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Oxidative stress: Normal pregnancy versus preeclampsia☆

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ABSTRACT

The role of oxidative stress in the physiopathology of human pregnancy is of particular interest. Pregnancy is well-known to increase the oxidative stress, mainly produced by a normal systemic inflammatory response, which results in high amounts of circulating reactive oxygen species (ROS) and reactive nitrogen species (RNS). Both ROS and RNS play an important role as secondary messengers in many intracellular signalling cascades. However, they can also exert critical effects on pathological processes involving the pregnant woman. ROS, RNS and antioxidants establish a balance that determines the oxidation status of animals and humans. This review focuses on the mechanism of oxidative stress in pregnancy as well as its involvement and consequences on the human pregnancy-specific clinical syndrome preeclampsia.

1. Introduction

Normal pregnancy is a series of temporary complex events finely orchestrated that includes decidualization, placentation, and partum [1,2]. The chronological transitions are critical for a normal pregnancy and any alteration may have consequences in the mother and foetus health [2]. Pregnancy is well-known to increase the oxidative stress, a phenomenon generated by a normal systemic inflammatory response, which results in high amounts of circulating reactive oxygen species (ROS). The major source of ROS during pregnancy is the central organ that regulates this condition, *i.e.* the placenta [3]. In this regard, the increased oxidative stress seen in pregnancy could lead to potential tissue damage [4,5]. However, increased oxidative stress is counterbalanced by the increase in the synthesis of antioxidants [6]. When the oxidative stress surpasses the antioxidant defence in the placenta, the oxidative damage could propagate to distal tissues.

Preeclampsia is a pregnancy-specific clinical syndrome with multisystem involvement [7,8]. The classic definition of preeclampsia includes both new-onset of hypertension plus new-onset proteinuria ≥ 300 mg/24 h after 20 weeks of gestation, most often near term. However, in the absence of proteinuria, preeclampsia is diagnosed as hypertension in association with thrombocytopenia, impaired liver function, renal insufficiency, pulmonary oedema, or new-onset cerebral or visual disturbances [9]. Although the aetiology of preeclampsia is not clear, placental insufficiency due to inadequate remodelling of the maternal vasculature perfusing the intervillous space plays an important role in the developing of this syndrome [8,10,11]. This may lead to a complex process of ischemia-reperfusion in the placenta with the release of cytotoxic factors into the maternal circulation. The placental alternance between an environment with low oxygen and reoxygenation, *i.e.*, hypoxia/reoxygenation is linked to an imbalance in angiogenesis, vascular endothelial damage, cardiovascular complications and an exaggerated inflammatory response [12–14]. The uteroplacental hypoxia/reoxygenation during preeclampsia increases the

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oxidative stress, which has consequences for the mother and foetal health [11,15,16].

Free radicals released from the poorly perfused fetoplacental unit initiate oxidative stress in placental cells [15,17,18]. The plasma membranes of the circulating blood cells can be oxidized when passing through the ischemic placenta contributing to propagate in this way the oxidative stress to distal tissues [17–19]. Also, the antioxidant defence is reduced in preeclampsia, probably due to a lower efficiency of free radical scavengers and the activity of antioxidant enzymes [20]. Although oxidative stress has an implication in the human health and pregnancy and it is a general feature of placental pathologies such as preeclampsia, spontaneous pregnancy loss, intra-uterine growth restriction (IUGR), and gestational diabetes mellitus [21], this review will focus on the significance of this phenomenon in the cells and its effects and involvement in preeclampsia.

2. Oxidative stress in pregnancy

2.1. Free radicals and cell physiology

Oxidative stress is defined as an imbalance between the generation of ROS or reactive nitrogen species (RNS) and the cellular antioxidant capacity [22]. ROS include free radicals, such as, superoxide ($\cdot O_2^-$), hydroxyl radicals ($\cdot OH$) and non-radical intermediates, like hydrogen peroxide (H_2O_2) and singlet oxygen $^1O_2$. RNS include the nitric oxide ($NO\cdot$), which is of relatively low reactivity, and its derivative peroxynitrite ($ONOO^-$). These species are part of normal cellular metabolism produced by enzymatic reactions (respiratory chain, phagocytosis, prostaglandin synthesis, and cytochrome P450 system) and non-enzymatic reactions (involving oxygen reaction with organic compounds or the exposition to ionizing radiations) taking place in peroxisomes and endoplasmic reticulum but mostly in the mitochondria [23–25].

The mitochondrial function is intimately linked to the enzymatic generation of superoxide ($\cdot O_2^-$) and H_2O_2 formed mainly by complex I (NADH dehydrogenase) and complex III (ubiquinone cytochrome c reductase) of the electron transport chain [26]. Meanwhile, H_2O_2 is formed as a product of enzymatic reactions that could yield hydroxyl radicals through a non-enzymatic way such as metal-catalysed Haber-Weiss reaction and the Fe(II)-catalysed Fenton reaction [27]. On the other hand, $\cdot O_2^-$ is highly reactive and it can combine with transition metals and other chemical species, *e.g.* $NO\cdot$, generating highly oxidant species such as $ONOO^-$ [28]. Another non-enzymatic process known as Maillard reaction, involves multiple steps, including the interaction of reducing sugars with amine groups of proteins, lipid or nucleic acids. These glycation reactions form Schiff bases that can rearrange into Amadori products, which form highly reactive carbonyl compounds progressing to the formation of advanced glycation end-products (AGEs) and $\cdot O_2^-$ generation [29,30].

