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Review

SARS-CoV-2, Endothelial Dysfunction, and the Renin-Angiotensin System (RAS): A Potentially Dangerous Triad for the Development of Pre-Eclampsia

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Abstract: SARS-CoV-2 represents the greatest epidemiological, clinical, and social challenge the human being has had to face in this century. SARS-CoV-2 is not merely a respiratory virus, as its target cells range from upper airway respiratory cells to pulmonary cells but also and above all to the cardiovascular cells, such as pericytes and endothelial cells. Indeed, the pathology related to SARS-CoV-2, COVID-19, may be defined as a thromboinflammatory syndrome in its most severe form, characterized by sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulopathy (DIC), which is prevalent in individuals already presenting a chronic level of inflammation (e.g., obese individuals, elderly) and hypertension. Pregnancy is not only an inflammatory-prone condition but is characterized by a consistent rearrangement of the blood circulation and coagulation profile. Cardiac output increases while arterial systolic and diastolic pressure decrease, regardless of the activation of the RAS system. ACE2, the SARS-CoV-2 entry receptor into the host cells, which transforms Ang II in Ang 1–7, is highly expressed in endothelial, smooth muscle cells and pericytes of placental villi, regulating blood pressure and fetal development. Pre-eclampsia is a pregnancy disorder characterized by hypertension and low levels of ACE2, endothelial dysfunction, and a high production of pro-inflammatory cytokines, resembling COVID-19 manifestations. Whereas pre-eclampsia and COVID-19 have overlapping clinical features, a role for SARS-CoV-2 as a leading cause of pre-eclampsia in COVID-19 positive pregnant women has not been clarified yet. In this mini-review, we will explore the possibility of the existence of such a link, focusing on the role of endothelial dysfunction and RAS in both pre-eclampsia and SARS-CoV-2-induced COVID-19 pathogenesis.

Keywords: pre-eclampsia; SARS-CoV2; hypertension RAS system

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1. Introduction

Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), the viral agent causing *Coronavirus disease-19* (COVID-19), is a RNA-enveloped β-coronavirus with a high degree of similarity–from 95 to 96%–at the level of the genomic sequence with the bat coronavirus RaTG13 [1]. The most striking difference is the presence of a cleavage site for the human protease furin, which is used by other respiratory viruses to better infect the target cells [2,3]. The acquisition of this cleavage site boosted SARS-CoV-2 capacity to enter in a wide variety of cells and tissues, probably after a period of cryptic spread in the human population. The first targets of SARS-CoV-2 are upper and lower airways and even the lungs. Therefore, among the principal clinical manifestations of COVID-19, interstitial pneumonia was reported, which in some cases may evolve into *Acute Respiratory Distress*

Syndrome (ARDS). However, in many COVID-19 patients, mechanical lung performance is conserved, with a good respiratory compliance, but these phenomena are counterbalanced by a severe hypoxemia, suggesting a decrease in pulmonary perfusion, because of a hyperinflammation-induced thrombosis of the pulmonary microcirculation. Indeed, hyperinflammation, which characterizes COVID-19 in its severe form, may locally activate the complement cascade, which, in turn, may directly damage the alveolar endothelium and recruit leukocytes which amplify the inflammatory response [4]. These local phenomena are believed to expand broadly to other organs in the body, like kidneys and brain. Indeed, coagulation abnormalities, such as *Sepsis Induced Coagulopathy* (SIC) or *Disseminated Intravascular Coagulopathy* (DIC), characterize 71% of COVID-19-affected individuals [5] and are typical of life-threatening disease. These events highlight the importance of SARS-CoV-2's impact on the cardiovascular system in the deterioration of COVID-19 patients' clinical conditions.

