***Review***

**COVID-19 and preeclampsia: the unique and the**

**mutually nonexclusive clinical manifestations**

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**Abstract**

**In brief**

Both preeclampsia (PE) and COVID-19 share multiple risk factors, laboratory and clinical features posing a problem in differential diagnosis. The present review discusses the shared and unique features of PE and COVID-19 and the probable mechanisms of their association.

**Abstract**

PE is a serious, unpredictable hypertensive disorder of pregnancy present in around 8-10% of all pregnancies resulting in high rate of maternal and fetal morbidity and mortality. With the pathophysiology partially known, delivery is the only cure for PE. The disease sets due to multiple pathologic processes involving endothelial cell activation, inflammation, and syncytiotrophoblast stress.  Though the primary target organ is lungs in COVID-19, other systemic manifestations which include endothelial dysfunction, dysregulated angiogenesis, thrombosis, liver injury, thrombocytopenia, hypertension, and kidney damage overlap with PE. COVID-19 patients show a higher incidence of PE as compared to their noninfected counterparts and vice versa. It is possible that in majority of the cases, the diagnosis of PE is related to the shared clinical features and possibly a misdiagnosis. Few reports do support a biological association between PE and COVID-19 with an etiological interaction between the two. Differential diagnosis of these two disorders with the help of unique clinical and laboratory markers is challenging but is important for appropriate therapeutic intervention. In the absence of adequate evidence to prove these hypotheses, the clinicians should be aware of the additional risks of adverse events posed by pregnant women infected with COVID-19.

***Key words*** : Preeclampsia; COVID-19; differential diagnosis ; angiogenic factors; proinflammatory markers

**Introduction**

Pregnant women show an increased incidence of COVID-19, ranging between 1.3% and 27% (Jering *et al* 2021, Pérez-López *et al* 2022). On the other hand, higher incidence of PE or eclampsia is also seen in severe COVID-19 cases as compared to noninfected people (Di Mascio *et al* 2020).The differential diagnosis is always difficult, as the clinical manifestations often overlap between the two conditions. A specific diagnosis is critical, since there is a difference in the treatment of these two disorders.

Throughout pregnancy, the semi-allogenic fetus is protected from a highly regulated maternal immune response. Physiological changes which take place during pregnancy, mainly alterations in immunity, can predispose pregnant women to viral infection. During pregnancy, sequential changes in the immunological mileu of pregnant women have been observed i.e. pro-inflammatory in the first trimester to anti-inflammatory in the second trimester, and again back to pro-inflammatory response in the last trimester (Mor *et al* 2017). Any disequilibrium in the fine balance of physiological adaptations at any point of time during pregnancy due to viral infection can lead to maternal and fetal complications.

PE is a pregnancy specific disorder ; new onset of hypertension (BP ≥140/90mmHg) developed beyond 20 weeks of pregnancy in the presence or absence of proteinuria ((≥ 300 mg/24 hours urine) is the diagnostic marker (Sibai *et al* 2005). PE alone is responsible for about 70000 maternal deaths and 500000 fetal deaths every year. Multiple mechanisms have been proposed to explain the pathogenesis; reduced oxygen tension, hypoxia, abnormal remodelling of spiral arteries, endothelial dysfunction, immune mechanism, imbalance between angiogenic and anti-angiogenic factors and genetic background are some of the proposed mechanisms attributed to PE (Poston *et al* 2006). However, the knowledge about the exact pathophysiology of the disorder is still limited ; delivery is the only treatment. Individuals infected with SARS-CoV-2 present wide spectrum of clinical symptoms i.e. from asymptomatic infection to acute respiratory failure and even death ; but endothelial dysfunction has been shown to play a significant role in the pathophysiology of the disease.

