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SARS- CoV-2 infection and oxidative stress in early-onset preeclampsia

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ABSTRACT

SARS-CoV-2 causes coronavirus disease 2019 (COVID-19) also in pregnant women. Infection in pregnancy leads to maternal and placental functional alterations. Pregnant women with vascular defects such as preeclampsia show high susceptibility to SARS-CoV-2 infection by undefined mechanisms. Pregnant women infected with SARS-CoV-2 show higher rates of preterm birth and caesarean delivery, and their placentas show signs of vasculopathy and inflammation. It is still unclear whether the foetus is affected by the maternal infection with this virus and whether maternal infection associates with postnatal affections. The SARS-CoV-2 infection causes oxidative stress and activation of the immune system leading to cytokine storm and next tissue damage as seen in the lung. The angiotensin-converting-enzyme 2 expression is determinant for these alterations in the lung. Since this enzyme is expressed in the human placenta, SARS-CoV-2 could infect the placenta tissue, although reported to be of low frequency compared with maternal lung tissue. Early-onset preeclampsia (eoPE) shows higher expression of ADAM17 (a disintegrin and metalloproteinase 17) causing an imbalanced renin-angiotensin system and endothelial dysfunction. A similar mechanism seems to potentially account for SARS-CoV-2 infection. This review highlights the potentially common characteristics of pregnant women with eoPE with those with COVID-19. A better understanding of the mechanisms of SARS-CoV-2 infection and its impact on the placenta function is determinant since eoPE/COVID-19 association may result in maternal metabolic alterations that might lead to a potential worsening of the foetal programming of diseases in the neonate, young, and adult.

Abbreviations: $^{\bullet}O_2^-$, superoxide anion; $^{\bullet}OH$, hydroxyl radicals; $^1O_2$, singlet oxygen; ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; ADAM17, a disintegrin and metalloprotease 17; Ang 1–7, angiotensin 1-7; Ang II, angiotensin II; AT1, angiotensin receptor 1; CAT, catalase; COVID-19, coronavirus disease 2019; CTB, cytotrophoblast; eoPE, early-onset preeclampsia; H_2O_2, hydrogen peroxide; HIF-1α, hypoxia-inducible factor 1 alpha; HIF-2α, hypoxia-inducible factor 2 alpha; IL-10, interleukin 10; IL-6, interleukin 6; IL-8, interleukin 8; loPE, late-onset preeclampsia; NADH, nicotinamide adenine dinucleotide reduced form; NADPH, nicotinamide adenine dinucleotide phosphate; $NO^{\bullet}$, nitric oxide; NF-κB, nuclear transcription factor-kappa B; $ONOO^-$, peroxynitrite; PlGF, placental growth factor; RAS, renin-angiotensin system; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sFlt-1, soluble fms-like tyrosine kinase-1; SOD, superoxide dismutase; STB, syncytiotrophoblast; TMPRSS2, transmembrane serine protease type 2; TNF, tumour necrosis factor; TNF-α, tumour necrosis factor-alpha; VEGF, vascular endothelial growth factor.

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1. Introduction

The coronavirus disease 2019 (COVID-19) results from the infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This coronavirus belongs to the Family *Coronaviridae*, genus *Betacoronavirus*, subgenus *Sarbecovirus*. It shares this subgenus with its predecessor, the atypical pneumonia-causing virus, SARS-CoV, which appeared in late 2002 and was eradicated in August 2003. The name of this group of viruses is due to their crown-like appearance under the electron microscope [1,2].

SARS-CoV-2 is a lipid-enveloped virus. It has a long positive-sense, single-stranded RNA (almost 30,000 kb) encoding four structural proteins, *viz*, spike protein (S), membrane protein (M), an envelope protein (E) and nucleocapsid (N), sixteen non-structural proteins (nsp), and eight accessory proteins. The accessory proteins are involved in virus replication and defence against the immune system (but are not included in the virion), including an RNA-dependent RNA polymerase and two viral proteases [3–5].

The viral cycle begins with the interaction between S and the cellular receptor angiotensin-converting enzyme 2 (ACE2). After this interaction, the virus enters the cell cytoplasm by at least two mechanisms, *i.e.* early and late endocytosis. In the early stages, priming processing by cellular proteases results in the exposure of the viral fusion motif of the S protein. The transmembrane serine protease type 2 (TMPRSS2) is a key enzyme in this activation process for the virus to gain access to the cell *via* the early endosome pathway. This pathway appears to predominate in lung cells. After membrane fusion, viral RNA is released into the cytoplasm and protein synthesis and replication of the viral genome occurs through a process that is characteristic of this group of viruses favouring recombination [3–5].

Although RNA viruses show a high mutation rate, in the case of coronaviruses their RNA polymerase has proofreading activity. This activity allows that these viruses can have such a long continuous genome. Without the proofreading activity, the excessive number of produced mutations would affect viral viability. In addition, recombination is common in coronaviruses, which favours virus jumping from one animal species to another, including humans. Another mechanism generating diversity in SARS-CoV-2 is due to the action of host enzymes where deaminases play a crucial role [3–5].