One of the major controllers of the whole body's homeostasis is *Angiotensin Converting Enzyme 2* (ACE2). In fact, it is the starter of the depressor axis of the *renin-angiotensin system* (RAS) [6] which controls blood pressure, plasmatic sodium concentration, and the extracellular volume [7]. Membrane-bound ACE2 is also the human gate that allows the SARS-CoV-2 virus to invade host cells [8]; a characteristic of SARS-CoV-2 infection is the decrease in the expression levels, malfunctioning, and irregular consumption of ACE2 [9]. ACE2 converts *Angiotensin II* (AngII) in Ang1-7 and has an organ-protective effect, such that it has been hypothesized that the decrease of ACE2 expression during a lifetime may be a predisposing risk to the development of a severe disease. Furthermore, in critically-ill patients, an imbalance between ACE2 and AngII may be directly responsible for the severity of the disease [10].

Pre-eclampsia (PE) is a hypertensive disorder of pregnancy (>140/90 mmHg), occurring after 20th week of gestation associated to proteinuria and/or other complications. Although its etiology is not completely clear, this condition seems to be linked to a hyperinflammatory response, leading to damage of the maternal endothelium [11]. As a hyperinflammatory syndrome, PE is also characterized by over-production of pro-inflammatory cytokines, such as *Tumor Necrosis Factor-α* (TNF-α), *Interleukin-6* (IL-6), and *Interferon-γ* (IFN-γ) [12] which are, intriguingly, among others, responsible for the so-called SARS-CoV-2-induced cytokine storm [13]. During normal pregnancy, there is an overexpression of the rulers of the RAS system due to hormonal changes, in particular of estrogens. In fact, liver stimulation by estrogens increase angiotensinogen plasma level during normal pregnancy [14,15]. On the contrary, in women with PE many studies report that the increase in angiotensinogen plasma level does not occur [16]. The increase in AngII levels, typical of normal pregnancies, is lacking during PE as well [17]. Furthermore, despite the fact that some papers describe no modification or even up-regulation of ACE2 expression in pre-eclamptic placental vasculature and cells [18,19], plasmatic levels of Ang1-7 have been found to be lower in pre-eclamptic versus normal pregnancies [20], underlying the importance of the correct functioning of the RAS system for the adequate development and completion of pregnancies. Indeed, proper RAS activation is indispensable to respond to the increasing demands of the developing fetus [21], and dysregulation of the RAS system has been proposed as a leading cause of PE [22]. Therefore, RAS dysregulation, endothelial damage, and hyperinflammation seem to represent common biological phenomena characterizing both COVID-19 and PE.

In this mini-review, we focus on the cardiovascular mechanisms malfunctioning in both COVID-19 and PE, possibly underpinning a role of SARS-CoV-2 in the pathogenesis of PE and pre-term-birth in COVID-19 pregnant women, based on the current—although poor—available data.

2. SARS-CoV-2 and the Cardiovascular System: ED and RAS

Cardiovascular disease (CVD) is one of the most prevalent and deadly conditions clinicians have to face when treating COVID-19 affected individuals. Therefore, thera-

