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The Trends of Progesterone Hormone in Advancing Pregnancy of Human Immunodeficiency Virus-infected Women: A Cohort Study in Western Kenya

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ABSTRACT
Despite many studies on Human Immunodeficiency Virus (HIV) and pregnancy, there is still insufficient information regarding the effect of HIV on progesterone in advancing pregnancy. In a prospective cohort study, 44 antiretroviral therapy naïve adult asymptomatic HIV-infected pregnant women and 44 healthy HIV-non-infected pregnant women matched by age, parity, CD4 count and gestational time were recruited in western Kenya to test for the trends of progesterone hormone levels in advancing pregnancy of HIV-infected and non-infected women. Blood sample from all study participants was collected, and progesterone hormone levels determined using Enzyme Linked Immunosorbent Assay method at first (baseline), second and third trimesters. The changes of progesterone were assessed using repeated measures regression models and presented alongside the graphical exploratory graph. Significance levels were tested at P≤0.05. The progesterone hormone levels of the HIV-negative, 26.7 ng/ml. (95% CI: 15.5-35.9) were significantly (P=0.033) higher than those of the HIV-positive, 21.7 ng/ml (95% CI: 915.8-29.9) participants at baseline. In addition, the difference of progesterone hormone levels between HIV-positive and HIV-negative participants continued to increase significantly from first (difference of -4.3(95% CI: -8.2, -0.5) ng/ml, P=0.028), second (difference of -6.6(95% CI: -10.3, -3.0) ng/ml P=0.001) and third (difference of -11.6 (95% CI: -17.2, -6.1) ng/ml, P=0.0001) trimesters. Present study findings suggest that HIV infection may lead to lower progesterone hormone levels in all trimesters of HIV infected pregnant women compared to HIV-non-infected pregnant women. The study recommend more research should be encouraged to give a clear understanding of the effect of HIV on the hormonal balances among the pregnant women for any possible effects on the outcome of pregnancy and development of strategies to manage pregnancy in HIV infection.
Key words: *HIV Infection, Pregnancy, Progesterone, Trimesters*

INTRODUCTION

Progesterone hormone is increasingly produced for pregnancy to succeed and, as a result, many complementary changes occur in a pregnant woman to protect the fetus while maintaining maternal defense against pathogens [1,2]. After conception, the *Corpus luteum* produces and maintain high levels of progesterone in the first 12 weeks of pregnancy to sustain a pregnancy through the first trimester [3,4]. Any significant drop in progesterone hormone levels during the first weeks of pregnancy may result into miscarriage [5,6]. At around 12 weeks of normal pregnancy, the production of progesterone is by the placenta [6]. This production of progesterone by placenta continues for the remaining period of the pregnancy, and the levels rise to just before delivery [6]. These observations confirms the importance of progesterone hormone as a crucial reproductive hormone during pregnancy [7]. Furthermore, increase in progesterone hormone levels during pregnancy is thought to be partly responsible for an immune regulation seen during pregnancy [1,8], thus enhancing success of the fetus survival during the period. The levels of plasma progesterone have been reported to be comparable in HIV patients on anti-retroviral (ARV) drugs and those not yet on drug [9, 10], thus the use of ARV therapy may not make a difference on the progesterone levels. Even though the exact causes of low progesterone levels during pregnancy remains unclear, some health specialists speculate that poor nutrition, lack of exercise and stress might contribute to low progesterone levels[11]. Despite many studies on HIV and pregnancy, insufficient data exists on the effect of HIV on progesterone hormone levels in different trimesters of advancing pregnancy. Pregnant HIV-infected women have been reported to have a significantly higher risk of complicated outcomes of pregnancy and childbirth [12]. As much as progesterone is a key hormone that maintains pregnancy [1,4,13], it is unknown whether conjoint cases of HIV infections and pregnancy alters the levels of this hormone. The rationale of the current study is thus based on the fact that progesterone is essential in promoting the immunological adaptation and fetal development [14] during pregnancy. As such, the aim of the current study was to investigate the trends of progesterone hormone levels in different trimesters of advancing pregnancy of HIV-infected and non-infected women resident in western Kenya. The present study results provide a critical initial evidence that may act as a pointer to the fact that any significant drop in progesterone hormone levels during early pregnancy may result into miscarriage [5,6]. Clinicians working with HIV-infected women therefore need to understand the trends of progesterone hormone in advancing pregnancy in order to properly manage and counsel patients.

