

# Immune evaluation of HIV-infected and noninfected pre-eclamptics

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**To the Editor:** It is widely known that an individual's immune status is debilitated by HIV infection. In the early stages of HIV infection, when few symptoms are seen, there may be a slight depression in CD4 T cells, which is temporary at this stage. Immune abnormalities appear during the second stage, when the virus begins to replicate rapidly, which results in a decrease in the percentage and total number of CD4 T cells. The decrease in CD4 T cells remains the most widely used parameter to assess disease progression.<sup>1</sup>

Further to this, the immune responsiveness of women is altered during pregnancy in order to retain protective properties against disease and also to allow tolerance of the fetus. Diseases such as pre-eclampsia have been suggested to arise as a result of maladaptations in these immune response alterations.<sup>2</sup> Studies have demonstrated that the rates of CD4 T cells in pre-eclamptic women begin to decrease in the early stages of pregnancy before the occurrence of pre-eclampsia and normal levels are only reached several weeks after delivery. In another study, it was found that the rates of CD4/CD8 T cells in pre-eclamptic women were lower when compared to normal pregnant women.<sup>1</sup> The immune system is altered during pregnancy and this is exacerbated in pre-eclampsia.

Haematological markers are also affected by HIV infection and disorders of all three major haematological lines (anaemia, leucopenia and thrombocytopenia) may occur, while in pre-eclampsia, circulating platelet counts are reported to be reduced. Platelets may either be consumed in thrombus formation or may suffer membrane damage from contact with abnormal surfaces or may be prematurely removed from the circulation.<sup>3-5</sup>

The aim of this study was to evaluate the haematological parameters and immune markers in women with both pre-eclampsia and HIV.

Institutional ethical permission was obtained and all participants gave written informed consent. Confidentiality was maintained by not including participants' names in the research records and by pooling the data.

The study population consisted of participants in whom the diagnosis of pre-eclampsia was made according to the International Society for the Study of Hypertension in Pregnancy

guidelines. The study was conducted at a regional hospital in Durban, South Africa. None of the participants required immediate delivery and all had agreed to HIV testing, followed by voluntary counselling. For each HIV-positive woman with pre-eclampsia an HIV-negative participant, matched for age, parity and grade/severity of hypertension, was enrolled.

Venous blood samples for a complete blood count and CD3, CD4 and CD8 counts were obtained at the same time as blood samples for routine blood investigations to avoid unnecessary venepuncture and participant discomfort. The immune markers were processed on a Coulter Epics MCL flow cytometer and the full blood counts were carried out on the Beckman Coulter® HmX Haematology Analyser. In addition, demographic and clinical data and delivery details were recorded.

SPSS Version 13 (SPSS Inc, Chicago, Illinois) was used to analyse the data. Bivariate analysis was undertaken to assess associations between HIV status and various outcomes. Categorical outcomes were assessed using Pearson's Chi-square tests or Fisher's Exact tests where appropriate. Quantitative outcomes were tested for normality and found to be significantly skewed. Therefore, nonparametric Mann-Whitney tests were used to compare median values between the HIV-negative and HIV-positive groups. A p-value of < 0.05 was considered as statistically significant.

Forty-five participants with pre-eclampsia were recruited and divided into two groups, viz non-HIV-infected (n = 25) and HIV-infected (n = 20) patients. The clinical data (age, parity, blood pressure, proteinuria, gestational age and mode of delivery) showed no significant statistical differences between the groups. In addition, there were no significant differences between the two groups in respect of neonatal outcomes. All participants had blood pressure values of > 140/90 mmHg (range 140/90–170/115 mmHg) and at least two pluses of proteinuria tested by urinary dipstick.

There were no differences between the groups in respect of red blood cell parameters. The lowest haemoglobin level was found in the HIV-positive group. There were no differences in platelet count. The lowest platelet count was  $21 \times 10^9/L$  in the HIV-negative group. Similarly, there were no differences in the groups in respect of white cell counts, neutrophils and absolute lymphocyte counts.

