomerase activity.[41] The absence of functional telomerase or loss of telomerase activity leads to progressive telomere shortening during cell division.[34,40] Telomere shortening may also be associated with a lack of adequate damage repair mechanisms that protect against DNA damage.[39] Due to their high oxidation potential, the guanine-rich residues in telomeres are extremely susceptible to free radical attack.[42] There is a clear relationship between OS and telomere length and telomerase activity, the indicators of cellular senescence and ageing.[43] Therefore, measurement of telomere length and telomerase activity can be used as biological markers for tissues suffering OS and age.[43–45]

4.2 | OS and placental ageing

OS is an important contributing factor in the pathophysiology of complicated pregnancies. OS is described as an imbalance in the generation of reactive oxygen species (ROS) and the ability of antioxidant defences to scavenge them. OS can arise from increased ROS production and/or defects in antioxidant defence mechanisms.[46] These ROS are oxygen free radicals that contain one or more unpaired electrons, produced from the reduction in molecular oxygen and generated as by-products of aerobic respiration and metabolism. These molecules have diverse chemical properties and are capable of activating and modulating various signalling pathways, including those involved in cell growth, differentiation and metabolism.[47] They can also induce cellular oxidative damage by interacting with DNA and intracellular macromolecules such as proteins and membrane lipids, leading to cellular malfunction that may initiate pathological processes. The free radical theory of ageing[48] postulates that ageing and degenerative diseases associated with ageing are due to the oxidative damage by ROS on cellular components. Moreover, the mitochondrial free radical theory of ageing[49] proposes that ROS damage mitochondrial DNA (mtDNA), proteins and other macromolecules that lead to respiratory chain dysfunction. Mutant mtDNA induces an increased production of ROS, further facilitating mtDNA damage and creates a self-amplifying deterioration.[49] The increased generation of ROS can cause lipid peroxidation, protein damage and several types of DNA lesions in cells, which may result in altered or complete loss of cellular function, compromised tissue and organ function, and ageing. Mechanistically, OS induces activation of processes, including repair pathways, inhibition of cell proliferation (transient cell-cycle arrest or senescence) or apoptosis.[50] OS activates a specific p53 transcriptional response, mediated by p44/p53 and p66, which regulates the cellular response to DNA damage, leading to a halt in proliferation via senescence or apoptosis and contributes to ageing.[51] To counterbalance the ROS, cells have endogenous antioxidant systems, including non-enzymes, for example vitamin C and E, and glutathione (GSH), enzymes, for example superoxide dismutase (SOD), glutathione peroxidases (GSH-Ps), glutathione S-transferase (GSH-T) and catalase (CAT), and trace elements, for example copper, zinc, manganese and selenium.[52]

Pregnancy itself is a state of OS, arising from the increased metabolic activity in placental mitochondria and an increased ROS production due to the higher metabolic demand of the growing foetus.[53,54] Superoxide anions produced by placental mitochondria appear to be a major source of ROS and lipid peroxidation that contribute to the OS in the placenta.[55] Although a physiologic balance between ROS and antioxidant activity is maintained in normal pregnancies,[56] an imbalance may increase OS. The placenta experiences a heightened level of OS in certain pathologic pregnancies, especially those that are complicated by maternal smoking, gestational diabetes, foetal growth restriction, pre-eclampsia and miscarriage.[42,57,58] Often antioxidant activity is upregulated in response to OS. However, persistent, overwhelming OS leads to consumption and decline of antioxidants, and affects placental antioxidant capacity and reducing systems.[54] In the post-mature placenta, the accumulation of OS damage to lipids, proteins and DNA in the placental tissue may induce a form of advanced ageing.[42] Premature ageing can occur when the intrauterine environment is affected by conditions that increase OS, causing irreversible changes in placental tissue.[8,59] It has been hypothesized that ageing of the placenta is usually associated with placental insufficiency, preventing this organ from meeting the needs of the foetus, and as a consequence, the viability of the foetus is compromised.[42] Figure 2 summarizes the effect of oxidative stress on placental function and pathological events at different stages during pregnancy.

5 | OS, PLACENTAL AGEING AND ADVERSE PREGNANCY OUTCOMES

5.1 | OS and spontaneous preterm birth

Preterm birth is defined as birth before 37 weeks of gestation, affects 5%-18% of pregnancies and is a leading cause of infant morbidity and mortality. Most of the preterm births occur after the spontaneous onset of labour (with or without preterm premature rupture of the membrane, pPROM), but the precise mechanisms of onset of preterm labour remain unclear.[60] Labour induces changes of gene expression in chorioamniotic membranes that are consistent with the localized acute inflammatory response, despite the absence of histologically detectable inflammation.[61] It has been hypothesized that cellular apoptosis transmits an inflammatory signal that stimulates parturition.[62] Although they are resistant to apoptosis, senescent cells may transmit both inflammatory and senescence-promoting signals to induce labour.[35] It has also been suggested that labour is associated with senescence-associated changes in the placental membranes mediated by the p38 MAPK pathway, including telomere shortening, p38 MAPK activation and increased expression of p21 and SA-β-galactosidase.[63] OS at term induces DNA damage and telomere shortening, which

