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PREECLAMPSIA (V GAROVIC, SECTION EDITOR)

A Review of Angiogenic Imbalance in HIV-Infected Hypertensive Disorders of Pregnancy

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Abstract

Purpose of Review This review provides a comprehensive insight into the angiogenic profile of hypertensive and normotensive pregnancies compromised by HIV infection. Furthermore, we evaluate the economic implementation of the sFlt-1/PlGF ratio and review the reports on therapeutic apheresis in limiting sFlt-1 production.

Recent Findings In preeclampsia, an increased expression of sFlt-1 triggers angiogenic imbalance. Women of African ancestry have high levels of angiogenic factors than other racial groups. The sFlt-1/PlGF ratio shows promise in the early assessment of preeclampsia, while sFlt-1 apheresis restores angiogenic imbalance. Studies suggest antiretroviral therapy does not impact the angiogenic shift in preeclampsia development.

Summary The angiogenic profile in pregnant women of different races influences preeclampsia development. Despite the opposing immune response in HIV infection and preeclampsia, the HIV *tat* protein strongly mimics vascular endothelial growth factor (VEGF); hence, it is plausible to assume that HIV infection may ameliorate the angiogenic imbalance in preeclampsia.

Keywords Angiogenesis · Preeclampsia · Soluble fms-like tyrosine kinase 1 · Vascular endothelial growth factor · Placental growth factor · HIV

Introduction

Angiogenesis involves the development of new blood vessels from pre-existing ones. Angiogenic factors regulate placental vasculogenesis, the process being initiated by a variety of growth factors such as vascular endothelial growth factor (VEGF), placental growth factor (PlGF), and endoglin (Eng) [1]. The switch from vasculogenesis to angiogenesis is regulated by a dynamic shift in equilibrium between angiogenic factors and their inhibitors [2]. In pregnancy, a balance between angiogenic and anti-angiogenic factors exists; while in hypertensive disorders of pregnancy (HDP), this imbalance is tipped in favor of anti-angiogenesis that contributes to endothelial dysfunction and end organ damage [3].

Approximately 6–8% of all pregnancies are affected by HDP [4]. According to the International Society for the Study of Hypertension in Pregnancy, HDP are classified into (i) chronic hypertension, i.e., BP > 140/90 mmHg taken on two occasions 4 h apart before 20 weeks of pregnancy or pre-existing hypertension; (ii) gestational hypertension (GH) which is elevated BP of > 140/90 mmHg occurring for the first time after the 20th week of pregnancy; (iii) preeclampsia (PE), i.e., BP > 140/90 mmHg at least one plus proteinuria measured by urinary dipstick; PE with severe features such as BP > 160 mmHg systolic and OR > 110 mmHg diastolic blood pressure, nausea and vomiting, epigastric pain, and headaches; (iv) eclampsia (high BP associated with convulsions); and (v) the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet counts) [5••].

Globally, HDP is a major cause of maternal morbidity and mortality [6]. The prevalence of HDP, GH, and PE are 5.2–

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8.2%, 1.8–4.4%, and 0.2–9.2%, respectively [7]. Preeclampsia and GH are the main sub-types of HDP. In Sub-Saharan Africa, HDP and HIV infections are the commonest causes of maternal deaths [8••]. Due to the high HIV prevalence setting (12.7%) [9], and subsequent risk of infection, South Africa remains burdened with 19% of the global HIV-infected population, 15% of new infections, and 11% of AIDS-related deaths [10].

Severe PE and eclampsia account for the majority of deaths associated with HDP. The exact etiology of PE remains unknown. However, current views suggest it is a two-stage disorder [11•]. The first stage is poor placentation emanating from inadequate trophoblast invasion that results in impaired uterine spiral artery remodeling with consequential decrease in blood flow and placental oxidative stress; the second stage is associated with a heightened maternal inflammatory response, systemic endothelial dysfunction, and the clinical signs and symptoms of PE [11•, 12].

It is commonly accepted that PE is a heterogenous entity of two sub-types based on disease onset. Early-onset PE (EOPE) is diagnosed as < 33 gestational weeks and late-onset > 34 weeks [13]. The early-onset sub-type is the most severe clinical variant of PE and contributes to adverse maternal and perinatal outcomes [13]. Failed transformation of the maternal spiral arteries leads to hypoperfusion of the placenta resulting in signs of fetal growth restriction (FGR) [14]. The latter sub-type is not associated in most cases with placental hypoperfusion, as there are minimal changes to the spiral arteries. Both PE entities show an enhanced systemic inflammatory response resulting in exposure of vessels to excessive oxidative stress [15].

