Pre-eclampsia and HIV repercussions for development of the renal diseases- review

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Abstract

Pre-eclampsia (PE), is an endothelial condition that impairs renal function in pregnancy, and is associated to a higher risk of developing cardiovascular and chronic renal diseases in future. Guidelines of the Kidney Disease Improving Global Outcomes highlights the joint relevance of glomerular filtration rate and albuminuria in defining the regularity of renal function surveillance. The objective of this study to review the pre-eclampsia and HIV repercussions for developing the renal diseases. As per the review, it is believed that acute kidney injury persists and continues during and after postnatal period among the women suffered with pre-eclampsia, HELLP syndrome and HIV infection. HIV-1 infections, preeclampsia and ARTs all have varied effects on endothelium function. Endothelial dysfunction prevails in the combination of both diseases.This information will aid in our understanding of the impact of HIV and ART on immunological restoration in preeclampsia. However, further research studies could be advancedand reinforced by deployment of the specific validation definitions and categorical systems. Researchers may require to develop a refined animal model that assists the futuristic researchers to further explain the mechanism and consequent problems associated with the preeclampsia, HIV infection and renal diseases.

Keywords: *Pre-eclampsia, HIV, Acute renal injury, renal diseases, repercussions.*

1. INTRODUCTION

Preeclampsia (PE) is an endothelial dysfunction distinguished by high blood pressure and albumin, and it is one of the leading cause of maternal deaths. Pre-eclampsia causes maternal mortality in 3.5 out of every one lakh births, contributing for 39% of all pregnancy associated deaths. [1]. Pre-eclampsia impairs renal capacity throughout the gestation and raises the chance of developing chronic hypertension, chronic renal failure, and coronary heart disease later in life. [2-3]. Pre-eclampsia is correlated to a 4-fold increase in the probability of having end-stage renal disease (ESRD) during 10 years following childbirth. [4]. Experiencing more

than one pre-eclamptic pregnancies, progeny with lower birth weight, or a pre-term birth raises that probability even more. [4].

Glomerular endotheliosis in a pre-eclamptic pregnancies could be completely revocable if the condition does not progress to an extent of renal fibrosis. [5]. The recurrence is evidently contingent on the source of endothelial damage being removed. In case of pre-eclampsia, this is accomplished through quick decision of pregnancy termination and placental delivery. The fibrinous and granular material collects in the glomerulus can take months to completely dissipate. [6].Data on these women's renal function follow-up are lacking. According to several case-control and cohort's trials, majority of women with a history of Pre-eclampsia maintained strong renal function following PE [7-8]. However, a subset of women who have a lower glomerular filtration rate (GFR) and/or recurrent urine protein leakage.

At any GFR, significantly elevated albuminuria is regarded as a distinct high risk for the development of heart disease. [9-10]. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines emphasise the importance of GFR and albuminuria in determining chronic renal disease's prognosis. The guidelines provide us broad evidence-based recommendations for monitoring chronic disease patients. We looked into the incidence of chronic renal failure in a large cohort of women with a history of Pre-eclampsia in this investigation.

Acute renal damage in gestation is related with significant maternal deaths and foetal loss rates that series from 30 to 60%, rendering it a potentially fatal event[11]. Acute kidney damage was formerly thought to be a comparatively rare and diminishing pregnancy complication related mostly with sepsis, complex termination of pregnancy, and living in developing countries [12]. The lack of consistent clinical guideline makes it difficult to precisely establish the prevalence of acute renal damage in pregnancy and measure its impact on morbidity and death. However, current statistics indicate that the prevalence of acute kidney damage is rising. Acute renal damage raises the peril of chronic kidney disease, increased blood pressure, and coronary heart illness. [13]. Acute kidney injury in pregnancy is frequently accompanied with hypertension disorders in pregnancy, that is linked to a higher risk of cardiac later in lifecycle [14].