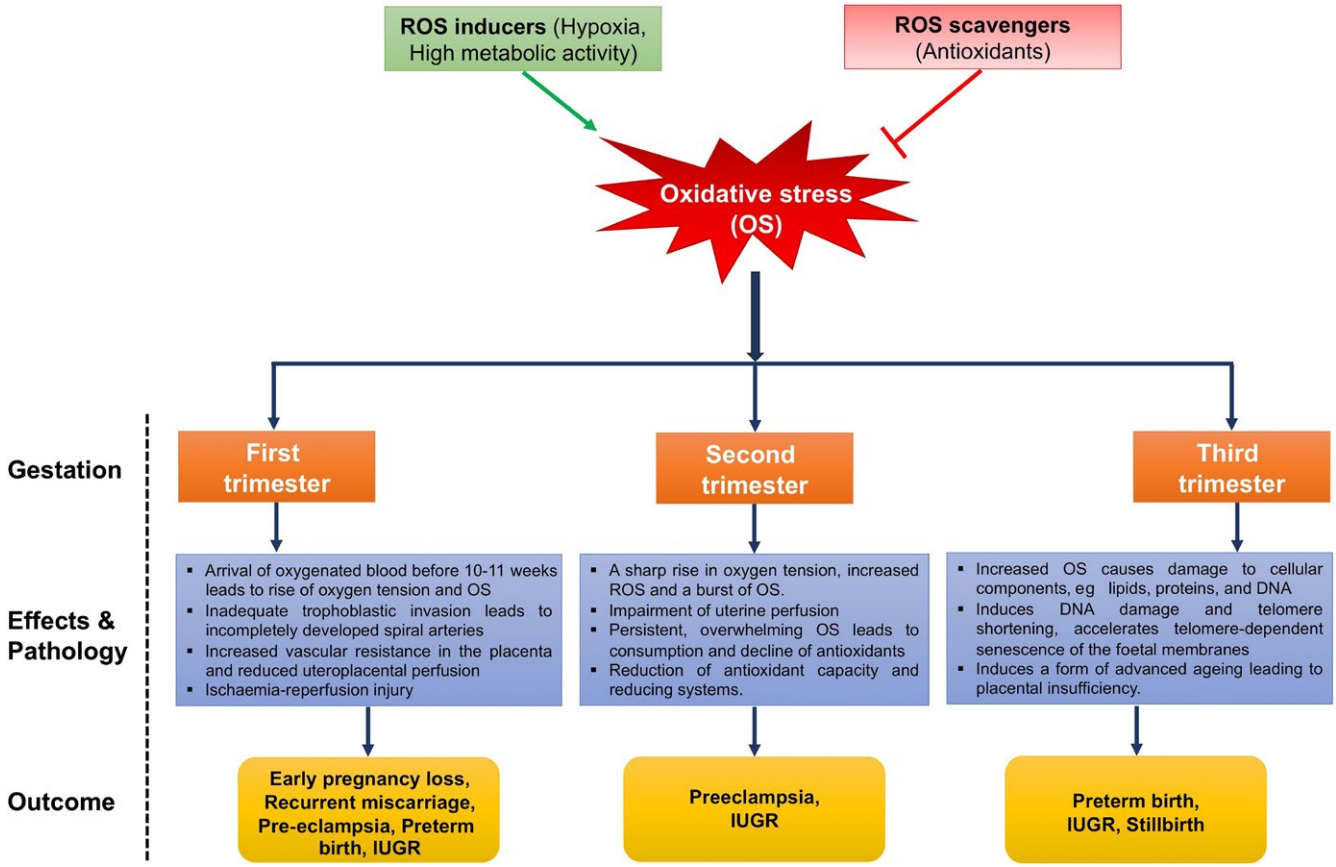

FIGURE 2 Effect of oxidative stress on placental function and pathological events in pregnancy

accelerates telomere-dependent senescence of the foetal membranes, resulting in senescence-associated inflammatory activation that may contribute to parturition.[64] It has long been thought both term and preterm labour have similar processes that occur through a "common pathway". The activation of this common pathway through physiologic signals results in term labour, while preterm labour is a "syndrome," which occurs from spontaneous activation of one or more of the components of the common pathway induced by multiple pathologic processes or risk factors.[60] Spontaneous preterm labour or pPROM is likely to be triggered by premature placental ageing caused by OS-induced damage and premature senescence of the intrauterine tissues, especially the foetal membranes of the placenta,[65–67] and vascular, endocrine or immune system dysfunction.[68] ROS activates NF-kappa B, which stimulates COX-2 expression and systemic inflammation. Infection, inflammation or exogenous factors (eg lead) upregulate ROS, resulting in OS-induced tissue injury, and the consequent decrease in antioxidant defences is likely to increase the risk of preterm birth.[69] Preterm birth is also associated with ROS-mediated redox imbalance (balance between pro- and antioxidants). In preterm birth, increased placental and maternal serum levels of oxidized metabolites (malondialdehyde) with reduced levels of antioxidant (GSH, selenium, GSH-T) are observed compared to term labour.[70–73] However, the expression of Mn-SOD in foetal membranes of women in preterm labour is increased, likely to constrain the inflammatory processes and OS.[74]