MATERIALS AND METHODS

Study population. The recruitment of study participants was at Academic Model for Providing Access To Healthcare (AMPATH) center and Moi Teaching and Referral Hospital (MTRH) - Mother Child Health Care (MCH) clinics situated in Eldoret, western Kenya. AMPATH is under MTRH and is the largest HIV treatment and care facility in Kenya. At the study site, a complete physical examination and history were taken prior to enrollment and symptom-directed exams at each follow-up visit documented. In a prospective cohort study between June 2013 and June 2014, 44 adult asymptomatic HIV-infected pregnant women were recruited from the HIV care outpatient clinics at the AMPATH center. In addition, 44 healthy HIV-non-infected pregnant women matched by participants' age, gestational age, parity and CD4 count at baseline were also enrolled from MTRH-MCH clinics. Gestational age was determined by use of the last monthly period. All participants in the study were antiretroviral naïve before recruitment to avoid any previous effects by anti-retroviral (ARV) therapy given before pregnancy. To prevent mother-to-child transmission of HIV, as part of their clinical care, all HIV-infected pregnant women were started on a simplified once-daily regimen of tenofovir DF (TDF), lamivudine

(3TC), and efavirenz (EFV) (EFV600mg+3TC300mg+TDF300mg). The demographic characteristics of the participants were collected from their medical records. Patients meeting eligibility criteria (asymptomatic HIV-positive pregnant women for study group and healthy non-HIV-infected pregnant women for control group and both with a cut-off CD4 cell count of 500 cells/µl, and aged between 18 and 40 years) were enrolled, and a complete clinical examination and history taken at recruitment point by a qualified medical officer. Study participants who smoked, used illegal substances, had poor nutrition, stress and did not do exercise were also excluded from the study. A guided questionnaire was used to ensure eligibility of the study participants and to obtain the demographic data (age, gestational age, marital status parity and CD4 count). A random sampling technique was used to enroll the study participants until the required sample size was achieved.

Laboratory procedures. After an informed and voluntary consent from each study participant was obtained a blood specimen (~5 ml) was collected. The blood collection was performed before 9 am to minimize diurnal variation in blood cell counts[15]. Immediately after blood collection, aliquots (200 microliters) were separated for laboratory analysis. Progesterone hormone levels were measured longitudinally by trimester in each participant. The first blood sample for analysis from the participants was collected at the time of recruitment during the first trimester. The second blood sample collection and analysis was done after 12 weeks, a time in the second trimester. The third and final blood sample collection was also performed 12 weeks after the second blood sample collection, a time in their third trimester. Commercially available Enzyme Linked Immunosorbent Assay (ELISA) kits (Human Company, Wiesbaden, Germany) were used to measure progesterone hormone levels as per the manufacturer's instructions.

Data analyses. Data analysis was performed using STATA version 13 (Statacorp, Timberlake, UK). Categorical variables were summarized as frequencies and corresponding percentages. Continuous variables were summarized as median and the corresponding inter-quartile range (IQR), if they failed to satisfy the Gaussian assumption; otherwise they were summarized as mean and the corresponding standard deviation (SD). Normality assumption was assessed using Shapiro Wilks test. The test for association between categorical variables was done using Pearson's Chi Square test while the test for differences between continuous variables was done using Mann Whitney U test, in cases where the variables failed to satisfy the Gaussian assumptions. The change in the progesterone hormone within study participants over time accounting for matched factors was investigated using repeated measures analysis of variance since the residual checks only showed mild violation of the normality assumption and homogeneity of variance. The change was reported alongside the corresponding 95% Confidence Intervals (95% CI). Interaction effect was included to assess the change by group over time. Results were presented using tables and graph. *P*-values ≤ 0.05 were considered statistically significant.