pies supporting the cardiovascular system represent one of the first lines of treatment of COVID-19 patients. COVID-19 cardiovascular manifestations may include thrombosis, coagulopathies, and till myocardial infarction, all sustained—at least in part—by a shared mechanism, endothelial dysfunction (ED), which also characterizes CVD and diabetes, major COVID-19 co-morbidities. At the very beginning of the pandemic, little attention was paid to the vascular contribution to the pathogenesis of COVID-19. Nevertheless, that endothelial cells (ECs) may be involved in viral-related pathological manifestations was already known [23]. Indeed, ECs play pivotal roles in organ homeostasis and in regulating the immune system. They enhance the immune response, as they are provided with class I and II Major Histocompatibility Complex molecules [24] and, therefore, are able to present antigens and to stimulate $CD4^+$ and $CD8^+$ memory T lymphocytes [25]. Furthermore, ECs regulate vascular permeability and the access of the immune cells to the site of inflammation, amplifying this process also because they are centrally responsible for the cytokine storm [26]. Dysfunctional ECs possess pro-thrombotic properties which may account for the deep venous thromboembolism and pulmonary thromboembolism, typical of critically ill COVID-19 patients [27,28]. SARS-CoV-2-dependent alterations of ECs have been extensively reported [29] and endotheliitis has been proposed as the main cause of the generalized microcirculatory dysfunction and multi-organ failure in critically ill COVID-19 patients. Viral structures have been detected within ECs, with massive recruitment of neutrophils and monocytes to the vasculature and inflammation of the endothelium [29]. All the vascular cells, including ECs, smooth muscle cells, and accessory pericytes express ACE2, as well as the *Transmembrane Serine Protease 22* (TMPRSS2) protease [30,31], which cuts Spike, the SARS-CoV-2 protein mediating the binding of the virus to ACE2 and cell infection, at the S1/S2 and S2′ sites and is responsible for the full entry of the virus within the cells [3]. Indeed, experimental evidence has documented direct ECs infection by SARS-CoV-2, which may be prevented by a *human recombinant ACE2* (hrACE2) in capillary and kidney organoids. Nevertheless, the neutralizing activity of hrACE2 is not complete, indicating alternative routes for CoV-2 to infect target cells [32]. Intriguingly, SARS-CoV-2 Spike protein also possess the ACE2 binding site upstream, in the *receptor binding domain* (RBD), an RGD (arginine-glycine-aspartate) motif [33] which is the docking site for integrins. Integrins are heterodimeric, ubiquitously expressed, cell surface receptors, mediating cell adhesion, migration, and signaling and are particularly important for the physiology of the endothelium [34].

Although COVID-19 ED pathogenesis is still an object of investigation, it has been recently hypothesized that CoV-2-dependent coagulopathy may be promoted by an imbalance between pro-angiogenic and anti-angiogenic factors. In particular, in COVID-19 patients a high ratio of *soluble fms-like tyrosine kinase 1* (sFlt-1)/*Placental Growth Factor* (PlGF) has been detected [35]. CoV-2 represses ACE2 expression, increasing Ang II levels which, in turn, promotes the growth of sFlt-1 levels. sFlt-1 acts as a decoy for PlGF and impairs nitric oxide (NO) production, leading to ED. The decrease in NO production, a hallmark of ED, may also depend on the lack of *endothelial Nitric Oxide Synthase* (eNOS) phosphorylation on *serine 1177* (ser1177), due to the SARS-CoV-2-dependent decrease in ACE2 expression and the consequent impaired activation of the Mas receptor signaling [36] along the RAS pathway. The actors of the RAS pathway are two axes with opposite function, mediating vasoconstriction/dilation. Starting from renin-dependent production of AngI from Angiotensinogen made in the liver, AngI is processed by *Angiotensin Converting Enzyme* (ACE) in AngII. The ACE/AngII/Angiotensin 1 (AT1R) pressor axes promote sympathetic nervous system tension, increasing vasoconstriction and blood pressure and inducing inflammation, fibrosis, and myocardial hypertrophy, through the activation of various kinases (e.g., JNK, p38, MAPKs) [37]. AngII may also bind AT2R, which has different functions and distribution with respect to AT1R, but retains vasoconstriction activity [38]. The counterpart of this axis is the ACE2/Ang1-7/Mas-a *G-protein-coupled receptor* (GPCR), as well as AT1R and AT2R, which mediates vasodilation and has an organ protective effect. ACE2 may cleave AngI to Ang1-9 and, most importantly, cleaves AngII in Ang1-7,

which activate Mas. In turn, the Mas-dependent PI3-kinase/AKT pathway leads to eNOS ser1177 phosphorylation, NO production, activation of phospholipase C, and increase in intracellular calcium levels [36]. These events are responsible for the anti-inflammatory and anti-fibrotic responses of ECs and for the organ protective effects of this axis. Decreasing ACE2 levels [9], SARS-CoV-2 deregulates RAS pathways, affecting the homeostasis of whole organs. Based on these data, it may be suggested that the direct EC infection by SARS-CoV-2 and a detrimental remodeling of the endothelium, together with reduced levels of ACE2, leading to a decrease in NO production, may contribute to ED. Furthermore, an unbalanced ACE2/AngII ratio may promote vasoconstriction, fibrosis, and organ damage because of an impaired production of Ang1-7 and Mas activation.