5.2 | OS and IUGR

IUGR, also known as foetal growth retardation, is a failure of a foetus to reach its genetic growth potential. IUGR is a leading cause of foetal, neonatal and perinatal morbidity and mortality.[75] IUGR is defined as an estimated foetal weight of less than the 10th percentile for gestational age.[18] Most intrauterine deaths, in particular, those that are classified as unexplained, are associated with IUGR. Around 76% of intrauterine deaths are associated with IUGR.[76,77] IUGR also strongly affects the long-term health of survivors.[78] Some potential risk factors for IUGR include maternal smoking, infection, obesity, malnutrition and chromosomal abnormalities, but the majority of cases remain unexplained.[79] The most common aetiology for IUGR is uteroplacental dysfunction, due to diminished maternal uteroplacental blood flow.[80] The placenta is the central organ for transporting nutrients and oxygen from the mother to the foetus. Inadequate function of this organ limits the supply of critical substrates to support the normal aerobic growth of the foetus.[81] Recently, it has been hypothesized that placental insufficiency originates in the early stage of gestation when the trophoblast invades spiral arteries in the placental bed.[81] This process requires high energy availability for cell growth, proliferation and metabolic activity that generates ROS and OS. Inadequate trophoblastic invasion to the spiral arteries may occur when the chorioallantoic villi encounter an injury caused by stimuli or mediators.[82] Among the diverse number of stimuli or mediators, OS has the leading role.[22]

Consequently, incompletely developed spiral arteries cause ischaemia (hypoxia)-reperfusion that exacerbates the OS and contributes to damage of the placental tissue.[18]

Damage resulting from OS predominantly occurs to membrane lipids, proteins and nuclear and mitochondrial DNA. Plasma and tissue levels of malondialdehyde (MDA), an end product of fatty acid oxidation, are frequently measured as indicators of lipid peroxidation and OS. The levels of MDA and xanthine oxidase (XO, an enzyme that generates ROS) are higher in maternal plasma, umbilical cord plasma and placental tissues of the patients with IUGR pregnancy compared to healthy pregnancies,[83] which suggest that OS has a role in IUGR. In nuclear and mitochondrial DNA, 8-hydroxy-2'-deoxyguanosine (8-OHdG, an oxidized derivative of deoxyguanosine) is one of the predominant forms of free radical-induced oxidative lesions, and has therefore been widely used as a biomarker for oxidative DNA damage, as well as OS. The levels of 8-OGdH and redox factor-1 (ref-1) are significantly higher in placentas from IUGR compared to normal pregnancies.[84–86] Ref-1 is a redox regulator that repairs oxidative DNA damage, and its concentration increases in response to oxidative damage. Placental antioxidant levels and antioxidant activity are also altered in pregnancies complicated by IUGR. In IUGR, the SOD and GSH-Px activities in maternal plasma, cord blood and placental tissues are increased, while CAT activity is decreased.[83] The mRNA levels of the reducing systems, glutaredoxin and thioredoxin, are also depleted in placentas with IUGR.[87] Moreover, the IUGR placenta shows signs of ageing markers, including shortening of telomere length and reduced telomerase activity. A significantly shorter telomere and/or an absent or reduced telomerase activity are observed in the placentas from IUGR pregnancies[41,88–90] with a reduced expression of hTERT, which is the rate-limiting factor in the telomerase activity.[41] Also, the expression of telomere-induced senescence markers p21 and p16 is elevated, and anti-apoptotic protein Bcl-2 is decreased in IUGR placentas.[88] Together with increased OS markers and reduced antioxidants capacity, the evidence of ageing markers supports the concept of the role of OS in placental ageing and IUGR.

5.3 | OS and pre-eclampsia

Pre-eclampsia is a hypertensive disorder of human pregnancy, and it frequently occurs in association with IUGR. Pre-eclampsia affects 5%-7% of all pregnancies worldwide and remains a leading cause of foetal growth retardation, premature delivery and maternal death.[54,91,92] The main features of pre-eclampsia are new-onset maternal hypertension (blood pressure ≥140/90 mmHg), reduced uteroplacental blood flow, proteinuria (≥300 mg/24 h), oedema and occurrence primarily in nulliparous women in their third trimester.[54] Among the two distinct subtypes, early-onset pre-eclampsia (occurs before 34 weeks) confers a higher risk of life-threatening maternal complications and foetal and perinatal death, than the late-onset (occurs at 34 weeks or later), and early delivery is the only treatment.[93] This disorder develops during pregnancy, and the rapid and complete recovery after childbirth indicates that the placenta has a pivotal role in the pathogenesis of this disease.[94] Although the aetiology of pre-eclampsia is still subject to debate, the basic pathologic event in pre-eclampsia is an injury to the vascular endothelium[95] that is mediated by OS from increased placental ROS or decreased antioxidant activity.[96] Consequently, trophoblastic invasion to the spiral arteries is inhibited that limits the spiral artery remodelling to the decidual portions and the myometrial segments of the arteries remain narrow and contractile.[97] Therefore, in pre-eclampsia, increased vascular resistance in the placenta leads to reduced uteroplacental perfusion.[97,98] The resultant hypoxia or ischaemia, together with intermittent perfusion, is associated with the conversion of xanthine dehydrogenase to XO and the increased XO activity provokes ROS synthesis in the placenta.[99,100] Both pre-eclampsia and IUGR share similar pathophysiology that is associated with defective placentation, but pre-eclampsia (with or without IUGR) is distinguished from IUGR (without pre-eclampsia) by extension of disturbances into the maternal vasculature.[97,101]

