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REVIEW ARTICLE

Maternal endothelial dysfunction in HIV-associated preeclampsia comorbid with COVID-19: a review

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Abstract

This review assesses markers of endothelial dysfunction (ED) associated with the maternal syndrome of preeclampsia (PE). We evaluate the role of antiretroviral therapy (ART) in human immunodeficiency virus (HIV)-infected preeclamptic women. Furthermore, we briefly discuss the potential of lopinavir/ritonavir (LPV/r), dolutegravir (DTG) and remdesivir (RDV) in drug repurposing and their safety in pregnancy complicated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In HIV infection, the trans-activator of transcription protein, which has homology with vascular endothelial growth factor, impairs angiogenesis, leading to endothelial injury and possible PE development despite neutralization of their opposing immune states. Markers of ED show strong evidence supporting the adverse role of ART in PE development and mortality compared to treatment-naïve pregnancies. Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 infection, exploits angiotensin-converting enzyme 2 (ACE 2) to induce ED and hypertension, thereby mimicking angiotensin II-mediated PE in severe cases of infection. Upregulated ACE 2 in pregnancy is a possible risk factor for SARS-CoV-2 infection and subsequent PE development. The potential effectiveness of LPV/r against COVID-19 is inconclusive; however, defective decidualization, along with elevated markers of ED, was observed. Therefore, the safety of these drugs in HIV-positive pregnancies complicated by COVID-19 requires attention. Despite the observed endothelial protective properties of DTG, there is a lack of evidence of its effects on pregnancy and COVID-19 therapeutics. Understanding RDV-ART interactions and the inclusion of pregnant women in antiviral drug repurposing trials is essential. This review provides a platform for further research on PE in the HIV-COVID-19 syndemic.

Keyword Antiretrovirals · Endothelial dysfunction · HIV · Preeclampsia · SARS-CoV-2

Introduction

Maternal mortality is a major concern worldwide, with its prevalence being particularly high in low- and middle-income countries (LMICs) [1, 2]. Sub-Saharan Africa bears the brunt of maternal deaths, namely, 66% of the global estimate [3]. The leading direct cause of maternal mortality in South Africa (SA) is preeclampsia (PE) [3].

Hypertensive disorders of pregnancy (HDP) are classified as follows: chronic hypertension (high blood pressure predating pregnancy or present at/or before 20 weeks of gestation); gestational hypertension, which is persistent de novo hypertension that develops at/or after 20 weeks of gestation without evidence of other organ involvement; PE without severe features; and PE with severe features [4]. PE is defined as new-onset hypertension presenting after 20 weeks of gestation in conjunction with one or more characteristic features, such as proteinuria and/or acute kidney injury, persistent headache, visual disturbances, epigastric pain, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), eclampsia (hypertension-associated seizures in pregnancy), and uteroplacental dysfunction, including fetal growth restriction [4]. Maternal mortality is present in all categories of HDP with eclampsia and PE, with severe features being the most common

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diagnosis before death [5]. It has been reported that PE accounts for >70,000 maternal deaths and 500,000 fetal deaths worldwide every year [4]. Globally, PE complicates 5–7% of pregnancies, and this incidence often increases to >10% in LMICs [6].

Although the exact etiology of PE remains elusive, endothelial dysfunction (ED) initiates the maternal syndrome of PE as a result of placental hypoxia, a reduction in uterine natural killer (uNK) cells, oxidative stress (OS), angiogenic imbalance and an exaggerated inflammatory response [7]. Human immunodeficiency virus (HIV) infection and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection also impact the inflammatory response and endothelial function. It is unclear whether HIV infection increases or decreases the frequency of PE. Nonetheless, the synergistic effect of these inflammatory conditions occurring concurrently requires investigation.

Pathophysiology of preeclampsia

In a normal pregnancy, the uteroplacental vasculature undergoes a significant morphological and physiological transformation to sustain fetal development [8]. Usually, cytotrophoblast (CT) cells derived from the tips of the chorionic villi migrate into the decidua and the inner myometrium in a set-time sequence [9, 10]. Thereafter, they fuse to form the multinucleated syncytiotrophoblast (ST) layer, which encloses the floating villi of the placenta and establishes the maternal-fetal interface for efficient gaseous and nutrient exchange [9, 11]. Extravillous trophoblast cells infiltrate fibrinoid-type material that replaces the musculo-elastic media of the spiral arteries, converting them into low-resistance large flaccid sinusoidal-like arteries [11, 12]. In the decidua, uNK cells regulate the depth of placentation and spiral artery remodeling [7]. The lumen of the spiral arteries is dilated five- to tenfold, ensuring an adequate supply of blood to the developing fetus [13]. These changes are typically achieved by 20 weeks of gestation [14].