Ethical considerations. Prior to initiation of the study, ethical approval was sought from Moi Teaching and Referral Hospital Ethical Review Committee (ERC) for research on human participants (#000915). In addition, written informed consent was obtained from the study participants and they could withdraw anytime from the study with no consequences as to access to medical services. Confidentiality was ensured throughout the study period.

RESULTS

Demographic and baseline characteristics of the study participants. A total of 88 pregnant participants, median age 28(IQR: 25-31) years with a minimum of 19 and a maximum of 38 years, were studied. The cohort was made up of equal numbers of HIV-negative (n=44) and HIV-positive (n=44) participants. At baseline, thirty-six participants, 41%, were parity one, and 37(42%) were parity two. The remaining 15 were

distributed as 12(14%) parity three and 3(3%) parity four. A total of 73/88 (83%) were married. The median gestation age at enrollment was 8(IQR: 7-9) weeks. Progesterone was assessed at baseline and during the second and third trimesters of advancing pregnancy. The progesterone level at baseline was 24.2(IQR: 15.8-31.6) ng/ml. The median age for the HIV-negative [27(IQR: 24-30)] and HIV-positive [29(IQR: 26-31)] years (P=0.053) and parity (P=0.058) were comparable. Furthermore, the proportion of the married in the HIV-negative 39(89%) and the HIV-positive 34(77%) participants were comparable (P=0.156). The average pregnancy period of the HIV-negative participants was similar to the median gestation age of the HIV-positive participants, 8(IQR: 7-10) *vs.* 8(IQR: 7-8) (P=0.147). However, the progesterone hormone levels of the HIV-negative [26.7(IQR: 15.5-35.9)] were significantly higher than those of the HIV-positive [21.7(IQR: 15.8-29.9)] participants (P=0.033). Collectively, these results demonstrate that despite similarities in age, parity, gestational age and marital status of the study groups, the baseline progesterone level was significantly lower in HIV-positive compared to the HIV-negative pregnant women.

Change in progesterone hormone levels across the trimesters of HIV-positive and -negative pregnant women. In order to determine the trends of progesterone hormone levels across the trimesters of both HIV-positive and -negative pregnant women, the progesterone hormone levels were measured during the baseline and thereafter in the second and third trimesters of advancing pregnancy (Figure 1). Among the HIV-negative participants, the mean progesterone hormone levels in the first, the second and the third trimesters were 25.8, 55.9, and 123.2 ng/ml, respectively. Among the HIV-positive, the mean progesterone hormone levels in the first, the second and the third trimesters were 21.5, 49.3, and 111.6 ng/ml, respectively. These data demonstrates an increasing trend in progesterone hormone levels across the three trimesters in both the HIV-positive and –negative groups.

In order to determine the mean change in progesterone hormone levels across the trimesters of both HIV-positive and -negative pregnant women, the mean change in progesterone hormone levels were also measured during the baseline and in the second and third trimesters of advancing pregnancy (Table 1). The changes in progesterone hormone levels were assessed using repeated measures regression models.

Among the HIV-negative, the mean change of progesterone during the second, 67.3(95% CI: 64.1, 70.5) ng/ml and the third, 97.4 (95% CI: 94.1, 100.6) ng/ml, trimesters, were significantly higher (P<0.0001 in both cases) than that of the first trimester, 30(95% CI: 26.8, 33.3) ng/ml. The mean change of progesterone for the third trimester was also significantly higher (P<0.0001) than that of second trimester 67.3(95% CI: 64.1, 70.5) ng/ml.

Likewise, among the HIV-positive, the mean change of progesterone during the second, 62.3(95% CI: 59.0, 65.5) ng/ml, and the third, 90.1 (95% CI: 86.9, 93.3) ng/ml, trimesters, were significantly higher (P<0.0001 in both cases) relative to that of the first trimester, 27.8(95% CI: 24.6, 31.1) ng/ml. The mean change of progesterone for the third trimester was also significantly higher (P<0.0001) than that of second trimester, 62.3(95% CI: 59.0, 65.5) ng/ml.

