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Review

Analogies between COVID-19 and Preeclampsia: Focus on Therapies

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Abstract: Preeclampsia is an obstetric pathology with striking similarities to COVID-19. The renin-angiotensin system plays a key role in the pathogenesis of both diseases. This report reviews the pharmacological strategies that have been suggested for the prevention and treatment of preeclampsia and that are potentially useful also in the treatment of COVID-19. Of note, both pathologies have in common an Angiotensin II-mediated endothelial dysfunction secondary to an angiogenic imbalance, with effects on vasculature, coagulation, and inflammation. These considerations are drawn from cases of the initial SARS-CoV-2 primary infection and may not apply to more recent SARS-CoV-2 variants or infections after COVID vaccination. The treatment options discussed included albumin infusion, aspirin, corticosteroids, the monoclonal antibody eculizumab, hydroxychloroquine, low molecular weight heparin, magnesium, melatonin, metformin, nitric oxide, proton pump inhibitors, statins, therapeutic apheresis, and vitamin D.

Keywords: COVID-19; SARS-CoV-2; preeclampsia; renin-angiotensin system; angiogenic factors; PlGF; sFlt1; biochemical marker; angiogenesis; therapy

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1. Introduction

Preeclampsia (preE) is a systemic syndrome of the second half of pregnancy which occurs in 2–8% of pregnancies. It is a major cause of maternal and perinatal morbidity and mortality. The disease typically presents with new-onset hypertension and proteinuria in the mother, and it can progress to multi-organ dysfunction with hepatic, renal, and cerebral manifestations, as well as systemic coagulopathy [1]. Despite being an obstetric pathology, preE shows striking similarities to COVID-19 caused by the original SARS-CoV-2 virus [2] (Figure 1). This virus has changed over time, leading to the advent of new variants that are more contagious but less dangerous. The initial pathology of COVID-19 and preE takes place respectively in the lung and the placenta, but both conditions eventually involve the endothelium in a systemic way. Both diseases are characterized by significant alterations in the renin-angiotensin system (RAS) [3], which are responsible for the thrombo-inflammatory state typical of the most severe forms of both conditions. Both COVID-19 and preE have a heterogeneous clinical course, ranging from mild to severe, and share common risk factors, such as chronic hypertension and obesity. Of note, a preE-like syndrome can be induced by severe COVID-19 [4], and an increased incidence of preE has been reported in pregnant women infected with SARS-CoV-2 infection, confirming the strong link between the two pathologies [5].

Vaccines have been the most effective weapon in the fight against the COVID-19 pandemic, and they have reduced serious manifestations of COVID-19 as well as related mortality [6]. At the beginning of the pandemic, there was no specific therapy for COVID-19;

when it became clear that COVID-19 was not just a respiratory disease, therapeutic efforts focused on three key aspects of the pathogenesis of the disease: direct viral cytotoxicity, endothelial dysfunction, and the "cytokine storm" [7]. The turning point in the reduction of mortality was the introduction of antithrombotic drugs and corticosteroids [8]. Currently, COVID-19 infection can be divided into four phases: phase 1, called the "early stage", which has a predominant viral replication; phase 2, called the "pulmonary" phase, characterized by pulmonary involvement; and phase 3, called the "hyperinflammatory phase", in which systemic inflammation prevails. Recently, a fourth phase has been described, namely "long COVID", with subacute to chronic symptoms [9]. Pharmacologic treatment is needed not only to prevent the severe forms of the disease but also to better treat patients in stages 2–3 and to prevent long COVID. A combinational therapy for COVID-19 should be based on the simultaneous use of agents with different mechanisms of action. Currently, COVID-19 therapy includes antiviral drugs, immunomodulatory medications, anticytokines, monoclonal antibodies, and miscellaneous agents. Antiviral drugs block the viral replication cycle; therefore, they are effective if administered soon after the onset of infection (by 5 days) [10]. In preE, the definitive treatment is delivery, particularly in severe forms with multiorgan alterations and placental insufficiency; however, a therapy would be desirable to prolong pregnancy in the case of early-onset forms and to prevent or reduce the rates of maternal and perinatal complications. Since the RAS plays a key role in the pathogenesis of both conditions, treatment options should focus on blocking the thrombogenic and inflammatory properties of Angiotensin II (ANG II) and ameliorating the angiogenic imbalance. RAS components have been shown to regulate angiogenesis, and our group was the first to show an angiogenic imbalance in COVID-19 non-pregnant individuals with features similar to preE [3].