3. Pre-Eclampsia: A COVID-19 Mimicry

PE is a complex medical disorder which affects 2–8% of the general pregnant population. After 20 weeks' gestation, pregnant individuals affected by PE present several symptoms characterized by de novo hypertension, (ISSHP), proteinuria, and signs of damage to different organ system: the liver, kidneys, the Central Nervous System (CNS) and fetal growth [39]. PE may be a serious disease if not monitored. Its rapid evolution can progress to serious complications, including death of both mother and fetus [39]. There are two types of PE definitions depending on the weeks of gestation: early-onset PE before 34 weeks of gestation and late-onset PE after 34 weeks of gestation. The difference between early and late-onset PE is associated with a different healthy status. In fact, early-onset PE present an impaired placentation in early pregnancy while late-onset PE is associated with metabolic and cardiovascular maternal risk [40,41]. For these reasons, the maternal and neonatal outcomes are different and look like two maternal hemodynamic different entities.

The impairment of placentation during early-onset PE is mostly related to fetus complications resulting in prematurity and growth restriction or in severe cases perinatal death. On the contrary, late-onset PE, derived by maternal pre-existing risks, is more associated with maternal complications. For these reasons and for the different etiologic backgrounds, early- and late-onset PE are often assessed separately in pathophysiologic studies [42]. Untreated PE can lead to serious complications, not only for the baby but even for the pregnant individual. In fact, PE is the main cause of maternal mortality worldwide [43]. Although the first paper in Medline about PE is dated 1914 [44], after more than a century of exhaustive research efforts, it is still not clear how PE may occur in pregnancies with no apparent risk factors [45]. However, one of the most accepted theories is that a poor or inadequate placentation in early pregnancy may result in PE [46]. In fact, since early 1940 placental lesions have been associated with PE [47] and the placenta remained the major focus of PE research for many years. Lately, the role of the placenta has been revised and the role of the cardiovascular system has gained more and more importance; although the placenta is necessary for the occurrence of PE, the problem resides probably in the response of the whole maternal cardiovascular system [41]. Different cardiovascular profiles may account for different forms of pre-eclampsia and other complications of pregnancy in which placental perfusion may be only a part of the problem. Early onset pre-eclampsia associated with fetal growth restriction may be associated to elevated maternal Peripheral Vascular Resistance and low cardiac output; this condition may be at the basis of placental hypoperfusion. The so-called "three stage" model tries to explain pre-eclampsia onset: in the first stage occurring early during pregnancy, an incomplete immune–maternal toleration of the fetus provides an unbalanced intrauterine environment. The second and consequential stage leads to an abnormal placental development, a disrupted spiral placental artery remodeling with different problems such as, first, decreased placental blood flow, then decreased uteroplacental perfusion with risk of ischemia reperfusion injury [48]. The third stage derives from the production of different pro-inflammatory cytokines, which characterizes the second stage [49], and antiangiogenic factors by syncytiotrophoblasts in abnormal placental conditions. The overproduction of all these pro- inflammatory factors lead to the activation of the maternal inflammatory system and endothelial dysfunctions [42].

However, while dysfunctional placenta remains a good starting point to study PE, recent clinical findings show that placental lesions are not specific to PE diagnosis [50]. Moreover, this exclusively placental vision does not appropriately account for those forms of late onset pre-eclampsia with gestational-age fetuses without evidence of placental dysfunction, usually associated to normal or low peripheral vascular resistance and elevated cardiac output. This new point of view led researchers to look for other factors which may be associated with PE. Some predisposing and risk factors for CVD, like advanced maternal age, obesity, ethnicity, diabetes, and chronic hypertension, have been always considered to be related to poor placentation.

Some recent data have also shown that chronic hypertensive patients may be associated with altered cardiovascular parameters before and at the beginning of pregnancy, long before the placentation process is completed.