Aberrant vascular remodeling predisposes the individual to PE development. PE is considered a two-stage placental disease where stage 1, often referred to as the fetoplacental or asymptomatic stage, occurs during the first and second trimesters of pregnancy [15]. In this stage, CT cells fail to take on the invasive endothelial phenotype; hence, CT migration is deficient, and there is a lack of physiological transformation of the myometrial spiral arteries [16, 17]. The resulting small arterial lumen, surrounded by vasoactive medial cells, is unable to provide adequate blood to meet the oxygen and nutrient demands of the fetus [17, 18]. This reduction in blood flow creates a hypoxic-ischemic microenvironment that marks the second stage [7, 19]. Stage 2, also referred to as the maternal stage, prompts the release of antiangiogenic factors and other mediators that initiate systemic inflammation, OS, and endothelial cell (EC) dysfunction. These mediators pre-empt the maternal syndrome of PE (presence of hypertension, proteinuria, liver dysfunction, cerebral edema, eclampsia, etc.) [4, 20]. An imbalance in circulating angiogenic factors persists during the pathogenesis of maternal syndrome [7].

Pathogenesis of the maternal syndrome in preeclampsia

Neovascularization (new blood vessel formation) results from either vasculogenesis or angiogenesis [21]. Vasculogenesis is the de novo construction of blood vessels from precursor cells, such as angioblasts, which differentiate into ECs that shape lumens to form simple blood vessels. In contrast, angiogenesis is the formation of new capillaries from the pre-existing vasculature [21, 22]. Angiogenesis is strongly associated with female reproductive conditions such as decidualization, implantation, and embryonic development [23]. Proangiogenic factors such as vascular endothelial growth factors (VEGFs) and placental growth factor (PlGF) are released into circulation, thereby increasing vascular permeability and promoting proteolysis of the extracellular matrix via proteases, leading to EC proliferation, migration and infiltration into the lumen and subsequent endothelial maturation [24, 25]. An array of VEGF isoforms, namely, VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PlGF, are present in the blood circulatory system and are responsible for various vascular processes. VEGF-A binding to VEGFR-1 does not produce significant receptor activation (in this case, the receptor acts as a decoy), whereas VEGF-B binding to VEGFR-1 promotes cell survival [26]. VEGF-A can also bind to VEGFR-2, with a lower affinity, in the presence of NRP-1, a coreceptor of VEGF, thereby promoting EC migration and proliferation (Fig. 1) [26, 27]. However, VEGFs and their receptors are significantly downregulated in preeclamptic conditions due to the overexpression of their antiangiogenic counterparts [28].

Soluble fms-like tyrosine kinase (sFlt-1), also known as sVEGFR-1, is the soluble form of endothelial-bound VEGF receptors and functions as a VEGF antagonist to maintain angiogenic homeostasis [29]. Elevated sFlt-1 prevents VEGF and PlGF binding to VEGFR-2 on ECs, thus hindering angiogenic signal transduction leading to EC injury [30]. Concentrations of sFlt-1 are markedly elevated in pregnancy and are even higher in PE [31, 32]. Studies have demonstrated that the overexpression of sFlt-1 in rats induces PE-like syndrome early in pregnancy, supporting the role of antiangiogenic factors in PE development [33].

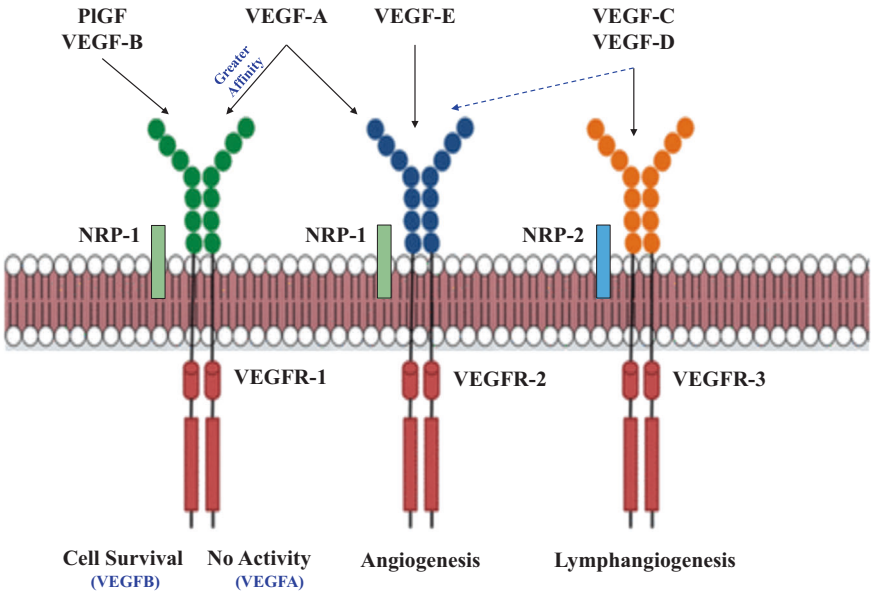

Fig. 1 Differential functions of vascular endothelial growth factor receptors. Adapted from Pandey et al. [27]. Vascular endothelial growth factor-A, B, C, D, and E (VEGF-A, B, C, D, and E), VEGF receptor-1, 2, and 3 (VEGFR-1, 2, and 3), Neuropilin-1 and 2 (NRP-1 and 2), Placental growth factor (PlGF)

Assessment of the imbalance in the sFlt-1/PlGF ratio is currently used in the diagnosis and management of PE; however, more accurate and effective modes of early detection are urgently needed [34].