The angiogenic markers of preE currently used in the clinical setting are PlGF (placental growth factor) and sFlt-1 (soluble fms-like tyrosine kinase 1). PlGF is an angiogenic protein expressed primarily in the placenta that promotes placental angiogenesis and vascular homeostasis. sFlt-1 is an anti-angiogenic protein expressed as an alternatively spliced variant of VEGFR-1 (vascular endothelial growth factor receptor-1) that lacks both the transmembrane and cytoplasmic domains. sFlt-1, also known as sVEGFR-1, antagonizes VEGF (vascular endothelial growth factor) and PlGF (pro-angiogenic factors) in the circulation by binding and preventing their interaction with the endothelial receptor and, therefore, inducing endothelial dysfunction (Figure 2).

sFlt-1 is produced by a number of tissues, including the placenta, in response to various stressors such as hypoxia and oxidative stress. In a healthy pregnancy, maternal serum levels of PlGF rise steadily until 29–32 weeks and then decrease until delivery, while sFlt-1 concentrations increase towards the end of pregnancy. Women with preE already have lower PlGF and a higher level of sFlt-1 before the clinical manifestations [11,12].

In patients with pneumonia due to COVID-19, the levels of sFlt-1 are significantly higher when compared to patients with pneumonia from other causes or with healthy controls [3]. sFlt-1 has been proposed as a biomarker to predict survival and thrombotic events in COVID-19 patients [13,14]. Of note, excessive amounts of the circulating antiangiogenic sFlt-1, which binds PlGF and VEGF, also appear to have a pathogenic role in COVID-19 [3].

Long-term outcomes among women with a history of preE and long COVID suggest that the endothelial changes are not limited to pregnancy or infection, respectively. Endothelial dysfunction is potentially reversible, and antagonizing endogenous sFlt-1 or enhancing angiotensin converting enzyme 2 (ACE 2) activity may be a therapeutic approach for these patients. The ACE 2 receptor is the entry receptor for the SARS-CoV-2 virus into human cells. Angiogenesis is currently the target for therapies in a wide range of diseases, including cancer, retinopathy, and heart disease [15]. Moreover, since immune activation and inflammation have been implicated in the pathogenesis of preE and COVID-19, suppressing inflammation and the resulting oxidative stress is another approach to halt or slow the progression of clinical symptoms [16].