2. Incidence of Acute kidney injury(AKI) during pregnancy

From 1998 to 2008, the prevalence of acute kidney injury in pregnancy augmented from 2.3 to 4.5 per ten thousand pregnancies [15]. The prevalence of Acute Kidney Injury due to obstetric factors is estimated to be one among the twenty thousand deliveries [16]. Retrospective researches have compared the prevalence of acute kidney injury from 1998-1999 to 2008-2009, discovered that the incidenceis amplified from 2.29/10,000 to 4.52/10,000 child births, and in postnatal women from 0.48/10,000 to 2.17/10,000 pregnancies with in the same time duration [16]. These findings were consistent with Canadian studies, which found that the prevalence of PR-AKI is rising [17].Severalresearches reportthe frequencies of PR-AKI ranging from 50 to 61% in critically ill obstetrics women, with a direct relation among symptom sternness and fatality. The incidence of acute kidney injury in pregnancy shows higher among emerging economies, as per the reports of WHO, MMR in underdeveloped nations is 239/100,000 women comparing to 12/100,000 in well advanced nations [18].

A research study executed on pregnancy related complications, 97.26% of PR-AKI was observed between 1998-1999 to 2008-2009, and a 351% rise in postnatal ARF patients, highlighting the idea of Acute kidney injury in pregnancy can develop in both the postnatal

and antenatal periods. A retrospective cohort research investigation intended to evaluate the development of maternal Acute renal failure in the US and discovered a 10% annual raise was noticed between 1999-2001 and 2010-2011 (95% CI 8-11%).The researchers noted a rise in ARF, as well as an elevation in maternal deaths and dialysis therapy, although there was a reduction in the enhance the impact of ARF. The prevalence of acute renal failure due to obstetrical factors is estimated to be 1 in 20,000 pregnant women.Pregnant women aged 35 or the above, overweight, metabolic syndrome such as diabetes, high blood pressure, multiple pregnancy, caesarean section delivery, past history of LSCS, induction of labour, polyhydramnios, APH such as abruptio placenta or placenta Previa, heart failure, lupus erythematosus, and chronic kidney diseases have been linked to an increase in PR-AKI . Improvements in the care of maternal diseases or the detection of AKI, on the other hand, might be involved.[15,16]

3. Diagnosis of Acute Kidney Injury in Pregnancy

Kidney changes begin early prenatally. These substantial alterations have consequences the normal clinical values, which may impact the acute kidney injury diagnosis and treatment.

Anatomical alterations

Increased renal diameter and capacity as a result of increased volume of blood and collecting system capacity. Smooth muscle relaxation caused by hormonal changes causes dilation of the collecting system. Hydronephrosis and hydroureter occurs among eighty percentage of pregnant mothers by 5-7 months of pregnancy.Ureteral dilatation at right side is higher than ureteral dilatation at opposite sidebecause of a tilted womb and the arterial network at the pelvic brim.

Physiological changes

Parameter	In pregnant women compared to non-pregnant women	Normal ranges
Serum creatinine	Lower	~ 0.5 mg/dL (<0.9 mg/dL)
Blood urea nitrogen (BUN)	Lower	~9.0 mg/dL
Plasma uric acid	Lower	2.0-3.0 mg/dL
pCO2	Lower	27-32 mmHg
pH	Higher	7.40-7.45
Serum bicarbonate	Lower	18-20 mEq
Creatinine clearance	Higher	~25% above baseline (>100 cc/min)
Urinary protein excretion	variable to higher	<300 mg/24 hours
Urinary glucose excretion	variable to higher	may be present

Definitive changes in Acute Kidney injury during pregnancy

The diagnosis of PR-AKI confirmed, if the serum creatinine levels raised up to 0.3mg/dl or the above and the output of urine is less than 5 ml per kg body weight per hour for more than 6 hours' period.

Preeclampsia affects between 3 and 10% of pregnant women. The diagnosis is based on high blood pressure and albumin in urine after 20 weeks of gestation. The illness can harm the mother's neurological system, respiratory system, renal system, hepatic system and platelets, placental circulation and foetal well-functioning in severe cases. Repeated checking of blood pressure, urine collection on a regular basis for excreting albumin, creatinine, hepatic enzymes , and platelets contribute in detection and sternness categorization.Specified significance from a rise in serum creatinine to the requirement for dialysis. This is complicated even more by the normal reduction in creatinine levels occurring during pregnancy. For the non-pregnant populations, the commonly referenced acronym is RIFLE (risk, injury, failure, loss and end stage). [19] andnetwork of acute kidney injury categories have been thoroughly verified in gestation. Nevertheless, in more recent obstetric investigations, these classifications have been used. [20]. A high RIFLE class, can predict expected morbidity and mortality rate among

the women with PR-AKI. Using Acute kidney injury network criterion, researchers found that the majority of the cases were in the AKIN stage 1 classification, only with temporary elevations in blood creatinine. Furthermore, these patients with Acute kidney injury are more likely to have concomitant illnesses including hypertension, gestational diabetes, or chronic renal failure, as well as obstetrical complications problems including preeclampsia/HELLP (Haemolysis, Elevated Liver Function Tests, Low Platelets), bleeding, or infections. As more research apply these criteria, researchers can better determine if they can use on risk-stratify maternal women.