The physiological concentrations of ROS and RNS may play beneficial roles in cellular metabolism since they act as signalling molecules in different biological process. For instance, ROS participate in the induction of genes involved in oxygen sensing, cell differentiation, and proliferation, in the host defence system and on the mitogenic pathway [24,25,31]. Furthermore, during pregnancy low levels of ROS promote angiogenesis through the upregulation of transcription factor E26 transformation-specific oncogene homolog 1 (Ets-1) that upregulates vascular endothelial growth factor (VEGF) expression and invasion through the upregulation of Kruppel-like factor 8 (KLF8) that promotes the activation of the matrix methaloproteinase 9 (MMP-9) [32,33]. Regarding the mitogenic pathway, ROS could activate mitogen-activated protein kinases (MAPK) [34]. MAPK signalling is required for proper development, differentiation and morphogenesis of the placenta [35–37]. Nevertheless, MAPK excessive activation by oxidative stress might decrease MMPs activity, leading to unfavourable effects in the invasion of trophoblast cells [38]. It is well known that excessive production of ROS and RNS have detrimental effects on the cell physiology. ROS and RNS can inhibit the physiological function of lipids by the oxidation of fatty acid residues of the membrane phospholipids. These products can also lead to the oxidation of different amino acid residues of proteins, which can result in the formation of protein-protein cross-linkages and carbonyl acid derivatives. ROS can also induce DNA damage by the formation of DNA-adducts and single and double stranded breaks in DNA [23,39].

2.2. Oxidative stress regulation and placentation

The development and maturation of the placenta is a complex process, which requires a coordinated regulation of invasion of the trophoblast, and its differentiation and proliferation in the maternal decidua [40]. At early gestation (8–10 weeks), trophoblast cells are exposed to low oxygen concentration, since the partial oxygen pressure (pO_2) at the placental bed is ~18 mm Hg (2.5% O_2) [41,42]. This physiologically low oxygen condition represents a key regulator of placental function since it activates the cellular response to hypoxia primarily mediated by hypoxia-inducible factors (HIF-1α and HIF-2α proteins) [41,42]. The low oxygen environment leads to down-regulation of the mitochondrial oxygen consumption [43]. Whilst the D-glucose consumption by endometrial glands is enough to support a plentiful supply of ATP to embryo and placenta [44]. Therefore, during the first trimester the metabolic requirement of the conceptus is adequately met still under an environment of 2.5% O_2 [41]. Down-regulation of the mitochondria aims to prevent the teratogenic effects of mitochondrial-derived ROS [45]. Similarly, HIF-1α increases the activity of the endothelial NOS (eNOS) isoform in the extravillous trophoblast [46,47]. The latter results in increasing $NO\cdot$ generation, which delays or inhibits trophoblast apoptosis, leading to extravillous trophoblast proliferation, migration, and invasion processes [48,49].

As the embryo grows, the metabolic requirement increases thus needing a more efficient system which will lead to the development of the uteroplacental circulation [50]. At the end of the first trimester, i.e., between 10 and 12 weeks, the trophoblastic plugs are progressively dissolved, thereby establishing a continuous low-flow perfusion of oxygenated blood into the placenta [51,52]. The intervillous blood flow increases, and there is a concomitant increase of the oxygen tension to ~60 mm Hg (8.5% O_2) [53]. The process begins at the peripheral margin of the placenta expanding to the central area of the placenta and producing a gradual increase in maternal blood flow and thus oxygen tension. Invasion of extravillous trophoblast (EVT) to the spiral arteries is deeper in the central region of the placenta compared to the periphery, taking longer to dissolve the plugs explaining the gradual increase in oxygen tension [54]. This phenomenon results in a shift from low to a higher oxygen tension in the intervillous space at the end of the first trimester [51,52]. This increase in oxygen level promotes differentiation of the trophoblast as well as the maturation of the placenta to become an exchange organ [40].

The increase of the metabolic rate ensuring adequate foetal growth and development comes together with increased oxidative stress in the placental tissues, but also with increased level of antioxidant enzymes to maintain the oxidative balance [55,56]. Simultaneously, the mitochondrial activity increases and therefore elevated levels of ROS are present especially in the syncytiotrophoblast (STB) [26]. The STB is a specialized and multinucleate epithelium originated by the fusion of a progenitor cell population of villous cytotrophoblasts (CTB) and it has important functions including solute transporting to the foetus and hormone production to sustain pregnancy [57,58]. STB and CTB have different types of mitochondria in terms of morphology and function [59]. The STB-mitochondria acquire a steroidogenic capacity and have dense matrix, atypical cristae structure, and are smaller and irregular in shape compared with mitochondria from the CTB. It has been suggested that the morphological features of this type of mitochondria is necessary to improve the steroidogenic activity of the STB [59–61]. The rate-limiting step of steroidogenesis is the translocation of cholesterol to

cytochrome P450 located in the inner membrane of mitochondria and this step is involved with the generation of $\cdot O_2^-$ and other ROS in STB [60,62]. The lipid metabolism and calcium homeostasis are mainly regulated by the mitochondria and endoplasmic reticulum, organelles that in the STB form an integrated unit [63] by keeping a close physical contact between their plasma membranes [64]. There is a close interaction between ROS, mitochondrial and endoplasmic reticulum function, where the Ca^{2+} release plays a crucial role [65]. Particularly, the endoplasmic reticulum coordinates the cellular responses to several stressors, finely tuning the energy expenditure to oxygen and nutrient availability. This is important for the placenta since ~30% of the total placental oxygen consumption is used for protein synthesis [66]. Besides, the oxidative environment in the lumen of the endoplasmic reticulum is critical for the formation of disulphide bonds during the protein folding process [67].