Endoglin (Eng), a coreceptor for the transforming growth factor (TGF) group of factors, is involved in vascular remodeling and hemostatic events via the activation of the endothelial nitric oxide synthase (eNOS) pathway that facilitates angiogenesis. In contrast, soluble endoglin (sEng), an extracellular variant of Eng, is highly expressed by trophoblasts and opposes TGF-β interactions with its receptor, thereby preventing vasodilation [35]. Upregulation of sEng impedes potent production of the vasodilator nitric oxide (NO) in ECs via its binding with TGF-β [36]. Therefore, exaggerated levels of sEng observed in PE may be central to the characteristic hypertension encountered during the maternal syndrome of the disease [35].

OS and nitrosative stress (NS) that causes endothelial injury in PE emanates from an imbalance between pro-oxidants and their therapeutic antagonists (antioxidants) [37]. This stress includes an increase in reactive oxygen species (ROS) and reactive nitrogen species production and/or diminished availability of antioxidant mechanisms [38]. The release of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6 and IL-8 from the ischemic placenta is intensified by syncytiotrophoblast microparticle (STMB) recruitment of monocytes and neutrophils to damaged EC sites [36]. These inflammatory cytokines not only decrease the bioavailability of NO and prostaglandin I2 (PGI2) but also produce ROS, which stimulates the elevation of endothelin-1 (ET-1), a potent vasoconstrictor. Vascular smooth muscle contraction results from an imbalance of endothelial vasodilators (NO and PGI2) and vasoconstrictors [Angiotensin II (Ang II), ET-1, and thromboxane A2 (TXA2)] during EC damage [39]. Vasoconstrictors decrease calcium ion efflux from smooth muscle cells through protein kinase C and Rho-kinase activation [39]. This leads to sustained vascular resistance and the hypertensive hallmark of endothelial injury observed in PE [33], depicted in Fig. 2.

Maternal antioxidant imbalance and oxidative/nitrosative stress in preeclampsia

The EC activation encountered during PE exacerbates systemic inflammation and increases the expression of leukocyte adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), P-selectin (SELP), and E-selectin (SELE) [40, 41]. Leukocytes such as neutrophils and macrophages express nicotinamide adenine dinucleotide-phosphate (NADPH) oxidase, which generates superoxide (O_2^-) with subsequent production of other free radicals leading to a respiratory burst [42]. Usually, this process is tightly regulated; however, an increase in this phenomenon greatly overwhelms reducing agents such as glutathione, glutathione peroxidase, superoxide dismutase and catalase, resulting in OS and endothelial damage [43]. Elevated proinflammatory cytokines, such as TNF-α, observed in PE not only promote NO degradation leading to O_2^- generation but also induce free radical production during oxidative phosphorylation, further contributing to EC injury [44, 45]. Moreover, increased levels of proinflammatory cytokines such as IL-1 and TNF-α upregulate lectin-like oxidized low-density

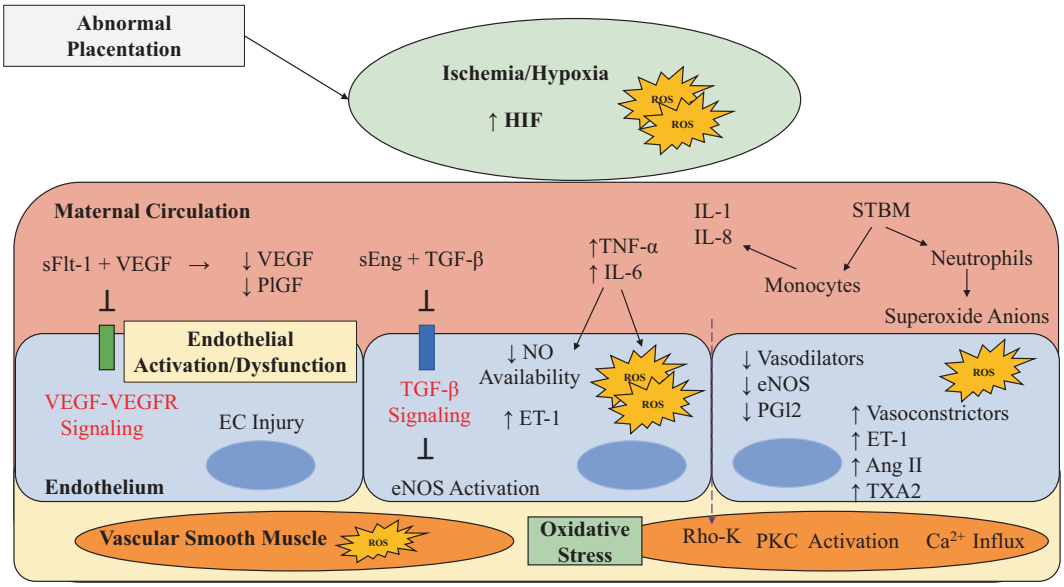

Fig. 2 Endothelial dysfunction in Preeclampsia. Adapted from Moghaddas et al. [36]. Angiotensin II (Ang II), Endothelial nitric oxide synthase (eNOS), Endothelin-1 (ET-1), Hypoxia-inducible factor (HIF), Interleukin-1, 6, and 8 (IL-1, IL-6, and IL-8), Nitric oxide (NO), Prostaglandin (PGI2), Protein kinase C (PKC), Placental growth factor (PlGF), Reactive oxygen species (ROS), Soluble endoglin (sEng), Soluble fms-like tyrosine kinase-1 (sFlt-1), Syncytiotrophoblast microparticles (STBMs), Transforming growth factor-β (TGF-β), Tumor necrosis factor-α (TNF-α), Thromboxane A2 (TXA2), Vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR)

