Pro-Inflammatory Cytokine Levels in HIV Infected and Uninfected Pregnant Women with and without Preeclampsia

Niren Ray Maharaj¹,², Alisa Phulukdaree¹, Savania Nagiah¹, Prithiksha Ramkaran¹, Charlette Tiloke¹, Anil Amichund Chuturgoon¹*

¹ Department of Obstetrics and Gynaecology, Prince Mshiyeni Memorial Hospital, KwaZulu-Natal, South Africa, ² Discipline of Medical Biochemistry, College of Health Sciences, University of KwaZulu-Natal, South Africa

¤ Current address: Department of Physiology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa

* chutur@ukzn.ac.za

Abstract

Introduction

Preeclampsia and HIV/AIDS are inflammatory conditions that contribute significantly to adverse maternal and foetal outcomes. The immune reconstitution effects of HAART on inflammatory mediators has not been adequately studied in pregnancy and may impact on the inflammatory cytokine network in women with co-morbid preeclampsia. Our study evaluated changes in pro-inflammatory cytokines IL-2, TNF-α, IFN-γ and IL-6 in HIV infected preeclamptic women on HAART.

Methods

A prospective experimental study was conducted at Prince Mshiyeni Memorial Hospital between July 2013 and September 2014. One hundred and ninety three pregnant women were recruited into 4 groups: uninfected normotensive (50; 26%), infected normotensive (45; 23%), uninfected preeclamptic (53; 28%) and infected preeclamptic women (45; 23%). Serum levels of cytokines TNF-α, IFN-γ, IL-2 and IL-6 were determined using commercially available kits and a Cytometric Bead Array (CBA). Comparative data was recorded and analysed descriptively.

Results

In the control groups (normotensive), significantly lower values were found in IL-2 (p = 0.010), TNF-α (p = 0.045), and IL-6 (p = 0.005); and a non-significant decrease was observed in IFN-γ (p = 0.345) in HIV infected women on HAART compared to uninfected controls. In the experimental group (preeclamptic) women, significantly reduced levels were observed in IL-2 and TNF-α (p = 0.001; p = 0.000) and non-significant decreases were observed in IFN-γ and IL-6 (p = 0.023; p = 0.086) in HIV infected women on HAART.
compared with uninfected preeclamptic women. Non-significant differences were observed between uninfected preeclamptic and normotensive women.

**Conclusion**

In uncomplicated/normotensive pregnancies, HIV/HAART is associated with significant decreases in IL-2, TNF-α and IL-6, and in preeclamptic women significant decreases in IL-2 and TNF-α were observed. These findings suggest that HIV/HAART impacts on pro-inflammatory cytokines in women with co-morbid preeclampsia. This provides a platform for further research on immune reconstitution effects of HAART during pregnancy, and the development of potential immune modulation therapies for the management of preeclampsia.

**Introduction**

Preeclampsia (PE), a multi-organ hypertensive disorder of pregnancy, and Human immunodeficiency virus/Acquired immunodeficiency syndrome (HIV/AIDS) are associated with significant maternal and perinatal morbidity and mortality, especially in poor resourced countries [1–3]. The treatment of PE still remains empiric and resolution is achieved by delivery [4]. Highly active antiretroviral therapy (HAART) has been shown to successfully reduce plasma HIV-1 viral load and vertical transmission rates in pregnancy [5, 6], and is now integrated with the management of HIV infection in pregnancy [7].

There is no consensus on the relationship between these conditions since data on the impact of HIV on the rate of PE are conflicting [8]. HAART may influence the postulated effect of HIV on the development of hypertensive disorders during pregnancy [9]. Although the underlying immunological changes in PE and HIV is not completely understood, it is generally accepted that both conditions are associated with inflammation [10, 11]. Inflammation is mediated by a variety of soluble factors, including a group of secreted polypeptides known as cytokines [12].