A meta-analysis and systematic review involving the spectrum of corona virus infections during pregnancy showed that approximately half of the women infected with the SARS-CoV-2 had preterm delivery, PE and premature rupture of membranes when compared to non-infected women (Di Mascio *et al* 2020). The meta-analysis by Conde-Agudelo and Romero showed that SARS-CoV-2 infection during pregnancy increases the risk of PE by 62% (Conde-Agudelo & Romero 2021). The INTERCOVID cohort study, a multicentric study involving 43 centers from 18 countries, assessed 706 and 1424 pregnant women with and without COVID-19 respectively and showed that women with COVID-19 had an increased risk of PE and other adverse pregnancy outcomes. Women with COVID-19 and known risk factors or comorbidities for PE i.e. increased body mass index (BMI), diabetes, hypertension were found to have the highest risk of developing PE as compared to women without COVID-19. Women with severe COVID-19 had a higher risk of developing adverse pregnancy related events compared to asymptomatic women (Villar *et al* 2021). In a systematic review involving 790954 pregnant women which included 15524 COVID-19 positive women, it was demonstrated that women with COVID-19 showed an increased odds ratio (OR) for developing PE and other associated conditions (Conde-Agudelo *et al* 2021). Both these analyses showed the strongest association between PE and COVID-19 in nulliparous women. Thus the association between PE and COVID-19 is unequivocal but it is not certain whether this association is mutually causal; the underlying mechanism needs to be unravelled for an appropriate distinction and specific therapeutic intervention.

The present review summarises the overlapping and distinctive features of PE and COVID-19 and also highlights the probable mechanisms of the association between these two disorders.

**Renin-angiotensin system (RAS)**

The most logical way of explaining the relation between COVID-19 and PE is the breakdown of RAS system. The angiotensin-converting enzyme 2 (ACE2) is densely expressed in the syncitiotrophoblast, cytotrophoblast, endothelium and villi. The important role of ACE2 is to degrade Ang-I to Ang-([1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9108291/#B1)-[9](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9108291/#B9)) and Ang-II to Ang-([1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9108291/#B1)-[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9108291/#B7)). Thus, besides the vasodilatory, and anti-proliferative effects, ACE2 has a role in preventing organ damage from the pro-inflammatory actions of Ang II. The circulating RAS also has a role of maintaining fluid and electrolyte homeostasis and blood pressure during normal pregnancy. Increased levels of ACE2 receptors during pregnancy also facilitates the conversion of Ang II to Ang (1-7) resulting in lowering of blood pressure. The SARS-CoV-2 virus enters the host cell through ACE2 receptor; on binding to ACE2, the virus causes its downregulation with a consequential reduction in Ang (1-7) levels, which in turn will lead to vasoconstriction, inflammation, and pro-thrombotic effects, which are the classic manifestations of PE (Ashary *et al* 2020).Junus *et al* have reported increased levels of ACE2 during mid-term pregnancy in women who developed PE subsequently as compared to those who continued with healthy pregnancy and term delivery (Junus *et al* 2022). Contrary to this report , there is another report which showed a decrease in the levels of ACE2 when women were examined after 28 weeks of gestation; majority in this group had already a diagnosis of PE (Tamanna *et al* 2020). It is not clear whether the ACE2 levels increase prior to the development of PE and subsequently get reduced. In addition to ACE2, SARS-COV-2 requires another key factor in the host cell i.e. TMPRSS2,which proteolyses the viral spike protein and enables the fusion between virus and host cell (Hoffmann *et al* 2020).The expression of both ACE2 and the cofactor TMPRSS2 increases with the progression of pregnancy (Pavličev *et al* 2017).

Along with ACE2, SARS-CoV2 affects other components of the RAS such as ADAM17 which mainly regulates the ACE2 levels on cell membrane and thus downregulates its expression (Lambert *et al* 2005).The role of ACE2 receptor in COVID-19 infection is evident by the work of Zhang et al, wherein the authors infected the humanized mice i.e. ACE2 (hACE2) with an engineered ACE2 molecule, sACE22.v2.4-IgG1, which prevented the virus from getting into lung epithelial cells (Zhang *et al* 2022). The histopathological studies from COVID-19 patients have also shown upregulation of ACE2 protein expression in lung tissues as compared to noninfected patients (Gheware *et al* 2022). Abnormal ACE2 levels is thus an important biomarker common for both PE and COVID-19.