The STB does not show enough concentration of antioxidant defence molecules such as manganese superoxide dismutase (MnSOD). Therefore, STB is more vulnerable to oxidative stress [68]. STB is sensitive to ROS since their plasma membranes have abundant unsaturated fatty acids, which are a target for ROS [48]. Interestingly, a deterioration of STB in the presence of a high oxygen level, without damaging CTB and stromal cells, has been reported [38].

The first line of defence against ROS consists of antioxidant enzymes such as SOD, glutathione peroxidase (GPx), and catalase (CAT) which metabolize these reactive species to innocuous by-products [69]. The non-enzymatic antioxidants represent the second line of defence against ROS and include low-molecular-weight compounds, such as vitamins C and E, α tocopherol, β-carotene, lipoic acid, ubiquinone, carotenoids, ascorbic acid, uric acid, and glutathione. These molecules act by reducing and rapidly inactivating radicals and oxidants [70]. Other scavengers and metal chelators, *e.g.* ceruloplasmin, albumin, ferritin, and lactoferrin, contribute to maintain the antioxidant status [69].

The oxidant status is a key factor regulating the gene expression and activity of antioxidant enzymes [69]. In addition, many antioxidant enzymes, including SOD, GPx and CAT, show circadian rhythmicity [71]. The master clock in the suprachiasmatic nucleus of the hypothalamus influences the peripheral clock genes expressed in tissues with metabolic, endocrine, and reproductive function, resulting in modulation of the placental function [72]. In fact, in a normal pregnancy the human chorionic gonadotropin (hCG) [73], blood pressure [74], and uterine contraction [75], show circadian rhythms. However, few studies has reported a clock gene expression in full-term human placenta and trophoblast cell lines [76,77]. In addition, melatonin (hormone responsible of chronobiotic effect) stimulates GPx activity in the human chorion [78]. Even more, placental melatonin (an extrapineal source of melatonin) could act as a direct scavenger of radical species to modulate the redox status in this tissue [79].

2.3. Endothelial function and oxidative stress

In the placental-umbilical unit, the eNOS and inducible NOS (iNOS) are expressed in the STB and in endothelium from the macrovasculature (human umbilical vein and arteries) and microvasculature (human placental microvascular endothelial cells) [80,81]. NO· is responsible for the maintenance of vascular homeostasis ensuring constant uterine blood flow and uterine myometrial quiescence [82,83]. It is proposed that oxidative stress acts as a disruptor factor of the placental endothelial function [21]. Also, excessive production of ROS induces oxidation of tetrahydrobiopterin (BH_4), a cofactor of eNOS that allows the conversion of a nitrogen component of L-arginine to NO· [84]. Reduced bioavailability of BH_4 results in uncoupling of eNOS in placental endothelium, a phenomenon favouring $\cdot O_2^-$ generation instead of NO·. The latter results in the synthesis of $ONOO^-$ as a product of the reaction between $\cdot O_2^-$ and NO· [85,86]. Additionally, ROS and RNS induced the neutrophil adhesion to the endothelium as well as the release of cytokines and activation of the inflammatory response-associated signalling pathways [87,88].

3. Oxidative stress and preeclampsia

3.1. Placental ischemia and oxidative stress

Early-onset preeclampsia is associated with impaired vascular remodelling of spiral arteries and shallow trophoblast invasion [89]. The failure in the remodelling of the spiral arteries in the placental bed of pregnant women affected by preeclampsia was demonstrated for the first time by Brosens *et al.* [90]. Later studies associated this pathology with partial failures in the invasion phenomenon of the trophoblast [91]. Preserving the muscle layer of the spiral arteries resulted in intermittent placental perfusion [92] and repeated hypoxia/reoxygenation, which significantly affects the placenta in pregnancy. Furthermore, hypoxia/reoxygenation represents a powerful stimulus for the conversion of xanthine dehydrogenase to xanthine oxidase, an important source of generation of $\cdot O_2^-$, which is abundantly expressed in CTB and STB cells [93]. Xanthine oxidase plays a fundamental role in tissue damage induced by free radicals in the human placenta [94]. Studies in placental ischemia show that the balance between ROS and antioxidants is disrupted, leading to oxidative stress-associated damage to proteins, lipids, and DNA [95]. Even more, placenta-derived lipid peroxides affect the circulating blood with lipoproteins, particularly low-density lipoprotein (LDL), and promote its peroxidation contributing to propagate the systemic lipid peroxidation and maternal vascular dysfunction [96].