Cytokines can be classified as pro and anti-inflammatory and are considered important initiators and mediators of inflammation and endothelial dysfunction [13]. Cytokines such as interferon gamma (IFN-γ) and tumour necrosis factor alpha (TNF-α) are characteristic of T helper 1 (Th1) type immunity and mediate several cell mediated cytotoxic and inflammatory reactions [14, 15]. Interleukin (IL)-2 plays a critical role in regulating cellular and humoral chronic inflammatory responses; whilst IL-6, although possessing some anti-inflammatory properties, is observed in many chronic inflammatory and autoimmune diseases and serves as a marker for the systemic activation of pro-inflammatory cytokines [12, 16].

Preeclampsia is associated with a generalized systemic inflammatory response and subsequent release of pro-inflammatory cytokines that may trigger the maternal disease [17]. An increase in the IL-2/IL-4 and IFN-γ /IL-4 ratios, as well as elevated circulating levels of IL-6 and TNF-α have been reported in previous studies, suggesting a pro-inflammatory systemic environment in PE when compared to normal pregnancy [18].

During the progression of HIV infection, a Th1 (pro-inflammatory) to Th2 (eosinophilic/anti-inflammatory) cytokine shift has been observed, which appears to be counteracted with the usage of HAART [19]. Data on the immune reconstitution effects of HAART on pro-inflammatory cytokines in HIV infected women with PE is lacking. To further understand the
effects of HAART on the inflammatory cytokine network in HIV infected PE women, we investigated IL-2, TNF-α, IFN-γ and IL-6 in women during the third trimester of pregnancy.

**Materials and Methods**

**Study population and sample collection**

Institutional ethical and hospital regulatory permission was obtained for the study (Biomedical Research Ethics Committee, University of KwaZulu-Natal, South Africa; reference number BE 119/11). After written consent was obtained, participants were recruited over a 14-month period from July 2013 to September 2014 from the maternity unit at Prince Mshiyeni Memorial Hospital in Durban, South Africa. This hospital is a regional level facility and serves a predominantly semi-urban African population from where the participants were recruited. Normotensive (n = 95, age range: 18–46 years) and PE patients (n = 98, age range: 18–42 years) were enrolled into the study. Maternal venous blood samples were then taken. To maintain ethno-graphic and anthropometric consistency, all patients recruited were of African descent, resident in the same geographical location and of Zulu ethnicity. All patients were non-smokers, non-consumers of alcohol or recreational drugs, and all HIV infected patients were on HAART (tenofovir, emtricitabine, efavirenz) as per the National guidelines [7]. Calcium supplementation was administered routinely to all patients attending the clinic. Women with gestational hypertension, renal disease, diabetes mellitus, chronic hypertension and collagen vascular disease were excluded from this study. Preeclampsia was defined as a blood pressure ≥140mmHg systolic or ≥ to 90 mmHg diastolic on 2 occasions at least 4 h apart after 20 weeks of gestation in a woman with previously normal blood pressure [20]. All patients had proteinuria ≥+1 on urine dipstick testing. Data on all patients was obtained from the institution’s maternity case records and laboratory data from the National Health Laboratory Services computerised database at the institution, and HIV was diagnosed on a rapid test kit. Weight was categorised as: normal weight (BMI: 18≤25), overweight (BMI: 25≤30) and obese (BMI: 30+).

**Cytokine quantification**

The BD Cytometric Bead Array Human Th1/Th2/Th17 Cytokine kit (catalog no.560484) was used to measure the IL-2, TNF-α, IFN-γ and IL-6 levels in serum samples. Briefly, lyophilized standards were prepared by reconstitution and serial dilution (1:2–1:256) in assay diluent immediately before staining with Capture Beads and Phycoerythrin Detection Reagent. All serum samples were also diluted in assay diluent (1:4) before staining with Capture Beads and Phycoerythrin Detection Reagent. For the staining procedure, 50μL of each standard and unknown sample was added to appropriately labelled sample tubes followed by 50μL of the Human Th1/Th2/Th17 Phycoerythrin Detection Reagent and incubated (3 h, RT, protected from light). Following incubation 1 mL of Wash Buffer was added to each assay tube and centrifuged at 200 xg for 5 minutes. The supernatant from each assay tube was then carefully aspirated and 300 μL of Wash Buffer was added to each assay tube to resuspend the bead pellet. Flow cytometric data was acquired using the BD AccuriC6 Sampler counting 2,100 gated events. This ensures that the sample file contains approximately 300 events per Capture Bead. Data analysis was performed using the FCAP Array analysis software. All cytokines are represented as pg/mL as extrapolated from standard curves.