lipoprotein receptor-1 (LOX-1), which consequently elevates the receptor for oxidized low-density lipoprotein (oxLDL), thereby facilitating O_2^- production via NO degradation [46, 47]. In maternal circulation, STBMs evoke ED via the activation of LOX-1 with an increase in O_2^- and a subsequent reduction in NO-mediated vasodilation [48]. However, contradictory studies demonstrate a significant upregulation in oxLDL with reduced concentrations of LOX-1 in PE [49]. Elevated agonist autoantibodies against angiotensin receptors (AT1-AA) due to placental ischemia enhance Ang II sensitivity via angiotensin II type I receptor (AT1) in PE [50]. Higher levels of AT1-AA have demonstrated increased placental OS [51] due to superoxide production through NADPH activation [52], which may result in vascular injury, deficient trophoblast invasion, placental hypoxia, inflammation, angiogenic imbalance, and reduced bioavailability of NO [53]. In addition, free fetal hemoglobin and circulating xanthine oxidase induce ROS production through various mechanisms [38]. These pathways can lead to eNOS uncoupling, generating O_2^- [54], which may prompt NO-O_2^- interactions and the production of the potent oxidant peroxynitrite, which inevitably predisposes cells to damage and DNA fragmentation and alteration [55]. Peroxynitrite can also hinder eNOS activity and disrupt endothelium-dependent vasodilation [56]. ROS have also been shown to downregulate the calcium-activated potassium channels KCa2.3 and KCa3.1, which are vital for electrical stimulation of vascular smooth muscle to ensure effective vasodilation [38].

Severe acute respiratory syndrome coronavirus-2 and preeclampsia

The outbreak of coronavirus disease 2019 (COVID-19) was declared a pandemic in March 2020 by the World Health Organization (WHO) [57]. At present, over 43.3 million cases of COVID-19 have been confirmed, with ~1.15 million deaths in over 218 countries and territories [58]. Genetic analysis of the novel beta-coronavirus revealed that its entry mechanism exploits the renin-angiotensin system (RAS) [59, 60]. The virus thereafter induces an array of symptoms, including vasoconstriction, elevated blood pressure and profibrotic pathway activation via coagulation [61]. An observational study conducted on COVID-19-infected pregnant women revealed that severe to critical cases of COVID-19 present with PE-like symptoms exclusive to placental maladaptation [62]. PE mimicry by COVID-19 was confirmed following the alleviation of preeclamptic symptoms without delivery of the placenta, which is currently the only known method for obtaining resolution of the clinical signs and symptoms of PE [62]. This prompted further insight into COVID-19's role in PE.

During normal RAS activation, renin catalyzes the conversion of angiotensinogen into angiotensin I (Ang I). Ang I is further cleaved by angiotensin-converting enzyme (ACE) to form Ang II [63]. The physiological antagonist of ACE and Ang II, ACE 2, serves to cleave Ang I and Ang II into angiotensin 1-9 and angiotensin 1-7 [Ang (1-7)], respectively, bringing about vasodilatory, anti-inflammatory, and

