EUROX 20 (2023) 100257

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology: X

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Is the central complement component C3 altered in the synergy of HIV infection and preeclampsia?

Mikyle David *, Shoohana Singh, Thajasvarie Naicker

Optics and Imaging Centre, Doris Duke Medical Research Institute, Nelson R. Mandela School of Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa

ARTICLE INFO

Keywords:
Complement
C3
HIV
Hypertension
Preeclampsia
Inflammation

ABSTRACT

Objective: In light of complement activation in preeclampsia and HIV infection, this study evaluates the concentration of complement component 3 (C3) in HIV-associated preeclampsia.
Method: The study population (n = 76) was equally stratified by pregnancy type (normotensive pregnant and preeclampsia) and by HIV status (HIV positive and HIV negative). The plasma concentration of C3 was determined using a Bioplex immunoassay procedure.
Results: We report a significant increase in C3 concentration in the HIV-negative *versus* the HIV-positive groups ($p < 0.05$), regardless of pregnancy type. However, based on pregnancy type and irrespective of HIV status, C3 concentration was similar between normotensive *versus* preeclampsia. Concentration of C3 was significantly increased in the HIV-positive preeclamptic compared HIV-negative preeclamptic groups ($p = 0.04$). The correlation of C3 with all study groups was non-significant.
Conclusion: This study demonstrates that C3 was upregulated in HIV-associated PE compared to HIV- associated normotensive pregnancies. The dysregulation of C3 expression by HIV infection may be attributed to antiretroviral therapy.

Introduction

Preeclampsia (PE), a multi-system and placentally-derived hypertensive disorder of pregnancy, affects 4–6% of pregnancies worldwide [1]. It is characterised by new-onset gestational hypertension (sBP ≥ 140 mmHg or dBP ≥ 90 mmHg), with/without proteinuria, maternal end-organ dysfunction, uteroplacental dysfunction, and systemic inflammation ≥ 20 weeks of gestation [2]. Whilst the pathophysiology of PE remains unresolved; it is widely accepted that trophoblast invasion is deficient early in pregnancy [3]. The trophoblast fails to take on an endothelial phenotype, with the resultant absence of physiological remodelling of myometrial spiral arteries [4]. This pre-empts placental ischemia and the release of anti-angiogenic factors that cause widespread endothelial damage, vasoconstriction, and immune dysregulation [5].

Notably, for successful implantation and development of the foetus, immunological and physiologic changes of the maternal immune system are activated [6]. This includes the complement system, which comprises of more than 50 cell membrane-bound and secreted proteins, that form an integral part of the body's innate immune system [7]. It is the first line of defence against the elimination of pathogens, cell and tissue debris, antigen-antibody complexes and regulation of tissue inflammation [7].

Three canonical pathways activate the complement system; the classical, alternative and the lectin pathway [8]. These pathways interlink at a common amplification step, which involves the central complement component 3 (C3). C3 is an essential protein in the complement system, responsible for complement activation, pathogen killing, apoptotic clearance, immune complex handling, inflammation triggering and modulation of the adaptive immune system [9].

Notably, the Human Immunodeficiency Virus (HIV) causes the degradation of cellular immunity, thereby increasing one's susceptibility to opportunistic pathogenic infection [10]. HIV is a major public health challenge, with 38.4 million people currently living with the virus and 1.5 million newly infected at the end of 2022 [11]. The relationship between HIV infection and PE emanates from an antagonistic immune response, where an exaggerated immune response in PE is neutralised by the impaired response in untreated HIV infection [12,13].

* Correspondence to: Optics & Imaging Centre, Doris Duke Medical Research Institute, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa.
E-mail address: mikyledavid101@gmail.com (M. David).

https://doi.org/10.1016/j.eurox.2023.100257
Received 4 May 2023; Received in revised form 26 September 2023; Accepted 17 October 2023
Available online 20 October 2023

Preeclampsia and HIV infection work antagonistically to induce aberrant immune responses, mediated by the complement system and resulting in the hyperactivation of C3. Moreover, the administration of ART restores immune function by inhibiting the viral load, thus preventing CD4 + T cell destruction [12].

In light of the high prevalence of antenatal HIV infection (30%) [11] and PE (14%) in South Africa [14], this study examines the expression of C3 using an immunoassay procedure in the duality of HIV infection and PE stratified by pregnancy type and HIV status, whilst taking into account ART and prevention of mother to child transmission (PMTCT).

Materials and methods

Study design

This prospective study received institutional ethics approval (BREC/00003028/2021.) This study utilised retrospectively collected samples stored at − 80 °C (BCA338/17).