**Statistical analysis**

Statistical analysis was done using SPSS® version 22. Correlation between continuous variables was assessed using the Spearman rank correlation coefficient. The Wilcoxon rank-sum
(Mann–Whitney) test was used to compare difference in sum of ranks (i.e. cytokine concentration) by dichotomous group, mainly between PE HIV− and PE HIV+. Comparisons of mean across 3 or more groups were done using the Kruskal–Wallis test. Non-parametric approaches were employed above as cytokine distributions were not normally distributed with evidence of asymmetry. The Pearson Chi-square ($\chi^2$) test was used to test association between group(s) and categorical explanatory variables. In the determination of significance, a p-value <0.05 was deemed statistically significant.

**Results**

The clinical characteristics of participants are shown in Table 1. The average duration of HAART was 16.6 weeks in the control group and 14.5 weeks in the PE group. All women were in the third trimester of pregnancy and the mean gestational age was 36.5 weeks. There was a significant difference in the parity across all groups ($p = 0.006$) but not among the PE women ($p = 0.400$).

There was a significant difference in age across the groups, however there was little or no correlation between cytokine levels and age, negating age as a confounding factor; hence age was not factored into the cytokine comparison by group. The overall quantitative evaluation of cytokines is shown in Tables 2 and 3. Significant differences were found in many of the circulating cytokines investigated. In the control groups i.e. normotensive groups, significantly lower levels of IL-2 ($p = 0.010$), TNF-α ($p = 0.045$), and IL-6 ($p = 0.005$), and a non-significantly lower level of IFN-γ ($p = 0.345$) in HIV infected women on HAART compared to uninfected controls.

In the experimental group i.e. PE women, significantly lower levels of IL-2 ($p = 0.000$) and TNF-α ($p = 0.000$) and non-significantly lower levels in IFN-γ ($p = 0.023$) and IL-6 ($p = 0.086$) were observed in HIV infected women on HAART compared with uninfected women. No significant differences were observed in uninfected PE women when compared with uninfected normotensive women.

**Discussion**

Our study demonstrates that both normotensive and PE HIV-infected women on HAART display lower cytokine levels than both PE and normotensive uninfected pregnant women. The data presented shows significantly lower levels of pro-inflammatory cytokines IL-2, TNF-α, and IL-6, and non-significantly lower IFN-γ among HIV positive normotensive women on HAART compared with uninfected normotensive pregnant women (Table 3). A similar profile was observed in PE women, with significantly lower IL-2 and TNF-α levels and non-significant lower IFN-γ and IL-6 (Table 2) in HIV infected PE women on HAART relative to uninfected PE women. This is suggestive of HIV in combination with HAART having suppressive effects on these inflammatory cytokines during pregnancy in both uncomplicated and PE pregnancies. Similar findings were observed in a local study among Black African participants receiving HAART, although this study involved non-pregnant participants [21].

Cytokines have been implicated as potential mediators in PE, where endothelial dysfunction is considered the hallmark of the syndrome [22]. Cytokines may also be involved with abnormal inflammatory responses caused by syncytiotrophoblast molecules (STBM) shed into maternal blood in PE [13]. The alteration between pro-inflammatory/regulatory responses does not occur in PE, or may be reverted in very early stages of the disease, leading to a pro-inflammatory state [23].

In our study, we did not find significant differences in IL-2, TNF-α, IFN-γ or IL-6 in PE women compared to normotensive women. Our findings do not reflect the pro-inflammatory
environment in PE shown in other studies [24–26], however differences in study designs exist in relation to sample population, pregnancy status, and sampling techniques.