The Coronavirus Resource Center from Johns Hopkins University & Medicine shows that by November 2021 there are almost 260 million people worldwide infected with SARS-CoV-2 [6]. However, the impact of this infection during pregnancy is still under debate. Although the clinical course distribution of the illness among pregnant women is typically mild (86%), severe (9%), or critical (5%), which is similar to that seen in the nonpregnant population [7,8], pregnancy itself may manifest increased complications and morbidities among women with severe and critical COVID-19 [9]. In this regard, preterm birth and caesarean deliveries are common complications for pregnant women with severe and critical cases of COVID-19 [10–15]. Besides, there is little understanding of pregnancy outcomes associated with SARS-CoV-2 infection. Preliminary studies point out to higher rates of preterm birth, preeclampsia, and caesarean delivery as a consequence of SARS-CoV-2 infection during pregnancy [16]. Abnormalities in the placenta are described in pregnant women with COVID-19 including placental vasculopathy and inflammatory infiltrates [17,18]. In addition, pregnant women with chronic inflammation or vascular defects, including obesity, hypertension or preeclampsia may be more susceptible to SARS-CoV-2 infection [19]. In the current review, we contrast the characteristics of pregnant women with early-onset preeclampsia (eoPE) with those with COVID-19, since both pathologies share common characteristics.

2. Viral infection and oxidative stress

The imbalance between the generation of reactive oxygen species (ROS) or reactive nitrogen species and the cellular antioxidant capacity leads to oxidative stress and potential cellular damage [20]. ROS include free radicals, such as superoxide ($^{\bullet}O_2^-$), hydroxyl radicals ($^{\bullet}OH$), and non-radical intermediates like hydrogen peroxide (H_2O_2) and singlet oxygen $^1O_2$. Reactive nitrogen species include nitric oxide ($NO^{\bullet}$), which is of 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 P_{450} system) and non-enzymatic reactions (involving O_2 reaction with organic compounds or the exposure to ionizing radiations) taking place in peroxisomes and endoplasmic reticulum but mostly in the mitochondria [21–23].

The mitochondrial function is intimately linked to the enzymatic generation of $^{\bullet}O_2^-$ and H_2O_2 formed mainly by complex I (NADH dehydrogenase) and complex III (ubiquinone cytochrome *c* reductase) of the electron transport chain [24]. Meanwhile, H_2O_2 is formed as a product of enzymatic reactions that could yield $^{\bullet}OH$ through a non-enzymatic way such as metal-catalysed Haber-Weiss reaction and the Fe(II)-catalysed Fenton reaction [25]. On the other hand, $^{\bullet}O_2^-$ is highly reactive and it can combine with transition metals and other chemical species such as $NO^{\bullet}$ generating the high oxidant species $ONOO^-$ [26]. Another non-enzymatic process known as the Maillard reaction, involves multiple steps, including the interaction of reducing sugars with amino groups of proteins, lipid, or nucleic acids. These glycation reactions form Schiff bases that can rearrange into Amadori products forming highly reactive carbonyl compounds progressing to the formation of advanced glycation end-products and $^{\bullet}O_2^-$ [27,28]. The uncontrolled ROS production could result in tissue damage, inflammation response, and cell death because of an indiscriminate oxidative attack on lipids, proteins, and cellular DNA [22,29].

It is known since 1979 that viral infections can induce oxidative stress through increased levels of ROS [30]. Many DNA and RNA viruses as well as retroviruses can cause ROS-mediated cell death [31–33]. The pathogenesis of viral infections is shown or are suspected of having a component of several host mechanisms such as excessive cytokine production, lipid mediator release, complement activation, and lipid peroxidation. ROS are generated when fighting pathogens through cells of the immune system (macrophages, neutrophils, and dendritic cells). These cells are activated showing a significant increase in the activities of myeloperoxidase, NADPH oxidase, and inducible NO synthase [34,35]. This phenomenon results in modulation of gene expression, cell metabolism, cell adhesion, cell cycle, and cell death pathways [36]. In addition, the primary antioxidant defence system is represented by superoxide dismutase (SOD), glutathione peroxidase, and catalase as well as non-enzymatic antioxidants such as vitamin C, vitamin E, carotenoids, glutathione, and flavonoids, are affected by viral infections [33,37,38].

Another aspect to consider in the pathogen-host interaction regards the alteration of the host's metabolism. The intracellular release of various molecular compounds of pathogens causes that some enzymes such as a few isoforms of cytochrome P_{450} (CYP3A4), which are responsible for the biotransformation of these compounds mostly through the generation of $^{\bullet}O_2^-$ [39]. Biomolecules from pathogens can also induce ROS production involving intracellular enzymes such as spermine oxidase [40] or interaction with the endoplasmic reticulum and mitochondria [41]. It should be noticed that because of oxidative stress, cellular regulatory processes can be altered since oxidation products can interact with molecular damage pattern recognition receptors changing the activation of transcription factors and gene expression. This phenomenon can lead to cell death processes or activate survival mechanisms. Thus, viral replication is promoted or facilitated by ROS depending on the type of virus and cells that are affected [33,42,43].

Within this scheme of oxidative stress, activated cells of the immune system can release pro-oxidant cytokines such as tumour necrosis factor (TNF) [44]. The oxidative environment, in addition, may favour the

activation of redox-sensitive transcription factors, including the hypoxia-inducible factor 1 alpha (HIF-1α) [44,45]. TNF stimulates the release of nuclear transcription factor-kappa B (NF-κB) from the cytoplasmic inhibitory of NF-κB, which translocate to the nucleus and binds to DNA increasing the viral replication through cellular and viral gene transcription [46]. In addition, viral infections promote local hypoxia in which phagocytic cells would activate HIF-1α, which promotes the expression of genes related to phagocytic function [47].