On the other hand, the oxidative stress increases the heterogeneous group of extracellular vesicles (EVs) shedding continuously from the STB [97]. These EVs include exosomes (~50–200 nm, of endosomal origin and released by exocytosis), microvesicles (~0.1–1 μm, released by outward budding process and fission of the plasma membrane) and apoptotic bodies (~1–5 μm, produced during programmed cell death) [98–101]. These EVs and particularly the exosomes could encapsulate damage-associated molecular pattern molecules (DAMP) in their cargo [102]. Indeed, BeWo choriocarcinoma cells with tunicamycin or thapsigargin, compounds inducing endoplasmic reticulum stress, leads to the release of extracellular vesicles containing DAMPs, specifically, high mobility group protein B1 (HMGB1), heat shock protein 70 (hsp70) and histone H3 [103]. These molecules have been found increased in the circulation in women with preeclampsia [104,105]. DAMP molecules are highly pro-inflammatory and may contribute to propagate and to exacerbate the inflammatory response seen in preeclampsia [103,106].

3.2. Markers of oxidative stress and preeclampsia

A physiological increase in lipid peroxidation products is detected in the maternal serum in a healthy pregnancy [107], a phenomenon balanced by increasing the activity of antioxidant systems [108,109]. The activity of GPx in maternal erythrocytes and platelets, as well as extracellular SOD activity, increases progressively throughout pregnancy until the third trimester [110,111]. However, this antioxidant capacity is absent in women with preeclampsia leading to an imbalance between the existing pro-oxidant and anti-oxidant systems resulting in oxidative stress [112–114].

The placenta represents the main target organ of complications during pregnancy. Its failure is the main cause of development of obstetric syndromes such as preeclampsia [115]. In this regard, it is well-known that the antioxidant balance is disturbed in preeclamptic pregnancies, as evidenced by increased placental production of ROS, RNS and lower level of antioxidants, which act as scavengers of free radicals and inhibitors of ROS [6,116]. In addition, preeclampsia is associated with lower SOD activity [17] and mRNA expression of CuZn-SOD of isolated trophoblast in preeclampsia [117]. In this regard, several studies show decreased CAT and SOD activity, and increased lipid

peroxidation by-products in the blood plasma from women with pre-eclampsia [118]. There are also studies showing decreased activity of GPx, SOD and glutathione *S*-transferase in placentas from preeclampsia [119]. Alterations in non-enzymatic antioxidants in preeclampsia such as total thiols in plasma, ascorbic acid, α-tocopherol and carotenoids (vitamin A, β-carotene and lycopene) have also been described [20,120–124]. In addition, Bharadwaj *et al.* [125] showed a decrease in the maternal total antioxidant status (M-TAS) in women with pre-eclampsia. This is a clear indication of a reduction of the antioxidant capacity of the preeclamptic women, which is one the characteristics of this clinical syndrome.

During the last 50 years, oxidative stress biomarkers have been detected in the blood of women with preeclampsia [126]. Thus, women with preeclampsia show increased levels of thiobarbituric acid reactive substances (TBARS), measured as the production of malondialdehyde (MDA), a breakdown product of lipid peroxidation, in erythrocytes, blood plasma, and placental tissue [17,127,128]. Moreover, the severity of the disease is related to the level of TBARS both in serum [129] and erythrocytes [130]. Besides, other markers of lipid peroxidation such as F2-isoprostanes, conjugated dienes, and antibodies against modified LDL are present in women with preeclampsia [112]. The usage of protein CO groups as biomarkers of oxidative stress has some advantages compared with the measurement of other oxidation products because of the relative early formation and stability of carbonylated proteins. In this regard, markers of lipid peroxidation and protein carbonyl maternal levels are elevated in preeclampsia [125,131].

Four major sources of $\cdot O_2^-$ are the mitochondrial electron transport chain, NADPH-oxidase (NOX), NOS, and xanthine oxidoreductase (XO) [132]. In addition, reduction of heme oxygenase protein abundance [133], an indirect source of $\cdot O_2^-$ and increased activity of xanthine oxidase [93] is reported in preeclampsia. Furthermore, the level of paraoxonase (PON-1), an enzyme found in high-density lipoprotein (HDL) that protects HDL and LDL from oxidative stress, is lower in serum from women with preeclampsia [134,135]. Additionally, oxidative stress induces DNA and RNA damage. Indeed, the cellular concentration of 8-hydroxy-20-deoxyguanosine (8-OH-dG), a marker of oxidative DNA damage, is higher in placental DNA from preeclampsia as compared to placentas from normal pregnancies [136,137]. Also, immunohistochemical labelling with H2AX (a marker of DNA double-strand breaks) show increased number of H2AX-positive cells in placentas from preeclampsia, especially in decidual cells, as compared to healthy placentas [138]. Moreover, a high level of DNA fragmentation, as seen in placentas from preeclamptic women, can lead to trophoblast apoptosis [139,140]. Altogether, these reports indicate that the antioxidant defence in tissues from women with preeclampsia is reduced compared with normal pregnancies [141].