**Immune and proinflammatory markers**

A healthy pregnancy is in a state of controlled inflammatory state which is required for normal placentation during early stages of pregnancy. Inflammation is the hallmark clinical manifestation of both PE and severe COVID-19. The common laboratory abonormalities are thrombocytopenia, increased serum ferritin levels and pro-inflammatory cytokines which include IL-1b, IL-2, IL-6, IL-7, IFN-g and tumor necrosis factor-α (TNFα) resulting in a cytokine storm and multi-organ failure (Sathiya *et al* 2022). Additionally, increased caspase-1 levels has been reported in women with COVID-19 and PE as compared to healthy controls (Cornelius *et al* 2022). Inflammasomes which are multiprotein complexes, have an important role not only in innate immune responses but also in regulating inflammation which makes them crucial in hyper-inflammatory diseases like PE and COVID-19. Among the various inflammasomes, NLRP3 is the most widely studied inflammasome in inflammation and antiviral action (Nieto-Torres *et al* 2015). Another important player in the pathophysiological association of COVID-19 and PE is exosomes, which are released from various cell types. Exosomes are extracellular vesicles formed by the budding of endosomal membranes and play an important role in cell to cell communication, viral spread as well as disease pathology. They are also important markers of inflammation, activation and apoptosis. A significant enhancement of NLRP3 inflammasomes was observed in endothelial cells after exposure to exosomes from severe COVID-19 patients compared to that from patients with mild disease or healthy individuals (Sur *et al* 2022). Further studies should investigate inflammasome inhibition, through direct or indirect approaches as an important and novel therapeutic approach in such patients, which may reduce the risk of pregnant women with COVID-19 to develop PE.

During inflammation, neutrophils also release certain substances i.e. neutrophil extracellular traps (NETs) by a special neutrophil response called NETosis . These NETs are chromatin structures consisting of DNA-histone complexes , antimicrobial proteins and enzymes (Arcanjo *et al* 2020). The composition of NETs varies depending on the triggering factor which induced NETosis (Brinkmann *et al* 2004). Both PE and COVID-19 show increased NETosis as both these disorders have inflammatory processes as the denominator, though underlying pathophysiology is different in both these disorders. While in COVID-19 it may be the virus itself, in PE, placental derived factors are known to be involved in NETosis (Palomo *et al* 2022). NETs are also known to be prothrombotic in nature.

**Coagulation markers**

A striking difference observed between PE and COVID-19 is in the VWF levels, which is also a marker of endothelial injury. However, these levels seem to be dependent on gestational age of the pregnant women during which the blood samples are collected. The severity of both COVID-19 and PE has been found to correlate with increased levels of VWF (Fernandez *et al* 2022). Palomo et al observed an increase of VWF levels in COVID-19 patients but an inverse relationship was observed between severity of PE and VWF levels (Palomo *et al* 2022). They have further confirmed these observations by exposing endothelial cell culture to PE sera and shown an increased release of VWF in the supernatant.

One of the important laboratory features of COVID-19 is decrease in the levels of ADAMTS13 activity and resultant increase in high molecular weight (HMW) multimers. PE too is associated with decreased levels of ADAMTS13, independent of VWF. The activity/Ag ratio, however did not differ between the cases and controls, and seems to be dependent on inflammation (Alpoim *et* *al* 2011, Stepanian *et al* 2021). Similar to VWF, there are contradictory findings to this observation; no association between ADAMTS13 and PE was observed in another study (Molvarec *et al* 2009). The difference between the two studies apart from the sample size is the gestational age. Palomo *et al* report a qualitative VWF defect in PE with a reduced VWF:GPIbM/VWF:Ag ratio which was further confirmed by the absence or highly reduced HMW multimers. The ADAMTS13 being normal in these groups, there may be other mechanisms in the degradation of HMW multimers (Palomo *et al* 2022).

**Angiogenic markers**

Both angiogenic and antiangiogenic factors have been reported to be highly accurate in predicting and diagnosing PE. The disruption of angiogenic balance is more pronounced in PE as compared to COVID-19. Besides being involved in the pathophysiology and diagnosis of PE , they have also been considered as important biomarkers for predicting the disease. The sFlt1/ PlGF ratio has been found to be a distinctive biomarker aiding in a differential diagnosis between PE and COVID-19. The levels of both sFlt1 and Ang2 levels are increased and PlGF markedly reduced in PE in contrast to COVID-19 patients who show reduced PlGF levels but normal sFlt1 levels without much alteration in sFlt1/ PlGF ratio. The changes in the levels of sFlt-1 and PlGF were dependent on the time of PE diagnosis with early- onset PE showing more pronounced changes as compared to late-onset PE (Verlohren *et al* 2022).Increase in uterine artery pulsatility index (UtAPI) is also an important marker for differential diagnosis of PE; however the predictive potential of this marker varies in different gestation periods (Wu *et al* 2021).