Study population

The study population was recruited from a large regional hospital in eThekwini, South Africa. Study groups included healthy normotensive pregnant women and preeclamptic women. Preeclampsia was diagnosed as a new sudden onset of hypertension at 20 weeks of gestation. (Systolic blood pressure ≥140 mmHg and or diastolic blood pressure of ≥90 mmHg) with or without proteinuria (300 mg in a 24-hour quantitative urine test or at least 1 + on a urinary dipstick test). Normotensive pregnant (n = 38) and preeclamptic women (n = 38) were stratified by their HIV status into HIV negative (H-) and HIV positive (H+) women. To maintain the homogeneity of the preeclamptic group, only early onset preeclampsia was selected. To detect a large effect size of 0.95, a sample size of 19 was required in each sub-group. The study population (n = 76) was used to determine a moderate effect size of 0.66 between the groups.

All HIV positive participants in this study received ART and PMTCT therapy (regardless of CD4 count) during pregnancy and breastfeeding, with the continuation of ART after breastfeeding for women with CD4 counts less than 350 cells/mm^3. The ARV treatment that was administered to women were either a single drug such as Zidovudine, also known as Azidothymidine (AZT) or a combination of multiple drugs [Tenofovir disoprovil fumarate (TDF, Viread), Emtricitabine (FTC, Emtriva) and Efavirenz (EFV)]. The alternative drug combination administered to some of the patients was [Abacavar (ABC, Ziagen), Lamivudine (3TC, Epivir) and Efavirenz (EFV)] and PMTCT (nevirapine) as per South African National HIV guidelines. HIV-exposed infants received nevirapine prophylaxis for 4–6 weeks.

Inclusion criteria

All blood pressure readings were measured at the time of screening, and women with BP ≥ 140 mmHg systolic and ≥ 90 mmHg diastolic were included, measured 4 h apart on at least two separate occasions. The cut off for CD4 + count in HIV positive participants was 350 cells/mm^3.

Exclusion criteria

Exclusion criteria for the groups were eclampsia, chronic diabetes, chronic hypertension/previous history of hypertension, chorioamnionitis, sickle cell disease, eclampsia, polycystic ovarian syndrome, abruption placentae, intrauterine death, pre-existing seizure disorders, active asthma that requires medication during the period of gestation, unknown HIV status and patients that are not booked into the hospital.

Bioplex immunoassay

A MILLIPLEX MAP™ Human Complement Panel one was performed according to the manufacturer's instructions (Millipore by Sigma-Aldrich, catalogue no: HCMP1MAG-19 K). The standards were prepared in a 1:100 dilution series. In a 96 well plate, C3 capture antibody-coupled magnetic beads were added to each well and washed twice. Standards, samples and blanks were then added into their designated wells and left to incubate before washing three times. After that, a biotinylated detection antibody was pipetted into each well and allowed to incubate. The plate was then washed three times before adding streptavidin-phycoerythrin throughout the wells. Finally, the plate was washed for a further three times before resuspending each well with assay buffer. The plate was then ready to be placed into the Bio-Plex™ system for reading. The Bio-Plex1MAGPIXTM Multiplex Reader (Bio-Rad Laboratories Inc., USA) was utilised to read the experiment plate. Bio-Plex Manager™ software version 4.1 was used to obtain the data from the multiplex analysis.

Statistical analysis

Data was analysed using GraphPad Prism 5.00 for Windows (GraphPad Software, San Diego, California, USA). Results are represented as the median and interquartile range (IQR) due to a non-parametric distribution. A Mann-Whitney U test was used to determine statistical significance according to pregnancy type (normotensive *vs* PE) and HIV status (negative *vs* positive). Statistical significance was determined across all groups using a one-way ANOVA test; a Kruskal-Wallis test in combination with Dunn's multiple comparison *post hoc* test was used. A Spearman's *r* data analysis for non-parametric distribution was used to determine correlation between gestational age and C3. Statistical significance was reported as $p < 0.05$.

Results

Patient demographics and clinical characteristics

The patient demographics and their clinical characteristics are shown in Table 1. Gestational age ($p < 0.0001$), systolic blood pressure (BP) ($p < 0.0001$) and diastolic BP ($p < 0.0001$) were significantly different across pregnancy groups. Additionally, baby weight ($p < 0.001$) significantly differed across the pregnancy groups. There was no significant difference in maternal weight and age across the study groups.

Plasma concentrations of C3

Pregnancy type- There was a non-significant increase in C3 concentration in the PE (median = 95,825 pg/mL, IQR = (160,963–54,764 pg/mL) *vs* the normotensive pregnant group (median = 83,548 pg/mL, IQR = (164,162–37,506 pg/mL), irrespective of HIV status (Mann-Whitney U = 669, *p* value = 0.4408; Fig. 1A).

HIV status- The concentration of C3 was significantly lower in the HIV-negative (median = 69,397 pg/mL, IQR = (153,737–36,827 pg/mL) *vs* the HIV positive (median = 108,319 pg/mL, IQR = (193,525–69,049 pg/mL) groups, irrespective of pregnancy type (Mann-Whitney U = 526, *p* value = 0.0423; Fig. 1B).