3.3. Endothelial dysfunction, oxidative stress and preeclampsia

Two potentially interrelated events appear to underlie the clinical features of preeclampsia: placental hypoxia/ischemia and diffuse maternal endothelial cell activation [142]. It is possible that pre-existing altered vascular function resulting from a systemic response to inflammation and oxidative/nitrative stress in the mother arising from an inadequately perfused placenta is one of the fundamental causes of preeclampsia [142]. Normal pregnancy itself is characterized by systemic inflammation, oxidative stress and alterations in the level of angiogenic factors and vascular reactivity. This is exacerbated in pre-eclampsia with an associated failure of compensatory mechanisms, eventually leading to placental and vascular dysfunction [116,142]. The local damage in placenta in preeclampsia seen as disturbed production of angiogenic and anti-angiogenic factors results in systemic inflammation, endothelial activation, systemic oxidative stress and altered endothelial NO· generation [143,144]. When this vascular endothelial activation and dysfunction occurs at the level of liver, kidney, brain, and placenta, the clinical presentation of preeclampsia worsens [115]. Abnormal expression of endothelial receptors on invading CTB is the cause of defective invasion of both endovascular and interstitial trophoblasts found in preeclampsia [145,146]. VEGF and the interactions with its receptor, Flt-1 (VEGF-Flt-1), manage the transformation from epithelial to endothelial phenotype on the invading CTB [147]. The immunostaining of CTB for VEGF and Flt-1 is reduced in pre-eclampsia [148]. Activation of Flt-1 by VEGF increases the release of NO· and the fall during preeclampsia leads to defective NO· synthesis causing vasoconstriction and inadequate perfusion [149,150]. The resultant placental hypoperfusion and intermittent perfusion creates an environment of hypoxia-reoxygenation that favours the oxidative damage [142]. The synthesis and action of angiogenic growth factors such as, VEGF, soluble fms like tyrosine kinase (sFlt-1), placental growth factor (PIGF) and endoglin and their receptors in the uterine bed and placenta are then crucial for normal placental development and pregnancy [151,152]. Changes in levels of these factors in placenta and circulation may identify those pregnancies that develop preeclampsia [142].

sFlt-1 is produced by alternative splicing of VEGF-R1 mRNA (Flt-1A mRNA) [153] and appears to be a central regulator of angiogenesis by its binding to potent angiogenic and mitogenic factors such as VEGF and PIGF [154]. Interaction of VEGF with its receptors (Flt-1 and Flt-2) [155] is prevented by sFlt-1 [115,156], which in turn results in low circulating maternal level of free or bioactive VEGF in preeclampsia [157]. In addition, endoglin, a co-receptor for transforming growth factor (TGF), increased the vascular permeability inducing modest hypertension in overexpression assays performed in rodents [158]. An increase in the circulating level of soluble endoglin in the onset of preeclampsia is associated with an increased sFlt1/PlGF ratio [154].

The link between abnormalities in trophoblast invasion and generalized maternal endothelial dysfunction seen in preeclampsia may also result from the release of placental factors [159]. Placental hypoxia resulting from inadequate trophoblast invasion accelerates the apoptotic cascade in villous trophoblast that ends with formation of syncytial knots and shedding of STB basement membrane fragments into the maternal circulation. Several other factors, including leukocyte and platelet membrane particles, ROS, activated neutrophils, cytokines, growth factors, angiogenic factors and hormones are also released in the abnormal trophoblast invasion. These factors will then interact with maternal vascular endothelium which may be already damaged [142].

Abnormal endothelial function, indicated by increased circulating levels of fibronectin and von Willebrand factor, which are markers of endothelial cell injury, is reported in women with preeclampsia [160]. Decreased generation of NO·, prostacyclin and increased production of thromboxane, endothelin and increased vascular reactivity to Ang II in preeclamptic women suggest abnormal endothelial function during preeclampsia [160,161]. The decrease in the level of NO· could be the result of an increased $\cdot O_2^-$ formation leading to NO· degradation and $ONOO^-$ formation [86]. $ONOO^-$ can also nitrate proteins, altering their crucial vascular function, such as NOS [162], prostacyclin synthase [163] and cyclooxygenase [164]. In addition, nitrotyrosine is higher in placental [165] and maternal vasculature [166] during pre-eclampsia altering the vascular bed reactivity.

An imbalance in the nitroso-redox state could be considered a causative element in preeclampsia-induced hypertension and other vascular diseases. Reports by Doridot *et al.* [167] suggested that a winged-helix transcription factor, storkhead box 1 (STOX1), induces opposite O_2-dependent effects on ROS and RNS production *in vitro* as well as *in vivo* in a murine model of preeclampsia. The results in the latter study showed a predominance of RNS in STOX1 transgenic placentas, suggesting that NO· is rapidly associated with ROS and generates $ONOO^-$. This could explain the lower circulating levels of NO· detected in preeclampsia, and therefore the rationale to the systemic hypertension of preeclamptic women.

Fig. 1 shows a summary of the sources of oxidative stress during preeclampsia as well as its influence on the exacerbated endothelial cell