**Endothelial markers**

The most significant pathophysiological process in both PE and COVID-19 is endothelial injury and dysfunction. The symptoms in COVID -19 are due to the direct impact of the virus resulting in endothelial injury with a series of sequential effects causing a vicious cycle which results in the severity of the disease. In severe disease, there is a series of pathological events which include leukocyte inflammation, altered vessel integrity and thrombotic tendency (Bermejo-Martin *et al* 2020).

Differential patterns of biomarkers of endothelial activation and damage have been reported for PE and COVID-19. In patients with PE, there is a significant increase in the levels of adhesion molecules like VCAM-1 and ICAM-1 and proinflammatory cytokine i.e. soluble TNF-receptor I (sTNFRI) (Crispi *et al* 2006), but normal levels of heparan sulfate (HS) (Cornelius *et al* 2022). In comparison, COVID-19 patients show marginally increased VCAM-1, ICAM-1 and sTNFRI, but there is significant increase in HS levels (David *et al* 2020, Palomo *et al* 2022). HS is a biomarker for endothelial barrier disruption and the levels of HS directly correlate with the severity of COVID-19 ; more studies should confirm these observations to utilize these markers for the differential diagnosis of PE and COVID-19.

**Neurological markers**

SARS-COV-2 is found in brain endothelial cells. Two proteins i.e. neurofilament light chain protein (NFL) and glial fibrillary acidic protein (GFAp) have been found to be important as biomarkers for both PE and COVID-19. These serve as important diagnostic markers as they develop much before the development of any clinically significant neurological problems. There are reports to indicate that these markers help in disease stratification in COVID-19 (Aamodt *et al* 2021, Bergman *et al* 2022).The significance of sNFL as a biomarker has already been reported earlier in PE with the sensitivity and specificity almost similar to the two well-established biomarkers for PE i.e. sFlt-1 and PlGF. In general, the level of sNFL increases with increasing maternal age ; but this increase has been found to be more pronounced in women with PE compared to controls (Evers *et al* 2018) . In another study, women with PE without clinically detectable neurological complications had increased CSF and plasma concentrations of NFL compared to women with normotensive pregnancies (Andersson *et al* 2021).

**Probable mechanisms of association between COVID-19 and PE**

With the onset of the COVID-19 pandemic and the simultaneous increase in the incidence of PE, there is a need to identify the pathophysiological mechanisms of this association and possible therapeutic targets for this devastating maternal disorder. Several questions arise from the observational data with regard to the association between COVID-19 and PE. Is the observed association just a confounding effect or is there some biological interaction? Is it that the SARS-CoV-2 itself triggers PE and other adverse events during pregnancy or is there a placental predisposition for PE? As per the confounding or association hypothesis, either the SARS-CoV-2 infection results in clinical manifestations which are similar to that of PE or pregnancy may be a predisposing risk factor for SARS-CoV-2 infection . As per the causal hypothesis, each of these disorders is an etiological factor for the other .

PE is referred to as the “disease of theories,” mainly because the underlying biological mechanisms are still far from clear.  There is growing evidence now to show that a defective maternal cardiovascular function leading to uteroplacental hypoperfusion may result in placental dysfunction in PE. Both PE and cardiovascular disorders share similar risk factors like diabetes, pre-existing chronic hypertension and studies have also shown that several abnormal cardiac parameters precede much before the development of clinically evident PE (Garcia-Gonsalez *et al* 2020). It has also been proposed that SARS-CoV-2 may injure the myocardium which in turn leads to uteroplacental malperfusion and predisposes patients to PE (Melchiorre *et al* 2021). Failure of the maternal cardiac system to adapt to pregnancy thus seems to be an important pathophysiological mechanism for the development of PE. The myocardial injury caused by SARS-CoV-2 is evident by elevated troponin and pro-B-type natriuretic peptide concentrations and left ventricular dysfunction, both in and outside pregnancy (Gul *et al* 2022). Most of the preventive therapeutic drugs like aspirin, statins and antihypertensives used for PE are the ones also used for cardiovascular disorders. However, more evidence is required to propose a causal association between PE and COVID-19.