The changes in the inflammatory response in HDP and the immunosuppressive effects of HIV infection upset the equilibrium between pro- and anti-angiogenesis with an increased susceptibility to PE development. By describing observed changes in the circulating angiogenic factors in HDP, this review aims to provide further insight on the angiogenic profile in HDP with HIV infection. Data on angiogenic levels based on race are limited; therefore, this paper evaluates the impact of race on angiogenic equipoise. We also provide an extensive review of the role of the sFlt-1/PlGF ratio in establishing PE diagnosis together with its economic implementation in addition to examining the effect of sFlt-1 therapeutic apheresis.

The Altered Angiogenic State in HDP

Circulating Angiogenic Factors: VEGF, PlGF, sFlt-1

Non-pregnant hypertensive women exhibit a loss of endothelial cell integrity through impaired flow-mediated dilatation and the upregulation of von Willebrand plasma factor (vWF) and soluble E selectin [16]. Microvascular rarefaction (reduced number of arterioles and capillaries) is associated with the pathogenesis of high blood pressure in hypertension [17]. Additionally, capillary size reduction contributes to increased peripheral vascular resistance causing blood pressure [18]. As angiogenic growth factors are major regulators of blood vessel formation, abnormal angiogenesis exacerbates these structural changes [16].

In PE, the ischemic microenvironment leads to the overproduction of soluble factors released into the maternal circulation that causes endothelial cell dysfunction [19]. Maynard et al. confirmed that excess soluble fms-like tyrosine kinase 1 (sFlt-1) or soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) leads to a decreased production of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), that result in increased systemic levels of sFlt-1 in PE which remits after delivery. Several other research groups have also reported that increased circulating sFlt-1 in PE is associated with decreased circulating levels of free VEGF and PlGF [20, 21].

Vascular endothelial growth factor and PlGF are known to promote vascular endothelial cell proliferation that is vital for normal placentation [22]. Evidence of abnormal angiogenesis in hypertension however, includes increased expression of VEGF, suggesting deregulation of VEGF balance [23]. The VEGF family comprises of various isoforms, namely VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PlGF [24]. VEGF-A is the most commonly studied isoform; however, there is a paucity of data on VEGF-B, VEGF-C, and VEGF-D [25•]. High-affinity receptor tyrosine kinases for VEGF includes VEGFR-1 (also known as fms-like tyrosine kinase receptor (Flt-1) and VEGFR-2 (also known as kinase insert domain receptor (Flk-1/KDR) [21]. Structurally, these receptors comprise extracellular, transmembrane, and intracellular domains. VEGF-A and VEGF-B bind to VEGFR-1 (Flt-1); however, in PE, binding is prohibited by the antagonist sFlt-1 or sVEGFR-1, a spliced soluble variant of VEGFR-1 that lacks the transmembrane and intra-cytoplasmic domains [11•]. VEGFR-2 is an antagonist to VEGF, in that it increases mean arterial pressure [26••]. VEGF-C and VEGF-D bind to a third receptor, VEGFR-3, to facilitate lymphangiogenesis [27].

The predominant sources of VEGF are endothelial, stromal, and hematopoietic cells. VEGF synthesis occurs in response to hypoxia and stimulatory mediators including transforming growth factor (TGF-β), interleukins, and platelet-derived growth factors [26••]. VEGF causes vasodilatory effects via the production of nitric oxide and prostacyclin. Decreased nitric oxide production and increased endothelin secretion by the antagonizing effects of sFlt-1 is a contributing factor to HDP [28, 29]. Importantly, VEGF supports vasculogenesis and angiogenesis and is involved in regulating vascular permeability and homeostasis [26••].

Additionally, VEGF induces glomeruli endothelial fenestration formation, hence regulating vascular permeability

[26••, 30•]. Eremina et al. demonstrated that VEGF is involved in regulating endothelial fenestral density in genetically modified mice by reducing VEGF expression, thereby producing a PE-like phenotype such as proteinuria and endothelial damage [31]. Moreover, loss of endothelial fenestrae in PE is due to the excess circulation of sFlt-1 that has an inhibitory effect on VEGF signaling [30•].

Felmeden et al. tested the relationship between endothelial damage and angiogenesis by assessing plasma levels of vWF, VEGF, and sFLt-1. Plasma VEGF and vWf levels were higher while sFlt-1 levels were reduced in the hypertensive group compared with the controls. After intensified cardiovascular risk factor management, VEGF and vWf levels decreased substantially as opposed to an increase of sFlt-1 [16]. These findings suggest dysfunctional angiogenesis and subsequent endothelial damage in hypertension. However, upon initiation of anti-hypertensive and pharmacologic treatment, management of hypertension may be improved.

