Progesterone And Immunological Changes In Human Immunodeficiency Virus Infection During Pregnancy

Stanslaus Kiilu Musyoki, Eric Omori Omwenga, Stephen Mwaura Kariuki, Edson Kipyegon Kemoi

Abstract: Immune responses during pregnancy are specifically regulated to allow fight against infections and prevent any damage to the growing fetus. HIV infections, a pro-inflammatory infection, present a challenge to the enhancement of pregnancy specific immuno-modulation of pro-inflammatory immunity. HIV Infection during pregnancy remains a health concern in regard to immune response and status. The immunological outcome of HIV-infected pregnant mothers and their effect on the health status and pregnancy outcome are areas of paramount importance in public health. In the current article, we review current data about the characteristic progesterone and immune responses in conjoint cases of HIV infection and pregnancy and present an immunological hypothesis to explain the findings. In conclusion HIV infection in pregnant women is associated with lower progesterone and increased cellular immunity compared to HIV-non-infected women. There is a clear indication that HIV infection may cause lower levels of progesterone among the HIV-infected pregnant women compared to the HIV-non- infected women. Most of the highlighted studies have indicated that HIV-infection during pregnancy is characterized by an elevation of both inflammatory and regulatory immune responses in response to both HIV infection and pregnancy concurrently. The reviewed studies have shown varied results regarding the lymphocyte counts during pregnancy and HIV infections. It, therefore, remains unclear how HIV infection would affect lymphocytes counts as pregnancy advances considering all arms of the immune response in a single study. Further researches are thus required to address the mechanism of interaction of the two opposing immune responses; pro-inflammatory (Th1) response as a result of HIV infection and the immune regulation (Th2) response during pregnancy that can define the delicate balance of immune response in conjoint cases of HIV infection and pregnancy. Further research is required to address the mechanism of interaction of the two opposing immune responses against HIV infection and the immune regulation during pregnancy that defines the altered immune response.

Index Terms: Progesterone, T- Lymphocytes, CD3+, CD4+, CD8+, Pregnancy, HIV infections, Trimesters.

1 INTRODUCTION

Progesterone levels and immune response of HIV-infected women may be different from that of HIV-infected women during pregnancy. Previous studies have suggested a progesterone-cytokine-T cell network during pregnancy [1, 2]. Progesterone promotes TH2 cell development hence increasing the production of anti-inflammatory cytokines [3]. Progesterone levels have been reported to be similar in HIV infected on antiretroviral drugs and those who have not been put on drugs [4, 5]. Immune responses during pregnancy are specifically regulated to allow fight against infections and prevent any damage to the growing fetus. HIV infections, a pro-inflammatory infection, present a challenge to pregnancy specific immuno-modulation of pro-inflammatory immunity is enhanced. The fetal-placental unit produces TH2 cytokines to avoid damaging TH1 mediated immune responses [6]. Thus, the type of cytokine produced during pregnancy determines the success or failure of gestation. Cytokines produced during pregnancy favors antibody production (mediated by TH2 cytokines) over T-cell responses (mediated by TH1 cytokines) [7]. Regarding this, it remains a fact that cell-mediated responses are suppressed during pregnancy, as an effect of suppressive mechanisms of cytokines produced by T-regulatory cells that favor the survival of fetus in successful pregnancies [8, 9]. Furthermore, it has been shown that failure to regulate cytokine production during pregnancy has been associated with abortions mediated by maternal NK and TH1 cells [10]. In cases of asymptomatic HIV infection, the levels of TH1 cytokines remain high [11] and patients have no clinical problems except for possible lymphadenopathy. In HIV infections, T-cells are responsive to the negative regulation by Tregs both spontaneously and upon stimulation [12]. Interleukin-2 is a cytokine that is majorly secreted by CD4+ T-cells, and it is dominant during HIV infections. Interleukin-2 has also been known to induce the secretion of INF-γ, TNF and IL-4 [13]. It induces the proliferation and activation B and T cells, as well as enhancement of the function of the NK cells. A previous study has indicated that IL-6 influence the progression of HIV disease [14]. In this scenario, a change in the repertoire towards TH1 cytokines in HIV infections during pregnancy may disturb the balance of the progesterone-cytokine-T cell network, which may cause complications and abortions during pregnancy.