Across all groups- There was a significant elevation of C3 concentration in the HIV positive PE (median = 108,702 pg/mL, IQR = (207025–87280 pg/mL) *vs* HIV negative PE (median = 63,605 pg/mL, IQR = (153,200–37988 pg/mL) groups. Additionally, a significant decrease was noted in the normotensive HIV negative (median = 67,320 pg/mL, IQR = (156,170–66,930 pg/mL) *vs* normotensive HIV positive groups (median = 107,300 pg/mL, IQR = (232,838–133050 pg/mL) (Kruskal-Wallis H = 9.216, $p = 0.0266$; Fig. 1C).

Table 1
Demographic data and clinical profile of participants across all study groups.

	Normotensive HIV Negative n = 19	Normotensive HIV Positive n = 19	Preeclamptic HIV Negative n = 19	Preeclamptic HIV Positive n = 19
Maternal Body Weight (kg)	75 (86.90–71.00)	74 (80.00–68.00)	73 (92.00–66.10)	77 (96.45–68.00)
Gestational Age (weeks)	40 (40.00–39.00)	38 (40.00–37.00)	31 (32.00–26.00)	31 (33.00–27.00)
Parity	1 (1.00–0)	3 (3.00–1.00)	1 (2.00–1.00)	1 (2.00–1.00)
Systolic blood pressure (mmHg)	124 (127.0–114.0)	115 (122.0–109.0)	164 (178.0–155.0)	160 (170.0–148.0)
Diastolic blood pressure (mmHg)	78 (86.00–65.00)	71 (76.00–70.00)	104 (112.0–96.00)	100 (108.0–92.00)
Maternal Age (years)	23 (28–19)	28 (36–23)	29 (31–26)	30 (35–22)
Baby weight (kg)	3 (3.700–3.068)	3 (3.335–2.928)	1.5 (3.335–2.928)	3 (2.625–1.193)

Patient demographics amongst study groups (n = 76). Results are represented as the median and interquartile range (IQR).