While VEGF-A acts through two principal receptors, PlGF facilitates the action of VEGF by competitively binding to the VEGFR-1 receptor only [32]. VEGF-A controls angiogenesis in the first 25 weeks of gestation, while PlGF takes over until term [33]. PlGF displaces the shift of VEGF from VEGFR-1 to VEGFR-2 as the kinase activity of this receptor is tenfold more potent than VEGFR-1, thereby enhancing angiogenesis [34]. PlGF expression predominantly occurs in the placenta, while a lower expression occurs in other tissues including the heart, lung, thyroid, liver, skeletal muscle, and bone. However, decreasing levels of PlGF may emanate during syncytiotrophoblast stress [35].

As a spliced mRNA variant of VEGFR-1 or the Flt-1 gene, sFlt-1 protein is an antagonist of pro-angiogenic factor signaling in the maternal vasculature [24, 30•]. Flt-1 encodes proteins and is capable of interacting with free-circulating growth factors rather than binding them [21]. During normal pregnancy, Flt-1 predominantly occurs in the form of sFlt-1, produced by the syncytiotrophoblast layer of the chorionic villi [36••, 37]. Modest concentrations of VEGF, PlGF, and sFlt-1 are produced in normal pregnancy. However, in PE, an excess of sFlt-1 in the maternal plasma binds to VEGF and PlGF thereby preventing their interaction with their two main endothelial cell-surface receptors, Flt-1 and fetal liver kinase 1 (Flk-1). Increased levels of sFlt-1 are released from placental syncytiotrophoblast microparticles in response to a hypoxic microenvironment with resultant placental ischemia [3]. The lack of physiologic remodeling of spiral arteries is the main contributor to this hypoxic microenvironment and the overproduction of sFlt-1 [38].

A study by Rajakumar et al. reported that in PE, syncytial knots of the syncytiotrophoblast are enriched with sFlt-1 protein. Moreover, the presence of syncytial knots are enhanced in the third trimester of preeclamptic compared with normal pregnancies, with concomitant sFlt-1 increase. Syncytial knots detach from placental villi through fission, resulting in free, multinucleated syncytial aggregates heavily loaded with sFlt-1, as well as being able to synthesize additional sFlt-1 from endogenous stores of mRNA [37]. Correa et al. noted similar placental pathologic features between PE and GH pregnancies, although the placentae from of PE women were populated with a greater number of syncytial knots.

Circulating sFlt-1 levels increase at 5–6 weeks gestational age before clinical symptoms appear and culminate with the onset of disease [20, 39, 40]. Moreover, sFLt-1 is significantly elevated in women with established PE, as demonstrated by Chaiworapongsa et al. However, a fall in sFlt-1 concentration following delivery correlates with improved clinical symptoms [19]. Govender et al. demonstrated elevations in both sFlt-1 and sEng compared with PlGF and TGF-β in Black South African PE compared with normotensive pregnant women at term [41]. These results are corroborated by previous reports [19, 41–43]. Furthermore, sFlt-1 levels are highest among women with severe forms of the disease, including pre-term PE or in women who gave birth to small for gestational age (SGA) babies [20, 42, 44].

Jakovljevic et al. investigated serum sFlt-1, VEGF, and PlGF levels at 11–14 gestational weeks between different HDP sub-groups PE, GH, CH, miscarriage, and a control group. They report an upregulation of sFlt-1 in PE and the miscarriage sub-groups, with a significant decrease of VEGF across the entire study population. Similar high levels of sFlt-1 with a concurrent decrease in VEGF were observed in the chronic and GH sub-groups compared with controls [22], thereby suggesting that an angiogenic imbalance in early pregnancy may impact on the pathophysiology of placental dysfunction that influences the development of HDP.

Moreover, Jakovljevic et al. suggests that the low levels of VEGF across the sub-groups of HDP correlate with reduced trophoblast invasion in abnormal placentation. As a result, uteroplacental hypoperfusion and ischemia persists, causing the pathognomonic lesion of endothelial dysfunction and subsequent clinical development of HDP.

sEng, PECAM, and the Angiopoietins

Endoglin (Eng) is a co-receptor for the TGF family, including TGF-β1 and TGF-β3. Endoglin mediates TGF activity via the regulation of vascular remodeling and hemostasis. This is achieved through the activation of the endothelial nitric oxide synthase pathway [26••], which induces cell migration and proliferation to control vascular remodeling [24]. However, a truncated variant of Eng, sEng, expressed by trophoblast cells antagonizes TGF-β binding to its receptor, thereby preventing vasodilation [41].