In pre-eclampsia, both the circulating and placental tissue levels of markers of OS are elevated and antioxidant capacities are compromised.[100,102] Polyunsaturated fatty acids, which are found in abundance in the cell membrane and in circulating lipoproteins, are highly susceptible to oxidation by free radicals to form lipid peroxides, and the process is called lipid peroxidation.[103] When lipid peroxidation is initiated, it becomes self-propagating and continues until it is interrupted by an antioxidant. Normal pregnancy is associated with increased free radical production, lipid peroxidation and OS; however, antioxidant activity is also upregulated[56] that counterbalances free radical generation and oxidative damage. In contrast, pre-eclampsia is associated with increased lipid peroxidation in the maternal circulation and the placenta and decreased antioxidant activity.[103–105] Superoxide anions produced by the enzyme XO in the placental mitochondria appear to be a major source of OS and contribute to an overall increase in maternal blood and placental lipid peroxidation in pre-eclamptic women.[55,104] Two major end-products of lipid peroxidation, MDA and 4-hydroxynonenal (4-HNE), are frequently measured as indicators of lipid peroxidation and OS. Increased placental and serum levels of MDA and 4-HNE and placental XO expression of pre-eclamptic women are observed compared with normotensive subjects,[55,99,103,106,107] whereas maternal circulating and placental levels of antioxidants, for example, CAT, GPX and SOD, are decreased in pre-eclampsia compared to healthy pregnancy.[103,105,106,108] Also, the expression of 8-OHdG is increased in both maternal blood and the placental trophoblast in pregnancy complicated by pre-eclampsia with or without IUGR.[84–86] The level of ref-1 that repairs oxidative DNA damage is also higher in the pre-eclamptic placenta.[84–86] Serum levels of derivatives of reactive oxygen metabolites (d-ROMs), for example, organic hyper oxides, are also increased in pre-eclamptic women,[85,86] indicating increased ROS in maternal circulation from which they are produced. The increased ROS in the maternal circulation may originate from the placenta, as the d-ROMs decrease following delivery.[85] Additionally, in pre-eclamptic placentas with or without IUGR, telomeres are shorter, and telomerase activity is reduced compared to healthy placentas.[38,41]

5.4 | OS and early pregnancy loss

OS has been implicated in early pregnancy loss. There is a sharp increase in oxygen tension when the maternal blood enters into the placenta, and this associated with a burst of OS.[15] It is not until about 11-12 weeks of gestation that the maternal blood invades into the intervillous space. The arrival of oxygenated blood before 10-11 weeks leads to deterioration of the syncytiotrophoblast caused by OS, resulting in loss of pregnancy, including spontaneous miscarriage and recurrent pregnancy loss.[12,69] The high levels of OS markers, such as nitrotyrosine residues, 4-HNE adducts and heat shock protein 70 in the placentas from early pregnancy loss,[15] suggest that increased ROS generation is due to premature establishment of maternal-placental perfusion, resulting in oxidative damage to the trophoblasts with subsequent termination of the pregnancy.[46] The expression of these markers is induced in vitro by exposing early placental villi to 21% oxygen and is associated with increased ROS production.[109] This OS in early stage of pregnancy can impair a number of cell functions, including matrix remodelling, angiogenesis, cytotrophoblast proliferation, migration and fusion, and endocrine function,[110] resulting in pregnancy loss.

5.5 | OS, placental ageing and stillbirth

Stillbirth, which is intrauterine foetal death at or after 20 weeks of gestation, is a major obstetric complication. Although a number of risk factors for stillbirth have been identified including advanced maternal age, obesity, smoking, late gestational age and IUGR,[111,112] most cases remain unexplained. Recently studies on stillbirth have postulated an association between stillbirth and placental pathology, including infarction, vessel wall thickening and calcification and dysfunction.[42,113–115] A 2016 study shows a significant reduction in telomere length in placentas associated with unexplained stillbirth indicating a telomere-dependent senescence in the placenta, suggesting that this may cause premature placental ageing and placental dysfunction leading to foetal death.[113] We have hypothesized that OS causes changes in proteins, lipids and DNA in the placenta, which may induce a form of advanced ageing, leading to placental insufficiency and an inability to meet the demands of the growing foetus that ultimately causes foetal demise.[42]

6 | SUMMARY

There is accumulating evidence that demonstrates an association between OS and placental ageing that contribute to poor pregnancy outcomes. Altered cellular metabolism is observed in several pathological situations, and these metabolic shifts that elevate ROS generation can increase telomere shortening or induce telomerase dysfunction leading to premature senescence and ageing. Conversely, dysfunctional telomerase may itself induce altered metabolic and mitochondrial functions that may, in turn, cause further OS deregulation. OS also activates processes or mediators that cause inhibition of cellular proliferation or increased apoptosis. Premature placental ageing is the consequence of OS-induced damage to lipids, proteins and DNA in the placental tissue that may cause cellular senescence or cell death in the placenta, leading to placental dysfunction and insufficiency. OS-induced endothelial dysfunction contributes to the pathogenesis of pregnancy complications, including pre-eclampsia, IUGR, preterm birth and recurrent pregnancy loss. Alteration of antioxidant capacity or changes apoptosis regulation in the placenta are also significant factors that contribute to the pathophysiology of abnormal pregnancies.