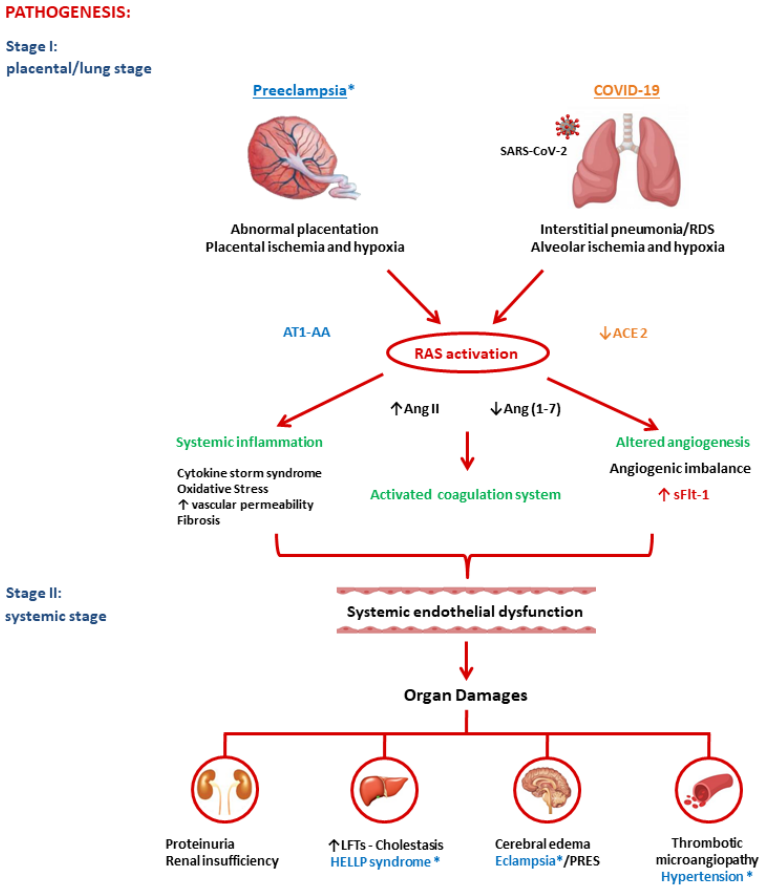

Figure 1. Schematic summary of the pathogenesis of preE and COVID-19. Legend: AT1-AA: angiotensin II type 1 receptor agonistic autoantibody; ACE2: ang-converting enzyme 2; RAS: renin-angiotensin system; Ang II: angiotensin II; Ang 1–7: angiotensin 1–7; sFlt-1: soluble FMS-like tyrosine kinase-1; LFTs: liver function tests; HELLP Syndrome: hemolysis, elevated liver enzymes, low platelets; PRES: posterior reversible encephalopathy syndrome. * refers to manifestations typically associated with preE. *Image taken from our article about similarities between the pathogenesis of preE and COVID-19* [2].

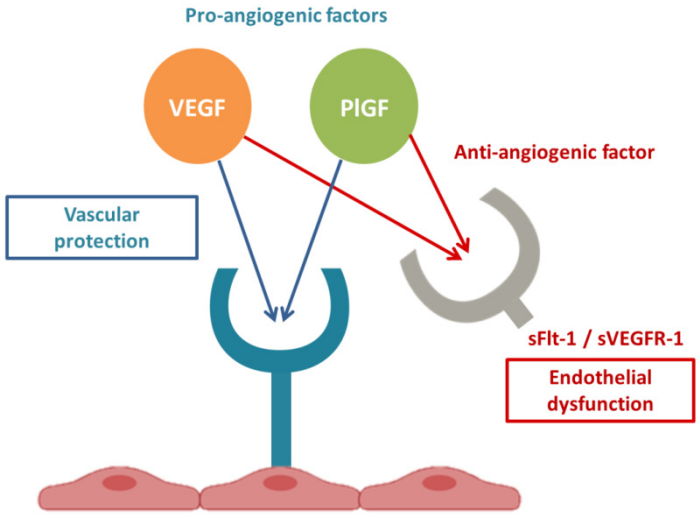

Figure 2. Angiogenic factor interactions. *Image taken from our article about similarities between the pathogenesis of preE and COVID-19* [2].

This review aims to evaluate the pharmacological strategies that have been suggested for the prevention and treatment of preE and that are potentially useful also in the treatment of COVID-19. Drug repurposing is a crucial strategy to shorten times for the development of new drugs, reduce costs, and ensure equity in care.

2. Therapeutic Strategies for Preeclampsia and COVID-19

The treatment options proposed include albumin infusion, aspirin, corticosteroids, the monoclonal antibody eculizumab, hydroxychloroquine (HCQ), low molecular weight heparin (LMWH), magnesium, melatonin, metformin, nitric oxide (NO), proton pump inhibitors (PPIs), statins, therapeutic apheresis, and vitamin D (Table 1).

Table 1. Therapeutic strategies proposed for preE and COVID-19.

Treatments	
1.	Albumin infusion
2.	Aspirin
3.	Corticosteroids
4.	Eculizumab
5.	Hydroxychloroquine
6.	Low molecular weight heparin
7.	Magnesium
8.	Melatonin
9.	Metformin
10.	Nitric Oxide
11.	Proton pump inhibitors
12.	Statins
13.	Therapetic apheresis
14.	Vitamin D

2.1. Albumin Infusion

Albumin downregulates the expression of the ACE 2 receptors and suppresses the production of proinflammatory prostaglandins, free radicals, and cytokines. Plasma albumin level is an indicator of severity for both preE and COVID-19 [17,18]. The use of albumin to correct or improve hypoalbuminemia remains controversial [19]. A recent study suggested that human albumin combined with LMWH could reduce the severity of preE and promote angiogenesis in the placenta [20]. Another study has shown that albumin administration is associated with a positive effect in critically ill patients with COVID-19 and hypoalbuminemia, reducing the risk of death [21].