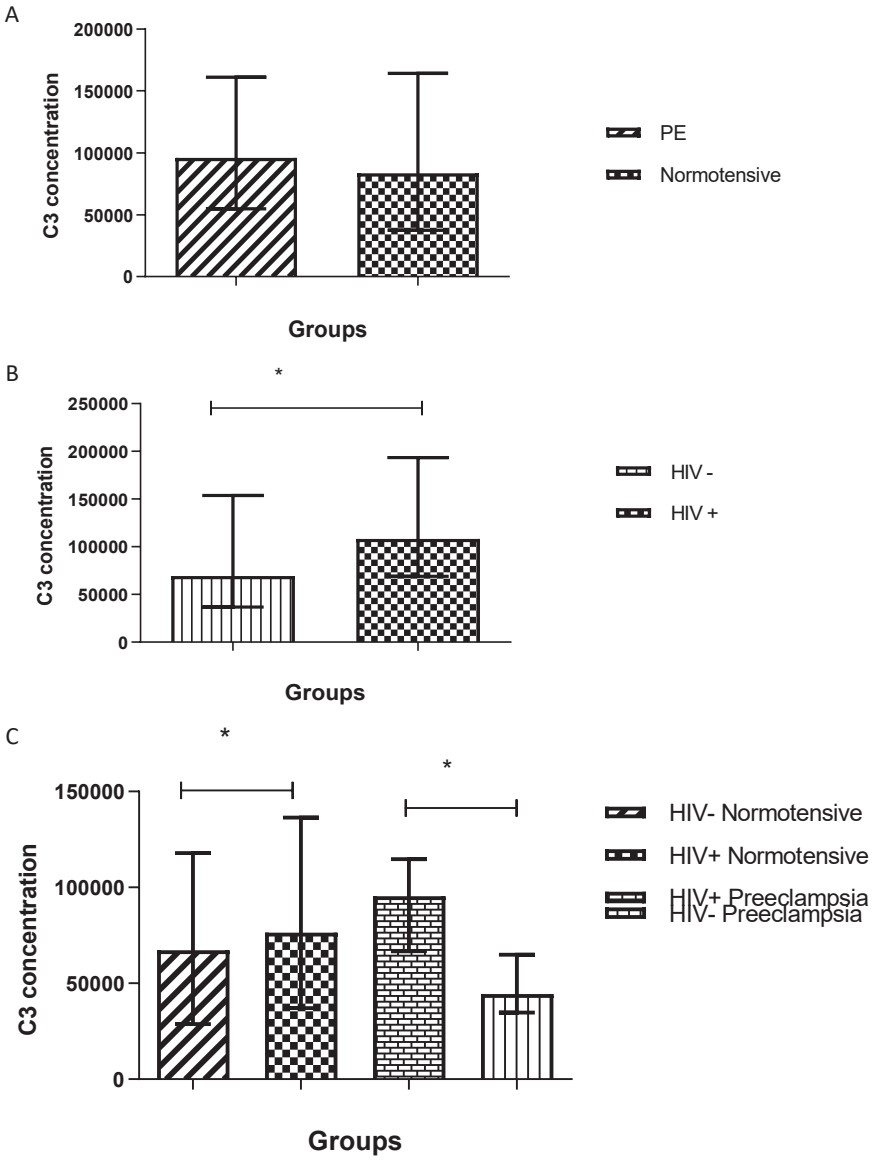

Fig. 1. Histogram illustrating plasma concentration of C3 across all study groups (A), *viz*, HIV- Preeclamptic *vs* HIV- Normotensive groups; (B) HIV + *vs* HIV - groups; Data is represented by median and interquartile range. * p value < 0.05.

Gestational age (GA) correlation of C3

There was no significant correlation between the C3 expression of the normotensive pregnant group with gestational age ($r = -0.036$, $p = 0.09972$; Table 2). Similarly, there was a non-significant negative correlation that was moderate in strength between C3 level of the PE group with gestational age ($r = -0.0215$, $p = 0.1813$; Table 2). The correlation between the C3 concentration of the HIV negative PE group with gestational age was negative and moderate in strength ($r = -0.477$, $p = 0.3895$; Table 2). Furthermore, the correlation of C3 level between HIV positive PE group and gestational age was positive and moderate in strength ($r = 0.0528$, $p = 0.7452$; Table 2; Fig. 2A).

Table 2
Gestational Age correlation of serum C3 across all study groups.

	Gestational age (weeks)	*R* value	*P* value
Normotensive HIV Negative (n = 19)	40 (1)	$r = -0.036$	0.09972
Normotensive HIV Positive (n = 19)	38 (3)	$r = -0.0215$	0.1813
Preeclamptic HIV Negative (n = 19)	31 (6)	$r = -0.477$	0.3895
Preeclamptic HIV Positive (n = 19)	31 (6)	$r = 0.0528$	0.7452

Gestational age correlation amongst study groups (n = 76). Data is represented by median and interquartile range. *r value < 0.05 *p value < 0.05

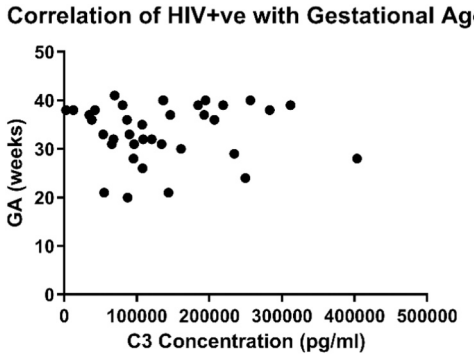

Fig. 2. A: Scatterplot illustrating the correlation between the HIV positive group and Gestational age, showing a positive and moderate strength relationship. Pearson's r = 0.0528.

Discussion

The main finding of this novel study was a significant up-regulation of C3 in the synergy of PE and HIV infection; more specifically between HIV positive PE group compared to the HIV negative PE groups (Fig. 1C; $p = 0.04$).

HIV concentration

In HIV infection, a combination of chronic inflammation and immune suppression, leads to the exhaustion of the immune response [15]. More specifically, the HIV virus confronts the complement-mediated attack by various mechanisms, including possession of the host's complement regulators during the budding process, acquisition of complement regulators from the plasma, inhibition of complement synthesis, increase of complement regulators on infected cells and cellular entry by the complement receptors [16–18]. The complement system activates the effector functions of T-helper cells; with consequential synthesis and release of the anaphylatoxins C3a and C5a during T cell-antigen-presenting cell and viral interactions [19]. During viral infections, the anaphylatoxins communicate *via* their receptors, thereby inducing a Th1/Th17 response [20,21], resulting in an elevated inflammatory response. These findings of an up-regulation of C3 regardless of pregnancy type concurs with our study, the increase being exacerbated in PE.

HIV infection affects all three pathways of the complement system, *i.e.*, the CP, where HIV-1 surface protein gp41 binds to and adheres to C1q; the LP, where the HIV-1 envelope protein gp120 binds to Mannose binding lectin (MBL) and lastly, the AP, where HIV-1 is activated through the binding of C3 to HIV-infected lymphocytes and monocytes [22]. Thereafter, HIV exploits complement regulatory proteins (CD55, CD59 and Factor H) and binds to C3 fragments, enabling HIV to escape complement-mediated lysis and amplify its dissemination and infectivity [23]. Notably, HIV-specific antibodies also increases complement activation by binding to the viral surface [17,24].