T cells are cytokine producing cells that are infected by HIV via CD4\(^+\) receptors present on the cell surface [27]. Studies conducted earlier have revealed that HIV-infected individuals have a weaker immune system and the inability of CD4\(^+\) T cells to proliferate, due to the decrease in the levels of IL-12 [28]. As a result, decreases in IL-2 and IFN-\(\gamma\) occur, leading to

Table 1. Clinical characteristics of participants.

| Variable          | PE HIV uninfected | PE HIV infected | Normo-tensive uninfected | Normo-tensive HIV infected | Total | \(p\) value | \(p\) value |
|-------------------|-------------------|-----------------|--------------------------|---------------------------|-------|-------------|-------------|
| Group             | 1                 | 2               | 3                        | 4                         | all   | all         | 1 vs. 2     |
| \(n\)             | 53 (100)          | 44 (98)         | 50 (100)                 | 45 (100)                  | 192 (99) | 0.002  | 0.003       |
| **Age** (n, %)    | 24.8 ± 5.3        | 28.7 ± 7.3      | 24.6 ± 6.4               | 28 ± 6.4                  |       |             |             |
| range (yrs)       | 16–40             | 16–42           | 16–42                    | 17–46                     |       |             |             |
| **Parity** (n, %) | 0                 | 26 (39.4)       | 18 (27.3)                | 17 (25.8)                 | 5 (7.6) | 66 (100)   |             |
| 1–5               | 27 (22)           | 26 (21.1)       | 31 (25.2)                | 39 (31.7)                 | 123 (100) |             |             |
| > 5               | 0 (0)             | 1 (25)          | 2 (50)                   | 1 (25)                    | 4 (100) |             |             |
| **GA** (wks)      | 35.8 ± 3.5        | 34.7 ± 4.6      | 38.2 ± 1.6               | 37.6 ± 2.7                | 36.5 ± 3.6 | < 0.001 | 0.086       |
| \(n\), %          | 0                 | 42 (93)         | 0                        | 40 (89)                   |       |             |             |
| mean ± SD         | 436 ± 181         | 39 ± 87         | 35 (70)                  | 36 (80)                   | 145 (76) |             |             |
| **BMI** (n, %)    | 24.3 ± 13         | 39.4 ± 12.4     | 29.7 ± 12                | 30.1 ± 15.4               | 31 ± 7.4 | 0.391  | 0.229       |
| **MOD** (n, %)    | ELCS              | 9 (17)          | 9 (20)                   | 25 (53)                   | 27 (61) | 70 (37)    |             |
| \(n\), %          | 436 ± 181         | 39 ± 87         | 35 (70)                  | 36 (80)                   | 145 (76) |             |             |
| mean ± SD         | 24.3 ± 13         | 39.4 ± 12.4     | 29.7 ± 12                | 30.1 ± 15.4               | 31 ± 7.4 | 0.391  | 0.229       |
| **GA@sample** (wks) | 35.6 ± 3.3       | 34.2 ± 4.5      | 38.2 ± 1.6               | 35.7 ± 2.7                | 189 ± 98 | 0.945  | 0.837       |
| \(n\), %          | 14 (26.4)         | 18 (40)         | 98 (100)                 | 98 (100)                  | 98 (100) | 0.153  |             |
| **Proteinuria**   | 18 (34)           | 21 (47)         | 98 (100)                 | 98 (100)                  | 98 (100) | 0.2     |             |
| **Systolic BP** (mm Hg) | 157.1 ± 17.1   | 159 ± 14.2      | 98 (100)                 | 98 (100)                  | 98 (100) | 0.304  |             |
| **Diastolic BP** (mm Hg) | 101.9 ± 9.8    | 104.5 ± 9.8     | 89 (91)                  | 89 (91)                   | 89 (91) | 0.993  |             |
| **Alanine transaminase** (units/L) | 26.3 ± 56.8    | 26.4 ± 53       | 65 (66)                  | 65 (66)                   | 65 (66) | 0.429  |             |
| **Aspartate transaminase** (units/L) | 33.4 ± 34.7    | 64.2 ± 20.9     | 87 (89)                  | 87 (89)                   | 87 (89) | 0.001  |             |
| **\(\gamma\)-Glutamyl transferase** (units/L) | 17.1 ± 14    | 26.9 ± 40.9     | 43 (44)                  | 43 (44)                   | 43 (44) | 0.39    |             |
| **Lactate dehydrogenase** (units/L) | 630 ± 207.2   | 1052.7 ± 2047.6 |                     |                           |       |             |             |