The “dosage effect” of the virus is a strong indication of the biological association between COVID-19 and PE. Pregnant women with COVID-19 have a 2-fold higher risk of severe PE; the risk is higher i.e. 5-fold in symptomatic than in asymptomatic cases with COVID-19, even after adjusting for pre-existing risk factors for PE (Lai *et al* 2021). Put together, these results provide some evidence to show that maternal COVID-19 predisposes and triggers the development of PE (Conde-Agudelo & Romero 2021).

The convincing evidence for the etiological link between COVID-19 and PE comes from the fact that the entry point for SARS-CoV-2 is ACE2 receptor and its co-receptor TMPRSS2, which are present on various cell types including lung epithelium, placental villi and syncitiotrophoblast. On binding of the spike protein to the ACE2 receptor, the virus enters the cell and there is a subsequent downregulation of the enzyme. This in turn reduces the conversion of Ang II to Ang (1–7), resulting in increased concentration of Ang II in blood. This downregulation of ACE2 in the placenta may lead to placental oxidative stress and the release of anti-angiogenic factors, including soluble sFlt-1 and a reduction in proangiogenic factors, leading to PE or PE-like symptoms ( Espino-Y-Sosa *et al* 2021). Since there is overexpression of ACE2 receptors in placental villi and syncitiotrophoblast during normal pregnancy, there may be a higher chances of pregnant women getting infected with SARS-CoV-2, which subsequently can lead to PE or PE-like manifestations. Histopathological studies in women infected with COVID-19 have shown placental injury, maternal malperfusion, lymphohistiocytic villitis and decidual arteriopathy (Shanes *et al* 2020). Placental changes seem to be more common in women in acute phase of COVID-19 infection (Linehan *et al* 2021).

On the other hand, it is also possible that the shared risk factors, clinical and laboratory features between PE and COVID-19 may have a confounding effect, rather than each being a mutual etiological factor. Both COVID-19 and PE share at least few systemic risk factors; for instance, pre-existing hypertension, advanced maternal age, diabetes and BMI. Similarly, the risk factors for severe COVID-19 during pregnancy are similar to those in non-pregnant women i.e. ethnicity, obesity and chronic comorbidities like hypertension and asthma (Allotey *et al* 2020). SARS-CoV-2 causes systemic complications like hypertension, renal and liver dysfunction, platelet activation, thrombocytopenia and acute respiratory distress syndrome (ARDS), which are also the symptoms of severe PE. The overlap in risk factors favours the proposition of confounding of clinical symptoms rather than causal association. Abnormal ratios of sFlt1 and PlGF , thrombocytopenia, platelet activation, endothelial damage, cytokine storm, thrombosis are some other laboratory and clinical attributes of both PE and COVID-19. Thus it is possible that PE in COVID-19 patients may often be due to misdiagnosis. Another important observation which goes against the causal hypothesis is that the association between the two is very strong in nulliparous women. If the virus induces PE or PE like symptoms, significant association should have been observed even in parous women. Even the risk factors for developing more severe COVID-19 are similar in pregnant and nonpregnant women. The risk of adverse pregnancy events in COVID-19 positive pregnant women is much higher in advanced pregnancy. If the virus induces these events , they should have been equally associated in all gestational ages. Finally, the prevalence of COVID-19 is the highest between 33 and 37 weeks of pregnancy, which is also the time for the occurrence of PE (He *et al* 2022).

An important molecular link between PE and COVID-19 is neuropilin-1(NRP1),which is an important transmembrane signalling protein associated with angiogenesis, tumor progression, cell migration, entry of SARS-CoV-2 into the cells, apoptosis, and immune function, besides their role in maternal immune tolerance and placentation during pregnancy (Mayi *et al* 2021, Arad *et al* 2017).NRP1 is abundantly expressed in the respiratory and olfactory epithelium, synciotrophoblast with highest expression in endothelial cells of placental villous blood vessels, making them the key molecules in maintaining normal maternal-fetal microenvironment. Neuropilin-1 has also been shown as a cofactor required for ACE2 for the internalization of the SARS-Cov-2 virus (Cantuti-Castelvetri *et al* 2020). Abnormal Neuropilin-1 expression in PE and its upregulation in COVID-19 has also been reported in multiple studies (Maulik *et al* 2016, Mayi *et al* 2021). Post-transcriptional regulation of NRP-1 expression by miRNAs has been reported both in PE, and SARS-CoV-2 infection, implicating novel NRP1 targeted treatment strategies involving miRNA suppression (Naidoo *et al* 2022) .