In another study, it was observed that CD4+ counts are affected by use of simplified once-daily regimen ARV, the therapy given to the HIV-infected pregnant women, but only after 12 months [15]. This study was however done within the nine months of pregnancy, a time before the effects of ARVs could be established. There are no other studies that indicate the effect of ARV on systemic cytokines, CD8+, CD19+, CD56/16+, the other variables measured in the present study. Therefore the use of ARV by the HIV-positive women during pregnancy remain is a limitation of researches since it has been reported to improve the health of HIV-infected persons. It is known that progesterone, 1L-2, IL-4, IL-10, IL-6, TNF, IFN-γ, T-cells, NK and B-cells have a paramount role and immune feedback in both pregnancy and HIV infection independently [16, 17]. However, the impact of HIV infections on these key immune parameters as pregnancy advances remained unknown despite the reported cases of abortion among the HIV–infected pregnant women. The current article has reviewed on the progesterone and immunological changes in pregnancy and human immunodeficiency virus infection..

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2 REVIEW DISCUSSION

2.1 Progesterone levels in pregnancy and HIV infections

During pregnancy, progesterone is increasingly produced and as a result several changes occur in the immune system of a pregnant woman to secure the fetus and at the same time maintain a maternal immunity against infections [1, 2]. Corpus leuteum is known secrete and maintains high levels of progesterone in early pregnancy in order to maintain pregnancy in the first twelve weeks of pregnancy [18]. A drop in the levels of progesterone hormone in the early weeks after conception may lead to miscarriage [19]. By the end of the first trimester of a healthy pregnancy, the placenta begins to produce progesterone in place of the Corpus leuteum [16]. During pregnancy, the placenta continues to produce progesterone, and continues to increase till term before delivery of the baby [16]. Approximately seventy percent reduction of progesterone secretion was noted in HIV-infected cell line cultures compared to controls in a study which investigated HIV infection of human placenta [20]. However, this study did not determine blood progesterone levels in advancing pregnancy, used in the routine monitoring of progesterone. Complicated pregnancies and abortions have also been reported among women with low progesterone levels [19]. These studies did not consider doing a follow-up on the study participants and were unable to show if HIV could affect the levels of progesterone in pregnancy. Other study findings have shown that HIV positive pregnant women had lower levels of progesterone in all trimesters of pregnancy compared to HIV-non-infected pregnant women [21]. Based on these review, there are few studies that have studied the changes of progesterone in conjoint cases of HIV infection and pregnancy. However, there is a clear indication that HIV infection may cause lower levels of progesterone among the women with HIV-infection during pregnancy compared to the HIV-negative women.