The first suggested link between COVID-19 and PE is RAS dysfunction. During pregnancy, there are many functional adaptations in the hemodynamic systems. Plasma volume is increased and to keep blood pressure in normal range, body adaptation involves: decreased sensitivity to RAS [51], increased compliance of the vascular wall [52], and increased NO production by ECs [53]. Moreover, cardiac output is increased together with glomerular filtration [42]. All these phenomena lead to a complex mechanism of adaptation whose impairment leads to PE. For these reasons, pre-eclamptic pregnant woman have lower levels of components of RAS (AngII) than healthy pregnant women do. However, importantly, AngII sensitivity is increased in pre-eclamptic women compared with healthy pregnant women [51]. The importance of AngII adaptation is strictly dependent on its role. In fact, Ang II is a vasoconstrictor agent and lack of AngII adaptation during pregnancy may develop hypertension [42]. The reason why AngII is increased during PE is unknown. One hypothesis leads to the alteration of placental and/or vascular AT1R expression, or heterodimerization of AT1R with bradykinin receptors [54]. Other mechanisms, such as increased angiotensin 1–7 expression, *AT1-R autoantibodies* (AT1R-AAs), and hemopexin could also be involved [54]. That RAS dysregulation is one of the main factors leading to PE is well established [55,56]. In this regard, it has to be highlighted that all the components of renal RAS are also present at local levels at the uteroplacental unit [57,58] and very recently it has been hypothesized that renin and RAS molecules secreted by the placenta may contribute to the development of PE via the activation of intrarenal RAS (iRAS). This phenomenon could rely on exosome shedding, which not only contains RAS molecular components but also microRNAs (miRNAs) which may target mRNA encoding for RAS proteins and ATR1/AAs, agonists of AngII. Both miRNAs and ATR1/AAs lead to the suppression of circulating RAS and to the activation of iRAS [22]. Indeed, a role for mir155 in PE has already been suggested, although discordant results have been reported [59,60] as well as for mir663, upregulated in the pre-eclamptic condition, which targets renin [61].

Although recent studies suggest that SARS-CoV-2 infection does not have a severe course in pregnant women [62], an increased incidence of PE has been reported among pregnant women infected with SARS-CoV-2 compared with the general population. ACE2 upregulation confers protective effects in acute lung injury. Nevertheless, SARS-CoV-2 downregulates ACE2 expression [63]. In women of reproductive age and especially in the second and third trimester of pregnancy, high level of estrogens could be protective by increasing the expression of ACE2 counteracting SARS-CoV-2-dependent ACE2 downregulation. In vivo experimental studies have demonstrated that during pregnancy, the placenta and uterus increase ACE2 levels. ACE 2 generate the vasodilator Ang1–7 inhibiting the vasoconstrictor AngII. During the third trimester of pregnancy, there is an increase in plasma levels of Ang-1-7 [64] which are different between healthy pregnant women and pre-eclamptic pregnant women [20]. This may contribute to the systemic vasodilation and decrease in blood pressure and to other physiological adaptations that occur in normal pregnancy. ACE2 regulates blood pressure and fetal development. Previous reports record that especially maternal viral infections contribute to the development of PE inducing maternal systematic inflammatory response [65]. In fact, PE induces an exaggerated in-

flammatory response leading to endothelial damage [11]. In addition, severe COVID-19 is characterized by a systemic hyperinflammatory response. The same proinflammatory cytokines typical of the COVID-19 cytokine storm are overexpressed in mesenchymal stromal cells of pre-eclamptic placentas [12,66] Possibly, SARS-CoV-2 intrauterine infection may alter the expression of ACE2. This alteration raises AngII levels in the placenta, inducing PE [67]. Finally, thrombocytopenia (<100,000/mL), which characterizes pre-eclamptic conditions, is a parameter used to evaluate the severity of COVID-19 patients [68].