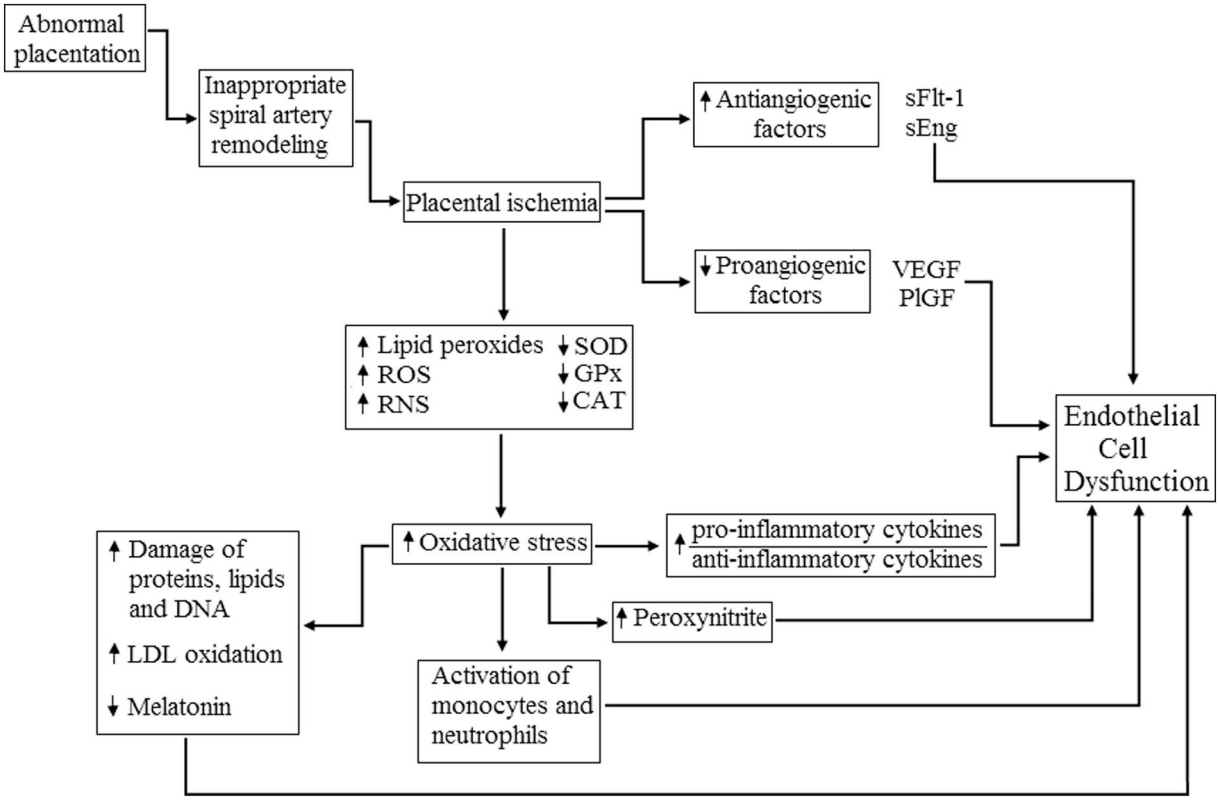

Fig. 1. Physiopathology of preeclampsia. Abnormal placentation, a common feature of preeclampsia, triggers several events leading to chronic placental ischemia or intermittent flow through the narrow muscular arteries thereby creating a process of ischemia-reperfusion. Reactive oxygen species (ROS), reactive nitrogen species (RNS), and lipid peroxides release is increased (↑) from the ischemic placenta, while the antioxidant defence is reduced (↓), including superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) leading to an increased systemic oxidative stress condition. The increase of oxidative stress together with a rise of pro-inflammatory cytokines lead to an exaggerated inflammatory reaction and angiogenic imbalance (higher antiangiogenic and lower proangiogenic factors) that exacerbates endothelial cell dysfunction. Other factors resulting from oxidative stress, including damaged DNA, low-density lipoprotein (LDL) oxidation and melatonin levels, monocytes and neutrophil activation, and overgeneration of peroxynitrite, also result in endothelial dysfunction. Impaired endothelial function plays a central role in the clinical manifestations of preeclampsia such as hypertension and proteinuria. sFlt-1, soluble fms like tyrosine kinase; sEng, soluble endoglin; VEGF, vascular endothelial growth factor; PlGF, placental growth factor.

dysfunction characteristic of this clinical syndrome.

3.4. Melatonin and preeclampsia

Several reports suggest that alterations of circadian rhythms correlated with higher susceptibility to pregnancy disease and preeclampsia [2,75,168]. The disruption of the coordinated processes of circadian rhythms may compromise the placental function [168]. Melatonin (5-methoxy-*N*-acetyltryptamine) is a potent antioxidant acting as a direct scavenger of free radicals, especially the highly harmful ·OH, and indirectly through the upregulation of antioxidant enzymes [169] such as heme-oxygenase-1 (HO-1), SOD-2 and NADPH:quinone oxidoreductase-1 [169]. The placental receptors for melatonin have been reported to be diminished in preeclampsia [170]. In animal studies, melatonin reduces the damage induced by ischemia-reperfusion in the rat placenta [78] and up-regulates the placental antioxidants in pregnant undernourished rats [171]. The use of melatonin in animal models of placental ischemia reduced tissue and DNA damage from oxidative stress [78,172]. In human placental explants treated with the oxidatives stress inducers xanthine/xanthine oxidase (X/XO), melatonin reduced placental oxidative stress suggesting that it may have utility as an adjuvant therapy for established preeclampsia due to reduce the oxidative stress [173].