There are various reasons that make diagnosing Acute kidney injury in pregnancies greater difficult than in non-pregnant women, and evaluation kidney function tests employed among women without pregnancy does not necessarily produce an appropriate evaluation in pregnant women. Because of physical effects and a rise in GFR, serum creatinine decreases in gestationalperiod making a timely and correct diagnosis of acute kidney injury more difficult. It is a natural drop occurs in serum creatinine may conceal earlier or minor abnormalities in glomerular filtration rate. Because kidney function measurements are frequently not acquired in pregnancy until injury is clinically apparent, comparability to baseline levels is frequently impossible. Furthermore, expectant mothers might experience thirty to forty percent decrease in Glomerular Filtration Rate without seeing significant increases in creatinine levels [21]. In setting of hypertensive disorders of pregnancy, the American College of Obstetricians and Gynecologists (ACOG) defines renal insufficiency as a serum creatinine greater than 1.1 mg/dL or a double of serum creatinine content in the lack of kidney illness [22]. Nevertheless, at the time of the survey, there was no consensus on clinical guidelines for Acute Kidney Injury in pregnancy. Apart from affecting patient safety, the absence of rigorous clinical guidelines is still most probably contributing to a variation in Acute kidney Injury in Pregnancy incidence rates.

Acute renal failure in Pregnancy

Figure 1Eteology of AKI in Pregnancy

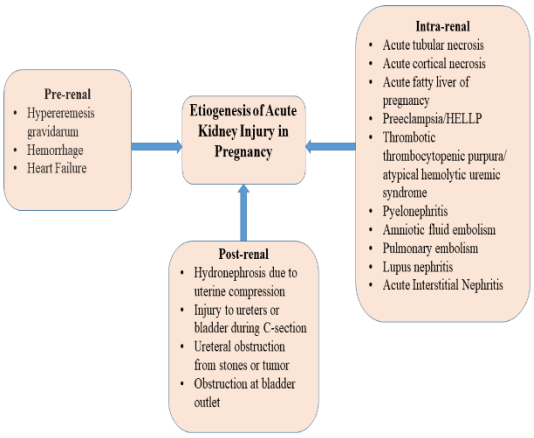
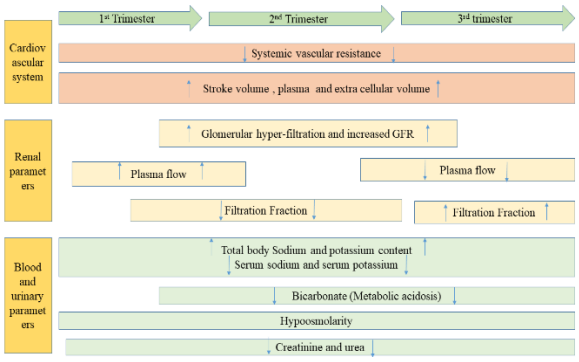


Figure 1Eteology of AKI in Pregnancy- PR-AKI can have prerenal, intrarenal, or postrenal aetiologies. Bleeding, hypovolemia due to excessive vomiting in pregnancy, inflammation that causes sepsis, or cardiac failure can all lead to pre - renal etiology. Acute necrosis, proximal tubular cell death, coagulant microangiopathy, pre-eclampsia continuum illnesses, hepatic complications including , glomerulonephritis, inflammation of the nephrons are examples of intrinsic renal causes, Technical blockage, tumour, or uteropelvic aetiology are examples of postrenal aetiologies.