4. Integrating SARS-CoV-2 Infection and Pre-Eclampsia

The experience with SARS-CoV and MERS-CoV showed different pregnancy outcomes, ranging from mild consequences to high pressure, PE, acute renal failure for pregnant women; from no consequences, to *intrauterine growth restriction* (IUGR) and preterm birth (PTB) [69,70] to death for newborns [71]. Despite the wide body of clinical and molecular evidence (see above) that underpins an interrelationship between COVID-19 and PE a causative role for SARS-CoV-2 in the development of pre-eclamptic conditions has still to be clearly demonstrated. However, it has been reported that in SARS-CoV-2-positive pregnant women, the incidence of PE was 15.7% with respect to 9.3% of non-COVID-19 pregnancies [72]. This may depend on potential intrauterine SARS-CoV-2 infection, leading to the increased expression of ACE2 and elevated AngII levels in placental villi with subsequently vasoconstriction and restricted fetal blood flow, all phenomena typical of early-onset PE [73]. Data related to SARS-CoV-2 entry molecules ACE2 and TMPRSS2 expression in the human placenta are contradictory. Indeed, ACE2 has been reported to be widely expressed in the human placenta, in particular in syncytiotrophoblasts, cytotrophoblasts, vascular cells of villi (ECs and smooth muscle cells (SMCs)) in the decidua and even in ECs and SMCs of umbilical cord [19,74]. Furthermore, a cytokine proinflammatory profile (IL-2, IL6, IL-7, and TNF-α) is found both in SARS-CoV2-infected and pre-eclamptic pregnant women, as well as ferritin plasma and low platelet count [12,75]. In particular, a low platelet count (<100,000/mL) is an independent risk factor used to determine the severity in PE [76], but it is also a useful parameter to determine COVID-19 severity [12]. Mendoza et al. report that six out of eight COVID-19 pregnant women with severe pneumonia revealed laboratory test results and biophysical and biochemical parameters typically occurring in late-onset pre-eclamptic women [77]. Moreover, a case report related to the analysis of the placenta of a COVID-19-affected pregnant woman with hypertension, coagulopathy, and PE, who underwent pregnancy termination of pre-viable pregnancy, by dilation and evacuation, at 22 weeks of gestation, demonstrated SARS-CoV-2 infection of the placenta—especially in syncytiotrophoblasts, overlapping ACE2 expression [74]—and the umbilical cord, both by real-time PCR and electron microscopy. Fetal tissues were, however, negative for SARS-CoV-2 at the molecular testing [78], confirming those reports assessing no vertical transmission of the infection. Other studies on the morphological characteristics of placentas derived from COVID-19-affected pregnant women testify a gross malfunctioning of the local vasculature, with diffuse fetal thrombi, arteriopathy of the decidua, and villitis of unknown etiology with respect to normal pregnancies [79]. These findings, together with the demonstration of the direct placenta infection by SARS-CoV-2, may suggest an involvement of ACE2/Ang1-7/Mas axis in determining the vascular pathology of COVID-19 placentas and in the SARS-CoV-2-dependent onset of early onset PE, which, as stated above, is characterized by decreased levels of Ang1-7 [20]. An interesting analysis of the expression of ACE2 and TMPRSS2 in placental tissues derived from non-COVID-19 affected women at different time of gestation and with different pathological features demonstrated an increase in ACE2 and TMPRSS2 in placentas from the first pregnancy trimester, to decline at later stages, suggesting a major susceptibility to SARS-CoV-2 infection early during pregnancy. No changes in the expression of these two SARS-CoV-2 entry molecules—which were barely detectable—have been found at the decidual interface in PTB and pre-eclamptic pregnancies, compared to uncomplicated pregnancies [80]. However, a decrease in ACE2 mRNA was detected in the uterus of a rat

model of pregnancy-induced hypertension, when compared to control pregnant rats [81]. Studies on the human placenta performed at the single cell level gave opposite results. In fact, Li et al. observed 32 cell types within a population of 65,000 cells, 4 of which expressed ACE2 at considerable levels, including decidual stromal and perivascular cells, cytotrophoblasts in villi, and syncytiotrophoblasts in placenta. Co-expression of ACE2 and TMPRSS2 was also observed in villous cytotrophoblasts and syncytiotrophoblasts, although TMPRSS2 was found at low levels in these latter [82]. Conversely, another publication reported negligible co-expression of these two molecules both at the single cell level and at single nuclear level in placental cells [83]. However, recently, another work confirmed the expression of both ACE and TMPRSS2 in human placenta at the single cell level, but most importantly, also at the protein level, by immunohistochemical analyses of placental tissues, with different degrees of expression according to the trimester of pregnancy and the cell type evaluated [84]. This last report suggests that, although limited, a vertical transmission of SARS-CoV-2 infection is possible, as recently described [85].