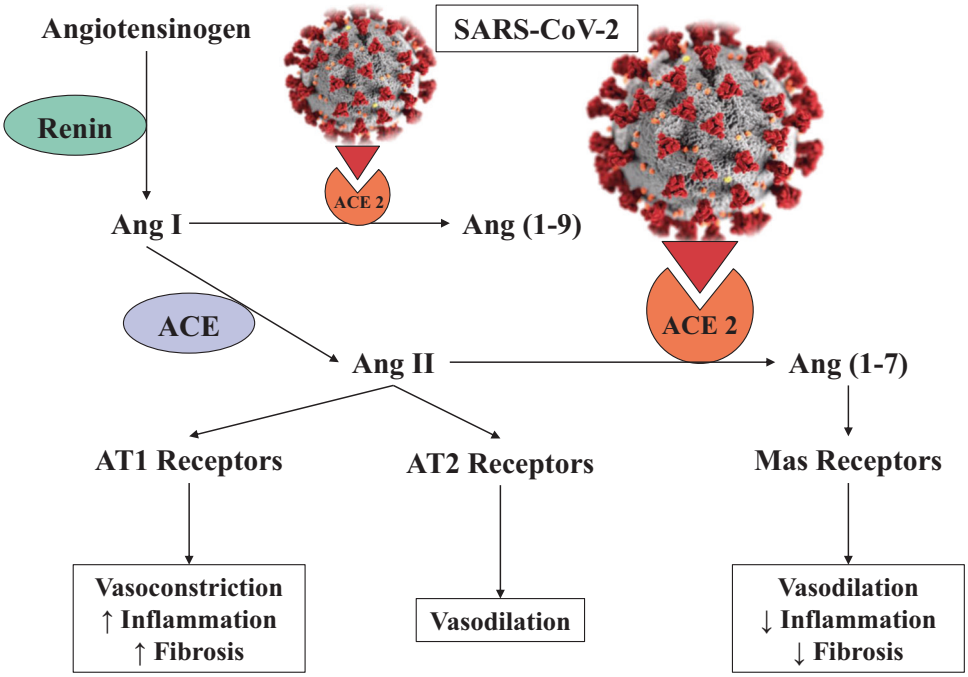

Fig. 3 Manipulation of RAS by SARS-CoV-2 in COVID-19. Angiotensin-converting enzyme (ACE), Angiotensin-converting enzyme 2 (ACE 2), Angiotensin (1-7), (1-9), I and, II [Ang (1-7), (1-9), I, and II], Angiotensin type 1 (AT1) receptors, Angiotensin type 2 (AT2) receptors, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

antifibrotic effects upon binding to its Mas receptor [61, 64]. RAS activation is, therefore, dependent on the balance between ACE and ACE 2. Pregnant women are partially unreceptive to circulating Ang II to maintain low vascular resistance. However, this adaptation is reversed in PE, leading to an angiogenic imbalance [65]. In SARS-CoV-2 infection, ACE 2 receptors are increased and exploited for effective viral infectivity, which decreases ACE 2 function, subsequently upregulating Ang II activity [66]. The decrease in ACE 2 function, along with an increase in the Ang II/Ang (1-7) ratio, may result in hypoxia-induced upregulation of sFlt-1 [67, 68], which further sensitizes ECs to Ang II [69]. Similar to PE, COVID-19 infection shows an increase in the sFlt-1/PlGF ratio due to the pathologic Ang II/Ang (1-7) imbalance [70]. Ang II acts through its receptors (AT1 and AT2) to induce vascular impairment, which is the initiator of the maternal syndrome of PE, thereby reinforcing Ang II-mediated ED [71], as depicted in Fig. 3.

The elevated expression of ACE 2 in STs, CTs, and the placental vasculature is imperative for blood pressure mediation for sufficient perfusion of the developing fetus. Therefore, SARS-CoV-2 infection and its alteration of ACE 2 expression may lead to dire adverse outcomes [72, 73]. A recent review highlighted that both normal pregnancy and COVID-19 infection show upregulation of ACE 2, IL-8, and IL-10; thus, pregnancy may be a risk factor for COVID-19 morbidity [74]. They also postulated that increased expression of ACE 2 receptors in the placenta might escalate the risk of vertical transmission of SAR-CoV-2 infection [74]. This suggestion is supported by the predominant localization of SARS-CoV-2 in STs at the maternal-fetal interface of the placenta, potentiating severe comorbidity among COVID-19-complicated pregnancies [75]. Conflicting evidence has revealed no significant differences in ACE 2 expression between normotensive pregnant women and preeclamptic women in the third trimester; however, the data are inconclusive, as PE onset occurs earlier in gestation [76]. Another study showed no significances in the prevalence rates of intrauterine growth restriction (IUGR) and PE between COVID-19-negative and COVID-19-positive pregnant women. The observed ED in this study was attributed to the 'cytokine storm' of COVID-19, similar to the proinflammatory state of PE. This is further supported by Shanes et al., who showed altered maternal vascular perfusion following placental hypoxia, conceivably due to systemic inflammation, in sixteen placentae obtained from COVID-19-infected women [77]. In contrast to PE, acute lung injury and acute respiratory distress syndrome (ARDS) have upregulated VEGF levels, which increases vascular permeability. Moreover, the same study identified VEGF-D as the most prominent indicator related to the severity of clotting in COVID-19 [78].

Soluble angiotensin-converting enzyme 2 in the therapeutic intervention of covid-19

Unlike the ACE 2 receptor, soluble angiotensin-converting enzyme 2 (sACE 2) is unable to facilitate SARS-CoV-2 entry into cells due to its lack of cell membrane interactions along with the absence of transmembrane serine protease 2

(TMPRSS2), a corequisite for SARS-CoV-2 endocytosis [79]. sACE 2 is formed through ACE 2 receptor cleavage/shedding by a disintegrin and metalloproteinase 17 (ADAM17) and is suggested to have protective effects against SARS-CoV-2 infection [80]. sACE 2 may serve as a competitive decoy for the coronavirus, thereby reducing the binding of viral particles to membrane-bound ACE 2 and consequently reducing viral infectivity [81]. Research on therapeutic interventions using sACE 2 has revealed its higher affinity for COVID-19, thereby neutralizing the virus without altering endogenous ACE 2 homeostasis [82]. However, research on the effects and safety of sACE, TMPRSS2 and ADAM17 manipulation in pregnancy and HIV-infected individuals comorbid with COVID-19 has yet to be established.