REFERENCES

1. Londero AP, Orsaria M, Marzinotto S, et al. Placental aging and oxidation damage in a tissue micro-array model: an immunohistochemistry study. *Histochem Cell Biol*. 2016;146:191–204.
2. Rosso P. Placenta as an aging organ. *Curr Concepts Nutr*. 1976;4:23–41.
3. Gude NM, Roberts CT, Kalionis B, King RG. Growth and function of the normal human placenta. *Thromb Res*. 2004;114:397–407.
4. Jirásek JE. The Embryo: Blastogenesis, Differentiation of the Inner Cell Mass and Formation of Germ Layers. In: Keith LG, ed. *An Atlas of the Human Embryo and Fetus: a photographic review of human prenatal development*. New York: Parthenon Publishing; 2000:27.
5. James JL, Carter AM, Chamley LW. Human placentation from nidation to 5 weeks of gestation. Part I: What do we know about formative placental development following implantation? *Placenta*. 2012;33:327–334.
6. 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;92:35–43.
7. te Velde EA, Exalto N, Hesseling P, van der Linden HC. First trimester development of human chorionic villous vascularization studied with CD34 immunohistochemistry. *Hum Reprod*. 1997;12:1577–1581.
8. Ahmed A, Perkins J. Angiogenesis and intrauterine growth restriction. *Best Pract Res Clin Obstet Gynaecol*. 2000;14:981–998.
9. Boyd JD, Hamilton WJ. *The Human Placenta*. Cambridge: W. Heffer & Sons;1970. p.
10. Rodesch F, Simon P, Donner C, Jauniaux E. Oxygen measurements in endometrial and trophoblastic tissues during early pregnancy. *Obstet Gynecol*. 1992;80:283–285.
11. Jauniaux E, Gulbis B, Burton GJ. The human first trimester gestational sac limits rather than facilitates oxygen transfer to the foetus - a review. *Placenta*. 2003;24:S86–S93.
12. Jauniaux E, Greenwold N, Hempstock J, Burton GJ. Comparison of ultrasonographic and Doppler mapping of the intervillous circulation in normal and abnormal early pregnancies. *Fertil Steril*. 2003;79:100–106.
13. Lim K-H, Zhou Y, Janatpour M, et al. Human cytotrophoblast differentiation/invasion is abnormal in pre-eclampsia. *Am J Pathol*. 1997;151:1809–1818.
14. Jaffe R, Jauniaux E, Hustin J. Maternal circulation in the first-trimester human placenta - myth or reality? *Am J Obstet Gynecol*. 1997;176:695–705.
15. Jauniaux E, Watson AL, Hempstock J, Bao YP, Skepper JN, Burton GJ. Onset of maternal arterial blood flow and placental oxidative stress. A possible factor in human early pregnancy failure. *Am J Pathol*. 2000;157:2111–2122.
16. Smith SC, Baker PN. Placental apoptosis is increased in post-term pregnancies. *Br J Obstet Gynaecol*. 1999;106:861–862.
17. Smith SC, Baker PN, Symonds EM. Placental apoptosis in normal human pregnancy. *Am J Obstet Gynecol*. 1997;177:57–65.