2.2 Systemic cytokines in pregnancy and HIV infections.

Pregnancy is known to contribute to the systemic change in cytokines toward TH2 dominance [22]. Some cytokines produced in pregnancy are beneficial for the foetal growth: IL-4 and IL-10, where others seem deleterious: IL-2, IFN-γ, and TNF [3, 23, 24]. During the growth of fetus , IL-23, IL-10,IL-6 and Th-17 associated immune responses, have been shown to increase while TNF-alpha and IL-1beta- and Th1-associated immune responses are decreased[25]. Interleukin-4 and IL-10 suppress TH1 responses [8]. The progress of pregnancy is shown to be linked with the secretion of IL-10 and IL-4, and both cytokines suppress the production and function of TH1 cells [26]. In a previous study, levels of IL-10 were shown to be low during early pregnancy and markedly increased in last days of pregnancy and post-partum [27]. This study also observed that IL-10 and IL-4 were promoting progesterone production in healthy pregnancies. The upregulated IL-10 cytokine levels may be an adaptation to control HIV associated inflammation-induced pathologies as a result of pro-inflammatory cytokines produced in HIV infection. In a different study IL-6 and TNF have been observed to be high in cases of spontaneous abortions [28]. Gravid is also associated with low levels of IFN-γ [29]. Despite this knowledge on the critical role of IL-4, IL-10, IL-6 and TNF and how they are affected by pregnancy, no study has shown the mechanism of how HIV infection could impact these cytokines during pregnancy. It, therefore, remains unclear if HIV infection is attributed to increasing or decrease of IL-4, IL-10, IL-6 and TNF as pregnancy advanced. Change in the TH2 and TH1 cytokines production in HIV infection could affect the HIV disease prognosis [30]. Predominance in high TH1 responses in early HIV infection is responsible for effective control of the virus [31]. In the advanced stages of HIV disease, TH1 cytokines production is reduced whereas secretion of TH2 cytokines is increased [32]. This change in cytokines contributes to the pathogenesis of the disease leading to AIDS. In HIV-infection, pro-inflammatory, and regulatory cytokines increase with higher T-regulatory cells, indicating that inflammation process and immuno-regulation have a similar pathophysiology in HIV infections [33]. Regarding HIV-infected women during pregnancy, higher levels of pro-inflammatory cytokines were noted in late pregnancy which may have contributed to an increased chance of maternal-fetal death [33]. A previous study observed that there was little difference in IL-2 between the HIV-infected patients and normal healthy volunteers [34]. However, a different study on pregnant women showed comparable levels of intracellular InterLeukin-2 production between HIV-infected and HIV-non-infected expectant mothers [13]. However, these studies did not do a follow-up on pregnant women to understand the longitudinal changes that occur across trimesters of pregnancy. Furthermore, other studies indicate that both pregnancy and HIV infection are biased towards a TH2-type response by T-cells [34]. Another study has also reported that conjoint cases of HIV infection and pregnancy significantly increase the risk of complicated pregnancy and abortions [35]. Despite the reported complications and abortions among the HIV-infected pregnant women, the effect of HIV infection on systemic cytokines as pregnancy advances remains unknown. Cytokines could be a cause of abortion and equally immune regulate immune responses. Therefore cytokines could also be used as supplement as a means of promoting immune responses in pregnancy and HIV-infection, and thus it was critical to determine how they are affected by HIV infection during pregnancy. In a different study HIV-infected women had higher IL-1, IL-8, IL-4, IL-10, TNF-alpha and IFN-gamma blood concentrations throughout pregnancy compared to non-infected women[25, 36]. Conjoint presence of HIV infection and pregnancy seem to favor the up regulation of IL-10 levels of cytokines as pregnancy advanced compared to cases of pregnancy without HIV infection. Therefore further investigation into the synergy effect of HIV and pregnancy in the production of IL-10 is greatly recommended. This will give a further insight in the possibility of treatment strategies of using IL-10 especially to pregnant women who are HIV-infected. The study also showed that inflammatory and regulatory cytokines are elevated with higher levels of Treg% in HIV-infected women compared to the non-infected. This may indicate that immuno-regulation and inflammation have a common origin during HIV infection. Most of the highlighted studies have indicated that HIV-infection during pregnancy is indicated by an elevation of both regulatory and inflammatory immune responses in response to both HIV infection and pregnancy concurrently.

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2.3 Lymphocytes in pregnancy and HIV infections

Some studies have reported that there is no alteration in the CD8+ and CD4+ levels in pregnancy[37–39], while others have clearly demonstrated that there are changes in CD8+

