ASSESSMENT OF SEX HORMONE LEVELS IN HIV SERODISCORDANT COUPLES IN JOS, NIGERIA.

ABSTRACT

This study adopted a cross sectional study design to assess the sex hormone levels in HIV serodiscordant couples in Jos, Nigeria. A total of 20 discordant HIV couples (40 patients) and 20 controls (40 non HIV couples) aged between 18 and 49 years were included in the study. 5ml of fasting venous blood sample was collected from each participant into plain containers for the evaluation of sex hormones levels. Female samples were taken two weeks prior to menstruation (follicular phase). Follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone, estrogen/estradiol (E_2), and testosterone (TT)were determined by using standard ELISA technique. The results revealed thatwhile there was no statistically significant difference in the mean serum levels of LH, Testosterone, progesterone, or estradiol between the HIV serodiscordant couples and the control group ($p>0.05$), FSH level in the HIV serodiscordant couples was significantly lower than in the control group (7.84±7.39 Vs 10.62±4.19; p=0.042).FSH, LH and progesterone levels in the male and female HIV discordant groups were not significantly different from those in the male and female control groups, respectively ($p>0.05$). TT level was significantly lower while E_2 was higher in the male HIV discordant group than in the male control group (p=0.000) whereas E_2 level was significantly lower in the female HIV discordant group than in the female control group (p=0.000). Furthermore, the mean serum TT levels was significantly lower in the male exposed HIV seronegative individuals compared to male control (p=0.000) while progesterone level was significantly lower in the male HIV seropositives than in the male control (p=0.021) as well as in the male exposed HIV seronegative individuals compared to the male HIV seropositive individuals (p=0.000). This study revealed significant alterations in the sex hormone levels in HIV-discordant couples, which is crucial for the desire to boost fertility through early detection and subsequent intervention in these individuals.

Comment [WU1]: I don't understand you exactly idea, above we say that FSH was low and few lines after that the hormone was not different; reefing you to the male and female serodiscordant vs males and females not discordant. You need a better explain

KEY WORDS: HIV, HIV Serodiscordant couple, Sex hormones, Gender.

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a public health problem that has an impact on the entire world's population; since the AIDS epidemic began, 36.3 million people have died from AIDS (World Health Organisation (WHO), 2021), and most recently, 37.7 million people were infected by HIV in the year 2020 (UNAIDS, 2022). It is the primary cause of morbidity and mortality in Sub-Saharan Africa (SSA), where it affects 71% of persons worldwide (James *et al*., 2018).Nigeria, the most populated nation in Africa (UNFPA, 2020), has the third-highest HIV load with 1.9 million persons living with the virus (with a prevalence of 1.4 percent) between the ages of 15 and 49 (UNAIDS, 2019).HIV makes the host susceptible to a wide range of infections and diseases as a result of declined immunity characterized by loss of CD4-T cells (Ezeugwunne*et al*., 2021; Ogbodo*et al*., 2021, Ezeugwunne*et al*., 2021) and may be responsible for changes in a number of biomarkers seen in HIV-infected people.

Reproductive hormones such FSH, LH, Testosterone, Estrogen, and Progesterone are essential for healthy reproductive function. Nevertheless, studies have shown significant alterations in these hormones which may undermine the reproductive function in these individuals (Ezeugwunne*et al*., 2019).HIV is known to have an adverse effect on women's reproductive health (Kumari*et al*., 2016; Ikechebelu*et al*., 2002; Fallahian and Ilkhani, 2006). Menstrual irregularities to complete infertility are among the detrimental effects on reproduction (Swaytha*et al*., 2014). Some of these conditions could come from abnormal ovarian function, which would have a significant impact on sex hormones (Swaytha*et al*., 2014).It cannot be overemphasized that antiretroviral therapy (ART) improves sex hormone and gonadal function in HIV-positive subjects; yet, controversial studies have indicated that antiretroviral therapy's long-term use can have a negative impact on sex hormones in infected individuals (Collazos*et al*., 2002; Hutchinson *et al*., 2000).Reduced ovarian function is another factor contributing to the significantly lower testosterone levels in HIV-positive female ART subjects compared to Control females.In the course of normal physiology, the ovaries of females produce very small amounts of testosterone that are used to maintain muscle mass and thus prevent weight loss (Ukibe*et al*, 2015). Hypogonadism in HIV-positive people has been documented with varying prevalence (Aggarwal *et al.*, 2018). Also, the prevalence of hypogonadism has been observed to be significantly correlated with the degree of immunodeficiency, with an increase in the prevalence of hypogonadism as CD4 levels decreases (Aggarwal *et al*., 2018).Since those who are HIV exposed but seronegative and involved in these relationships are at risk for contracting the virus, which could predispose them to the significant alterations in sex hormone levels, it is necessary to measure the levels of sex hormones in the HIV serodiscordant couples in Jos, Nigeria.

MATERIALS AND METHODS

Study Area and Location

Thestudy area for this work was Jos North Local Government Area of Plateau State and location includes APIN (Aids Preventive Initiative of Nigeria) section of Our Lady of Apostles (OLA) Hospital, Faith Alive Foundation Hospital and Plateau State Specialist Hospital where HIV screenings are carried out.