18. Scifres CM, Nelson DM. Intrauterine growth restriction, human placental development and trophoblast cell death. *J Physiol*. 2009;587:3453–3458.
19. Levy R, Smith SD, Chandler K, Sadovsky Y, Nelson DM. Apoptosis in human cultured trophoblasts is enhanced by hypoxia and diminished by epidermal growth factor. *Am J Physiol Cell Physiol*. 2000;278:C982–C988.
20. Heazell A, Lacey H, Jones C, Huppertz B, Baker P, Crocker I. Effects of oxygen on cell turnover and expression of regulators of apoptosis in human placental trophoblast. *Placenta*. 2008;29:175–186.
21. Soleymanlou N, Wu Y, Wang JX, et al. A novel Mtd splice isoform is responsible for trophoblast cell death in pre-eclampsia. *Cell Death Differ*. 2005;12:441–452.
22. Hung TH, Skepper JN, Charnock-Jones DS, Burton GJ. Hypoxia-reoxygenation: a potent inducer of apoptotic changes in the human placenta and possible etiological factor in preeclampsia. *Circ Res*. 2002;90:1274–1281.
23. Ishihara N, Matsuo H, Murakoshi H, Laoag-Fernandez JB, Samoto T, Maruo T. Increased apoptosis in the syncytiotrophoblast in human term placentas complicated by either preeclampsia or intrauterine growth retardation. *Am J Obstet Gynecol*. 2002;186:158–166.
24. Levy R, Smith SD, Yusuf K, et al. Trophoblast apoptosis from pregnancies complicated by fetal growth restriction is associated with enhanced p53 expression. *Am J Obstet Gynecol*. 2002;186:1056–1061.
25. Huppertz B. Placental villous trophoblast: the altered balance between proliferation and apoptosis triggers pre-eclampsia. *J Reprod Med Endocrinol*. 2006;3:103–108.
26. Kadyrov M, Schmitz C, Black S, Kaufmann P, Huppertz B. Pre-eclampsia and maternal anaemia display reduced apoptosis and opposite invasive phenotypes of extravillous trophoblast. *Placenta*. 2003;24:540–548.
27. Fedarko NS. The biology of aging and frailty. *Clin Geriatr Med*. 2011;27:27–37.
28. Blasco MA. Telomeres and human disease: ageing, cancer and beyond. *Nat Rev Genet*. 2005;6:611–622.
29. Harley CB, Futcher AB, Greider CW. Telomeres shorten during ageing of human fibroblasts. *Nature*. 1990;345:458–460.
30. Elks CE, Scott RA. The Long and Short of Telomere Length and Diabetes. *Diabetes*. 2014;63:65–67.
31. Saretzki G, Von Zglinicki T. Replicative aging, telomeres, and oxidative stress. *Ann N Y Acad Sci*. 2002;959:24–29.
32. Aviv A. The Epidemiology of Human Telomeres: Faults and Promises. *J Gerontol A Biol Sci Med Sci*. 2008;63:979–983.
33. von Zglinicki T, Saretzki G, Döcke W, Lotze C. Mild Hyperoxia Shortens Telomeres and Inhibits Proliferation of Fibroblasts: A Model for Senescence? *Exp Cell Res*. 1995;220:186–193.
34. Allsopp RC, Harley CB. Evidence for a critical telomere length in senescent human fibroblasts. *Exp Cell Res*. 1995;219:130–136.
35. Bonney EA, Krebs K, Saade G, et al. Differential senescence in feto-maternal tissues during mouse pregnancy. *Placenta*. 2016;43:26–34.
36. Raffetto JD, Leverkus M, Park H-Y, Menzoian JO. Synopsis on cellular senescence and apoptosis. *J Vasc Surg*. 2001;34:173–177.
37. Burton DGA. Cellular senescence, ageing and disease. *Age*. 2009;31:1–9.
38. Sukenik-Halevy R, Amiel A, Kidron D, Liberman M, Ganor-Paz Y, Biron-Shental T. Telomere homeostasis in trophoblasts and in cord blood cells from pregnancies complicated with preeclampsia. *Am J Obstet Gynecol* 2016;214:283. e281-283.e287.
39. Lombard DB, Schwer B, Alt FW, Mostoslavsky R. SIRT6 in DNA repair, metabolism and ageing. *J Intern Med*. 2008;263:128–141.
40. Greider CW. Telomeres, telomerase and senescence. *BioEssays*. 1990;12:363–369.
41. Biron-Shental T, Sukenik-Halevy R, Sharon Y, et al. Short telomeres may play a role in placental dysfunction in preeclampsia and intrauterine growth restriction. *Am J Obstet Gynecol*. 2010;202:e381–e387.
42. Smith R, Maiti K, Aitken R. Unexplained antepartum stillbirth: a consequence of placental aging? *Placenta*. 2013;34:310–313.
43. von Zglinicki T. Oxidative stress shortens telomeres. *Trends Biochem Sci*. 2002;27:339–344.
44. Houben JM, Moonen HJ, van Schooten FJ, Hageman GJ. Telomere length assessment: biomarker of chronic oxidative stress? *Free Radic Biol Med*. 2008;44:235–246.
45. Nicholls C, Li H, Wang JQ, Liu JP. Molecular regulation of telomerase activity in aging. *Protein Cell*. 2011;2:726–738.
46. Burton GJ, Jauniaux E. Oxidative Stress. *Best Pract Res Clin Obstet Gynaecol*. 2011;25:287–299.
47. Kurlak LO, Green A, Loughna P, Broughton Pipkin F. Oxidative stress markers in hypertensive states of pregnancy: preterm and term disease. *Front Physiol* 2014;5:310.
48. Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol*. 1956;11:298–300.
49. Lagouge M, Larsson NG. The role of mitochondrial DNA mutations and free radicals in disease and ageing. *J Intern Med*. 2013;273:529–543.
50. Johnson TM, Yu ZX, Ferrans VJ, Lowenstein RA, Finkel T. Reactive oxygen species are downstream mediators of p53-dependent apoptosis. *Proc Natl Acad Sci U S A*. 1996;93:11848–11852.
51. Gambino V, De Michele G, Venezia O, et al. Oxidative stress activates a specific p53 transcriptional response that regulates cellular senescence and aging. *Aging Cell*. 2013;12:435–445.
52. Mistry HD, Williams PJ. The Importance of Antioxidant Micronutrients in Pregnancy. *Oxid Med Cell Longev*. 2011;2011:841749.
53. Wisdom SJ, Wilson R, McKillop JH, Walker JJ. Antioxidant systems in normal pregnancy and in pregnancy-induced hypertension. *Am J Obstet Gynecol*. 1991;165:1701–1704.
54. Myatt L, Cui X. Oxidative stress in the placenta. *Histochem Cell Biol*. 2004;122:369–382.
55. Wang Y, Walsh SW. Placental mitochondria as a source of oxidative stress in pre-eclampsia. *Placenta*. 1998;19:581–586.
56. Wang YP, Walsh SW, Guo JD, Zhang JY. Maternal levels of prostacyclin, thromboxane, vitamin E, and lipid peroxides throughout normal pregnancy. *Am J Obstet Gynecol*. 1991;165:1690–1694.
57. Sbrana E, Suter MA, Abramovici AR, et al. Maternal tobacco use is associated with increased markers of oxidative stress in the placenta. *Am J Obstet Gynecol*. 2011;205:e241–e247.
58. Menon R, Fortunato SJ, Yu J, et al. Cigarette smoke induces oxidative stress and apoptosis in normal term fetal membranes. *Placenta*. 2011;32:317–322.
59. Ashfaq M, Janjua MZ, Nawaz M. Effects of maternal smoking on placental morphology. *J Ayub Med Coll Abbottabad*. 2003;15:12–15.
60. Romero R, Dey SK, Fisher SJ. Preterm Labor: One Syndrome, Many Causes. *Science*. 2014;345:760–765.
61. Haddad R, Tromp G, Kuivaniemi H, et al. Human spontaneous labor without histologic chorioamnionitis is characterized by an acute inflammation gene expression signature. *Am J Obstet Gynecol* 2006;195:394. e391-324.
62. Phillippe M. Cell-Free Fetal DNA, Telomeres, and the Spontaneous Onset of Parturition. *Reprod Sci*. 2015;22:1186–1201.
63. Menon R, Behnia F, Polettini J, Saade GR, Campisi J, Velarde M. Placental membrane aging and HMGB1 signaling associated with human parturition. *Aging*. 2016;8:216–230.
64. Polettini J, Behnia F, Taylor BD, Saade GR, Taylor RN, Menon R. Telomere Fragment Induced Amnion Cell Senescence: A Contributor to Parturition? *PLoS ONE*. 2015;10:e0137188.
65. Polettini J, Dutta EH, Behnia F, Saade GR, Torloni MR, Menon R. Aging of intrauterine tissues in spontaneous preterm birth and preterm premature rupture of the membranes: a systematic review of the literature. *Placenta*. 2015;36:969–973.
66. Menon R. Oxidative stress damage as a detrimental factor in preterm birth pathology. *Front Immunol*. 2014;5:567.