3. SARS-CoV-2 and oxidative stress in pregnant women

Normal pregnancy is a series of temporary complex events finely orchestrated that includes decidualization, placentation, and childbirth [48,49]. The chronological transitions are critical for a normal pregnancy and any alteration may have consequences in the mother and foetus health [49]. Pregnancy is well-known to increase oxidative stress, a phenomenon generated by a normal systemic inflammatory response, which results in higher amounts of circulating ROS. The major source of ROS during pregnancy is the placenta [50]. ROS are generated at the decidual, trophoblast and mesenchymal components of the maternal-foetal interface [51]. Physiological ROS generation is essential for signalling, regulation of redox-sensitive transcription factors and protein kinases for cell survival, proliferation, adaptive homeostasis, and apoptosis, as well as host defence mechanisms such as phagocytosis and microbicidal activities [52]. In this regard, excessive oxidative stress seen in pregnancy could lead to potential tissue damage [53,54]. However, excessive oxidative stress is counterbalanced by the increase in the synthesis of antioxidants [55]. When the oxidative stress surpasses the antioxidant defence in the placenta, the oxidative damage could propagate to distal tissues.

COVID-19 in pregnant women may complicate the outcome of pregnancy since infection by this virus associates with oxidative stress, a pro-inflammatory state, cytokine production, and cell death [56–58]. SARS-CoV-2 infection is also associated with activation of the innate immune system, which is one of the important effects of SARS-CoV-2, as it is associated with increased lung damage and a torpid clinical course. Thus, in severe cases of the disease, there is an activation of a large fraction of neutrophils, macrophages, and mast cells resulting in a higher release of pro-inflammatory cytokines [59] known as the cytokine storm. This phenomenon results in uncontrolled infection, lymphocyte depletion and increased tissue damage [60]. Pregnant women with cytokine storm produced by SARS-CoV-2 infection show similar clinical characteristics as those in non-pregnant counterparts [61]. However, since oxidative stress and cytokine storm is implicated in the pathogenesis of COVID-19, a pregnancy with this disease should be carefully monitored [62].

4. SARS-CoV-2 and the human placenta

The development and maturation of the placenta is a complex process, which requires coordinated regulation of invasion of the trophoblast, and its differentiation and proliferation in the maternal decidua [63]. It is well-known that at early gestation (8–10 weeks), trophoblast cells see low O_2 concentration since the partial O_2 pressure at the placental bed is ~18 mmHg (2.5% O_2) [64,65]. This hypoxic condition stands for a key regulator of placental function since it activates the cellular response mediated by hypoxia-inducible factors (HIF-1α and HIF-2α proteins) [64,65]. The hypoxic environment leads to down-regulation of the mitochondrial O_2 consumption [66], with the metabolic requirement of the embryo and the placenta being coped with the D-glucose consumption by endometrial glands [67]. Furthermore, HIF-1α increases the activity of the endothelial NOS isoform in the extravillous trophoblast [68,69]. The latter results in increasing $NO^{\bullet}$ generation, which delays or inhibits trophoblast apoptosis leading to extravillous trophoblast proliferation, migration, and invasion processes [70,71].

As the embryo grows the metabolic requirement increases, thus, needing a more efficient system that leads to the development of the uteroplacental circulation [72]. At the end of the first trimester, *i.e.* between 10 and 12 weeks, the trophoblastic plugs are progressively dissolved, thereby establishing continuous low-flow perfusion of oxygenated blood into the placenta [73,74]. As the intervillous blood flow increases there is a concomitant increase of the O_2 tension to ~60 mmHg (8.5% O_2) [75]. The process begins at the peripheral margin expanding to the central area of the placenta producing a gradual increase in the maternal blood flow and thus O_2 tension. Invasion of extravillous trophoblast 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 O_2 tension [76]. This phenomenon results in a shift from low to a higher O_2 tension in the intervillous space at the end of the first trimester [73,74]. This increase in the O_2 level promotes differentiation of the trophoblast as well as the maturation of the placenta to become an exchange organ [63].

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 an increased level of antioxidant enzymes to maintain the oxidative balance [77,78]. Simultaneously, the mitochondrial activity increases and therefore elevated levels of ROS are present especially in the syncytiotrophoblast (STB) [24]. 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 the transport of metabolic substrates to the foetus and hormone production to sustain pregnancy [79,80]. The architecture of the placenta allows fine control of what enters and leaves the foetus, presenting a defence against compounds and pathogens. The fused multinucleated STB layer does not have intercellular gap junctions and its cytoskeletal network is unusually dense, creating a protective brush border on the apical surface (maternal side) which is in direct contact with maternal blood [81,82]. The STB does not show enough concentration of antioxidant defence molecules such as manganese superoxide dismutase. Therefore, STB is more vulnerable to oxidative stress [83]. Also, STB is sensitive to ROS since their plasma membranes have abundant unsaturated fatty acids, which are a target for ROS [70].