Additionally, metalloprotease 14 (MMP14) stimulates the shedding of circulating sEng from membrane-bound endoglin which contributes to an upregulation of sEng in PE [42]. sEng

shedding is also triggered by inflammation, TNF-α, endothelial injury, and anti-Eng antibodies [45]. Furthermore, upon clustering of exosomes with MMP14, sEng may be released from the placenta [46]. Therefore, maternal sEng levels are upregulated prior to the onset of PE [20]. Govender et al. demonstrated an upregulation of sEng and sFlt-1 in PE, and it is presumed the presence of sFlt-1 is a direct stimulus for increased sEng expression [47].

Importantly, sEng correlates with disease severity and declines after delivery. In an animal model, using an adenoviral expression system in pregnant rats, the administration of both sFlt-1 and sEng led to endothelial dysfunction thereby inducing clinical symptoms of a severe PE-like multi-phenotype including the HELLP syndrome and FGR [48]. These results suggest that when sEng acts in concert with sFlt-1, the hallmark features of severe PE are induced.

Noori et al. found that sFLt-1 and sEng were significantly elevated in a PE group compared with a GH group, supporting the theory that PE is an anti-angiogenic state. When performing a sonographic measure of vascular endothelium function by flow-mediated dilatation, endothelial abnormalities were noted in PE, while endothelial function in the GH group were similar to the non-hypertensive control group [49]. These findings are corroborated by Yelumalai et al. who reported that sFlt-1 levels are not significantly increased in patients with GH. Therefore, it is possible to assume sFlt-1 is critical in PE but not in GH development [50].

Early and late-onset pre-eclamptic women at 26 and 29 gestational weeks with SGA neonates have a significant elevation of plasma sFlt-1 levels compared with normotensive women [51]. In the case of sEng, despite high plasma levels during normal pregnancy, sEng levels escalate significantly in early and late-onset PE at 23 and 30 gestational weeks respectively [51]. Previous studies have shown that SGA pregnancies disturbed by abnormal anti-angiogenic factors correlate with preterm delivery [52].

Platelet endothelial cell adhesion molecule-1 (PECAM-1) is another significant angiogenic receptor in vascular development [53]. PECAM-1 is expressed on the surface of circulating monocytes, platelets, and neutrophils and functions as a constituent of the endothelial intercellular junction thereby facilitating angiogenesis and trans-endothelial migration of leukocytes. Notably, cytotrophoblasts lack PECAM-1 expression as it is decreased in PE placentas compared with controls [54]. Albeit non-significant, Thakoordeen et al. observed a lower trend of PECAM-1 expression in PE compared with normotensive controls, indicative of the shallow trophoblast invasion in PE [55]. Shallow trophoblast invasion is also associated with abnormal expression of cell adhesion molecules on trophoblast cells [54]. Lyall et al. reported similar findings of an absence of a significant difference of PECAM-1 concentration between PE and normotensive pregnancies [56].

During normal pregnancy, the angiopoietin/Tie system plays a critical role in regulating the survival of endothelial cells and maternal vasculogenesis [57]. The angiopoietin system includes four ligands (Ang-1, Ang-2, Ang-3, and Ang-4) and two corresponding tyrosine kinase receptors (Tie-1 and Tie-2) [56]. Ang-1 and Ang-2 are the most well characterized of the angiopoietin family. Both Ang-1 and Ang-2 are specific to Tie-2 binding [58]. Tie-2 expression occurs on endothelial cells and embryonic hemopoietic cells and is required for vasculogenesis [59]. Ang-2 primarily acts as an antagonist of Ang-1 signaling involved in promoting angiogenesis in the presence of VEGF [60]. During normal pregnancy, the most likely source of circulating Ang-2 is the placenta [60]. Hirokoshi et al. observed increased Ang-2 serum levels in healthy pregnant women compared with non-pregnant controls. In the post-partum period however, Ang-2 levels returned to those of non-pregnant controls as Ang-2 serum levels decrease rapidly following delivery [60].

The expression of angiopoietins in PE is conflicting. Some authors have reported that in PE, circulating concentrations of Ang-2 [60, 61] and Tie-2 are downregulated [62, 63]. On the contrary, Leinonen et al. reported that in women who subsequently developed PE, an upward trend of Ang-2 concentrations occur during 16–20 gestational weeks [64]. Similarly, a study by Mbhele et al. demonstrated elevated levels of Ang-2 in PE compared with normotensive pregnancies [65]. These results indicate that the increased expression of placental anti-angiogenic factors has a strong association to the increase of circulating maternal factors [19].

The Immune Response in an Altered Angiogenic State

During pregnancy, the innate immune system is activated as the first line of defense [66]. Toll-like receptors (TLRS) have key attack mechanisms in innate immunity. Activation of TLR9, a member of the TLR family, triggers signaling pathways that stimulate various pro-inflammatory transcription factors (nuclear factor-κB (NF-κB), activated protein-1 (AP-1), and interferon regulatory factor 7 (IRF7)) [67, 68]. TLR9 expression is also substantially increased in the placenta and dendritic cells in PE compared with normotensive patients [66, 69, 70].