2.2. Aspirin

Aspirin has anti-inflammatory effects, induces antiplatelet aggregation, has anticoagulant properties, and has a pro-angiogenic effect. Recent evidence suggests that aspirin may also modulate cytokines, stimulating the production of the proangiogenic protein placental growth factor (PlGF) and inhibiting the apoptosis of endothelial cells [22]. Aspirin is a safe, cheap, universally available, and well-tolerated medication. Low-dose aspirin is recommended for the prevention of preE in women at high risk [23]. The evidence regarding the potential benefits of aspirin in COVID-19 patients is contradictory, with some publications supporting the use of aspirin in COVID-19 patients and others arguing against it [24,25]. The use of aspirin is associated with a reduced risk of mortality among patients with COVID-19 [26]. In the ASA-CARE study, pre-hospitalization treatment with aspirin was associated with better in-hospital outcomes among hospitalized COVID-19 patients [27]. However, the RECOVERY (randomised evaluation of COVID-19 therapy) trial has shown that in patients hospitalized with COVID-19, 150 mg of aspirin once daily was not associated with reductions in 28-day mortality or the risk of progression of the disease [28]. A confounding element in the trial was that the enrolled patients were administered other drugs simultaneously, especially corticosteroids and LMWH. Investigators have

demonstrated that treatment with an antiplatelet agent has a low likelihood of providing improvement in the number of organ support-free days within 21 days, among critically ill patients with COVID-19 [29]. The role of aspirin in the primary or secondary prevention of preE has been the subject of numerous studies and controversy [30,31]. Low-dose aspirin is effective in the prevention of preE in high-risk groups, but not for treatment. A randomized study is underway to evaluate if aspirin administration over 6 months in early postpartum in women with prior severe preE improves their future cardiovascular risk [32].

2.3. Corticosteroids

Corticosteroids are potent anti-inflammatory and immunosuppressive drugs that are used in the treatment of a wide range of medical disorders, including HELLP syndrome, a severe form of preE [33].

To date, there is insufficient evidence to support the routine use of steroids for the management of HELLP, although postpartum administration of dexamethasone can improve blood pressure, platelet counts, and liver enzyme values in these women, reducing hospital stay and the rate of blood transfusions [34–36]. Guidelines issued by the U.K. chief medical officers and by the National Institutes of Health in the United States recommend the use of glucocorticoids in patients hospitalized with COVID-19, after the publication of preliminary results of the RECOVERY trial, which showed a reduction in death rates associated with the administration of dexamethasone in hospitalized patients with COVID-19 requiring supplemental oxygenation [37]. This finding was then confirmed by multiple randomized trials [38–40]. Dexamethasone produces anti-inflammatory and immunomodulatory effects on the endothelium and vasculature; it decreases sFlt-1, soluble endoglin, IL-6, and TNF-alpha after 24 h and could have a profound effect on the suppression of immune factors known to play a pathophysiological role in both preE and COVID-19.

2.4. Eculizumab

Monoclonal antibodies are a type of therapy that has been studied for the prevention and treatment of COVID-19; antibodies targeting the spike protein of SARS-CoV-2 have been shown to have clinical benefits in treating SARS-CoV-2 infection [41]. Eculizumab is a humanized monoclonal antibody that acts as a complement inhibitor and is approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, generalized myasthenia gravis, and neuromyelitis optica spectrum disorder. In retrospective studies, eculizumab safely improved respiratory dysfunction and decreased the mortality in patients with severe COVID-19 [42,43]. These findings need confirmation in large, randomised trials [44]. There is a growing number of publications on the successful use of eculizumab in the severe forms of preE, such as HELLP syndrome, with pregnancy prolongation. Additional research is needed [45,46].

2.5. Hydroxychloroquine

Hydroxychloroquine (HCQ) is an antimalarial drug that is also used for the treatment of autoimmune diseases. It appears to have anti-inflammatory, anti-oxidant, and anti-thrombotic effects. HCQ was among the first therapies used at the start of the pandemic [47], although several recently published randomized trials have shown no benefit of HCQ on the clinical course or mortality in COVID-19, as well as side effects of HCQ in elderly patients with comorbidities [48]. HCQ is considered safe in pregnancy, and epidemiological studies suggest a potential use of HCQ in preventing preE, especially in women with autoimmune diseases. To date, several studies are underway to evaluate the impact of HCQ on the prevention of obstetric complications [49]. More research is needed to understand the role of HCQ in angiogenesis, as a recent study demonstrated that HCQ reduces anti-angiogenic sFlt-1 production by cytotrophoblasts but does not reduce endothelial dysfunction in vitro [50]. This finding, if confirmed in vivo, could further justify its therapeutic failure in COVID-19.