The STB is not always able to prevent all pathogens from damaging and crossing the placental barrier, particularly during the early stages of pregnancy where intercellular fusion in the placental barrier is not fully complete or during the late stages of pregnancy when there is a decrease in syncytium formation [82,84]. On the other hand, there are maternal disorders, such as preeclampsia, in which there is increased oxidative stress, causing suppression of intercellular fusion, syncytium formation, and damage to the syncytial membranes [85]. The damage to the placental barrier represented by STB can also be caused by the action of certain pathogens that cross the placental barrier, *i.e.* vertical mother-to-foetus transmission, or cause miscarriage, stillbirth, foetal sepsis, premature delivery, foetal growth restriction, and birth defects such as microcephaly or congenital heart disease, as well as perinatal mortality [86].

The main infectious agents responsible for 2% to 3% of all congenital anomalies because of their ability to cross the STB, are the so-called TORCH group (*Toxoplasma gondii*, varicella-zoster virus, parvovirus B19, human immunodeficiency virus, enteroviruses, *Listeria monocytogenes*, *Treponema pallidum*, rubella, cytomegalovirus, *Herpes simplex* virus, and Zika virus) [87–89]. The first aspect of determining the permissiveness of the placenta to SARS-CoV-2 infection is to assess whether this organ expresses canonical receptors for the virus. Hikmet et al. [90] assessed ACE2 expression in different tissues. ACE2 expression is particularly high in intestinal tissue. Interestingly, the ACE2 receptor is expressed in the placenta at levels comparable to the lung [90].

Immunohistochemical assays with an anti-ACE2 monoclonal antibody show that this receptor is present in the placenta throughout the gestational period [91]. Individual cell expression assays have identified expression of the ACE2 receptor and the TMPRSS2 not only in the

placenta but also in the trophectoderm, with implications for the possibility of intrauterine transmission [92]. Hosier et al. [17] reported evidence of SARS-CoV-2 infection of a placenta, with a high level of viral replication. Hecht et al. [93] tested 19 placentae from women with COVID-19 and found infection in two of the placentae. Viral RNA was found in the placenta focally in the STB and CTB. None of the placentae, infected or not, had any histopathology that could be associated with maternal infection. The authors concluded that the virus could infect the placenta albeit at a low frequency.

Initial observations of the effect of COVID-19 on the placenta seem to show that this organ is not greatly affected by the disease since no pathology associated with maternal disease was seen [94,95]. It is important to consider that the average age of pregnant women is precisely that which is not associated with severe disease progression, and this could decrease the frequency of pathology observed in the placenta. In fact, in a study of 65 placentae from mothers with COVID-19, no significant differences were observed as compared to 85 placentae from uninfected mothers; however, in three out of six cases of severe to critical disease, maternal vascular hypoperfusion was observed [96].

Histopathological observation of placentae from SARS-CoV-2 infected mothers showed an increase in factors associated with hypoperfusion (microcalcifications, fibrin thrombi, syncytial knots, and villous clumping). However, there was no significant effect on other variables, such as inflammation or coagulation [97]. Flores-Pliego et al. [98] studied three proteins in placentae from infected and uninfected mothers. They found an increased presence of von Willebrand factor (involved in coagulation) in blood vessels of placentae from mothers with moderate disease and an even higher elevation in cases of severe disease. Two other proteins, VE-cadherin and claudin-5, associated with endothelial adhesion, appeared instead to decrease with disease severity. Thus, COVID-19 severity may be associated with thrombotic and microvascular damage of the placental endothelium. A systematic review of studies on the impact of SARS-CoV-2 infection on the placenta showed an increased frequency of placental abruption and placenta previa [99]. Another observation, although rare, is placentitis in pregnant women with COVID-19, which could be associated with some form of foetal compromise in this disease [100]. Another study shows that COVID-19 in pregnant women could be causing microvasculopathy in the placenta [101]. One of the most frequent manifestations of COVID-19 in the placenta would be maternal vascular hypoperfusion, which could relate to an altered pathologic maternal blood flow leading to placental hypoxia and adverse perinatal outcomes such as miscarriage, stillbirth, premature delivery, foetal growth restriction, and preeclampsia [102–107].

5. Early-onset preeclampsia (eoPE)

There is a consensus that preeclampsia is triggered either by specific trophoblast defects (*i.e.* placental origin) or by maternal metabolic defects (*i.e.* maternal origin) [108–111]. A large number of studies have characterized and identified several features of this clinical syndrome, which led to defining specific subtypes of the syndrome. Since the late 1970s and early 1980s, several articles described preeclampsia as two specific subtypes of the syndrome [112]. This classification was based upon the time of onset of clinical signs and symptoms. (*i*) Early-onset preeclampsia (eoPE) with a start of clinical signs and symptoms and delivery before 34 weeks of gestation, and (*ii*) late-onset preeclampsia (loPE), with an onset of clinical signs and symptoms and delivery after 34 weeks of gestation. Although this classification implies knowing the onset of clinical signs and symptoms, which is hard to establish in a pregnant woman, the classification utilizes the time of delivery to identify the subtypes of preeclampsia. Both eoPE and loPE are pure maternal syndromes [113] associated with different clinical features, biochemical markers, prognosis, genetic risk factors, and heritability, although they share the maternal features, signs, and symptoms of preeclampsia [114,115].