A computational comparison between differentially expressed genes by SARS-CoV-2 infection and PE associated genes [86–88] reported that SARS-CoV-2 modulates the expression of several genes typical of pre-eclamptic conditions. Intriguingly, *Gene Set Enrichment Analyses* (GSEA) showed that one of the most affected pathways is related to defective vascular response. Indeed, many angiogenic/antiangiogenic and vasoactive molecules have been found to be deregulated by SARS-CoV-2 [86]. Of note, among them sFlt-1 and *endoglin* (ENG), two antiangiogenic molecules contributing to PE development, are upregulated by SARS-CoV-2. As stated above, sFlt-1 act as a decoy for PlGF, preventing its binding to membrane-bound Flt-1 [89] and impairing its angiogenic function. ENG impairs *Vascular Endothelial Growth Factor* (VEGF) and PlGF activity, cooperating with sFlt-1 [90,91]. Moreover, vasoconstrictive (Urotensin-2, Angioteninogen, Endothelin-1) and pro-thrombotic peptides (e.g., Thrombomodulin, Plasminogen Activator Inhibitor-1, *Sigma-1 ligand 4-phenyl-1-(4-phenylbutyl) piperidine* (PPBP)) are also deregulated [92], possibly suggesting at least one of the molecular mechanism–besides RAS dysfunction-for the vascular malformations detected in COVID-19 pregnant patients.

Another issue to take into account is the presence of genetic polymorphisms predisposing one either to PE or SARS-CoV-2 infection. To date, the one linked to the risk both to develop PE and COVID-19 is the *ACE I/D* (insertion/deletion) polymorphism. This polymorphism consists in the insertion or deletion of a 287 bp sequence in the intron 16 of *ACE* gene. The DD genotype results in higher ACE levels and risk to develop hypertension [93] due to an increase in AngII levels, whereas the II genotype is characterized by low ACE. Despite controversial results, some reports established a relationship between the DD ACE genotype and PE [94]. Intriguingly, the II ACE genotype is inversely correlated both to COVID-19 incidence and mortality [95], suggesting the DD genotype as a predisposing factor to develop the disease and confirming hypertension as an underlying clinical condition contributing to the pathogenesis of both COVID-19 and PE.

5. Conclusions

Both PE and COVID-19 are multifactorial diseases, whose pathogenesis relies on cardiovascular as well as immune dysfunction. Taking into account the vascular side of the story, the dysfunction of the RAS system, ED, the imbalance of angiogenic/antiangiogenic factors, the presence of *ACE* genetic polymorphisms, together with the detection of SARS-CoV-2 viral particles in placenta-derived cells and to the shared histopathological characteristics of pre-eclamptic and COVID-19 placentas, strongly supports a role of SARS-CoV-2 in promoting the development of pre-eclamptic-like conditions in pregnant women with severe COVID-19 symptoms (Figure 1). In fact, it has also to be considered that, despite the lack of an outstanding demonstration of SARS-CoV-2 entry into placental cells through ACE2 and TMPRSS2, SARS-CoV2-related systemic inflammation may contribute to the development of pre-eclamptic conditions. For these reasons, we suggest that an association between COVID-19 and development of PE may be possible, although thorough

studies are required to fully elucidate the underlying molecular pathogenic mechanisms, recommending a careful surveillance of SARS-CoV-2 infected pregnant women.