Figure 2 Pathophysiological changes during pregnancy



4. Outcome of the pregnancy with Acute Kidney Injury (AKI)

From 1998 and 2009, 17.4% of fatalities observed in antenatal women and 31.5% of mortality in postnatal hospitalisation reported amongst women with acute kidney Injury of any aetiology. Data shows that hypertension diseases of gestation, particularly pre-eclampsia and HELLP syndrome, constitute a significant contribution to the incidence of acute kidney injury in pregnant women, and that they are linked to higher rates of perinatal and maternal mortality [23-26, 27]. In comparison to expectant women who did not have AKI, those of with AKI had a higher risk of caesarean birth, perinatal haemorrhage, abruptio placenta, intravascular thrombosis, and a higher mortality. Those with AKI also had a prolonged intensive care stay, a higher incidence of pregnancy loss, a substantially lower gestational age at childbirth (0.70 week [95% CI 1.21 to 0.19 week]), and a reduced birth weight (740 g [95% CI 1,180 to 310 g]) than women lacking AKI. Same findings have indeed been observed in current additional study that highlight the influence of AKI in pregnancy on both maternal and foetal wellbeing [28]. PR-AKI has a massive effect on foetal mortality rates, in addition to maternal problems. The fatality rate among babies born to AKI mothers is predicted to be 23.5-38%.[29]. A scant data on the long-term outcomes of foetuses subjected to prenatal AKI. More research is needed to determine the lengthy repercussions for such new-borns. The obstetrical complications such as pre-eclampsia and HELLP syndrome are the common reasons of PR-AKI and which is also atypically seen in the conditions thrombolytic disorders, haemolytic illness and liver failure.

5. Pre-eclampsia, HELLP Syndrome and Acute fatty liver in the pregnancy

Pre-eclampsia, defined as new-onset with high blood pressure and high protein levels after 20 weeks of pregnancy, affects 3-5% of all pregnant women and is a primary cause of maternal, foetal, and neonatal morbidity and mortality worldwide [30-32]. Gestational hypertension is considered to develop due to insufficient cytotrophoblast penetration of the uterine vasculature, which results in placental ischemia and the subsequent production of pro-inflammatory cytokines, intrinsic immunological activation, and endothelial abnormalities [33]. It was believed to be largely a hypertensive condition, pre—eclampsia has become recognised as a multi system disorder Pre-eclampsia is defined by ACOG as raised systolic blood pressure upto 140 mmofHg/more and diastolic pressure up to 90 mmofHg /more on 2 separate occurrences minimum three to 4 hours gap after twenty weeks of gestation among pregnant women who were having the normal blood pressure, albumin levels in urine and serum creatinine.[34].

HELLP syndrome is frequently related with pre-eclampsia, as it affects up to 20% of women suffering with severe pre-eclampsia [35, 36]. Lactate dehydrogenase raised to 600 IU/L or higher, aspartate aminotransferase and alanine aminotransferase elevated more two times more than maximum values of the normal, and platelet tally 100,000 109/L are common diagnostic criteria. HELLP syndrome has a pathogenesis comparable with pre-eclampsia in that women with HELLP syndrome have dysfunctional placental implantation, immune cell stimulation, and vascular dysfunction. HELLP syndrome is also linked to higher incidence of maternal death rates [37, 38]. While the processes underlying pre-eclampsia and HELLP syndrome are not entirely understood, the inspecting of oedema, high blood pre, and high albumin levels in urine.

Only approximately 1% of pre-eclampsia patients get AKI as a complication. 25 AKI, on the other hand, is significantly more frequent when it is coupled with HELLP, appearing in 7-15% of patients. [39] Although new-onset

hypertension and proteinuria after 20 weeks of pregnancy are typically used to diagnose pre-eclampsia, these results can also be seen in various disorders such as acute fatty liver in pregnancy, aHUS, and nephritis. The clinical clues that can assist in making an accurate diagnosis. Moreover, angiogenesis variables including soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), and dissolved endoglin (sEng) amounts could be useful for distinguishing among pre-eclampsia and chronic hypertensive, renal, disorders and ESRD on dialysis. [40]

Acute fatty liver of pregnancy (AFLP) is an uncommon condition that affects 1 in 10,000 deliveries. It is caused by a foetal deficit of long chain 3-hydroxyl coenzyme A dehydrogenase (LCHAD), that results in an high of foetal unrestricted fats which pass the placental and are toxic to the liver . [41]. .In 3rd trimester, women typically appear with exhaustion, nausea, migraine, hypoglycemic, and lactic acidosis. Liver metabolic derangement, including elevations among transaminases, alkaline phosphatase, and bilirubin, as well as hematological irregularities, including leukocytosis, thrombocytopenia, and DIC, are examples of testing disorders. It can also cause AKI and proteinuria, which might be mistaken for pre-eclampsia/HELLP. [42] Low blood sugar and visceral effusion are distinct clinical characteristics of AFLP. Approximately to 50percent of the total of patients are with AFLP might also have simultaneous pre-eclampsia, finding an actual identification even more challenging. Interestingly, the therapies both for groups are frequently same as. A liver biopsy revealed microvesicular steatosis and cytoplasmic enlargement. A liver biopsy is generally rarely necessary for diagnosis and can be risky, particularly when there is concurrent coagulopathy, although it could be useful in the initial stages of sickness if indeed the diagnostic is questionable. The hallmarks of treatment include expedited delivery, palliative therapy, & thorough surveillance.