HIV status

Our study demonstrates a significant increase of C3 by HIV status, irrespective of pregnancy type. The study by Nitkiewicz et al. [25], corroborates our findings; they noted significantly increased levels of C3 induced by HIV-1 infection. This may be attributed to the cleavage of C3 into C3a, which is a strong anaphylatoxin and releases pro-inflammatory cytokines (IL-1β, IL-6, IL-12, IL-18, IFNγ, TNF-α) and inflammatory mediators (proteins, peptides, glycoproteins, cytokines, arachidonic acid metabolites); thus, causing a hyperinflammatory state in both HIV infection and PE [26].

It is conceivable that a compromised immune system emanating from HIV infection induces a compensatory feedback mechanism of C3, which causes excessive complement activation. This change in C3 concentration is likely caused by dysregulation of the complement system, brought about by HIV infection paired with ART and pregnancy [27].

ARV therapy

The mechanism of action for most ARV drugs is to inhibit one out of the two HIV enzymes, *viz.*, protease or transcriptase [28]. The most frequently recommended antiretroviral therapy for initial treatment is Efavirenz + 2 nucleoside reverse transcriptase inhibitors (NRTIs) [29], one of the drugs of choice administered as combination therapy in our study. They function by affecting the life cycle of HIV, including the HIV integrase and Tat mediated transactivation, thus modifying Gp120 post transcriptional maturation and reducing iron deposits on infected cells, effecting reverse transcription [30,31]. A recent study by Serrano-Rísquez et al. [32], correlated higher levels of C3 with HIV-1 infection. The HIV virus is able to escape complement-mediated lysis by attaching itself to the surface of complement regulatory proteins, such as CD59, CD55 and Factor H, thus enhancing and mediating its infectivity [23]. This effect may also possibly explain the higher concentrations of C3 due to HIV virions escaping complement-mediated lysis, resulting in the overcompensation of the complement system and the release of C3 and other pro-inflammatory mediators.

We also reported a significant difference of C3 expression between the HIV-negative and HIV-positive groups, irrespective of pregnancy type. This response is unexpected due to the fact that these women were receiving ARV treatment, which decreases the HIV viral load and neutralises the hyperinflammatory response mediated from the complement system [33]. Moreover, studies by Isaac et al. [28] and Datta et al. [34], have reported elevated C3 concentration levels following ARV therapy. ARV's reduce the viral replication drastically, resulting in decreased circulating viral antigens, antibodies and subsequently leading to the increase of C3. This increase may be attributed to the immune reconstitution inflammatory syndrome (IRIS), which is an inflammatory condition mediated against the presence of microbial antigens [35]. Previous literature is also in agreement [36,37]. A recent study by Seddiki et al. [38] reported that patients had developed immune reconstitution inflammatory syndrome following ARV therapy. These conflicting results may be attributed to the mechanism by which ARV therapy works.

Complement C3 activation

A study by He et al. [39] reported increased levels of C3 in pregnancy. Several other studies also noted elevated C3 levels during pregnancy [18, 40, 41]. However, Derzsy et al. [42] and Kestlerová et al. [43] reported C3 elevation in PE compared to normotensive pregnancy. The most plausible explanation for this up-regulation of C3, is its cleavage into C3a during hyperinflammatory conditions, such as PE. C3a is a potent anaphylatoxin known to increase vascular permeability and

smooth muscle contraction, which is most likely a compensatory response to the lack of spiral artery transformation in PE [44]. Furthermore, C3a is a chemotactic factor for leukocytes and may activate neutrophils and monocytes in the PE milieu, which promote the release of inflammatory mediators such as free oxygen radicals, proteases and pro-inflammatory cytokines [26]. This contributes to the hyperinflammatory state and excessive complement activation observed in PE. Nonetheless, this elevation in C3 levels favours excessive activation, thereby creating a hyperinflammatory state in PE [45].

Also, an increase in the synthesis of C3 may be part of the acute phase reaction in the third trimester of both normotensive and preeclamptic pregnancies. Additionally, Huang et al. [46] and Kennelly et al. [47] indicated that increased C3 concentration was associated with adverse pregnancy outcomes such as preterm birth and PE development. Nonetheless it is quite unexpected that we report similar C3 levels between PE *versus* normotensive pregnancy regardless of HIV status, a finding that may be attributed to gestational age during the third trimester. In our study, the women were in their third trimester.

In both PE and normal pregnancy, elevation of C3 occurs, from the onset of gestation until parturition [48]. In a prospective study by He et al. [6], it was reported that the concentration of C3 began to rise in the first trimester and continued throughout the second semester but decreased in the third trimester. Derzsy et al. [42] also demonstrated C3 levels to fluctuate throughout the gestation period. A plausible explanation is that during placental development in the first and second trimesters, numerous apoptotic cells and free DNA are generated, and the subsequent cellular debris and DNA fragments induce aberrant complement activation [6]. This activation facilitates the removal of apoptotic cellular fragments during the first and second trimesters. Therefore, the similar C3 levels in our study may be attributed to the complement clearance in the third trimester.