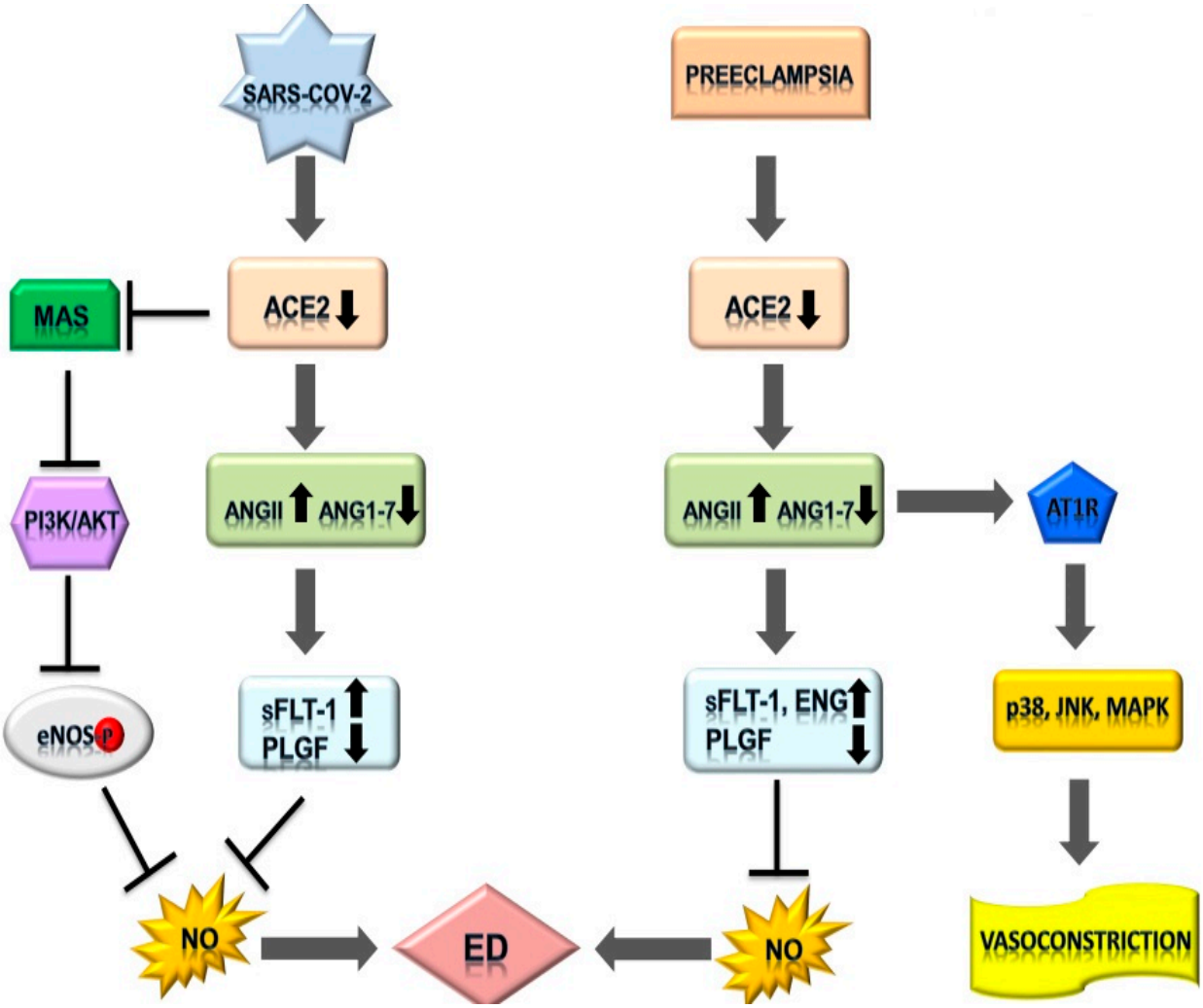

Figure 1. Comparison of activated RAS pathway leading to endothelial dysfunction (ED) during SARS-CoV-2 infection (**left**) and Preeclampsia (**right**).

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