67. Menon R, Boldogh I, Hawkins HK, et al. Histological evidence of oxidative stress and premature senescence in preterm premature rupture of the human fetal membranes recapitulated in vitro. *Am J Pathol*. 2014;184:1740–1751.
68. Romero R, Kusanovic JP, Chaiworapongsa T, Hassan SS. Placental bed disorders in preterm labor, preterm PROM, spontaneous abortion and abruptio placentae. *Best Pract Res Clin Obstet Gynaecol*. 2011;25:313–327.
69. Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S. The effects of oxidative stress on female reproduction: a review. *Reprod Biol Endocrinol*. 2012;10:49.
70. Cinkaya A, Keskin HL, Buyukkagnici U, et al. Maternal plasma total antioxidant status in preterm labor. *J Obstet Gynaecol Res*. 2010;36:1185–1188.
71. Ahamed M, Mehrotra PK, Kumar P, Siddiqui MKJ. Placental lead-induced oxidative stress and preterm delivery. *Environ Toxicol Pharmacol*. 2009;27:70–74.
72. Mustafa MD, Pathak R, Ahmed T, et al. Association of glutathione S-transferase M1 and T1 gene polymorphisms and oxidative stress markers in preterm labor. *Clin Biochem*. 2010;43:1124–1128.
73. Rayman MP, Wijnen H, Vader H, Kooistra L, Pop V. Maternal selenium status during early gestation and risk for preterm birth. *CMAJ*. 2011;183:549–555.
74. Than NG, Romero R, Tarca AL, et al. Mitochondrial manganese superoxide dismutase mRNA expression in human chorioamniotic membranes and its association with labor, inflammation, and infection. *J Matern Fetal Neonatal Med*. 2009;22:1000–1013.
75. Brodsky D, Christou H. Current concepts in intrauterine growth restriction. *J Intensive Care Med*. 2004;19:307–319.
76. Frøen JF, Gardosi JO, Thurmann A, Francis A, Stray-Pedersen B. Restricted fetal growth in sudden intrauterine unexplained death. *Acta Obstet Gynecol Scand*. 2004;83:801–807.
77. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet*. 2011;377:1331–1340.
78. Chan PYL, Morris JM, Leslie GI, Kelly PJ, Gallery EDM. The long-term effects of prematurity and intrauterine growth restriction on cardiovascular, renal, and metabolic function. *Int J Pediatr*. 2010;2010:280402.
79. Yung H-W, Calabrese S, Hynx D, et al. Evidence of placental translation inhibition and endoplasmic reticulum stress in the etiology of human intrauterine growth restriction. *Am J Pathol*. 2008;173:451–462.
80. Krishna U, Bhalerao S. Placental Insufficiency and Fetal Growth Restriction. *J Obstet Gynaecol India*. 2011;61:505–511.
81. Mandò C, De Palma C, Stampalija T, et al. Placental mitochondrial content and function in intrauterine growth restriction and pre-eclampsia. *Am J Physiol Endocrinol Metab*. 2014;306:E404–E413.
82. Huppertz B. Placental origins of preeclampsia challenging the current hypothesis. *Hypertension*. 2008;51:970–975.
83. Biri A, Bozkurt N, Turp A, Kavutcu M, Himmetoglu Ö, Durak İ. Role of oxidative stress in intrauterine growth restriction. *Gynecol Obstet Invest*. 2007;64:187–192.
84. Takagi Y, Nikaido T, Toki T, et al. Levels of oxidative stress and redox-related molecules in the placenta in preeclampsia and fetal growth restriction. *Virchows Arch*. 2004;444:49–55.
85. Fujimaki A, Watanabe K, Mori T, Kimura C, Shinohara K, Wakatsuki A. Placental oxidative DNA damage and its repair in preeclamptic women with fetal growth restriction. *Placenta*. 2011;32:367–372.
86. Kimura C, Watanabe K, Iwasaki A, et al. The severity of hypoxic changes and oxidative DNA damage in the placenta of early-onset preeclamptic women and fetal growth restriction. *J Matern Fetal Neonatal Med*. 2013;26:491–496.
87. Sahlin L, Ostlund E, Wang H, Holmgren A, Fried G. Decreased expression of thioredoxin and glutaredoxin in placentae from pregnancies with pre-eclampsia and intrauterine growth restriction. *Placenta*. 2000;21:603–609.
88. Davy P, Nagata M, Bullard P, Fogelson NS, Allsopp R. Fetal growth restriction is associated with accelerated telomere shortening and increased expression of cell senescence markers in the placenta. *Placenta*. 2009;30:539–542.
89. Kudo T, Izutsu T, Sato T. Telomerase activity and apoptosis as indicators of ageing in placenta with and without intrauterine growth retardation. *Placenta*. 2000;21:493–500.
90. Kim S-Y, Lee S-P, Lee J-S, Yoon S-J, Jun G, Hwang Y-J. Telomerase and Apoptosis in the Placental Trophoblasts of Growth Discordant Twins. *Yonsei Med J*. 2006;47:698–705.
91. Redman CW, Sargent IL. Latest advances in understanding pre-eclampsia. *Science*. 2005;308:1592–1594.
92. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet*. 2005;365:785–799.
93. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol* 2013;209:544. e541-544 e512.
94. Rajakumar A, Cerdeira AS, Rana S, et al. Transcriptionally active syncytial aggregates in the maternal circulation may contribute to circulating soluble fms-like tyrosine kinase 1 in preeclampsia. *Hypertension*. 2012;59:256–264.
95. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: an endothelial cell disorder. *Am J Obstet Gynecol*. 1989;161:1200–1204.
96. Hubel CA, Roberts JM, Taylor RN, Musci TJ, Rogers GM, McLaughlin MK. Lipid peroxidation in pregnancy: new perspectives on pre-eclampsia. *Am J Obstet Gynecol*. 1989;161:1025–1034.
97. Hubel CA. Oxidative Stress in the Pathogenesis of Preeclampsia. *Exp Biol Med*. 1999;222:222–235.
98. Trudinger BJ, Giles WB, Cook CM, Bombardieri J, Collins L. Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. *Br J Obstet Gynaecol*. 1985;92:23–30.
99. Many A, Hubel CA, Fisher SJ, Roberts JM, Zhou Y. Invasive cytotrophoblasts manifest evidence of oxidative stress in preeclampsia. *Am J Pathol*. 2000;156:321–331.
100. 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.
101. Redman CW. Current topic: pre-eclampsia and the placenta. *Placenta*. 1991;12:301–308.
102. Poston L, Igosheva N, Mistry HD, et al. Role of oxidative stress and antioxidant supplementation in pregnancy disorders. *Am J Clin Nutr*. 2011;94:1980S–1985S.
103. Madazli R, Benian A, Aydin S, Uzun H, Tolun N. The plasma and placental levels of malondialdehyde, glutathione and superoxide dismutase in pre-eclampsia. *J Obstet Gynaecol*. 2002;22:477–480.
104. Kaur G, Mishra S, Sehgal A, Prasad R. Alterations in lipid peroxidation and antioxidant status in pregnancy with preeclampsia. *Mol Cell Biochem*. 2008;313:37–44.
105. 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;22:206–212.
106. Sahay AS, Sundrani DP, Wagh GN, Mehendale SS, Joshi SR. Regional differences in the placental levels of oxidative stress markers in pre-eclampsia. *Int J Gynaecol Obstet*. 2015;129:213–218.
107. Morikawa S, Kurauchi O, Tanaka M, et al. Increased mitochondrial damage by lipid peroxidation in trophoblast cells of preeclamptic placentas. *Biochem Mol Biol Int*. 1997;41:767–775.
108. Wang Y, Walsh SW. Antioxidant activities and mRNA expression of superoxide dismutase, catalase, and glutathione peroxidase in normal and preeclamptic placentas. *J Soc Gynecol Investig*. 1996;3:179–184.