Finally, if SARS-CoV-2 infection can cause PE, then vaccination against COVID-19, antiviral therapies and COVID-19 pandemic mitigation measures would be expected to reduce the risk of PE. However, small series studies on comparison of pregnancy outcome between women who were vaccinated and those who were unvaccinated against COVID-19, vaccination was associated with a non-significant decrease in the incidence of PE (Theiler *et al* 2021). Ongoing clinical trials of COVID-19 vaccination in pregnancy will establish whether vaccination reduces the risk of SARS-CoV-2 infection and PE.

Figure 1 shows the common risk factors, laboratory and clinical features in PE and COVID-19 and the probable mechanism for the strong association between PE and COVID-19 .

**Discussion**

The relationship between COVID-19 and PE is mutually nonexclusive. COVID-19 has clinical manifestations , some of which match with the diagnostic criteria of PE. SARS-CoV-2 infection during pregnancy could be either an association with PE or it may well be an etiological factor for PE or PE could create the ground conducive for SARS-CoV2 infection.

A healthy pregnancy depends on how well the maternal system is adapted to face the multiple challenges it is exposed to. The major challenge is to develop tolerance to the semi-allogenic fetus. The immune system undergoes continuous changes as the pregnancy proceeds with proinflammatory state in the first trimester changing into anti-inflammatory state in the second trimester and going back into proinflammatory state in the third trimester again (Liu *et al* 2020).

In PE, there is a defective placental perfusion, increase in the levels of sFlt-1 and decreased levels of PlGF, which leads to an anti-angiogenic status with increased s-Flt-1/PlGF ratio. Since this imbalance can be detected in maternal plasma at least five weeks prior to the onset of PE, it acts as an important biomarker for the prediction of PE. The COVID-19 patients with normal placental implantation should present with normal values of sFlt-1/PlGF and uterine artery pulsatility index (UtAPI) even in severe cases (Mendonza *et al* 2020). This is an important differential marker unique to PE.

There are contradictory reports about the nature of association between PE and COVID-19. One of the important ways to find the nature of the association between COVID-19 and PE is to see the dosage effect i.e. whether severity of COVID-19 is directly correlated with pregnancy related complications specifically PE. The study conducted by Lai et al provides substantial evidence that there is an etiological link between PE and COVID-19 (Lai *et al* 2021). In a retrospective study involving 14 centers in UK and 1223 pregnant women, the authors have shown that the observed rate of PE in women is much higher than the expected rate and there was a graded increase in the incidence of PE with increasing severity of COVID-19 i.e. 1.9%, 2.2%, 5.7% and 11.1% in asymptomaic, mild, moderate and severe disease patients respectively (Ciapponi *et al* 2021). Papageorghiou et al. in a longitudinal prospective study, however have reported that COVID-19 in pregnancy is independently associated with PE especially among nulliparous women irrespective of severity of symptoms (Papageorghiou *et al* 2021).

Pregnant women could also be more susceptible to SARS-CoV-2 due to the immunological compromise that occurs during pregnancy (Abbas *et al* 2020). In addition, SARS-CoV-2 causes hypoxic injury to the placenta, which could contribute to the development of PE (Sibai *et al* 2009). In the study by Mendonza et al, among six COVID-19 infected pregnant women who were diagnosed with PE, only one patient showed placental under-perfusion and abnormal angiogenesis (Mendonza *et al* 2020). A careful analysis of all markers specifically the angiogenic markers will help in the differential diagnosis and appropriate treatment. A better understanding of the pathophysiology of SARS-CoV-2 infection in the placenta will provide important insights into possible intervention in this vulnerable group.