Complement component C3 is essential for activating the complement system by acting as a convergence point for the complement pathways [49]. Therefore, our similar levels may once again be accredited to ARV therapy in our study, and this plays a conflicting role, as it is known to re-establish the immune system [50], whilst other studies contradict this [51,52].

Disorders of complement regulation have been previously linked to pregnancy complications, including miscarriage, growth disorders and maternal complications such as gestational hypertension and PE [53]. Several studies have correlated an increase in complement components with body mass index (BMI) in PE compared to normotensive pregnant women; unfortunately, however, BMI was unavailable for our study population [54–56]. It is noteworthy that certain metabolic conditions, such as obesity and diabetes mellitus, results in chronic inflammation, characteristic of PE [57]. As such, it is plausible that the increase in C3 may be due to metabolic changes that occur during pregnancy and PE development [58].

One of the limitations of this study was the small sample size. Additionally, all the HIV-positive women were on ARV treatment, the duration of which was not known and may have possibly confounded analyte expression.

Conclusion

This study demonstrates a significant up-regulation of C3 by pregnancy type emanating from the elevated oxidative response and proinflammatory mediators that provoke the complement response. We also report an elevation of C3 by HIV status due to the anaphylatoxins action that occurs during infection and induces a Th1/Th17 response in PE. Nonetheless, these findings may also be attributed to the immunorestorative action of ART and to the escape of complement mediated regulation during HIV infection. Additionally, in the HIV positive preeclampsia and HIV negative preeclampsia group. in our study. Notably, our results may be influenced by the variability of complement proteins with gestational age attributed to removal of apoptotic and complement debris.

Declaration of Competing Interest

None.

Acknowledgments

Prof T. Naicker for her guidance and use of the optics and imaging facility. The National Research Foundation and College of Health Sciences for financial support.

Conflict of interest

All authors wish to declare no conflict of interest.

References

[1] Wang W, Xie X, Yuan T, Wang Y, Zhao F, Zhou Z, et al. Epidemiological trends of maternal hypertensive disorders of pregnancy at the global, regional, and national levels: a population-based study. BMC Pregnancy Childbirth 2021;21(1):364.
[2] Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens 2022;27:148–69.
[3] Naicker T, Dorsamy E, Ramsuran D, Burton GJ, Moodley J. The role of apoptosis on trophoblast cell invasion in the placental bed of normotensive and preeclamptic pregnancies. Hypertens Pregnancy 2013;32(3):245–56.
[4] Ives CW, Sinkey R, Rajapreyar I, Tita ATN, Oparil S. Preeclampsia—pathophysiology and clinical presentations: JACC state-of-the-art review. J Am Coll Cardiol 2020;76(14):1690–702.
[5] Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia. Circ Res 2019;124 (7):1094–112.
[6] He Yd, Xu Bn, Song D, Wang Yq, Yu F, Chen Q, et al. Normal range of complement components during pregnancy: a prospective study. Am J Reprod Immunol 2020; 83(2):e13202.
[7] Pekna M, Pekny M. The complement system: a powerful modulator and effector of astrocyte function in the healthy and diseased central nervous system. Cells 2021; 10(7):1812.
[8] Noris M, Remuzzi G. Overview of complement activation and regulation. Semin Nephrol 2013;33(6):479–92.
[9] Alcorlo M, López-Perrote A, Delgado S, Yébenes H, Subías M, Rodríguez-Gallego C, et al. Structural insights on complement activation. FEBS J 2015;282(20):3883–91.
[10] Maartens G, Celum C, Lewin SR. HIV infection: epidemiology, pathogenesis, treatment, and prevention. Lancet 2014;384(9939):258–71.
[11] UNAIDS. UNAIDS Global HIV & AIDS statistics—2022 fact sheet 2022 [cited 2022 22/12/2022]. Available from: ⟨https://www.unaids.org/en/resources/fact-sheet⟩.
[12] Kalumba V, Moodley J, Naidoo T. Is the prevalence of preeclampsia affected by HIV/AIDS? A retrospective case–control study. Cardiovasc J Afr 2013;24(2):24.
[13] Maharaj NR, Phulukdaree A, Nagiah S, Ramkaran P, Tiloke C, Chuturgoon AA. Pro-Inflammatory Cytokine Levels in HIV Infected and Uninfected Pregnant Women with and without Preeclampsia. PLoS One 2017;12(1):e0170063.
[14] Sebitloane HM, Moodley J, Sartorius B. Associations between HIV, highly active anti-retroviral therapy, and hypertensive disorders of pregnancy among maternal deaths in South Africa 2011–2013. Int J Gynecol Obstet 2017;136(2):195–9.
[15] Appay V, Sauce D. Immune activation and inflammation in HIV-1 infection: causes and consequences. J Pathol: A J Pathol Soc Gt Br Irel 2008;214(2):231–41.
[16] Banerjee A, Mazumdar B, Meyer K, Di Bisceglie AM, Ray RB, Ray R. Transcriptional repression of C4 complement by hepatitis C virus proteins. J Virol 2011;85(9): 4157–66.
[17] Li Y, Johnson JB, Parks GD. Parainfluenza virus 5 upregulates CD55 expression to produce virions with enhanced resistance to complement-mediated neutralisation. Virology 2016;497:305–13.
[18] West EE, Kolev M, Kemper C. Complement and the regulation of T cell responses. Annu Rev Immunol 2018;36:309–38.
[19] Strainic MG, Shevach EM, An F, Lin F, Medof ME. Absence of signaling into CD4+ cells via C3aR and C5aR enables autoinductive TGF-β1 signaling and induction of Foxp3+ regulatory T cells. Nat Immunol 2013;14(2):162–71.
[20] Ghannam A, Fauquert J-L, Thomas C, Kemper C, Drouet C. Human complement C3 deficiency: Th1 induction requires T cell-derived complement C3a and CD46 activation. Mol Immunol 2014;58(1):98–107.
[21] Weaver Jr DJ, Reis ES, Pandey MK, Köhl G, Harris N, Gerard C, et al. C5a receptor-deficient dendritic cells promote induction of Treg and Th17 cells. Eur J Immunol 2010;40(3):710–21.
[22] Hladik F, McElrath MJ. Setting the stage: host invasion by HIV. Nat Rev Immunol 2008;8(6):447–57.
[23] Roberts L, Passmore J-AS, Williamson C, Little F, Bebell LM, Mlisana K, et al. Plasma cytokine levels during acute HIV-1 infection predict HIV disease progression. AIDS 2010;24(6):819.
[24] Huber G, Bánki Z, Lengauer S, Stoiber H. Emerging role for complement in HIV infection. Curr Opin HIV AIDS 2011;6(5):419–26.