Difference of progesterone hormone levels between HIV-positive and HIV-negative participants across the trimesters of pregnancy. In order to determine mean difference of progesterone hormone levels between HIV-positive and HIV-negative participants across the trimesters of pregnancy, the mean differences in progesterone hormone levels between the two groups were measured during the baseline and in the second and third trimesters of advancing pregnancy (Table 2). The difference in progesterone hormone levels were assessed using repeated measures regression models.

The mean difference of progesterone hormone levels between HIV-positive and HIV-negative participants continued to increase significantly from first [difference of -4.3(95% CI: -8.2, -0.5)

ng/ml *P*=0.028)], second [difference of -6.6(95% CI: -10.3, -3.0) ng/ml, *P*=0.001] and third [difference of -11.6 (95% CI: -17.2, -6.1) ng/ml, *P*=0.0001] trimesters. Since gestational age can affect differences in progesterone hormone levels[7, 16, 17], the differences in gestational age between the two groups in all trimesters was also assessed to confirm if the difference of progesterone hormone levels would in any way be influenced by the age of pregnancy (Table 2). The findings reveal that there was no significant (*P*>0.058) mean difference between HIV-positive and HIV-negative participants in gestational age in all trimesters. Taken together, these results demonstrate that the mean difference of progesterone hormone levels between HIV-positive and HIV-negative participants continued to increase significantly from the first to the third trimester. In addition, we show that these observations were not influenced by the differences in gestational age across the trimesters.

Table 1: Assessing change in progesterone hormone across trimesters of pregnancy

	HIV-Negative		HIV-Positive	
	Mean Change (95% CI)		Mean Change (95% CI)	
Trimester	1	2	1	2
2	30.1(26.8, 33.3) *P*<0.0001	N/A	27.8(24.6, 31.1) *P*<0.0001	N/A
3	97.4(94.1, 100.6) *P*<0.0001	67.3(64.1, 70.5) *P*<0.0001	90.1(86.9, 93.3) *P*<0.0001	62.3(59.0, 65.5) *P*<0.0001

Table legend. The changes in progesterone were performed using repeated measures regression model and assessed at 95% confidence level (95% CI). Among the HIV-negative, the mean change of progesterone during the second trimester was significantly (*P*<0.0001) higher than that of the first trimester, 30(95% CI: 26.8, 33.3) ng/ml. The mean change of progesterone for the third trimester was also significantly higher than that of the first trimester, 97.4 (95% CI: 94.1, 100.6) ng/ml, *P*<0.0001 and second trimester 67.3(95% CI: 64.1, 70.5) ng/ml, *P*<0.0001. Among the HIV-positive, there was also a significant (*P*<0.0001) mean change in progesterone hormone levels between the second and the first trimesters 27.8(95% CI: 24.6, 31.1) ng/ml. The mean change of progesterone for the third trimester was significantly higher than both the first trimester, 90.1 (95% CI: 86.9, 93.3) ng/ml, and the second trimester, 62.3(95% CI: 59.0, 65.5) ng/ml (*P*<0.0001 for both cases). N/A=Not applicable.

Table 2: Assessing the differences in progesterone in the first, second and third trimesters between the HIV-Positive and the HIV-Negative participants.

Variable		HIV-positive	HIV-Negative	Difference(95% CI)	
	Trimester	mean(SD)	mean(SD)	(Mean HIV+) - (Mean HIV-)	*P-value*
Progesterone	1	21.5(8.4)	25.8(9.8)	-4.3(-8.2, -0.5)	0.028
	2	49.3(10.0)	55.9(6.8)	-6.6(-10.3, -3.0)	0.001
	3	111.6(11.3)	123.2(14.7)	-11.6(-17.2, -6.1)	0.0001
Gestation Age	1	7.7(1.3)	8.4(2.2)	-0.7(-1.4, 0.1)	0.079
	2	19.8(1.2)	20.4(2.2)	-0.6(-1.4, 0.1)	0.110
	3	31.5(2.0)	32.4(2.2)	-0.9(-1.8, 0)	0.058