The clinical implications of concomitant PE and COVID-19 infection have been analyzed in a multicentric study from Brazil. The study involved 203 COVID-19 positive pregnant women, 21 with PE and 182 without PE. The authors observed that women with PE had a higher risk for caesarean section compared to non-PE women (RR 5.54 [1.33 – 23.14]); similarly their neonates had higher risks for getting admitted in the intensive care unit (RR 2.46[1.06 – 5.69]). Pre-term birth, neonatal morbidity and mortality were more common in the PE group (Guida *et al* 2022). Marwah *et al* in an analysis of 38 women with PE and COVID-19 showed 36.84% premature delivery, 42.50% low birth weight, 28.57% NICU admission and 5% neonatal mortality ( Marwah *et al* 2022). A different analysis in COVID-19 positive pregnant women by Simon *et al* after adjusting all causes of premature delivery including PE has still shown an increased RR of 1.77 (Simon *et al* 2022). All these suggest that SARS-CoV2 infected pregnant women with PE develop a clinically severe disease and have increased maternal and neonatal morbidity compared to patients with only COVID-19 or PE. Both these being inflammatory disorders have a cumulative effect when present together in the same patient.

Both COVID-19 and PE, though presenting with overlapping clinical features, yet have contrasting treatment consideration. Besides a stringent follow-up in SARS-CoV2 infected pregnant women, low-dose aspirin prophylaxis (60-100 mg/day) is recommended, specifically for those women with a high risk of PE (Duley *et al* 2019). Since premature delivery is often an indication in pregnant women with both PE and COVID-19, use of corticosteroids for fetal maturation is considered, however its use should be balanced between the positive effect on fetal maturation recommended for preeclamptic women versus the probable negative effect in COVID-19 infected women (Bhimraj *et al* 2020). Along with anti-hypertensive drugs, Magnesium Sulphate (MgSo4 ) is one agent used in women with PE specifically to prevent convulsions due to its neuroprotective effect and has clearly shown to improve maternal morbidity and mortality ( Joudi *et al* 2020).  However, studies in women with PE and mild to moderate COVID-19 have shown that a loading dose of 4mg followed by the maintenance dose of 2mg/hour did not show any adverse effect in COVID-19 positive women with PE. (Goldshtein *et al* 2021). More data on the safety of MgSO4 in pregnant women with PE and severe COVID-19 is needed before it is recommended to be used in this vulnerable group of women.

The observational data on the safety of mRNA COVID-19 vaccines have shown that it is safe and effective in pregnant women (Dagan *et al* 2021). Considering the increased morbidity of women infected with SARS-CoV2 during pregnancy, pregnant women should systematically be included in all clinical trials of vaccines as vaccination during pregnancy protects not only the mother but also the fetus and the neonate.

**Conclusion**

The clinical evidence is inconclusive about an apparent link between COVID-19 and PE. It is not currently known whether PE and COVID-19 is mutually causal or consequential. Women who are at high risk for PE should also be considered at higher risk for COVID-19 and vice versa. They should be included in all preventive strategies during the pandemic. Differential diagnosis in COVID-19 pregnant women developing hypertension, thrombocytopenia, proteinuria, as well as increased levels of liver enzymes, might be challenging. Healthcare professionals should be aware that SARS-CoV-2 infection in pregnant women, even in those who remain asymptomatic, is a risk factor for subsequent development of PE. Pregnant women who test positive for SARS-CoV-2 should benefit from close monitoring of blood pressure and liver and renal function in order to allow early diagnosis of PE or other adverse events.

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**Legend**

**Figure 1. Common risk factors, laboratory and clinical features shared between COVID-19 and PE and probable mechanism of their association**

Severe COVID-19 during pregnancy and PE share risk factors, clinical and laboratory features which include placental hypoperfusion, increased levels of pro-inflammatory cytokines, inflammation, coagulation activation, endothelial, renal and liver dysfunction, increased serum ferritin levels, thrombocytopenia and altered s-Flt1 to PlGF ratio.The mechanism of the association between PE and COVID-19 is either by synergism of the clinical features or by biological interaction, the major link being the ACE-2 receptor which is over-expressed during pregnancy thus predisposing pregnant women to SARS-CoV-2 infection. Subsequent to virus entry, there is a downregulation of the enzyme resulting in excess of Ang-II and angiogenic imbalance.