He et al. reported that a TLR9-mediated inflammatory response interferes with spiral artery remodeling and has a suppressive effect on angiogenesis. TLR9 and sFLt-1 were upregulated in their study with a downregulation of VEGF-A, acquiescent of the limited trophoblast invasion in PE. TLR9 stimulates TNF-α expression which in turn fuels the release of sFlt-1 [71]. Thus, TLR-9 is capable of regulating the expression of VEGF-A and sFlt-1 at the maternal–fetal interface, implicating its role in PE pathogenesis [68]. Furthermore, VEGF-A and sFLt-1 are downstream pro/anti-angiogenic factors of TLR9 signaling.

Does Race Impact Angiogenesis?

Data on angiogenic and anti-angiogenic profiles and correlation to PE development among different racial groups is limited. Yang et al. investigated mid-trimester serum levels of angiogenic factors and their association to EOPE in 197 women (90 Whites, 67 Hispanics, and 40 Blacks) from 2000 to 2007. White and Hispanic women had higher adjusted sFlt-1 levels compared with controls, while a reverse trend for PlGF was observed in Black women.

Similarly, elevated sFlt-1 levels are associated with an increased risk of EOPE in both White and Hispanic races [72]. Black women have increased levels of PlGF in both case and controls compared with Hispanics and Whites. Interestingly, Hispanic cases had higher adjusted means of sEng than White and Black cases. Black women also had the weakest association of EOPE with PlGF and sEng compared with White and Hispanics, suggesting the strength of the relationship between angiogenic factors and their association to PE differs by race [72]. Conflicting results were found by Mijal et al. who observed higher levels of sFlt-1, sEng, and PlGF in Black women compared with women of different races [73]. Furthermore, studies from England reported that adjusted first trimester levels of PlGF were elevated in Black women compared with White women [74, 75]. Racial-ethnic differences of angiogenic markers suggest each racial group has its own key pathophysiological mechanism underlying PE development [72].

The Altered Angiogenic State in HIV Infection

The observations of Wimalasundera et al. suggest that the standard of care regimen of HIV-positive pregnant women affect the rate of PE development, due to the neutralized immune response that occurs when PE and HIV infection coexist [47].

However, in a study investigating angiogenic factors in HIV-positive preeclamptic women, Govender et al. reported that irrespective of HIV status and pregnancy type, anti-angiogenic factors were not affected in PE development as no significant difference for sFlt-1, sEng, and PlGF levels were detected [47].

Govender et al. investigated variations between pro-angiogenic (PlGF and TGF-β1) and anti-angiogenic (sFLt-1 and sEng) factors in a HIV-infected preeclamptic population. sFlt-1 and sEng were upregulated in PE compared with the normotensive pregnant groups. The elevated levels of these anti-angiogenic factors confirm previous reports [19, 51]. Increased PlGF levels were observed in HIV-negative normotensive pregnant women *vs* both the HIV-negative and HIV-positive PE groups. These results are expected as PlGF supplements the pro-angiogenic effects of VEGF, thereby supporting angiogenesis [41]. As this trend is reversed in the HIV-positive normotensive group, it is reasonable to assume that the immunodeficiency stimulated by HIV infection was effective in suppressing the hyperreactive milieu of the maternal inflammatory response, thereby increasing susceptibility to PE development. No significant expression was detected for TGF-β1 expression between the PE and normotensive pregnant groups [41].

In a novel study, Shange et al. correlated the association between HIV and circulating serum levels of pro-angiogenic factors (VEGF-A, VEGF-C, and VEGF-D) in PE. Based on HIV-status and irrespective of pregnancy type, no significant difference was detected in serum concentrations of 3 VEGF isoforms, *viz*., VEGF-A, VEGF-C, and VEGF-D [25•]. VEGF-A, VEGF-C, and VEGF-D serum concentrations were downregulated in HIV-positive compared with HIV-negative women [25•], possibly due to interferences in VEGF signaling, resulting in defective activity of the HIV *tat* protein [76]. The HIV-1 accessory protein, *tat*, is released from infected T cells and drastically enhances the efficiency of viral replication [76]. Moreover, *tat* is able to mimic VEGF activity through the specific binding and activation of the VEGFR-2 (Flk-1) tyrosine kinase receptor [22]. This decrease of serum VEGF in HIV-positive women may also be attributed to the downregulation of VEGF signaling via HIV protease inhibitors by obstructing the phosphatidylinositol 3-kinase/protein kinase B signaling pathway [77] (Fig. 1). Furthermore, previous studies revealed that HIV-1 *tat* protein induced the expression of ICAM-1 and VCAM-1, suggesting a possible mechanism by which HIV-1 infection contributes to endothelial injury and accelerated atherosclerosis [80, 81].