2.6. Low Molecular Weight Heparin

LMWH is an anticoagulant agent, but it also has many anticoagulant-independent properties that may be relevant in preE and COVID-19, including effects on angiogenesis and inflammation. LMWH improves maternal endothelial function, possibly mediated through increased PlGF bioavailability, favoring a proangiogenic state, and stimulating the production of nitric oxide. Heparin may suppress complement-mediated inflammation, modulate the activity of soluble inflammatory mediators, and prevent leukocyte adhesion to activated endothelial cells, which may contribute to endothelial dysfunction [51,52]. The role of LMWH in the prevention and treatment of preE remains unclear. A recent study found that a combination therapy of LMWH with low-dose aspirin started at $\leq$16 weeks' gestation is more effective than LMWH alone in the prevention of preE in high-risk women [53]. Other reports found that in patients with mild preE, LMWH prevented the development of severe preE, resulting in less maternal, fetal, and neonatal morbidity and mortality [54,55]. COVID-19 is characterized by a prothrombotic state; therapy with LMWH in severe COVID-19 has been associated with lower mortality and a reduced incidence of thrombotic complications [56,57]. These findings seem to confirm that the use of LMWH can improve microcirculatory function, especially in patients with pre-existing endothelial dysfunction. Thromboprophylaxis is currently recommended for all hospitalized patients with COVID-19 by all national and international guidelines [58].

2.7. Magnesium

Magnesium is essential in many important biological processes. Of note, it potentiates the production of local vasodilator mediators (prostacyclin and nitric oxide) and alters vascular responses to a variety of vasoactive substances (endothelin-1, ANG II, and catecholamines) [59]. Magnesium deficiency promotes inflammation, impairs angiogenesis, and induces a pro-thrombotic state, so that hypomagnesaemia has been associated with cardiovascular and chronic endothelial disease [60]. In the obstetric field, magnesium sulfate is the gold standard for the prevention of eclampsia in women with severe preE [61]. Both observational studies and randomized controlled trials suggest that the administration of magnesium reduces the risk of seizures and other complications in women with preE. Administration of magnesium sulfate lowers plasma levels of antiangiogenic proteins, so it could improve endothelial dysfunction induced by SARS-CoV-2. In addition, other symptoms reported in long COVID-19, such as asthenia, anxiety, and depression, might be attributable to magnesium deficiency [62]. Data on the predictive ability of serum magnesium levels and the therapeutic efficacy of magnesium supplementation on long COVID-19 are lacking.

2.8. Melatonin

Melatonin is a well-known hormone with anti-inflammatory, antioxidant, and immunomodulatory properties. Recent obstetric studies have found that melatonin can affect angiogenesis, reducing the production antiangiogenic factors such as sFlt-1, and it may improve placental and maternal endothelial function [63]. Such effects may also justify its benefits in COVID-19 patients [64,65]. The circadian pattern of melatonin secretion seems to be altered in pregnancies complicated by placental insufficiency: night-time levels of melatonin are lower in women with severe preE than in those with a healthy pregnancy [66,67]. Melatonin has been proposed as a safe agent to treat or prevent preE [68]. Several observational studies and a recent meta-analysis of randomized controlled trials have concluded that melatonin may improve the clinical outcomes of patients with COVID-19 [64,69,70]. Further large-scale research is required. In light of the above, melatonin could be an effective supplemental treatment for COVID-19, including long COVID [71].

2.9. Metformin

Metformin, an oral biguanide insulin sensitizer, is an effective and approved oral hypoglycemic agent for diabetes type 2 and is a treatment option for patients with ges-

tational diabetes [72]. Researchers have found that metformin can significantly improve the dysfunction of placental endothelial cells in preE, dilate and ameliorate injured vessels, promote angiogenesis, and reduce the secretion of antiangiogenic factors from the placenta [73,74]. The PI2 trial suggested that metformin can prolong gestation in women with preterm preE [75]. Metformin has been considered among the drugs that could be repurposed against COVID-19, with potential antiviral effects through activation of the AMP-activated protein kinase pathway, effecting the ACE-2 receptor, and blocking the entry of SARS-CoV-2 into host cells [76]. Data from observational studies have shown a reduction in mortality among people using metformin as treatment for diabetes at the time of their COVID-19 diagnosis [77]. Two randomized controlled trials (the TOGETHER and COVID-OUT trials) reported that metformin did not reduce the risk of hospitalization or death in outpatients with COVID-19, but recent data after a 10-month follow-up on COVID-19 outpatients showed that metformin can reduce the risk of long-term COVID by more than 40% [78–80].