Table I: Immune markers

| Immune markers | HIV positive (means)<br>(n = 20)  | HIV negative (means)<br>(n = 25)    | P-value |
|----------------|-----------------------------------|-------------------------------------|---------|
| CD3+ cells     | 978 cells/ $\mu$ l<br>(338–2 284) | 1 423 cells/ $\mu$ l<br>(674–2 712) | 0.02    |
| CD4+ cells     | 274 cells/ $\mu$ l<br>(96–782)    | 925 cells/ $\mu$ l<br>(176–1 716)   | 0.002   |
| CD8+ cells     | 633 cells/ $\mu$ l<br>(110–1 333) | 618 cells/ $\mu$ l<br>(114–921)     | 0.84    |

\*30% of HIV-infected patients had CD4+ cell counts  $\leq$  200 cells/ $\mu$ l.  
n = actual number

The results of the three immune markers measured are shown in Table I. The CD3 counts were lower in the HIV-infected group than in the noninfected group: 978 vs 1 423 cells/ml ( $p = 0.03$ ), respectively. CD4 counts were also lower in the HIV-infected group than in the noninfected group: 274 vs 925 cells/ml ( $p = 0.002$ ).

The results obtained did not show any severe haematological or immunological abnormalities when women had both pre-eclampsia and HIV infection. There was no statistical difference in haematological parameters, in other words anaemia, thrombocytopenia and leucopenia, key features in either pre-eclampsia or HIV infection. We found decreased levels of CD3+ cells in HIV-positive patients compared with HIV-negative patients (mean of 978 cells/ $\mu$ l vs 1 423 cells/ $\mu$ l;  $p$ -value = 0.015), and the CD4+ cell count was decreased in the HIV-positive group when compared with the HIV-negative group (mean of 274 cells/ $\mu$ l vs 925 cells/ $\mu$ l;  $p$ -value = 0.002). Therefore, there were HIV-infected pre-eclamptic patients with low CD4+ cell counts ( $< 500$  cells/ $\mu$ l) and CD3+ cell counts, and our mean values were much lower than previously described mean values by Wimalasundera et al and Mattar et al.<sup>3,4</sup>

This suggests that immune mechanisms involving CD estimations do not play a role in pre-eclampsia since the decline in the counts can be solely attributed to HIV infection. There was no statistical difference in CD8 among the two groups. This is in keeping with results reported by Cetiner et al<sup>1</sup> that show no statistical significance in CD4 and CD8 in pre-eclamptic patients when compared to normal pregnant controls.

However, contradicting results by Mahmoud et al (2003)<sup>2</sup> show a statistical significance in the number of T lymphocytes: CD2, CD3, CD4, CD8 and CD19. These findings suggest systemic alteration in maternal immunity associated with the pre-eclamptic state. The difference in results could be due to the small sample size used by Mahmoud et al<sup>2</sup>; of 54 women with pregnancy-induced hypertension, only 14 were proteinuric and therefore pre-eclamptic. Our results show that HIV infection lowers CD3 and CD4 during pregnancy. Ibrahim et al<sup>6</sup> found no deterioration in the CD4 count in any of the trimesters among HIV-infected pregnant women; it seemed to only increase post delivery. According to Ibrahim et al<sup>6</sup> this may have been due to the cross-sectional nature of the study. Further, with the exception of the third-trimester CD8 counts, among all the trimesters the CD4 and CD8 counts showed significant differences between the HIV-infected and noninfected pregnant groups. These lower CD4

counts in the HIV-infected group might reflect a longer period of infection prior to parturition.

These results suggest that more specific management is not required when women have both pre-eclampsia and HIV infection. Medical care should be administered on the basis of grade of pre-eclampsia (mild or severe) and stage of HIV infection, taking into account maternal and fetal well-being.

The results obtained from this study contradict the outcomes of other studies conducted. Further investigation is warranted in these areas. The limitations of this study may include the small sample size and neglected antiretroviral treatment history among the HIV-positive group, which may have played a role in the stability of the haematological parameters. Tracking the women over all three trimesters may also have produced more significant results. Due to the small sample size, this study may serve to determine the study size required for a larger study to evaluate the haematological parameters and immune markers among HIV-infected and noninfected pre-eclamptic women in South Africa.

The question does arise as to whether severe immunosuppression from HIV infection (CD4+ cell count  $\leq 200$  cells/ $\mu$ l) protects patients from the development of pre-eclampsia. A study that would follow up HIV-infected patients with severe immunosuppression and check for the incidence of pre-eclampsia would probably answer this question.

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