and CD4+ T cell levels during pregnancy [40, 41]. In regards to HIV infections, the marked depletion of CD4+ cells due to the cellular destruction by specific activated CD8+ cytotoxic T-cells [42]. The decline of CD4+ T-cell count in HIV infection can vary such that some patients may have a quick depletion of CD4+ counts for some months while others may experience relatively stable CD4+ counts for years [43]. In another study involving sex workers in Nairobi, Kenya, a significantly (P< 01) lower frequencies of CD4+ specific T cell activation was observed among the HIV-non infected compared to the HIV-infected women was observed. Among the HIV-negative women, lower CD4 T-cell specific, interferon (IFN)- gamma cytokine production was also observed in this study. The results of this study indicate that, CD4 T cells in HIV-non-infected women have good immune response in response to HIV infection compared with HIV-infected women [44] Regulatory cells (T-reg) have been reported to increase in pregnancy[33]. A previous study characterized Treg in HIV-positive and negative women in pregnancy and how they are related with inflammation, activation and cellular immune. The study observed that HIV-infected women presented higher proportion of Treg subpopulations in the first weeks of pregnancy. However, T-reg levels were lower in the last weeks of pregnancy compared with no-infected women, which include CD8+TGFbeta+%, CD4+CTLA4+% and CD8+CTLA4+%. Cellular immunity, measured by lymphocytes, was observed to be lower in HIV-positive cases compared to HIV-negative pregnant women. It was also inversely associated with CD8+FoxP3+%, CD4+FoxP3+%, and CD8+TGFbeta+% among the HIV-infected when compared to HIV-non-uninfected pregnant women. This results indicate that T-reg have varied changes in pregnancy in both HIV-infected and non-infected women. The higher frequencies of pro-inflammatory cytokines and reduced T-regs in the last weeks of pregnancy among the HIV-infected women may explain the higher incidences of mother-fetal morbidity. Among the HIV-infected pregnant women, a previous study observed that CD4+ counts decrease in pregnancy and after birth the HIV-positive women [39]. In this study, the CD8+ % counts increased at the last weeks of pregnancy and reduced to the first weeks after delivery in both HIV-negative and HIV-positive women. Another study has also shown HIV-infected pregnant women to have low CD4+ and elevated CD8+ compared to HIV-negative pregnant but remained stable throughout pregnancy and after delivery in both groups of women [45]. Other observational studies on HIV-infected women and men, found that women who became pregnant had better health in comparison to those who did not become pregnant [32]. Although the pregnant women in the study had higher CD4+ levels at start and were young compared to the non-pregnant women, their health remained better even after pregnancy. Additionally, women with repeated pregnancies during the study tended to have better immune status than did women with only one pregnancy. In different study done in Kenya, HIV infected pregnant women is were observed to be characterized by leukocytosis with low levels of lymphocytes but steady CD4 levels than the HIV-infected but non- pregnant women[46]. Another study in Kenya also did not support a synergy of pregnancy and HIV infection on immune response as designated by CD4+ and CD8+ counts [47]. The CD4+ % T-cells was lower after delivery than during pregnancy, in both HIV-positive and negative women; however this was different for CD8+ counts. Absolute CD8+ Counts and percentages were observed to be significantly higher after delivery than in pregnancy. In a different study HIV-infected pregnant women had lower activated CD8+ cells than HIV-infected non-pregnant women[48]. In this study activated CD8 were also shown to reduce in pregnancy in the second and third trimesters. Therefore, the study indicated pregnancy may significantly suppress CD8+ T cells activation in HIV-infected women. In B-lymphocytes, CD19+ biomarker is very crucial for B-cell immune activation by the T-dependent mechanisms of antigens and also the maturation of the activated cells or their selection into becoming B-memory-cells [49] and therefore an important marker for B-cell and humoral immune responses [50] . B-cells and the antibodies they produce have been evaluated and shown to have a crucial role in pregnancy success [51]. Regulatory B-cells, which is a subset of B-cells having powerful tolerance functions, expand during pregnancy [52]. However, another study showed almost no change in B-cells during pregnancy [53]. Natural Killer (CD56/16+) lymphocytes are also important in HIV disease and pregnancy [54]. Natural Killer cells which predominate in blood circulation have lower levels of cytokine production, but with an increased cytotoxicity [55] thus their suppression partly maintains the pregnancy to term. A decrease in absolute counts of CD56/16+ in the third trimester of gestation has also been shown [56]. Natural Killer cell cytotoxicity has also been observed to decrease in the decidua of normal early pregnancies [57] with low NK cell numbers [41]. Lower blood NK cell percentages have been shown to occur in women without recurrent miscarriages than in women with recurrent miscarriages [58]. Although research on lymphocytes in HIV infection and pregnancy has become more pronounced as per the highlighted literature, no study has measured all lymphocytes inclusively. The majority of the studies investigated HIV-infected pregnant women compared to HIV-infected non-pregnant women and never considered the HIV non-infected pregnant women in advancing pregnancy. A comparison of lymphocyte counts between HIV-infected pregnant and HIV-non-infected pregnant would give a better insight of the effect of HIV on lymphocyte counts as the pregnancy progressed. Despite the reported complications and abortions among the HIV infected pregnant women, the highlighted studies did not clearly indicate which arm of immunity dominates among the HIV-infected women since they did not consider all the lymphocytes in the studies. The reviewed studies have shown varied results regarding the lymphocyte counts during pregnancy and HIV infections. It, therefore, remains unclear how HIV infection would affect lymphocytes counts as pregnancy advances considering all arms of the immune response in a single study.

3 Conclusion and Future Strategies

Based on the reviewed articles HIV infection during pregnancy is associated with lower progesterone. There is a clear indication that HIV infection may cause lower levels of progesterone among the HIV infected pregnant women compared to the HIV non-infected women. Most of the highlighted studies have indicated that HIV-infection during pregnancy is indicated by an elevation of both pro-inflammatory and regulatory immune responses in response to both HIV infection and pregnancy concurrently. The reviewed studies have shown varied results regarding the lymphocyte counts during pregnancy and HIV infections. It, therefore, remains unclear how HIV infection would affect lymphocytes

counts as pregnancy advances considering all arms of the immune response in a single study. Further researches are thus required to address the mechanism of interaction of the two opposing immune responses; pro-inflammatory (Th1) response as a result of HIV infection and the immune regulation (Th2) response during pregnancy that can define the delicate balance of immune response in conjoint cases of HIV infection and pregnancy.

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