2.10. Nitric Oxide

Nitric oxide (NO) is a vasodilator released by endothelial cells to modify maternal vascular resistance, decreasing responsiveness to vasopressors and, therefore, increasing blood flow. It is also an inhibitor of platelet aggregation and adhesion and inhibits vascular smooth muscle cell proliferation and inflammatory cell activation. Impairment of its production is associated with diseases such as atherosclerosis, hypertension, cerebral and coronal vasospasm, and ischemic reperfusion injury [81]. PreE is associated with reduced NO bioavailability, and recent studies found significantly lower NO levels in patients with COVID-19 [82]. Therapies that increase NO, including the administration of NO precursors (L-arginine or L-citrulline) and the use of NO donors (such as glyceryl trinitrate), are seen as potential tools in the prevention and treatment of endothelial dysfunction [83]. A randomised controlled trial has shown that supplementation in pregnancy with L-arginine and antioxidant vitamins reduced the incidence of preE in a population at high risk for this condition [84]. Preliminary results from a randomized clinical trial seem to support a beneficial effect of L-arginine in COVID-19 [85]. The administration of sildenafil citrate, which enhanced the effects of NO, has also been tested as a promising therapy for placental insufficiency, although the fetal-neonatal safety of the drug is yet to be established [86]. A recent randomized trial of sildenafil in hospitalized patients with COVID-19 noted a reduction in hospital stay and need for mechanical ventilation with sildenafil treatment [87].

2.11. Proton-Pump Inhibitors

Proton pump inhibitors (PPIs) are medications for gastric reflux that can reduce sFlt-1 and thereby improve endothelial function [88]. Since they are safe drugs in pregnancy, PPIs may have the potential to treat or prevent preE [89]. However, large studies evaluating 40 mg of esomeprazole per day have found no evidence that PPIs may reduce the risk of preE [90,91]. PPIs may also play a positive role in the prevention and management of COVID-19 [92]. However, their effect is controversial: according to several studies, patients taking PPIs were at higher risk of serious clinical outcomes of COVID-19 [93], whereas other studies found a benefit in the use of PPIs in cases of COVID-19 [94,95].

2.12. Statins

Statins are hypolipidemic drugs, but they also have multiple beneficial anti-inflammatory and immunomodulatory properties. Of note, they affect RAS, increasing levels of ACE 2 receptor, the entry receptor for the SARS-CoV-2 virus [96]. A meta-analysis of retrospective observational studies showed that the use of statins prior to COVID-19 was associated with an approximately 35% decrease in the adjusted risk of mortality in hospitalized patients [97]. In contrast, randomized trials reported no benefit in treating COVID-19 patients with de novo introduction of statins after diagnosis of severe disease [98,99]. In obstetrics, statins may be useful in the prevention or treatment of preE [100]. Several groups have reported

that pravastatin can resolve the preE phenotype in various animal models by reducing circulating sFlt-1, reducing inflammation, and increasing nitric oxide synthase [101]. A randomized pilot clinical trial of pravastatin versus placebo in pregnant women at high risk of preE confirmed the overall safety and favorable pregnancy outcomes in the pravastatin group, but a larger clinical trial is needed [102].

2.13. Therapeutic Apheresis

Therapeutic apheresis is an extracorporeal treatment to remove various pathogenic factors from the blood, such as autoantibodies, immune complexes, and inflammatory mediators. It has been successfully used to treat many hematologic, neurologic, renal, rheumatic, and metabolic diseases, as well as severe preE [103]. Pilot studies show that therapeutic apheresis reduces the circulating serum levels of sFlt-1, prolonging pregnancy without severe adverse consequences for the mother or fetus [104]. Numerous clinical cases have described the success of this treatment in severe forms of COVID-19 [105,106].