Table legend. The mean difference in progesterone hormone was performed using repeated measures regression model and assessed at 95% confidence level. The mean difference of progesterone hormone levels between HIV-positive and HIV-negative participants continued to increase significantly from first (difference of -4.3(95% CI: -8.2, -0.5) ng/ml *P*=0.028), second (difference of -6.6(95% CI: -10.3, -3.0) ng/ml *P*=0.001) and third (difference of -11.6 (95% CI: -17.2, -6.1) ng/ml *P*=0.0001) trimesters. Difference in gestational age between the two groups in all trimesters was also assessed to confirm if the difference of progesterone hormone levels was influenced by the age of pregnancy. The study confirmed that there was no significant (*P* >0.058) mean difference between HIV-positive and HIV-negative participants in gestational age in all trimesters.

Fig 1

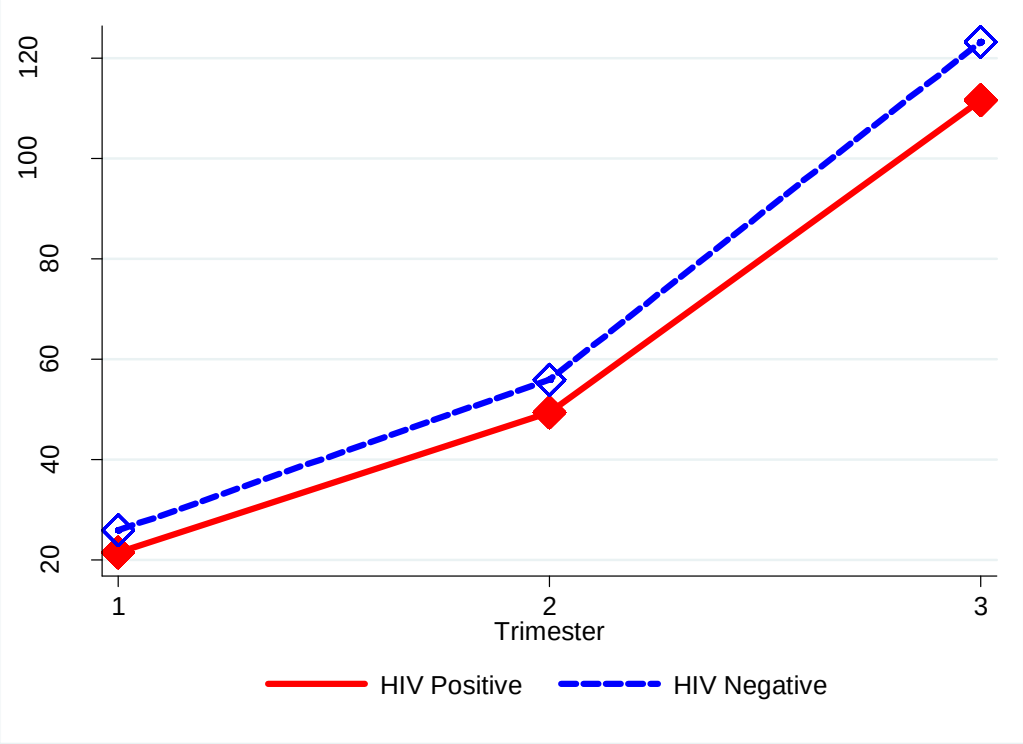

Figure 1: Progesterone (ng/ml) trends from the first trimester to the third trimester stratified by HIV status. The changes in progesterone were performed using repeated measures regression model and assessed at 95% confidence level. Among the HIV-negative participants, the mean progesterone hormone levels in the first, the second and the third trimesters were 25.8, 55.9, and 123.2 ng/ml, respectively. Among the HIV-positive participants, the mean progesterone hormone levels in the first, the second and the third trimesters were 21.5, 49.3, and 111.6 ng/ml, respectively. This is a clear demonstration of an increasing trend in both groups.