Evidence suggests that the interaction between VEGF and its receptor VEGFR-2 (Flk-1/KDR) plays a critical role in the pathogenesis of AIDS-Kaposi's sarcoma (KS) [76]. Kaposi's sarcoma cells secrete VEGF, and a major signaling component of VEGF signal transduction is Src kinase. The Src protein kinase family mediates downstream signals that activate the MAP kinase pathway required for VEGF-induced cell proliferation in different cell types [82]. In a study by Munshi et al., the c-Src kinase inhibitor PP1 inhibits VEGF-induced cell growth. Furthermore, this group reported that inhibiting Src kinase led to a significant decrease in MAP kinase activation, albeit lacking an effect on Flk-1/KDR. Therefore, c-Src, an inhibitor in AIDS-KS therapeutics impedes tumor growth and spread by targeting VEGF mitogenic signaling.

On another note, HIV infection is associated with immune suppression [83] while in normal pregnancies, there is a slight elevation in the maternal immune response to the fetal allograft. The chronic state of infection of HIV-positive individuals promotes chronic arterial inflammation and injury, subsequently stimulating dysfunction of the endothelium, atherosclerosis, and thrombosis [84]. Additional studies (Table 1) reveal low-grade systemic inflammation is not only central to PE development, but also in chronic and gestational hypertension [89, 90].

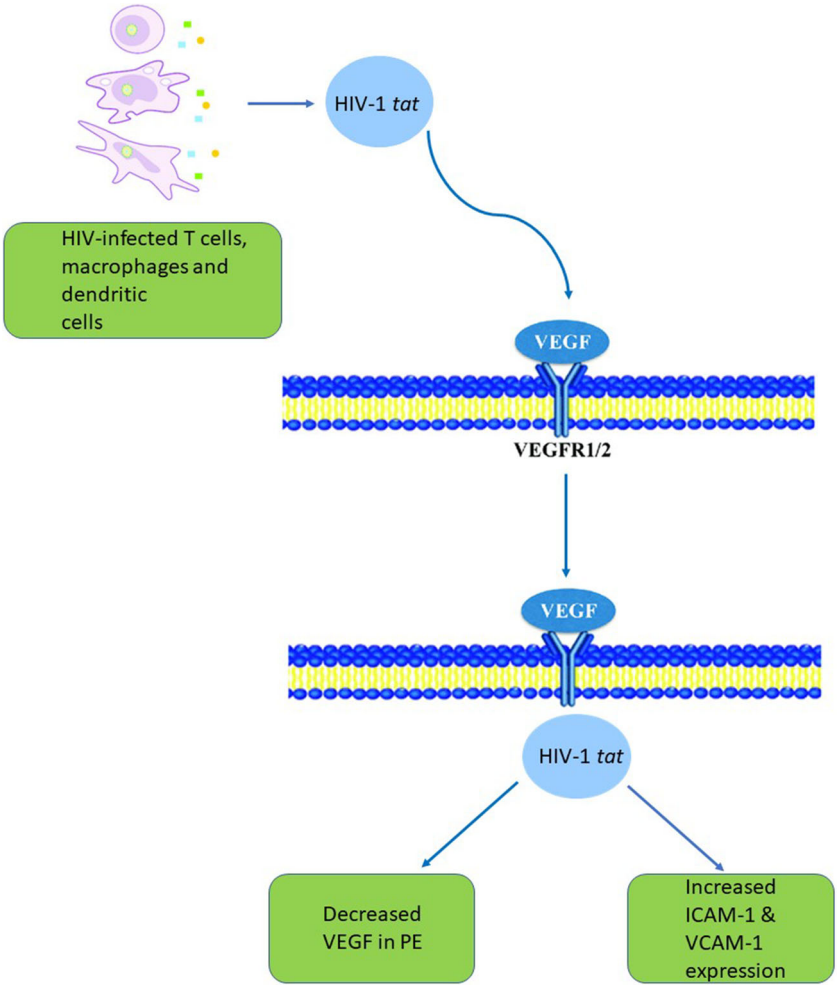

Fig. 1 HIV-1 *Tat* protein in VEGF activity. *Tat* protein is released from infected cells and mimics VEGF activity by binding to the VEGFR-2 receptor. As a result, serum VEGF is decreased in HIV-positive women, with an increased expression of ICAM-1 and VCAM-1. Image is adapted from Foreman [78] and Guo et al. [79]

sFlt-1 Prognostic Performance

In high-income countries, maternal and antenatal care revolve around early identification of PE facilitating better management. In these countries, clinical studies have initiated the use of angiogenic biomarkers to diagnosis pre-term PE as their systemic concentrations act as an index of disease severity [30•, 91]. Changes in these biomarker levels occur prior to the clinical manifestation of PE, *viz.*, sFlt-1 is upregulated 5 weeks before the onset of PE with parallel decreased concentration of free-circulating VEGF and PlGF [20]. The sFlt-1/PlGF ratio has recently been regarded as a promising tool for assessing angiogenic imbalance in the first and second trimester of pregnancy [24, 30•]. Verhloren et al. reported that the sFlt-1/PlGF ratio was significantly higher in women with PE compared with women with GH, indicating the reliability of the sFlt-1/PlGF ratio in distinguishing different cases of HDP.