2.14. Vitamin D

Vitamin D has an impact on inflammation, regulation of the immune response, and an effect on RAS, angiogenesis, and endothelial status. Indeed, vitamin D reduces the production of proinflammatory cytokines, enhances innate cellular immunity, inhibits RAS, and restores the angiogenic balance [107–109]. Although many observational studies have reported that low vitamin D levels were associated with an increased risk of SARS-CoV-2 infection and worse outcomes [110], and a recent meta-analysis has suggested that vitamin D insufficiency or deficiency increased the risk of preE, the data on the benefits of its supplementation in these two pathologies are still inconclusive. One reason for this is that several studies had significant biases, such as size and heterogeneity in dosages [111,112]. The effects of the vitamin D on long COVID are not known. Since vitamin D insufficiency is associated with increased cardiovascular disease, improving vitamin D status could reduce the risk for long-term sequelae from COVID-19 [113]. According to Vanherwegen et al., vitamin D may also enhance immunity associated with vaccination [114]. Vitamin D deficiency is very common; therefore, it may be prudent to correct vitamin D deficiency, as recommended by the Endocrine Society's Practice Guidelines on Vitamin D [115]. Changes in circulating angiogenic markers have been described after vitamin D supplementation [108]. More studies are needed to evaluate the angiogenic profile before and after vitamin D supplementation and the benefits of this vitamin for the prevention of preE.

3. Conclusions

We have reviewed the proposed or validated therapeutic options for the management of preE and those tested or potentially useful in the treatment of COVID-19. The two conditions share similarities in the pathogenic pathways involved, with ANG-II-mediated endothelial dysfunction secondary to an angiogenic imbalance, with effects on vasculature, coagulation, and inflammation [2,3]. A caveat is that the observations were derived from cases of the original SARS-CoV-2 primary infection; emerging SARS-CoV-2 variants as well as COVID vaccinations could alter various aspects of the virus biology, including human ACE-2 receptor binding affinity and, therefore, the RAS-mediated consequences [116,117]. Treatment options are still being defined, but understanding the factors involved in endothelial dysfunction could identify specific targeted therapies for the prevention and acute, and long-term phases of both conditions; some of the proposed drugs have been in use for decades, with proven safety profiles. Numerous pharmaceutical drugs have been repurposed for COVID-19 disease, and the same could be done for preE. Data on the angiogenic effect of many common drugs may provide the basis for their incorporation into therapeutic protocols for both COVID-19 and preE; for example, many of the treatment options mentioned above reduce circulating sFlt-1 concentrations and positively affect the course of both diseases. Peripheral blood biomarkers of endothelial cell activation/dysfunction may be clinically useful to guide treatment and monitor the therapeutic response. sFlt-1

and PlGF tests are already performed in many hospitals in obstetrics department, for the diagnosis and prognosis of placental dysfunction. sFlt-1 and PlGF can be measured in plasma and serum using automated immunoassays, with reference ranges according to gestational age. They are useful for risk stratification among women presenting with hypertensive disorders in pregnancy. The sFlt-1/PlGF ratio has a very high negative predictive value in ruling out the development of preE within 7 days among women with suspected preE, adverse maternal outcomes, or delivery within 14 days. Of note, women with a test result >85 are most likely to have, or will develop, preE and require intensive monitoring, whereas an sFlt-1/PlGF ratio <38 would rule out preE in the next 2 to 4 weeks [118]. Low PlGF discriminates between small fetuses with underlying placental pathology, also known as FGR (fetal growth restriction), and fetuses that are constitutionally small, also known as SGA (small for gestational age) [119].

There is also an urgent need to improve long COVID symptoms. The long term consequences of SARS-CoV-2 infection are little known; however, preliminary data suggest that these patients could have persistent microvascular dysfunction post-infection, mediated in part by increased sensitivity to ANG II, in a manner similar to preE. Immunomodulatory and anti-inflammatory agents, as well as therapeutic strategies directed at restoring the angiogenic imbalance, may prove beneficial.

We hope that these multidisciplinary considerations will shed light and increase knowledge for the management of both conditions, but also of all pathologies with underlying endothelial dysfunction. Evaluation of the angiogenic profile may soon become part of the routine tests for conditions associated with endothelial dysfunction, so as to detect its alterations and introduce drugs and supplements to restore an angiogenic balance.

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