DISCUSSION

The current study was designed to determine the trends of progesterone hormone levels in HIV-positive pregnant women compared to HIV-negative pregnant women. Results reveal that both HIV- positive and –negative women had increasing trends of progesterone hormone levels across trimesters of pregnancy. However, the mean change of progesterone hormone levels was significantly lower in all trimesters of pregnancy among the HIV-positive compared to the HIV-negative pregnant women. In addition the mean differences of progesterone hormone levels between HIV-positive and HIV-negative participants continued to increase significantly from the first to the third trimester.

The current study demonstrated a significant increase of progesterone hormone levels in the pregnant participants across trimesters in both HIV-infected and non-infected women. This is comparable to previous studies which showed that progesterone hormone remain significantly high throughout pregnancy in HIV-negative populations [1,2,7,18], despite the fact these studies did not consider the HIV-positive cases. The current finding and the reviewed previous studies, thus support the hypothesis that progesterone hormone continuously increase in advancing pregnancy. The continued increase of progesterone in advancing pregnancy irrespective of the HIV status could be explained partly by the fact that, progesterone is a key reproductive hormone during pregnancy produced to enhance the success of pregnancy [7]. In addition, progesterone is known to relax the uterus during pregnancy, which enables the retention of the fetus by inhibition of contraction-related protein[4,19] further explaining the continuous increase of this hormone as pregnancy advances. Among other mechanisms, the endocrine status have been observed to be at least part of the process responsible for the induction of immune-modulation in advancing pregnancy [20]. However, it remains to be determined whether additional roles and mechanisms exist for progesterone during pregnancy and whether or not there is any effect post-partum due to these levels in both HIV-negative and –positive groups.

This study also demonstrated significant lower progesterone hormone levels in all trimesters of pregnancy among the HIV-positive women compared to HIV-negative women. These results are consistent to those observed in previous studies [15,16]. For example, it was shown that HIV infection in human placenta decrease up to seventy percent (70%) in progesterone production in HIV-1-infected cultures in comparison with controls [21]. Similarly, it was observed in a different population that progesterone concentration was lowered in HIV-positive compared to HIV-negative women during their menstrual cycle, possibly implicating HIV infection as a contributing factor for the observed differences in progesterone hormone levels [22]. The mechanisms under which HIV infection can concomitantly lead to a reduction in progesterone production in pregnancy remains to be determined.

The present study also observed that the mean change of progesterone hormone levels was significantly lower in all trimesters of pregnancy among the HIV-positive relative to the HIV-negative pregnant women. In addition, the mean differences of progesterone hormone levels between HIV-positive and HIV-negative participants continued to increase significantly from the first to the third trimester. To our knowledge, this is the first study that has demonstrated this pattern in both HIV-positive and HIV-negative pregnant women across the trimesters. Potential clinical consequences of such differences in progesterone hormone levels could lead to complications and adverse birth outcomes of pregnancies associated with HIV-infection [12, 21]. However, in contrast to these earlier studies, the present study did not report any complication during pregnancy among the HIV-infected women despite the generally low progesterone hormone levels reported relative to HIV-negative women. Additional studies, focusing on the succinct roles of the endocrine response especially in HIV infection in pregnancy remain to be explored. The current study provides baseline data for similar future studies that would provide an in-depth exploration for a better understanding of the complex interaction of HIV and pregnancy.

CONCLUSION AND RECOMENDATION

We have shown that HIV infection in pregnancy may lead to lower progesterone hormone levels in all trimesters of pregnancy compared to pregnancy without HIV infection. Since limited information is available on how HIV affect progesterone hormone levels during pregnancy further research should be directed to give a clear understanding of the complex interaction between HIV and pregnancy.

AUTHORS' CONTRIBUTIONS

SKM designed the study and participated in the drafting of the manuscript. KC, SM and CO participated in the drafting of the manuscript. CO and SKM participated in the data analyses. All authors read and approved the manuscript for submission.

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