Human immunodeficiency virus infection and preeclampsia

The trans-activator of transcription (Tat) protein is a regulatory protein of HIV-1 that improves the efficiency of viral infectivity [83]. The rich arginine and lysine arrangement seen in Tat resembles the VEGF sequence [84]. Therefore, Tat mimics the role of VEGF by promoting EC adhesion and αvβ3 and α5β1 integrin expression [84, 85], which also binds osteopontin (an angiogenic factor involved in decidualization) [86]. A study conducted on HIV-1 Tat-induced angiogenesis demonstrated that Tat protein notably reduced endothelium-dependent vasorelaxation and eNOS expression and regulation in ECs of porcine coronary arteries [37]. The latter study also implicated Tat in coronary artery disease, which is associated with the long-term effect of PE [37]. In addition, Tat protein was also shown to induce the expression of ICAM-1 and VCAM-1, suggesting a possible mechanism by which HIV-1 infection contributes to endothelial injury and accelerates atherosclerosis [87, 88]. Therefore, it is plausible that Tat's homology with VEGF affects angiogenesis in PE.

In contrast to the exaggerated immune state of PE, there is significant immune suppression after HIV infection [89, 90]. Although infection has been shown to reduce the risk of developing PE, most studies show that pregnant women receiving highly active antiretroviral therapy (HAART) have an increased prevalence of PE development [90, 91]. This increase is believed to be due to immune restoration [92]. Recent studies show no difference in the risk of PE development between treated and untreated HIV-infected pregnant women [93], but others have reported findings that do not support the notion that HIV infection has protective qualities against HDP development [94].

Role of HIV therapy in maternal endothelial dysfunction

The WHO recommends that all individuals living with HIV infection receive HAART, regardless of their $CD4^+$ count and disease stage (including pregnant and breastfeeding women) [95]. HAART or antiretrovirals (ARVs) not only improve life expectancy but also decrease the risk of mother-to-baby (vertical) transmission of the infection in utero during birth and breastfeeding [95]. However, ARVs may trigger severe PE development [96]. A study conducted on nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), namely, azidothymidine, tenofovir disoproxil fumarate and lamivudine, revealed dysregulation of EC proliferation and migration [97]. The study also suggested that NRTIs induce mitochondrial OS, which hinders the activation and transduction of endothelial receptor tyrosine kinase signals and VEGFR-2 pathways in vascular ECs [97]. In addition, this adverse effect on angiogenesis may predispose the individual to PE development [98]. Excessive production of ROS is associated with increased trophoblast apoptosis, which may occur in placental-mediated disorders, such as PE and/or IUGR, overpowering antioxidant defenses with deleterious effects [98]. Protease inhibitors (PIs) deter HIV aspartyl protease, causing reconstitution of the immune microenvironment, which may predispose the individual to PE development [99]. In vivo, three PIs [atazanavir, lopinavir (LPV), and ritonavir (r)] significantly lower progesterone in trophoblast cells, thus indicating its hindrance of trophoblast proliferation and migration [100]. In a recent study, Kala et al. showed that LPV-based ART dysregulated uterine decidualization and spiral artery remodeling in both human ex vivo and mouse in vivo models [101]. Lower expression of the chemokines VEGF, PlGF, angiopoietin-2, granulocyte-macrophage colony-stimulating factor, interferon-gamma and matrix metalloproteinase (MMP) 9 was observed upon LPV exposure of primary decidual cell cultures [101]. They reported uNK cell depletion and deficient trophoblast invasion as a result of decreased expression of the transcription factor STAT3, which mediates decidualization [101]. These observations highlight the events that precede widespread ED in PE and its associated adverse neonatal outcomes. HAART impairs nuclear factor kappa B (NF-κB) transcription factors that decrease MMP and VEGF expression, which inevitably dysregulate angiogenesis, promoting ED and PE development [102]. The placentae of HIV-infected women receiving zidovudine-containing ART showed evidence of mitochondrial DNA depletion, elevated OS levels, and apoptosis, implicating secondary mitochondrial failure potentiating PE development and adverse perinatal outcomes [103].

Increased immune-expression of Flt-1 and sFlt-1 was observed within trophoblast cells during PE, regardless of HIV status, implying autocrine signaling in trophoblast invasion and differentiation [104]. This is believed to promote abnormal placentation with subsequent EC dysfunction in PE [104]. Pre-HAART exposure in HIV infection showed lower PlGF levels and increased sFlt-1 in women who developed PE compared to normotensive pregnant women [105]. Multivariate analysis demonstrated that PlGF and viral load were significantly related to PE development, and no significant shifts were observed in angiogenic factors following HAART among normotensive women [105]. Increased sFlt-1 and sEng levels were linked to PE regardless of HIV infection [106]. This study also elucidated a significant downregulation in PlGF levels in HIV-negative preeclamptic women compared to normotensive women. However, HIV infection downregulates PlGF in normotensive pregnant women compared to their HIV-negative counterparts ($p = 0.02$), thereby predisposing the individual to PE development [106]. TGF-β1 levels remain unchanged in HIV infection regardless of the increase in its coreceptor sEng [106, 107].