The plasma concentration of melatonin and its circadian production are modified in preeclampsia [174]. After delivery, the mothers kept altered the rhythm for production of melatonin [174]. The reduction in melatonin in the preeclamptic placenta may help to explain the lower level of blood melatonin measured in women with preeclampsia [175]. However, this correlation implies that placenta-derived melatonin is normally released into the blood, perhaps especially near-term pregnancies when the blood level of the indolamine is maximal [75]. Currently, depressed circulating melatonin level in pregnancy may be a biomarker for the diagnosis of preeclampsia [75,176] or melatonin may be useful as a treatment for preeclampsia [75,176]. In a recent study [177], it was reported that melatonin regulated inflammation and autophagy and reduced apoptosis in human trophoblasts exposed *in vitro* to hypoxia/reoxygenation conditions, a model that mimics the molecular modifications observed in preeclamptic placentas. Thus, exogenous melatonin treatment could afford protection in preeclampsia thereby enhancing placental cell survival and consequently improving pregnancy and foetal outcomes.

4. Oxidative stress and foetal programming

Epigenetics comprise post-translational modifications of amino acids on the amino-terminal tail of histones, histone variants and DNA methylation [178]. These modifications regulate gene expression and can be hereditary. However, since the genes are not mutated these modifications could be potentially reversible [179]. The epigenetic changes are controlled by different mechanism, DNA methylation, the most mechanistically understood epigenetic modification that incorporate a methyl ($-CH_3$) group on the cytosine base of CpG islands [180]. The post-translational modifications of histones related to dynamics nucleosome rearrangement [181] as well as non-coding RNAs, particularly microRNAs that bind to the target messenger RNA through

the RNA-induced silencing complex (RISC) leading to inhibition of its translation into protein [182]. These mechanisms are key regulators of cellular differentiation and organogenesis during foetal development, without DNA sequence changing [183]. According to Baker's hypothesis, foetal stressors can lead to cardiovascular diseases in adult life [184]. The epigenetic mechanisms are susceptible to being modified by stimuli such as dietary factors [185], metabolic disorders [186,187], oxidative stress [188], drugs and inflammation [189].

Oxidative stress links to changes in the DNA methylation pattern with subsequent impact on foetal programming [31,190,191]. Epidemiological and experimental data are correlated to the levels of oxidative stress in preeclampsia [192,193], preterm birth [194,195], GDM [196], obesity [187], low birth weight and IUGR [136,197,198]. Foetuses with these complications of pregnancy could have long-term consequences in their health later in life [199]. ROS can directly modulate the methylome from DNA and histones to histone modifiers, affecting global epigenetic landscape [188]. It is reported that peroxynitrites modify chromosomal histone proteins [200,201]. Furthermore, oxidative stress could alter the chromatin structure leading to nucleosome relaxation resulting in epigenetic alterations [202]. It has been hypothesized that ROS mediate activation of the ten-eleven translocation (TET) protein leads to global DNA hydroxymethylation [203]. This oxidation structure could achieve active DNA demethylation processes, leading DNA hypomethylation [204]. Additionally, assays in the colon carcinoma cell line RKO cells showed that a lipid peroxidation product, 4-oxo-2-nonenal (4-ONE) could bind to lysine-rich histone residues in the methylation sites forming ketoamide adducts which may alter the epigenetic pattern and the disruption of normal gene expression [205]. However, more studies are still needed to evaluate the role of this type of modifications in the epigenetic alterations associated with pregnancy pathologies. The link between oxidative stress and gene regulation via epigenetic modulation during pregnancy may represent a strong candidate contributing to the increased metabolic and cardiovascular risk in the offspring later in life [206–210].

5. Antioxidant-based therapy for women with preeclampsia

5.1. Antioxidant defence in preeclampsia

The definitive treatment for preeclampsia is delivery of the baby to prevent development of maternal or foetal complications. Nevertheless, therapies to attenuate symptoms and maintain pregnancy are necessary in order to prolong gestation. Prolonging the pregnancy has benefits for foetal growth and maturation. One of the focus of the therapies applied in women with preeclampsia is to increase their antioxidant status. Furthermore, epidemiologic studies link dietary deficiencies of antioxidant vitamins to an increased risk of preeclampsia, and antioxidant vitamins were proposed as possible prophylaxis against preeclampsia [170]. Supplementation with vitamins C and E are alternative treatments to prevent oxidative stress and endothelial dysfunction in preeclampsia. Vitamins C and E are well-known antioxidants. Vitamin C scavenges free radicals in the aqueous phase, whereas vitamin E acts to prevent lipid peroxidation. Small-randomized trials suggested that supplementation with these vitamins might be beneficial in the prevention of preeclampsia in women at increased risk of the disease *[211]*. Nevertheless, large randomized, placebo-controlled trials found that supplementation with these vitamins does not prevent the risk of preeclampsia [9]. This is in agreement with a recent meta-analysis of randomized controlled trials of Tenório *et al.*, who have shown that antioxidant therapy with vitamins C and E, selenium, L-arginine, allicin, lycopene and coenzyme Q10 had no effects in the prevention of preeclampsia [212].