eoPE is well-known to occur in 5% to 20% of all preeclampsia cases and its clinical impact makes it relevant [109,111]. This subtype of preeclampsia is known as "placental preeclampsia" because its primary cause is the placenta [110]. In eoPE both the mother and foetus show high morbidity and mortality [116]. It is a condition characterized by poor development of the cytotrophoblastic shell early in pregnancy, leading to impaired villous growth. This inadequate transformation of the spiral arteries makes the placenta an environment with alternating periods of hypoxia/reoxygenation with higher flow velocities of maternal blood entering the intervillous space [117]. It is accepted that hypoxia/reoxygenation is linked to an imbalance in angiogenesis, vascular endothelial damage, cardiovascular complications, and exaggerated inflammatory response. The uteroplacental hypoxia/reoxygenation during preeclampsia triggers oxidative stress, increases placental apoptosis, necrosis, and shedding of placenta-produced debris resulting in complications in the mother and foetal health [118–122]. It results in severe growth restriction of the foetus seen in pregnant women with this subtype of preeclampsia [115]. Maternal malperfusion of the placenta could result in infarcts of villous tissues at various stages of pregnancy, together with villous-free placenta lakes, fibrin deposition, and inflammation. These lesions are not specific to preeclampsia; however, they are four to seven times more common in preeclampsia than in normotensive gestational controls [123]. These placenta alterations are more severe in eoPE than loPE [124,125].

Also, there are high levels of placental senescence, maternal serum pro-inflammatory cytokines, cell-free foetal DNA, leptin, placental apoptotic debris, antiangiogenic soluble fms-like tyrosine kinase-1 (sFlt-1), and lower levels of proangiogenic vascular endothelial growth factor (VEGF), and placental growth factor (PlGF) during eoPE [110]. sFlt-1 is a splice variant of the VEGF receptor Flt-1 and it is well-known to act as an antagonist of VEGF and PlGF. In this regard, it is reported that serum concentration of sFlt-1 is elevated and relates to a reduced VEGF and PIGF level in preeclamptic women [126,127]. In addition, the antagonism of sFlt-1 with both VEGF and PlGF seems to be essential since the VEGF antagonist sFlk-1 does not lead to a preeclampsia phenotype in pregnant rats [126]. sFlt-1 can bind to VEGF, reducing its bioavailability in the maternal endothelial cells. This phenomenon leads to a diminution of their endogenous production of $NO^{\bullet}$ causing vasoconstriction. Moreover, sFlt-1 can bind PlGF in the second half of pregnancy of preeclamptic women with eoPE [128]. PlGF is proangiogenic as it enhances the activity of VEGF by competitively binding to the VEGFR-1 receptor, allowing VEGF to bind then to VEGFR-2 which has stronger tyrosine kinase activity [128]. There is a diminution of PIGF during preeclampsia, likely due to a combination between the diminution of expression of this factor and increased binding with sFlt-1, which is elevated in eoPE [110,128]. The excess of sFlt1 production could have a placental origin since placental sFlt1 mRNA is upregulated in preeclampsia and its levels fall within 48 h after delivery [126]. Thus, the sFlt-1/PlGF ratio is higher in preeclamptic women with eoPE as compared with women with a normal pregnancy [129,130].

6. COVID-19 and eoPE

Pregnant women with COVID-19 share abnormalities, such as elevated liver enzyme levels and thrombocytopenia, with those that occur in preeclampsia with severe features and HELLP syndrome [16]. Also, these pathologies can share several symptoms such as headache, acute cerebrovascular disease, acute kidney injury, and seizures [131]. Mendoza et al. [132] have suggested that pregnant women with severe COVID-19 can develop a preeclampsia-like syndrome. While there were no symptoms and signs of preeclampsia among the pregnant women who had mild COVID-19 infection, pregnant women with severe COVID-19 had symptoms and signs such as new-onset hypertension and proteinuria and/or thrombocytopenia and/or, elevated liver enzymes, which associates with placental maladaptation. The clinical improvement of the infection led to an alleviation of symptoms and signs of

preeclampsia, which was taken as a further indication of the preeclampsia-like syndrome since there was no delivery of the placenta [132]. In this regard, COVID-19 may mimic the inflammatory pattern seen in preeclampsia since both pathologies are associated with systemic inflammation [133,134].

There is no doubt that this proposal by Mendoza et al. [132] has to be analysed with care. In this particular, several authors have discussed this proposal by Mendoza et al. [135–137]. Evidently, as above-mentioned severe SARS-CoV-2 infection of pregnant women may mimic the inflammatory pattern seen in pre-eclamptic pregnant women [133,134]. However, the number of cases in the study of Mendoza et al. [132] is very low, which does not allow a robust conclusion to be drawn from an epidemiological point of view. Nevertheless, this study is very important as it allows us to analyse the possible consequences of the COVID-19/eoPE combination.

The reduced PlGF levels during preeclampsia are due to a combination of decreased expression of PlGF and/or increased binding with sFlt-1, which is an indication of placental malperfusion [110,128]. Interestingly, it has been shown that COVID-19 is associated with an increased sFlt-1/PlGF ratio possibly due to direct infection through ACE2, which is associated with global endothelial damage [138]. Consequently, one might expect that pregnant women with severe COVID-19 might develop a pre-eclampsia-like syndrome, as suggested by Mendoza et al. [132], with an associated placental malperfusion with the viral infection. However, Mendoza et al. [132] have indicated that the preeclampsia-like syndrome shown in pregnant women with severe COVID-19 does not seem to be associated with placental malperfusion since those women had normal values of both sFlt-1/PlGF ratio and uterine artery pulsatility ratio.