In contrast, a study of HIV-associated PE women revealed that HIV/HAART is linked to significant downregulation of IL-2, TNF-α and IL-6, with significant decreases in IL-2 and TNF-α observed in preeclamptic women [108]. Saums et al. found that integrase strand transfer inhibitor-containing ARTs had a greater frequency of HDP development than protease inhibitor-containing regimens [93]. Another study concluded that HIV infection, rather than its pharmacological treatment, induces alterations in markers of endothelial function [109]. The short-term duration of treatment with HAART reduces some markers of ED, including VCAM-1, with no differences between PIs and nonnucleoside reverse transcriptase inhibitors. However, SELP remained elevated upon exposure to both treatments [109].

The repurposing of various antiviral drugs (Table 1) has gained momentum as a desperate measure to prevent the deleterious effects of COVID-19 [110].

Antiretroviral therapy in pregnancy and coronavirus disease 2019

It is plausible to assume that HIV-infected individuals receiving ARVs have a lower risk of developing complications from COVID-19 infection [111–114]. Protease inhibitor-based ARVs, such as LPV/r, have shown potential against SARS-CoV-2 infection due to their ability to bind SARS-CoV-1. Studies have shown a strong sequence homology between SARS-CoV-1 and SARS-CoV-2 [115]. However, SARS-CoV-2 binds ACE 2 with a 10-20-fold

Table 1 Antiviral drug repurposing for COVID-19 therapeutics highlighted in this review

Drugs	Mechanism of action	Safety in pregnancy	Effectiveness in treatment of COVID-19[a]	Placental transfer	Clinicaltrials.gov: COVID-19 (including pregnant women)
Lopinavir/ Ritonavir	Antiretroviral (Protease inhibitor) SARS-CoV[b] 3-chymotrypsin-like cysteine protease inhibitor [144]	Considered safe in pregnancy [145, 146] despite contradicting data [100, 101]	Potential to reduce mortality, although no benefit beyond standard care is clinically proven [122]	Low [147, 148]	NCT04364022
Dolutegravir	Antiretroviral (Integrase strand transfer inhibitor) Possibly inhibits 2′-O-ribose methyltransferase involved in coronavirus infectivity [149]	Recommended for HIV[c]-infected pregnancies (International guidelines, 2020) [134] Potential risks of neural tube defects (initiation < 6 weeks gestation) [126]	No clinical evidence	Moderate to high [150]	None
Remdesivir	Broad-spectrum antiviral (Viral RNA-dependent RNA polymerase inhibitor)	Requires greater research	Potential to improve clinical improvement time [137] FDA[d] approved for compassionate use (22/10/2020) [141]	Unknown [148]	NCT04292899 NCT04292730 NCT04582266

[a]Coronavirus disease 2019

[b]Severe acute respiratory syndrome coronavirus

[c]Human immunodeficiency virus

[d]Food and drug administration

greater affinity than SARS-CoV-1, which explains the high human transmission and infectivity rates of SARS-CoV-2 [116]. LPV/r lowers the risk of patients developing ARDS and subsequently dying from SARS-CoV-2 infection [117]. In various subsequent clinical trials comparing prenatal exposure to LPV/r and prenatal exposure to efavirenz (EFV), there were no significant differences in adverse outcomes in pregnancy [118] or other control measures [119]. These drugs, therefore, have become the preferred drugs of choice for pregnancy complicated by COVID-19 in China [120].

Randomized controlled trials (RCTs) are essential for providing standard guidance on clinical management, even in an emergency setting, since RCTs offer data without bias due to confounding factors, as seen in nonrandomized studies [121]. RCTs of LPV/r in severe COVID-19 showed no benefit beyond standard care [122]. Other RCTs revealed that a combination of antiviral drugs (interferon beta-1b, ribavirin, and LPV/r) was more successful in symptom alleviation than LPV/r alone in mild to moderate COVID-19 cases [123]. A systemic review of RCTs of LPV/r in COVID-19 highlighted that ARVs may reduce mortality; however, this reduction varies across different risk groups [124].

The South African National ART guidelines employ LPV/r-based ARTs as the second-line therapy in HIV-infected adults [125]. The guidelines further recommend that women who become pregnant while receiving the LPV/r-containing regimen should continue treatment with monthly clinical observations [125]. Dolutegravir (DTG), the newly established ARV in SA, together with two NRTIs, is also recommended as a second-line ART after failing a non-NRTI-based first-line regimen since DTG is suggested to be better tolerated by HIV-infected individuals than PIs such as LPV/r [126]. SA has experienced over 716,700 confirmed cases of COVID-19 as of late October 2020 [58]. Considering the slow switch from previously approved ARVs to DTG, LPV/r-containing ARTs are still readily available in SA, and clinical trials may include women in their first trimester. Notably, LPV/r has a negative influence on decidualization and placentation; therefore, the safety of these drugs in HIV-associated PE complicated by COVID-19 infection requires urgent and intensive scrutiny.