Abbreviations: GA = gestational age, BMI = Body Mass Index, MOD = mode of delivery, ELCS = elective caesarean section, EMCS = emergency caesarean section, VD = vaginal delivery, SD = standard deviation PE = preeclampsia, \(n\) = total number (1): \(p\) = significance, * = Grp 2 vs Grp 4

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immunosuppressive effects and opportunistic infections, a marker of advanced disease. In a recent study of the cytokine milieu in untreated HIV infection, pro-inflammatory cytokines, IL-2, IL-12, and IFN-γ were shown to be significantly decreased. CD4 cell counts are an important biomarker for HIV progression, and are lower in HIV participants versus healthy participants [27]. In our study, we did not find a significant difference between the CD4+ counts in normotensive HIV infected women and those with PE, however, both groups were on HAART in terms of existing guidelines [7].

Due to HIV having immune—depressive effects, an association between PE and HIV has been suggested [29]. HAART suppresses HIV viremia, increases CD4+ cell counts, and is suggested to counteract the Th1 to Th2 shift in the disease progression of HIV [19]. The use of HAART in pregnancy provides significant benefits in delaying HIV disease progression and reducing the risk of mother-to-child transmission, and has been integrated into policy [7].

Our data suggests that immune reconstitution by HAART in these conditions includes alterations in pro-inflammatory cytokines. Although some clinical data is associated with a lower rate of PE among HIV positive women who receive HAART [30], a further prospective

### Table 2. Quantitative evaluation of cytokines.

| Cytokine   | Statistics | PE + HIV+ (2) vs. PE - HIV- (3) | PE - HIV+ (4) vs. PE - HIV- (3) |
|------------|------------|---------------------------------|---------------------------------|
| IL-2 (pg/mL) | p-value    | 0.0008                          | 0.9384                          |
|            | {group} [median] | [268.7] | [274.4] | [257.6] |
| TNF-α (pg/mL) | p-value    | 0.0001                          | 0.2792                          |
|            | {group} [median] | [172.2] | [198.8] | [174.8] |
| IFN-γ (pg/mL) | p-value    | 0.0233                          | 0.5534                          |
|            | {group} [median] | [214.1] | [217.1] | [214.1] |
| IL-6 (pg/mL) | p-value    | 0.0865                          | 0.7743                          |
|            | {group} [median] | [139.7] | [149.8] | [133.0] |

Abbreviations: PE = preeclampsia, HIV = Human Immunodeficiency Virus, IL-2 = interleukin 2, TNF-α = tumour necrosis factor alpha, IFN-γ = interferon gamma, i: Wilcoxon rank-sum (Mann-Whitney) test, IQR: interquartile range, vs = versus

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### Table 3. Comparative analysis of cytokine perturbations by groups.

| Cytokine | HIV+ vs. HIV- | PE vs. Normotensive | PE/HIV+ vs. PE/HIV- |
|----------|---------------|---------------------|---------------------|
| Units    | Δ median pg/mL (p-value) |
| IL-2     | -16.8 (0.010)* | -1.20 (0.938) | -4.5 (0.000)* |
| TNF-α    | -24.0 (0.045)* | -13.6 (0.279) | -13.0 (0.000)* |
| IFN-γ    | -3.0 (0.345)   | +1.2 (0.553)    | -4.2 (0.023) |
| IL-6     | -16.8 (0.005)* | -2.8 (0.774)   | -7.3 (0.086) |

*(p< 0.05 is deemed statistically significant); Δ = difference in values; PE = preeclampsia

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cohort study with sequential sampling is necessary to determine the clinical association. Currently there is a paucity of data on cytokine mediated immune reconstitution effects associated with HAART in pregnancy, possibly due to differences in drug regimens, patient profiles, study settings and rapidly evolving therapeutic regimens.