Leavitt et al. [136] have indicated that endothelial damage is a common feature of the pathophysiology of preeclampsia with severe features and severe infection with COVID-19, which could lead to multi-organ dysfunction. Furthermore, Leavitt et al. [136] have summarized three possible links between severe COVID-19 infection and pre-eclampsia: 1) Neutrophil extracellular traps (NETs), which are DNA and histones released by neutrophils when destroying bacteria, play an important role in both the endothelial damage seen in COVID-19 and preeclampsia [139]. In this regard, it should be noted that endothelial damage is not unique to loPE, but is also present in eoPE [140]. 2) Anti-phospholipid antibodies (aPLA) have been shown to be elevated in a significant number of patients with COVID-19 [141]. In addition, aPLA represent an elevated risk factor for pregnant women with preeclampsia [139]. 3) Alpha-1-antitrypsin is an inhibitor of SARS-CoV-2 infection and of two of the most important proteases in the pathophysiology of COVID-19: transmembrane serine protease 2 (TMPRSS2) and disintegrin and metalloprotease 17 (ADAM17) [142]. In addition, this compound prevents apoptosis, reduces oxidative stress and inflammation in endothelial cells, and has therefore been used as a protective agent in pre-eclampsia [143].

6.1. Renin-angiotensin system, COVID-19 and eoPE

Another element that should be considered when comparing the effect of both SARS-CoV-2 on pregnant women and preeclampsia is the behaviour of RAS in these pathologies. RAS primarily regulates blood pressure, fluid, and sodium homeostasis. It is a rather complex system, with endocrine, paracrine, and intracrine features [144], with systemic and local (tissue) activities that communicate with each other, involving different signalling pathways, leading to different outcomes depending on the pathway chosen [144,145]. RAS functions by setting up a balance between angiotensin-converting enzyme (ACE) and ACE2. If the balance shifts towards ACE, angiotensin II (Ang II) production is elevated along with activation of its receptors (AT1) and vasoconstriction, cell proliferation, inflammation, fibrosis, and thrombosis. If, on the other hand, the balance shifts towards ACE2, there is an increase in angiotensin 1-7 (Ang 1-7) production, with activation of Mas receptor [146] causing its vasodilatory, anti-inflammatory, anti-fibrotic and anti-thrombotic effects [144,147]. RAS is upregulated during pregnancy playing a key role since this is a state of marked vasodilation and increased plasma volume [148–150]. Pregnant women are partially unreceptive to circulating Ang II to keep low vascular resistance. In this regard, the mechanism that controls vascular refractoriness during normal pregnancy has been ascribed, in part, to progesterone and prostacyclin [151].

Both SARS–CoV-2 and preeclampsia are known to reduce ACE2 activity, leading to reduced tissue levels of Ang 1-7 [152–154]. The imbalance of the RAS system seen in COVID-19 patients may therefore contribute to hypertensive complications including preeclampsia in pregnant patients with COVID-19. Also, urinary and plasma Ang 1-7 levels are lower in preeclampsia as compared with normal pregnancy and that the balance between Ang II and Ang 1–7 is shifted towards Ang II [155,156]. This effect favours the vasoconstrictor action of RAS, regardless of the circulating levels of Ang II and aldosterone. Moreover, in preeclampsia, the normal vascular refractoriness to Ang II is reversed [157], perhaps as a consequence of reduced prostacyclin production or enhanced vasoconstriction due to endothelin or thromboxane A_2 [151,158,159]. In addition, the monomeric AT1-receptor, which is usually present in normal pregnancy, is in a heteromeric form in pre-eclampsia being highly sensitive to binding by Ang II [160].

ACE2 protein expression varies throughout human pregnancy, peaking in the first trimester and falling as the pregnancy progresses [161]. Surprisingly, ACE2 expression in the placenta at term appears to be significantly increased with COVID-19 compared to the low ACE2 expression seen in term placentae from women with normal pregnancies, a phenomenon that appears to be associated with the inflammatory process [162,163].

In SARS-CoV-2 infection, the changes that occur in the level of ACE2 expression and its regulatory mechanism after the SARS-CoV-2 S protein binds to the ACE2 receptor are not entirely clear. It may be that viral invasion down-regulates ACE2, which would inevitably lead to impaired RAS homeostasis. Conversely, if viral infection up-regulates ACE2, there would be greater availability of receptors for viral entry and thus greater viral invasion of host cells. What is clear is that SARS-CoV-2 infection and altered ACE2 expression can lead to severe adverse outcomes [164,165].

6.2. Cytokines, COVID-19 and eoPE

It is important to review the role of the cytokines since these agents play a role in both COVID-19 and preeclampsia. In this regard, the cytokine storm is present in severe cases of COVID-19 as it causes widespread inflammation and endothelial damage [59,60]. Interleukin 6 (IL-6) is produced by monocytes and macrophages [166] and is the main responsible for the cytokine storm with a hyper-innate inflammatory response in the lungs of COVID-19 patients.