Other compounds have been also evaluated in order to decrease oxidative stress in preeclampsia. In this regard, the effect of *N*-acetyl-cysteine on oxidative stress in preeclamptic pregnant women has been evaluated. *N*-acetyl-cysteine is a by-product of glutathione and it has a role on glutathione maintenance and metabolism. The results indicated that supplementation with *N*-acetyl-cysteine improved liver and kidney function, decreased blood pressure, decreased proteinuria and ameliorated the severity of oxidative stress in preeclampsia [213]. Other studies show that the intake of carotenoids provides positive health effects in adults, due to their antioxidant and anti-inflammatory properties [214]. In this regard, Cueto *et al.* showed that perfusion with beta-carotene of isolated human placental cotyledons, previously exposed to hydroperoxides, inhibited peroxide-induced vasoconstriction as well as the secretion of lipid peroxides and thromboxane [215]. Other line of studies show that parenteral magnesium sulfate ($MgSO_4$) is used to treat severe preeclampsia in order to prevent the seizures of eclampsia and for tocolysis in preterm labour [216]. The treatment with $MgSO_4$ is known to decrease the level of lipid peroxidation [217] of red cell ghosts from women with preeclampsia [218] as well as protecting endothelial cells [219]. Furthermore, in placental explants, $MgSO_4$ prevents the increase of lipid peroxidation levels induced by hypoxia [220]. In fact, Abad *et al.* showed the $MgSO_4$ acts as antioxidant in women with preeclampsia [221]. This salt acts as antioxidant since it reduces lipid peroxidation as described in human STB plasma membranes [222]. It is proposed that $MgSO_4$ reduces the bioavailability of free radicals by forming complexes with hydroxyl radicals (·OH) and lipid peroxides in the cell membrane hydrophobic microenvironment [223].

The oxidative stress generated by the mitochondria is also considered a potential therapeutic target. In preeclampsia, there is mitochondrial dysfunction due to increased mitochondrial lipid peroxidation and enhanced susceptibility to oxidation [224]. Mitochondrial ROS is markedly elevated in HUVECs treated with plasma from preeclamptic women compared to plasma from uncomplicated pregnancy. Pre-treatment of HUVECs with MitoTempo (a mitochondria-targeted SOD antioxidant mimetic) provided protection against ROS-induced cell death. MitoTempo significantly reduced mitochondrial ROS generation in cells exposed to plasma from women with preeclampsia. Mitochondrial-targeted antioxidant pre-treatment was more effective than general antioxidant at similar concentrations, highlighting the importance of a direct-targeted therapeutic approach [225].

5.2. Chronotherapy for preeclamptic patients

The main adaptation of the living organisms to cyclic changes in environmental variables *e.g.*, light, temperature, and food availability is the rhythmicity. In mammals, light is the major factor in the synchronization between many body functions and environment [226]. The rhythmic physiological processes that approximate a day are the most central rhythms in chronobiology [227]. These rhythms are regulated by endogenous circadian clocks which are characterised by a molecular response to light [228]. In this regard, some studies implicated circadian clock genes in the regulation of processes in the heart, kidney, vasculature, and the metabolic organs, which are important for the blood pressure rhythms in humans [229].

Several studies showed that preeclampsia appears to interfere with the normal circadian decrease in blood pressure at night [230,231]. In order to increase the positive effects of medications and manage their adverse effects, it is critical to take into account the circadian rhythms regulating the blood pressure. Ayala *et al.* [232] performed a prospective, randomized, placebo-controlled, double-blind trial on women at high risk for preeclampsia evaluating the chronotherapy with low-dose acetylsalicylic acid (ASA) (100 mg/d) starting early in pregnancy (≥16 weeks of gestation). This study showed that low-dose ASA has an effect on ambulatory blood pressure depending upon the ingestion time in a 24 h rest/activity cycle, being effective in the evening and bedtime, but not upon awakening. Besides, ingestion at bedtime of low-dose ASA starting as early as 16 weeks of gestation significantly reduced the incidence of preeclampsia.

ROS-induced molecular damage as well as the activity of several antioxidant enzymes (GPx, glutathione-disulfide reductase GSR, CAT, SOD and glutathione system) is modified by circadian rhythmicity [71,233,234]. Specifically, changes in circulating lipid peroxides and the activity of antioxidant enzymes are associated with circadian rhythms in pulmonary tuberculosis, liver cirrhosis, peptic ulcers, cardiovascular and neurodegenerative diseases, diabetes and cancer [71,235–237]. Therefore, more studies about the interaction between these two systems, oxidative stress and circadian rhythms during pregnancy, are needed to get more information about the prevention and treatment of preeclampsia.

6. Conclusions

Preeclampsia associates with abnormal placentation, intermittent blood flow to intervillous space, placental ischemia-reperfusion, material shedding from syncytiotrophoblast, decrease in the total terminal villi volume/surface area, oxidative stress, a rise of pro-inflammatory cytokines, exaggerated inflammatory reaction and angiogenic imbalance. All these alterations exacerbate endothelial cell dysfunction and leads to adverse foetal outcome. Several biomarkers of oxidative stress have been used to identify pathological processes related to ischemia-reperfusion seen in preeclampsia. The latter approach is the basis of the antioxidant-based therapy for women with preeclampsia. Although supplementation with vitamins C and E does not prevent the risk of preeclampsia, other compounds have been also evaluated in order to try to decrease the deleterious effects of oxidative stress in preeclampsia. The role of circadian therapies in this syndrome is still under controversy but it should be considered as a future research line aiming to reduce its incidence. It is expected that more studies will keep coming addressing potential effects and mechanisms of antioxidant therapies in preeclampsia. This will serve to minimize the risk associated with this syndrome for child, young and adulthood.

Conflict of interest

The authors confirm there are not conflict of interest.

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Disclosures

None.

Transparency document

The Transparency document associated with this article can be found, in online version.

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