6. Association between HIV infection, preeclampsia and renal disorders

Renin-Angiotensin-Aldosterone System (RAAS) and vasoconstrictor angiotensin II receptors are main responsible increasing the blood pressure in preeclampsia. Pathophysiology in preeclampsia and insulin resistance in HIV infection associated with irregular stimulation of the renin angiotensin. [48]. Because of the HIV infection, renin production in immune cells will be increased, thus, RAAS will be activated. Moreover, via renin signalling force causes the HIVreplication. Bouba et al.,stated that there is a substantialconnotationwith the circulation of angiotensin (AGT) gene polymorphisms and preeclampsia[49]. Aung et al. stated that there is drastic association in increasing the AGT variant in preeclampsia. [50]. Dissimilarly to the AGT gene polymorphisms, the ATR1 optional reported the significant relevance with preeclampsia. [51]. In addition, ATR II showed significant relation with preeclampsia among the women with BMI above 25 kg/m2 [52].

The prevalence of renal disorders such as acute renal injury, chronic renal diseases and renal treatment associated toxicity is high in the HIV infected patients. Identification of renal diseases at an early stage is important in these patients as chronic kidney diseases can lead high morbidity and mortality rates. Increasing number of cases with HIV noticed more chronic kidney diseases and also these patients require dialysis and kidney transplantations. [47]. Thus the early detection, timely screening and therapeutic measures help to reducing the existing burden of the chronic kidney diseases. The HIV associated nephropathy diseases are broadly reduced after using the antiretroviral therapy, however, other kidney diseases prevalence is still high. The tenofovirdisoproxil fumarate (TDF) is administered along with the other antiretroviral drugs for HIV patients and it is also used as pre-exposure prophylactic drug for preventing the sexually transmitted

HIV infections, and chronic Hepatic B treatment. [44,45] Due to the amplified benefits of the TDS, it is highly used as one of the anti-retroviral drugs [46].

The association between the HIV treatment and RAAS is not clear. Nevertheless, HIV infection can raise the risk of increasing blood pressure. In Cameroon study, 36.4 % of the HIV patients developed hypertension [53]. Moreover,preeclampsia has been reported in patients with HIV. In contrast, studies reported that, HIV infected pregnant women are protected against the preeclampsia but it is developed after initiation of ART.[54] . However, pathogenesis of this process and effect of ART on RAAS expression and its variants poorly explained, thus it requires further research evidence. Furthermore, in extreme instances of infection, SARS-CoV-2 infestation uses ACE2 to generate endothelial dysfunction and hypertensive, resembling angiotensin II-mediated PE [55]. ACE2 upregulation during pregnant may be a risk factor for SARS-CoV-2 infections and subsequent PE pathogenesis.

7. Management of preeclampsia women with AKI

Identification of the underlying source of injury, capacity restoration treatment, avoidance of future damage, early beginning of kidney replacement therapy, and rapid delivery of the foetus, if needed, are general strategies to treat prenatal AKI. Volume replacement is essential in pre-renal conditions, but the quantity of fluid restoration must be managed efficiently since patients with endotoxin-mediated damage or pre-eclampsia can develop the respiratory failure. Problems of acute kidney injury managed similarly to women without pregnancy, i.e. hyperkalemia with cation exchange beads for most cases, lactic acidosis with alkali treatment, overload volume problems are treated with the loop diuretics, and anaemia is managed with blood transfusion therapy. When these efforts are ineffective, or if the kidney damage worsens, renal replacement treatment would be required. Particular treatment options for AKI are determined by the fundamental factors for the illness. In patients of glomerulonephritis confirmed by biopsy treated with steroids. For severe pre-eclampsia, HELLP syndrome, and Acute fatty liver in pregancy, the foetus should be delivered as soon as possible. Plasmapheresis and the prescription of eculizumab are required for the treatment of TMAs, including TTP and atypical HUS (for atypical HUS). If the foetus must be delivered before 34 weeks of gestation, glucocorticoids must be administered to decrease the likelihood of new-born respiratory distress. [43]