[25] Nitkiewicz J, Borjabad A, Morgello S, Murray J, Chao W, Emdad L, et al. HIV induces expression of complement component C3 in astrocytes by NF-κB-dependent activation of interleukin-6 synthesis. J Neuroinflamm 2017;14(1):23.
[26] Lokki AI, Kaartokallio T, Holmberg V, Onkamo P, Koskinen LLE, Saavalainen P, et al. Analysis of complement C3 gene reveals susceptibility to severe preeclampsia. Front Immunol 2017;8(589).
[27] Yu QYR, Qin X. The good and evil of complement activation in HIV-1 infection. Cell Mol Immunol 2010;7:334–40.
[28] Isaac LM, del Carmen M-GM, Guillermo V-RJ, Enrique R-MM, Sergio F-H, César R-B, et al. Effect of Tenofovir/Emtricitabine/Efavirenz with and without chloroquine in patients with HIV/AIDS C3: double blinded randomized clinical trial. J Pharmacovigil 2015.
[29] Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray AL, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med 2011;365(16):1492–501.
[30] Ford N, Migone C, Calmy A, Kerschberger B, Kanters S, Nsanzimana S, et al. Benefits and risks of rapid initiation of antiretroviral therapy. AIDS 2018;32(1):17.
[31] Günthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA Panel. JAMA 2016; 316(2):191–210.
[32] Serrano-Rísquez C, Omar M, Gómez-Vidal MA, Real LM, Pineda JA, Rivero A, et al. CD46 genetic variability and HIV-1 infection susceptibility. Cells 2021;10(11): 3094.
[33] Chen S-B, Rajaee F, Yousefpour A, Alcaraz R, Chu Y-M, Gómez-Aguilar J, et al. Antiretroviral therapy of HIV infection using a novel optimal type-2 fuzzy control strategy. Alex Eng J 2021;60(1):1545–55.
[34] Datta PK, Rappaport J. HIV and complement: hijacking an immune defense. Biomed Pharmacother 2006;60(9):561–8.
[35] Shankar EM, Vignesh R, Murugavel KG, Balakrishnan P, Sekar R, Lloyd CA, et al. Immune reconstitution inflammatory syndrome in association with HIV/AIDS and tuberculosis: views over hidden possibilities. AIDS Res Ther 2007;4(1):1–7.
[36] Baranwal M, Gupta Y, Dey P, Majaw S. Antiinflammatory phytochemicals against virus-induced hyperinflammatory responses: Scope, rationale, application, and limitations. Phytother Res 2021;35(11):6148–69.
[37] Maggi P, Ricci E, Messina V, Salzillo A, Simeone F, Iodice A, et al. Dangerous liaisons? The role of inflammation and comorbidities in HIV and SARS-CoV-2 infection. Expert Rev Clin Immunol 2021;17(3):201–8.
[38] Seddiki N., French M. COVID-19 and HIV-Associated Immune Reconstitution Inflammatory Syndrome: Emergence of Pathogen-Specific Immune Fuel to the Fire Responses Adding. Infectious Agent-Induced Chronic Immune Activation: Causes, Phenotypes, and Consequences. 2022.
[39] He YD, Xu BN, Wang ML, Wang YQ, Yu F, Chen Q, Zhao MH. Dysregulation of complement system during pregnancy in patients with preeclampsia. Mol Immunol 2020;122:69–79.
[40] Buyon JP, Kim MY, Guerra MM, Laskin CA, Petri M, Lockshin MD, et al. Predictors of pregnancy outcomes in patients with lupus. Ann Intern Med 2015;163(3): 153–63.
[41] Laissue P, Lakhal B, Vatin M, Batista F, Burgio G, Mercier E, et al. Association of FOXD1 variants with adverse pregnancy outcomes in mice and humans. Open Biol 2016;6(10):160109.