The PROGNOSIS (Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study) to validate a serum ratio of sFlt-1/PlGF at defined cut-off points was conducted to diagnose PE development in singleton pregnancies. A low sFlt-1/PlGF ratio below a cut-off of 38 excludes the presence of PE within the following week (negative predictive value, 99.3%; sensitivity, 80%; and specificity, 78.3%), while a high sFlt-1/PlGF ratio above 38 within the next 4 weeks is an indication of possible PE development (positive predictive value, 36.7%; sensitivity, 66.2%; and specificity, 83.1%) [92]. It is therefore plausible to predict the absence of PE irrespective of gestational age, by an sFlt-1/PlGF ratio below 38 in a woman with suspected clinical signs [92]. On the contrary, high PE risk development requiring close clinical surveillance is indicated by a sFlt-1/PlGF ratio between 85 and/or 110, to establish early or late-onset PE, respectively [93].

The primary objective of the STEPS (The Study of Early Preeclampsia in Spain) study evaluated the sFlt-1/PlGF ratio in 729 women at risk of PE development, as a predictive marker for EOPE at 20, 24, and 28 weeks. Secondary objectives included evaluating the ratio for prediction of late-onset PE (LOPE) and using the sFlt-1/PlGF measurement for differentiating between hypertension and PE [94]. In women with EOPE at 20–28 weeks, the median sFlt-1/PlGF ratio was higher than normotensive controls respectively (14.5; < 7), and increased as gestation progressed from 18.4–51.9

Table 1 Summary of additional findings regarding the association between HIV and hypertensive disorders of pregnancy

Author, year	Ref.	Country	Study design	Main findings
Sansone, 2016	[85]	Italy	Retrospective cohort	• Pregnant women on HAART had a significantly higher risk of PE development compared with women without HIV (13.0% *vs* 4.0%) and compared with the non-HAART group (13.0% *vs* 4.6%) • HIV-infected women had an increased risk of pre-term birth < 37 gestational weeks • HIV-infected women had an increased risk of PE
Landi, 2014	[86]	Italy	Prospective cohort	• GH and PE were diagnosed in the following: 3/126 HIV-positive patients (2.38%); 14/140 HIV-negative patients (10%) • HIV-positive pregnant women may be protected against GH and PE • No association between HIV and PE
Machado, 2014	[87]	Latin America and the Caribbean	Prospective cohort	• HAART before conception was associated with PE (OR = 2.3; 95%CI 1.1–4.9) • HIV-positive women with a previous history of PE and use of HAART before contraception have an increased predisposition to PE development
Hall, 2014	[88]	South Africa	Prospective cohort	• Significantly fewer cases of PE in the HIV-positive *vs* HIV-negative group [$n = 35$ (3.2%) *vs* $n = 57$ (4.9%)] • Significantly fewer cases of GH in the HIV-positive *vs* HIV negative group ($p = 0.026$; OR = 0.53 95% CI 0.30–0.94) • PE and GH less common in women on mono- or triple anti-retroviral therapy
Kalumba, 2013	[83]	South Africa	Retrospective case-control	• The rate of HIV/AIDS was lower in the preeclamptic *vs* control group ($p = 0.005$, OR = 0.658) • Among 492 cases of PE, 130 (26.4%) were HIV-positive. In the control group, 183/500 (36.6%) were HIV-positive • HIV-positive women less likely to develop PE

between 24 and 28 weeks. No major changes were observed in women with LOPE between 20 and 28 weeks, remaining lower than 7 [94]. sFlt-1/PlGF ratios were significantly higher in EOPE women than those diagnosed with chronic or gestational hypertension and LOPE [94]. The sFlt-1/PlGF ratio may differentiate PE sub-type and other pregnancy-related hypertensive disorders [95].

Furthermore, comparative studies of serum sFlt-1, sFlt-1/PlGF ratio, and sEng are significantly elevated in PE compared with GH, with levels higher in women with GH than a normotensive population. Hence, a slight increase of sFlt-1, sFlt-1/PlGF ratio, and sEng may be a characteristic of GH development whereas a severe increase may be indicative of PE development [42, 96].