A systematic review about maternal serum cytokines during pre-eclampsia revealed a significant increase of maternal TNF-α, IL-6, and IL-10 as compared to normal pregnancies [167]. Moreover, maternal serum ferritin is much higher in women with preeclampsia compared to normotensive pregnant women which reflects a hyperinflammatory state [168]. Then, a preeclampsia-like syndrome in pregnant women with severe COVID-19 as shown by Mendoza et al. [132] could be a consequence of the cytokine storm in these women. In this regard, placental viral infections may activate the immune system of both mother and foetus, where high concentrations of inflammatory cytokines, such as TNFα, IL-1, IL-6 and IL-8 are released from the ischemic placenta [169]. These inflammatory cytokines are associated with a diminution of the bioavailability of $NO^{\bullet}$ and prostaglandin I_2 as well as a rise in the production of ROS, stimulating the elevation of the potent vasoconstrictor endothelin-1 (ET-1). Furthermore, IL-6, IL-10, and TNF-α can lead to a Foetal Inflammatory Response Syndrome [170]. This raises the possibility of major complications in preeclamptic pregnant women who become infected with SARS-CoV-2.

6.3. ADAM17, COVID-19 and eoPE

Diabetes, cardiovascular diseases, obesity, among other pathologies are important risk factors for COVID-19 [171,172]. All these pathologies have in common the presence of increased expression of a disintegrin and ADAM17 [173–176]. ADAM17 is a protease that is responsible for releasing extracellular domains of transmembrane proteins and thereby generating soluble bioactive signalling proteins playing a role in autocrine and paracrine signalling. ADAM17 substrates include adhesion proteins, transmembrane mucins, membrane-bound cytokines (*v.g.* TNF-α), growth factors (*v.g.* transforming growth factor-alpha) and cytokine receptors (*v.g.* IL-6 receptor, TNF receptor) [176,177]. ADAM17 exerts a proinflammatory and profibrotic role in chronic kidney disease and other pathological processes such as inflammatory diseases, neurological diseases, cardiovascular diseases, and diabetes mellitus [174]. ADAM17 also cleaves the ACE2 ectodomain producing soluble ACE2. Thus, elevated circulating levels of soluble ACE2 are indicative of different disease states characterized by increased RAS activity associated with a worse prognosis [178,179]. Cleavage of the ACE2 ectodomain by ADAM17 causes an imbalance in tissue RAS [174] and thereby generates decreased control of the ACE2/Ang 1-7 axis with the subsequent accumulation of Ang II. The pro-inflammatory role of ADAM17 and its action on the RAS interfering with the tissue balance of ACE2/ACE generates an inflammatory state leading to the appearance of comorbidity that causes an increase in ADAM17 expression levels.

In subjects with previous comorbidities, SARS-CoV-2 infection may potentiate the existing imbalance in the RAS causing further suppression of the ACE2/ACE activity balance. This mechanism favours the increase in Ang II levels leading to worsening the clinical picture of a patient with these comorbidities. It should be noted that the protease activity of ADAM17 on ACE2 does not occur in the same way on ACE [180–182]. Furthermore, ACE can regulate ADAM17 activity mediated by activation of the AT1 receptor by Ang II [183]. Therefore, ACE not only directly regulates Ang II formation from Ang I but through its ADAM17-mediated effect on ACE2 contributing to a lower formation of Ang 1-7 from Ang II. In the case of pathologies where there is higher tissue ACE expression and consequently higher Ang II production, they will show a decrease in tissue ACE2 and an increase in soluble (systemic) ACE2 due to increased activation of ADAM17 and cleavage of ACE2.

ADAM17 expression is increased in STB from eoPE pregnancies [184]. The increased ADAM17 expression occurs at the protein level, but not at the mRNA level, suggesting that ADAM17 expression/activity is mediated by post-transcriptional regulatory mechanisms. Uteroplacental hypoxia/reoxygenation during pre-eclampsia triggers oxidative stress [118–122]. Hypoxia promotes TNFα production leading to increased ADAM17 expression. ADAM17 plays a role in the release/scavenging of TNFα by placental trophoblasts. It is suggested that oxidative stress could be a causative factor in the up-regulation of ADAM17 expression and increased activity in trophoblasts [184]. Furthermore, increased ADAM17 expression may play a role in the increased production of TNF-α by the trophoblast during eoPE.

Women with eoPE have an insufficient decrease in vascular resistance in mid to late gestation together with endothelial cell dysfunction [110]. Considering the role of endothelial cells in the development and progression of COVID-19, pregnant women with eoPE may be at particular risk if infected with SARS-CoV-2 [13]. To the best of our knowledge, there is only one report of acute placental infection with SARS-CoV-2, which occurred in a pregnant woman with eoPE [17]. Obstetric surveillance of such patients is highly recommended.

Fig. 1 shows a schematic comparison of the main findings summarized in the current review for both severe COVID-19 in pregnant women and eoPE. Both conditions share several characteristics such as placental hypoperfusion, increased oxidative stress, increased levels of several cytokines, in particular IL-6, that is associated with widespread inflammation and endothelial damage.