Our study was limited by the lack of knowledge on the precise duration of HAART and detailed knowledge of drug adherence. Moreover, pregnancy is inherently immunogenic and is associated with longitudinal variation, posing further challenges to accurately contextualise changes. In our study, we did not include patients with untreated HIV infection, which is unethical under the current guidelines. In addition, we included patients that had proteinuria \( \geq +1 \) on urine dipstick testing which may have included patients without significant proteinuria \( \geq 300 \text{mg} \). The present study was conducted among African women, and our results may therefore differ in comparison to other HIV-infected populations. In the context of racial variation on cytokine responses, African–Americans have been shown to have higher baseline levels of inflammatory cytokines [31]. Differences in sample sizes, patient selection and techniques used, further contribute to heterogeneity among studies relating to PE and HIV. Furthermore, functional pleiotropy and redundancy are characteristic features of cytokines, and may show overlapping activities depending on the type and developmental state of the target cells involved [32].

**Conclusion**

The effects of HAART, in conjunction with HIV, during pregnancy include alterations in pro-inflammatory cytokines IL-2, TNF-\( \alpha \), IFN-\( \gamma \) and IL-6. We observed consistently lower levels of IL-2 and TNF-\( \alpha \) in HIV-infected pregnant women on HAART, regardless of PE or normotensive status; suggesting HIV/HAART has an inhibitory effect on these proinflammatory cytokines during pregnancy. Under normotensive conditions, IL-6 was significantly lower in HIV infected women on HAART. These findings highlight the need for further investigation on the immune reconstitution effects of HAART during pregnancy, and the potential of immune modulation therapy for the management of PE, where treatment still remains empiric.

**Author Contributions**

**Conceptualization:** AAC NRM.

**Data curation:** NRM AAC SN.

**Formal analysis:** AP SN PR CT.

**Funding acquisition:** NRM AAC.

**Methodology:** AAC NRM AP SN PR CT.

**Project administration:** AAC.

**Supervision:** AAC.

**Validation:** AP.

**Writing – original draft:** NRM AAC.

**Writing – review & editing:** AAC.
References

1. Backes CH, Markham K, Moorehead P, Cordero L, Nankervis CA, Giannone PJ. Maternal preeclampsia and neonatal outcomes. Journal of Pregnancy. 2011; 2011(2011):2011.

2. WHO. WHO report on the health of women: AIDS leading cause of death globally in women of reproductive age. In: Organisation WH, editor. Geneva: WHO Press; 2009.

3. Moodley J. Saving Mothers 2011–2013: Sixth report on the confidential enquiries into maternal death. In: Africa DoHS, editor. 2014.

4. Nääv Ä, Erlandsson L, Axelsson J, Larsson I, Johansson M, Wester-Rosenlöf L, et al. A1M Ameliorates Preeclampsia-Like Symptoms in Placenta and Kidney Induced by Cell-Free Fetal Hemoglobin in Rabbit. PloS one. 2015.

5. Autran B, Carcelain G, Li TS, Blanc C, Mathez D, Tubiana R, et al. Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease. Science. 1997; 277(5322):112–6. PMID: 9204894

6. Volmink J, Siegfried N, Van der Merwe L, Brocklehurst P. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection (Review). 2007.

7. NDH. The South African Antiretroviral Treatment Guidelines In: Africa NDoH-S, editor. South Africa 2013.

8. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annual review of medicine. 2011; 62:141. doi: 10.1146/annurev-med-042909-093756 PMID: 21090961

9. Shaikh PZ, Sharma M, Shah A, Sharma P, Darwehekar GN. INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES. Int J of Pharm & Life Sci(IJPL S). 2011; 2(10):1154–73.