Economic Implementation of the sFlt-1/PlGF Ratio

To test and verify the national impact of the ratio, health economic assessments are required for economic implementation [97]. Vatish et al. developed an Excel-based economic model based on PROGNOSIS data, from a taxpayer's financial perspective to evaluate costs for diagnosing and managing suspected preeclampsia. This UK-based model was aimed at stimulating the progress of a pregnancy, by determining a woman's risk of developing PE and consequent hospitalization or management to rule out possibility of PE development in an outpatient environment [97, 98]. Before PE diagnosis, 36% of women were hospitalized of whom 27% subsequently developed PE. If additional test information had initially been presented, hospitalization could have been reduced to 16%. Introducing the measurement of the sFlt-1/PlGF ratio to detect PE may reduce hospitalization at first presentation by half (56%), a substantial decrease from 36 to 16% [98].

As a consequence of the accuracy of the sFlt-1/PlGF ratio in PE predicting women at risk of PE development [92, 99], the test has since been extrapolated to English, Italian, and German healthcare systems where they also show economic and early identification of at risk patients [97, 98, 100].

Assessing sFlt-1 Therapeutic Apheresis

Potential antagonists of heightened sFlt-1 expression in PE include saturating the system with its own natural pro-angiogenic ligands, *viz*., VEGF or PlGF, administration of anti-sFlt-1 antibodies or small molecules such as statins to

limit sFlt-1 production, and removal of circulating sFlt-1 through an extracorporeal device [101]. Removal of circulating sFlt-1 avoids removing placental sFlt-1, required for maintaining placental health [102]. It is hypothesized that a possible reduction in circulating serum sFlt-1 levels could limit severity of disease as PE progresses [103]. Clinical trials in the UK and USA have recently been conducted using statins to reduce circulating sFlt-1 concentrations, to treat women with EOPE or prevent recurrent cases of the disorder [104, 105].

Also, positively charged sFlt-1 circulates in maternal blood. Through therapeutic apheresis, an open pilot study by Thadhani et al. was conducted using negatively charged plasma-specific dextran sulfate (PSDS) columns to remove positively charged circulating sFlt-1 by adsorption [101, 102]. This apheresis device separates plasma from whole blood before passing through a PSDS column [102]. These complementary negatively charged columns employed in apheresis devices are approved worldwide and are commercially available to facilitate treatment of familial hypercholesterolemia, even in pregnant women [101].

The study assessed 11 pregnant women with pre-term preeclampsia (< 32 weeks) and a sFlt-1/PlGF ratio < 85 who received 17 therapeutic apheresis treatments. Through therapeutic apheresis, mean sFlt-1 levels decreased by 18% (4 h following apheresis treatment) with a concomitant 44% decrease in protein/creatinine ratios. For women receiving single and multiple apheresis, pregnancy continued for 8 and 15 days respectively without adverse maternal or fetal outcomes, as compared with a shortened pregnancy for 3 days in untreated PE controls [102]. A transient drop in BP in the first half hour of initiating apheresis was the only primary side effect experienced by all treated women, who were successfully managed by saline infusion and by a reduction of blood flow [102].

Another inhibitor of sFlt-1 activity is heme oxygenase (Hmox), an endogenous system of the placenta with protective effects against placental cytotoxic damage associated with preeclampsia [105]. The Hmox1/carbon monoxide (CO) pathway negatively regulates sFlt-1 and sEng [106]. Furthermore, statins also induce Hmox1 expression and in an animal model of PE, the induction of Hmox1 or exposure to CO suppresses the release of sFlt-1 and sEng in the maternal circulation [107].

Khalil et al. investigated the effect of α-methyldopa treatment against angiogenic marker levels (sFlt-1 and sEng) in women with GH and PE and found that it significantly reduced sFlt-1 and sEng levels by 50% in PE compared with GH [108].

Conclusion

Different hypertensive disorders of pregnancy may stem from variations in angiogenic expression, while clinical manifestations and disease severity is primarily dependent on the extent of placental dysfunction [19]. Among the angiogenic factors involved in angiogenesis, sFlt-1 holds the most significance in reducing the bioavailability of free VEGF and PlGF to their receptors. However, therapeutic apheresis limits sFlt-1 production. In preeclamptic pregnancies with HIV infection, it is possible that the HIV *tat* protein influences angiogenic imbalance by interfering with VEGFR-2(Flk-1/KDR) receptor activity. The sFlt-1/PlGF ratio is the first successful automated biomarker test for preeclampsia development, although additional prediction and detection strategies are required to facilitate early assessment of the disease. Angiogenic imbalance in preeclampsia compromised with HIV infection is novel and still warrants further investigation.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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