109. Watson A, Palmer M, Jauniaux E, Burton G. Evidence for oxygen-derived free radical mediated damage to first trimester human trophoblast in vitro. *Placenta*. 1998;19:259–276.
110. Burton GJ, Jauniaux E. Placental oxidative stress: from miscarriage to preeclampsia. *J Soc Gynecol Investig*. 2004;11:342–352.
111. Stacey T, Thompson JM, Mitchell EA, Ekeroma AJ, Zuccollo JM, McCowan LM. The Auckland Stillbirth study, a case-control study exploring modifiable risk factors for third trimester stillbirth: methods and rationale. *Aust N Z J Obstet Gynaecol*. 2011;51:3–8.
112. Sutan R, Campbell D, Prescott GJ, Smith WC. The risk factors for unexplained antepartum stillbirths in Scotland, 1994 to 2003. *J Perinatol*. 2010;30:311–318.
113. Ferrari F, Facchinetti F, Saade G, Menon R. Placental telomere shortening in stillbirth: a sign of premature senescence? *J Matern Fetal Neonatal Med*. 2016;29:1283–1288.
114. Smith GC, Yu CK, Papageorghiou AT, Cacho AM, Nicolaides KH. Maternal uterine artery Doppler flow velocimetry and the risk of stillbirth. *Obstet Gynecol*. 2007;109:144–151.
115. Pinar H, Goldenberg RL, Koch MA, et al. Placental Findings in Singleton Stillbirths. *Obstet Gynecol*. 2014;123:325–336.

How to cite this article: Sultana Z, Maiti K, Aitken J, Morris J, Dedman L, Smith R. Oxidative stress, placental ageing-related pathologies and adverse pregnancy outcomes. *Am J Reprod Immunol*. 2017;77:e12653. https://doi.org/10.1111/aji.12653