Latest antiretroviral therapy effects on endothelial dysfunction

In 2017, SA and other low/middle-income countries agreed to launch a new high-quality ART, a single-tablet regimen containing an integrase strand transfer inhibitor (INSTI), DTG, which provides rapid viral suppression [127]. Notably, the 2019 ART guidelines in SA state that the preferred first-line ART regimen is a DTG-based drug (TLD) for patients experiencing EFV side effects or those who prefer to use DTG [125]. However, the EFV-containing regimen (TEE) is recommended for use in the first 6 weeks of gestation and in women of child-bearing age due to a high risk of neural tube defects associated with TLD [125]. In vivo studies of human coronary artery endothelial cells (HCAECs) showed that DTG reduced inflammation and IL-6, IL-8, VCAM-1, and ICAM-1 secretion via NF-κB pathway inhibition and decreased senescence by repressing apoptotic pathways [128, 129]. DTG also displayed protective properties in HCAECs, such as reduced OS, inflammation, and senescence and improved ED from an aged donor with persistently elevated levels of senescence [129]. The Stockholm pregnancy cohort showed that the PE rate was normal; however, the population size was too small to make any deductions [130]. In a study on treatment-naïve HIV-infected individuals, a significant decrease in TNF-α was observed 12 months following DTG initiation in comparison to PIs and other INSTIs, such as elvitegravir [131]. This study also revealed DTG's capacity to significantly reduce D-dimer levels [131], implicating a possible positive interaction in COVID-19-infected individuals since elevated D-dimer, a marker of clot formation, is associated with increasing severity of the disease [132]. A case study of a 63-year-old HIV-infected woman with an undetectable viral load on a DTG-containing ART showed improvement despite presenting with COVID-19 complications during admission [133]. However, the role of DTG in the treatment of COVID-19 requires further investigation.

In light of the lack of evidence that particular ARVs are clinically active against SARS-CoV-2, HIV-infected individuals are advised to refrain from changing their ART regimen in an attempt to prevent or treat COVID-19 [134].

Remdesivir in covid-19 and pregnancy

Remdesivir (RDV), initially used in the treatment of Ebola, is among the top contenders against the new coronavirus [110]. RDV is a broad-acting nucleoside analog drug that has shown inhibitory effects on pathogenic animal and human coronaviruses such as SARS-CoV-2 in vitro and inhibits Middle East respiratory syndrome coronavirus, SARS-CoV-1, and SARS-CoV-2 replication in nonhuman primates [135]. In a randomized, double-blind, placebo-controlled trial, RDV showed no significant difference in terms of clinical benefits [136]. However, a larger study population is needed to confirm the observed reduction in clinical improvement time following RDV treatment [136]. Another RCT's final report revealed that RDV was superior to placebo in decreasing recovery time among hospitalized

adults [137]. However, neither trial included pregnant women. A case report of RDV-based treatment showed the successful management of a COVID-19-positive critically ill obstetrics patient [138]. Another case report of RDV-treated COVID-19 in the third trimester of pregnancy showed no adverse outcomes apart from elevated transaminases, which is also associated with PE development [139]. PE was ruled out as a cause of transaminitis because the patient did not present with hypertension and proteinuria [139]. This report also noted that there was no clarity on whether the transaminitis observed was due to COVID-19 or RDV intake [139]. In a recent study, 86 pregnant and postpartum women with severe COVID-19 who received compassionate use of RDV showed a high rate of recovery with a low rate of serious adverse events, such as transaminitis, hypertension, and hypoxia [140]. In Ebola clinical trials, there were no adverse outcomes among pregnant women receiving RDV [80]. On October 22, 2020, the United States Food and Drug Administration (FDA) approved the emergency use of RDV for severe cases of COVID-19 [141]. However, the safety of RDV in pregnancy has not been elucidated; therefore, the inclusion of pregnant women in clinical trials is necessary to guide risk-benefit considerations of RDV treatment in COVID-19.

LMICs such as SA have a limited capacity to accommodate the daily rise in COVID-19 infections [142]. The use of RDV may be vital for the prevention of adverse outcomes and a decrease in clinical improvement time in severe COVID-19 cases while regulating intensive care unit bed capacity [142]. Recently, Gilead Sciences Incorporated, CIPLA was granted a license to manufacture and distribute a generic form of RDV for compassionate use against COVID-19 in 127 countries, including SA; however, RDV is still not readily available to all citizens [143]. There is also no knowledge of the interactions of RDV with ARVs.

Conclusion

An imbalanced angiogenic status, inflammation and OS/NS induced by placental maladaptation facilitate pervasive multiorgan ED in PE. Adverse effects associated with HIV infection and ART promote ED predisposing PE development; however, higher prevalence and mortality rates among PE cases are still associated with ART use. Pregnancies complicated by the COVID-19 exploitation of ACE 2 have a strong correlation with PE-like symptoms such as endothelial injury, implicating COVID-19 in PE onset. Despite the inconsistent data on LPV/r against COVID-19, its availability in LMICs suggests the need for further insight into its safety in HIV-associated PE complicated by COVID-19. The observed endothelial protective properties of DTG in pregnancy and its role in COVID-19 therapeutics, along with the approved compassionate use of RDV in pregnancy, have yet to be established.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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