Pre-eclampsia/HELLP syndrome/pregnancy acute fatty liver, considerable treatment is pregnancy termination. Expectant therapy may be undertaken in certain patients of pre-eclampsia without signs of end-organ engagement (neurological clinical features, hepatic or renal abnormalities, or low platelets) underneath the supervision specialised obstetricians at tertiary care hospital. Clinical and obstetric factors influence the mode of birth (vaginal vs. C-section). To prevent the development of AKI in complicated cases, intensive treatment with intravenous fluids and delivery of blood and other blood components when needed are required. To prevent maternal cerebrovascular and coronary accidents, blood pressure must be managed while keeping foetal well-being in mind. Systemic magnesium sulphate (4-gram IV bolus followed by 2 grams/hour) is used to avoid maternal seizures, with vigilant surveillance for signs of respiratory failure. To avoid toxicity, dosage may need to be modified and magnesium levels checked when there is malfunctioning of kidney. If a preterm foetus is delivered, paediatrician must be present.

8. Recommended guidelines for management of the HIV infection and preeclampsia

Because there is a paucity of information on medicine interactions in HIV-associated pregnancies, existing guidelines regarding the use of antihypertensive medications in preeclampsia are appropriate. Because there is no long-term data on the use of anti-hypertensive medicines in case with HIV with the treatment of HAART, scientific management ought to be scenario. In severe PIH , anti-hypertensive medications needs to be taken to reduce the instantaneouscomplications in women and foetus . Unlike HAART, an innate immunity can suppress viremia in gestation. [56]. Pregnancy, on the other hand, damages the immune system. As a result, momentarily discontinuing ARV use in pregnant women to avoid PE progression is not recommended since the immune system may not be robust enough to combat viremia. Further research in a pregnancy population is needed to evaluate antibodies neutralisation without the use of ARVs.

Clinically, it is recommended that people having Human immunodeficiency virus (HIV monitor their viral load precedingfor the pregnancy, as excessive viral load has no association with embryo or foetal loss. There is lack of information on the efficacy of antihypertensive medicines in pregnant; nevertheless, Labetalol, an alpha beta blocker, may be an acceptable option for the treatment of HIV-infected PIH mothers. Remarkably, there is presently no evidence that preeclampsia c raises the risk HIV transmission to mother and foetus.

9. Conclusion

Even though the general prevalence of acute kidney injury is decreasing across the globe, the actual amount of acute kidney deaths remains unacceptably large. The diagnosis AKI in pregnancy becomes difficult particularly in those with overlapped symptoms including pre-eclampsia/HELLP, and glomerulonephritis. In making an appropriate evaluation, clinical judgement and expertise becomes crucial. Monitoring angiogenic markers could be useful in determining the presence of pre-eclampsia. Advanced genomic or serologic tests may have the potential to aid in the identification of women with acute fatty liver and unusual HUS but they are not currently available for routine clinical usage. Research must concentrate on illness diagnostic biomarkers, only with understanding the fast accessibility to information is required to influence managerial decisions and impact outcomes. The mentioned difficulties are important when the prevalence of Acute KidneyInjury isaugmenting the well advanced nations, with the raise being linked with the tendency of postponing pregnancy, which may be associated with rises in mother co-morbidities. Moreover, an increased using assisted reproduction, which usually result in multiple stages of pregnancy, may raise the risk of acute kidney injury.

This review looks at available research that might help reduce the major effective (preeclampsia) and indirectly (HIV) reasons for maternal death worldwide. Both preeclampsia and HIV infection have conflicting immune responses; nevertheless, the immunological restoration that happens with ART use balances this out. Furthermore, these circumstances result in dysfunction of endothelial cells.HIV-1 accessory and matrix molecules each make contribution to oxidative, mortality, and the release of pro-inflammatory mediators, adhesion molecules, and angiogenesis. These events also occur in the hypoxic milieu of PE; thus, there is an intensification of these processes in the combination of HIV linked PE, impacting signalling pathways. It is probable that HIV-1 has acquired methods to avoid complement-mediated destruction while enhancing its infection rate of human host, disrupting foetal resistance at the parental contact.

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