6.4. COVID-19 and increased risk of hypertension disorders in pregnancy

A recent study [185] has revealed the causal association between COVID-19 and hypertensive disorders in pregnancy. In this regard, this study provided the direct evidence that genetically determined COVID-19 is causally associated with an increased risk of hypertensive disorders in pregnancy. However, the authors could not establish any relationship between COVID19 linked polymorphisms and eoPE. This is a very

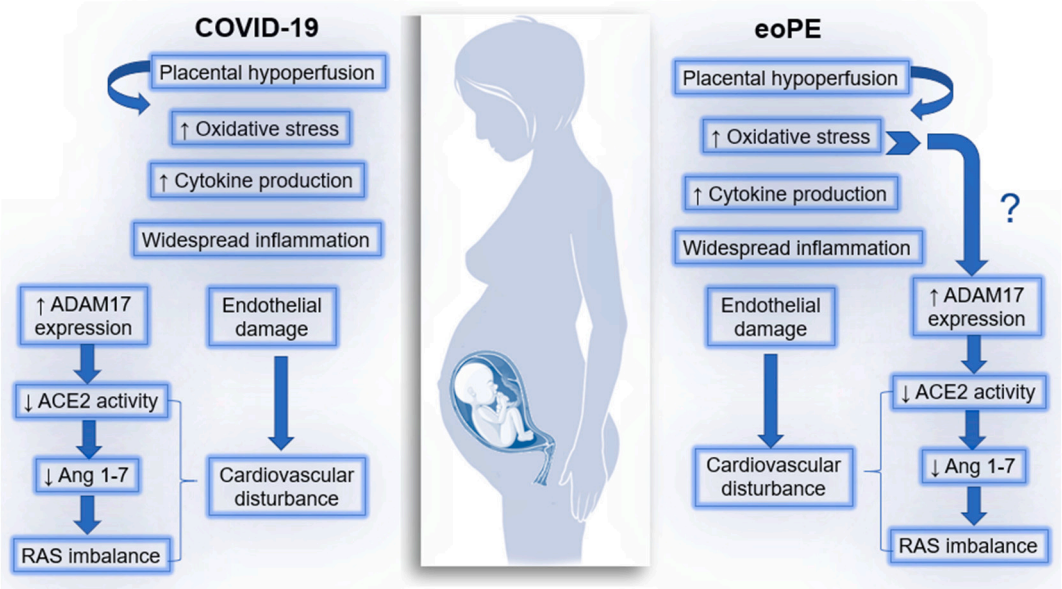

Fig. 1. Schematic comparison of several effects of COVID-19 in pregnant women and eoPE. Severe cases of COVID-19 in pregnant women and eoPE share several characteristics: placental hypoperfusion, increased oxidative stress, increased levels of several cytokines, in particular IL-6, that is associated with widespread inflammation and endothelial damage. Both pathologies have in common the presence of increased expression of ADAM17, cleaving the ACE2 ectodomain, producing soluble ACE2 and therefore generating decreased control of the ACE2/Ang 1-7 axis, with the accumulation of Ang II. Oxidative stress could be a causative factor in the up-regulation of ADAM17 expression and/or increased ADAM17 activity in the placenta from eoPE pregnancies. The RAS imbalance together with the endothelial damage can explain the cardiovascular disturbances that are present in severe cases of COVID-19 in pregnant women and eoPE.

important point especially for COVID-19 infection in early pregnancy, when it can be combined with eoPE.

The COVID-19/eoPE combination may have an impact on gestational public health. A multi-organ foetal infection and inflammation caused by SARS-CoV-2 during early pregnancy, in conjunction with specific trophoblastic defects, such as those in eoPE, should be taken into account by obstetricians in charge of the clinical management of these pregnant women. In this regard, it is essential to follow a strict antenatal control programme, which includes constant monitoring of oxygen saturation, body temperature and blood pressure. This additional monitoring opens the possibility of identifying the COVID-19/eoPE combination and possible foetal consequences as well as adverse perinatal outcomes.

7. Concluding remarks

Preeclampsia is a clinical syndrome of pregnancy that makes prone the patients to infection by SARS-CoV-2 causing COVID-19. Pregnant women with a diagnosis of COVID-19 have been increasing and comorbidities, such as preeclampsia, result in altered placental function with potentially harmful effects in the foetus development and growth, as well as a perinatal higher risk of developing metabolic alterations. Placental vasculopathy and influx of foamy macrophages lead to placental infarction in women with COVID-19. eoPE being a clinical syndrome that appears early in pregnancy becomes a condition where the foetus may get impacted for a considerable time in the uterus, leading to abnormal metabolism homeostasis. It is interesting that pregnant women with severe, but not mild COVID-19, can develop a preeclampsia-like syndrome. Severe SARS-CoV-2 infection results in increased ROS generation, inflammation and cell death associated with a cytokine storm triggered during this infection.

Canonical receptors for SARS-CoV-2 are ACE2 receptors that are expressed in the human placenta. However, it is still controversial whether the placenta acts as a reservoir of the virus and whether the STB, stromal environment and endothelial layer are physical and functional barriers for the mother-to-foetus viral transmission. Placentae from women with COVID-19 show increased microcalcifications, fibrin thrombi, syncytial knots, and villous clumping, which are factors associated with placental hypoperfusion. Severe cases of women with COVID-19 may result in placental abruption and placenta previa, perhaps, although not confirmed, altering the foetus. One key element in the placental function that secures foetus growth and development is the endothelium. Signs of placental endothelial dysfunction are reported in eoPE opening the possibility that severe SARS-CoV-2 infection may result in a lack of endothelial function homeostasis in patients with COVID-19. Clarifying the mechanisms of SARS-CoV-2 that impact the placenta is determinant since alterations of the intrauterine environment due to maternal metabolic stress results in the programming of adult diseases, including pathologies associated with placental dysfunction such as eoPE and gestational diabetes mellitus.

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