[42] Derzsy Z, Prohászka Z, Rigó J, Füst G, Molvarec A. Activation of the complement system in normal pregnancy and preeclampsia. Mol Immunol 2010;47(7):1500–6.
[43] Kestlerová A, Feyereisl J, Frisová V, Měchurová A, Šůla K, Zima T, et al. Immunological and biochemical markers in preeclampsia. J Reprod Immunol 2012;96(1–2):90–4.
[44] Sjöberg A, Trouw L, Blom A. Complement activation and inhibition: a delicate balance. Trends Immunol 2009;30(2):83–90.
[45] Regal JF, Burwick RM, Fleming SD. The complement system and preeclampsia. Curr Hypertens Rep 2017;19(11):87.
[46] Huang S, Tian J, Liu C, Long Y, Cao D, Wei L, et al. Elevated C-reactive protein and complement C3 levels are associated with preterm birth: a nested case–control study in Chinese women. BMC Pregnancy Childbirth 2020;20(1):131.
[47] Kennelly MA, Killeen SL, Phillips CM, Alberdi G, Lindsay KL, Mehegan J, et al. Maternal C3 complement and C-reactive protein and pregnancy and fetal outcomes: a secondary analysis of the PEARS RCT-An mHealth-supported, lifestyle intervention among pregnant women with overweight and obesity. Cytokine 2022; 149:155748.
[48] Girardi G, Lingo JJ, Fleming SD, Regal JF. Essential role of complement in pregnancy: from implantation to parturition and beyond. Front Immunol 2020;11: 1681.
[49] Ricklin D, Reis ES, Mastellos DC, Gros P, Lambris JD. Complement component C3 - The "Swiss Army Knife" of innate immunity and host defense. Immunol Rev 2016; 274(1):33–58.
[50] Landi B, Bezzeccheri V, Guerra B, Piemontese M, Cervi F, Cecchi L, et al. HIV infection in pregnancy and the risk of gestational hypertension and preeclampsia. World J Cardiovasc Dis 2014;2014.
[51] Lillegard KE, Johnson AC, Lojovich SJ, Bauer AJ, Marsh HC, Gilbert JS, et al. Complement activation is critical for placental ischemia-induced hypertension in the rat. Mol Immunol 2013;56(1–2):91–7.
[52] Youssef L, Miranda J, Blasco M, Paules C, Crovetto F, Palomo M, et al. Complement and coagulation cascades activation is the main pathophysiological pathway in early-onset severe preeclampsia revealed by maternal proteomics. Sci Rep 2021;11 (1):3048.
[53] Regal JF, Gilbert JS, Burwick RM. The complement system and adverse pregnancy outcomes. Mol Immunol 2015;67(1):56–70.
[54] Lynch AM, Eckel RH, Murphy JR, Gibbs RS, West NA, Giclas PC, et al. Prepregnancy obesity and complement system activation in early pregnancy and the subsequent development of preeclampsia. Am J Obstet Gynecol 2012;206(5): 428. . e1-. e8.
[55] Olson K, Reijnders-Most D, Douglas N, Redman LM, Sones JL. Inflammatory reproductive white adipose tissue characterises the obese Preeclamptic-like BPH/5 mouse prior to pregnancy. FASEB J 2018;32(S1):882. .13-.13.
[56] Olson KN, Redman LM, Sones JL. Obesity “complements” preeclampsia. Physiol Genom 2019;51(3):73–6.
[57] Rossheim AE, Cunningham TD, Hair PS, Shah T, Cunnion KM, Troy SB, et al. Effects of well-controlled HIV infection on complement activation and function. Journal of acquired immune deficiency syndromes (1999) 2016;73(1):20–6.
[58] Perez-Sepulveda A, Torres MJ, Khoury M, Illanes SE. Innate immune system and preeclampsia. Front Immunol 2014;5:244.