10. Catarino C, Santos-Silva A, Belo L, Rocha-Pereira P, Rocha S, Patrício B, et al. Inflammatory disturbances in preeclampsia: relationship between maternal and umbilical cord blood. Journal of pregnancy. 2012; 2012.

11. Dweikat I, Steer P, Ilievski M, Martin I, Parmar M, et al. Antiretroviral therapy and inflammation: a systematic review of the literature. J Intern Med. 2016; 280(3):245–63.

12. Sargent IL, Borzychowski AM, Redman CW. Immunoregulation in normal pregnancy and preeclampsia: an overview. Reproductive biomedicine online. 2006; 13(5):680–6. PMID: 17169180

13. Martinez-Varea A, Pellicer B, Perales-Marin A, Pellicer A. Relationship between maternal immunological response during pregnancy and onset of preeclampsia. Journal of immunology research. 2014; 2014.

14. Szarka A, Rigó J, Lázár L, Becs G, Molvarec A. Circulating cytokines, chemokines and adhesion molecules in normal pregnancy and preeclampsia determined by multiplex suspension array. BMC Immunology. 2010; 11(1):59.

15. Pinheiro MB, Martins-Filho OA, Mota APL, Alpoim PN, Godoi LC, Silveira AC, et al. Severe preeclampsia goes along with a cytokine network disturbance towards a systemic inflammatory state. Cytokine. 2013; 62(1):165–73. doi: 10.1016/j.cyto.2013.02.027 PMID: 23523008
24. Saito S, Umekage H, Sakamoto Y, Sakai M, Tanebe K, Sasaki Y, et al. Increased T-Helper-1-type immunity and decreased T-Helper-2-type immunity in patients with preeclampsia. American Journal of Reproductive Immunology. 1999; 41(5):297–306. PMID: 10378024

25. Bates MD, Quenby S, Takakuwa K, Johnson PM, Vince GS. Aberrant cytokine production by peripheral blood mononuclear cells in recurrent pregnancy loss? Human Reproduction. 2002; 17(9):2439–44. PMID: 12202438

26. Cemgil Arikan D, Aral M, Coskun A, Ozer A. Plasma IL-4, IL-8, IL-12, interferon-γ and CRP levels in pregnant women with preeclampsia, and their relation with severity of disease and fetal birth weight. The Journal of Maternal-Fetal & Neonatal Medicine. 2012; 25(9):1569–73.

27. Tudela EV, Singh MK, Lagman M, Ly J, Venketaraman V. Cytokine Levels in Plasma Samples of Individuals with HIV Infection. Austin Journal of Clinical Immunology. 2014; 1(1):5.

28. Noble A, Thomas MJ, Kemeny DM. Early Th1/Th2 cell polarization in the absence of IL-4 and IL-12: T cell receptor signaling regulates the response to cytokines in CD4 and CD8 T cells. European Journal of Immunology. 2001; 31(7):2227–35. PMID: 11449377

29. Hall D, Gebhardt S, Theron G, Grové D. Pre-eclampsia and gestational hypertension are less common in HIV infected women. Pregnancy Hypertension: An International Journal of Women’s Cardiovascular Health. 2014; 4(1):91–6.

30. Mattar R, Amed AM, Lindsey PC, Sass N, Daher S. Preeclampsia and HIV infection. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2007; 117(2):240–1.

31. Slopen N, Lewis TT, Gruenewald TL, Mujahid MS, Ryff CD, Albert MA, et al. Early life adversity and inflammation in African Americans and whites in the midlife in the United States survey. Psychosomatic Medicine. 2010; 72(7):694. doi: 10.1097/PSY.0b013e3181e9c1f6 PMID: 20595419

32. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro-and anti-inflammatory properties of the cytokine interleukin-6. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2011; 1813 (5):878–88.