Study Design and Subject Selection

An approach known as a cross sectional research was used for this experiment. The participants were partners who were known to be HIV positive and exposed seronegatives and are between the ages of 18 and 49 years old.In addition, controls consisting of HIV-negative couples in the aforementioned age group who appeared to be in healthy condition were used. The HIV-positive individuals were already taking antiretroviral drugs, but the negative individuals in the discordant relationship were not.

Comment [WU2]: what was the frequency of protected or unprotected sexual relations?

Study Population

The study population included male and female subjects in discordance relationship within the age of 18 to 49 years attending the APIN section of Our Lady of Apostles Hospital, Faith Alive

Foundation and Plateau State Specialist Hospital. A total of 20 discordant HIV couples (40 patients) and 20 controls (40 non HIV couples) were included in the study.

Sample Collection

Following sterilizing the collection site with 70% alcohol, five milliliters of venous blood were drawn into plain containers, allowed to clot, and then retracted while serum was recovered after centrifugation at 3,000 rpm for five minutes.Unanalyzed serum samples were kept frozen at -20°C for later analysis.All blood samples were taken while fasting, and female samples were taken two weeks prior to menstruation (follicular phase).

Inclusion criteria

HIV-negative individuals who had been in a committed, discordant relationship for at least three months were eligible to participate. Participants in the study were between the ages of 18 and 49, registered patients at the hospital under study, and have the required status documentation. A control group of participants in the same age range who seemed healthy was also included in the study (non HIV subjects).

Exclusion Criteria

Participants who were already bedridden due to AIDS, diabetics, contraceptive users, those who were not registered patients or had improper documentation with the institution under research, and those who refused to give informed consent were all excluded from the study.

Ethical Approval

Ethical approval was obtained from the Ethics Committees of the hospitals: Plateau State Specialist Hospital (PSSH/ADM/ETH.CO/2019/005); Faith Alive Foundation Hospital (FAFEC/08/34/25) and Our Lady of Apostles Hospital (dated 13th June, 2018) where the study was carried out.

Laboratory methods

Sex hormones (FSH, LH, Testosterone, Estrogen/Estradiol, and Progesterone were determined by using Enzyme linked immunosorbent assay (ELISA) method.

Statistical Analysis

The data obtained were analyzed using independent t-test and one-way analysis of variance (ANOVA) with the aid of SPSS statistics tool version 23.0 software. Significant level was assumed at $p<0.05$.

RESULTS

The mean serum FSH level was significantly lower in the HIV serodiscordant couples when compared to the control group (7.84±7.39 Vs 10.62±4.19; p=0.042), while there was no statistically significant difference in the mean serum LH (p=0.756), Testosterone (p=0.567), progesterone (p=0.248) and estradiol (p=0.319) levels in the HIV serodiscordant couples when compared to the control group. See table 1.

There was no significant difference in the mean serum FSH and LH levels in male and female HIV discordant group than in the male control group and female control group respectively (p=0.140; 0.452). See table 2.

Comment [WU3]: The paragraph result confused, since, before you said that there was difference only in FSH, so, you need an explanation above that.
Then, in different lines you can explain what happened with the LH.
At paragraph beginning, is a good idea to explain that it corresponds to other type or comparators.

There was significantly lower mean serum testosterone and higher E_2 levels in the male HIV discordant group when compared to the male control (p=0.000). Also, there was significantly higher mean serum testosterone level in the male HIV discordant group than in the female control group and female HIV discordant group (p=0.000). The mean serum testosterone level was also significantly higher in the male control group than in the female control group (p=0.000). See table 2.

Comment [WU4]: Require make a differentiation when you talk above serodescondant groups or when you talk above Genders groups avoid synonyms. Make a consistent document.

The mean serum progesterone levels did not differ significantly in the male and female HIV discordant groups when compared to the male and female control groups respectively (p>0.05) although the mean serum progesterone levels was significantly lower in the male HIV discordant group when compared to the female control group (p=0.021). See table 2.

The mean serum estradiol level was also significantly lower in the female HIV discordant group than in the female control group (p=0.000) but the mean serum estradiol level was not significantly different in the male HIV discordant group than in the male control group (p>0.05). See table 2.

There was no significant differences observed in the mean serum FSH and LH levels in the groups studied when compared between and across the groups respectively (p>0.05). There was no significant difference in the mean serum testosterone level observed in the male HIV seropositives compared to male control (p>0.05). The mean serum testosterone level was significantly lower in the male exposed HIV seronegatives than in the male control (p=0.000). The mean serum testosterone level was significantly higher in the male control than in the female control (p=0.000). The mean serum testosterone level was significantly lower in the female

Comment [WU5]: I don't understand, before you said: there was differences in FSH.

seropositives and female exposed HIV seronegatives than in the male control (p=0.000). See table3.

The mean serum progesterone level was significantly different compared amongst the groups (F=3.425, p=0.02). The mean serum progesterone level was significantly lower in male HIV seropositives compared to female control; male control, female HIV positive and female HIV negative respectively (p=0.021). The mean serum progesterone level was significantly lower in male exposed HIV seronegatives when compared to female HIV positive (p=0.021). See table 3.

Comment [WU6]: before you said there was no differences and table 1 shows no differences

The mean serum estradiol level in the male control was significantly lower compared to the female control (p=0.000) while the mean serum estradiol level in the female HIV seropositives was significantly higher compared to the male control (p=0.000). Also, the mean serum estradiol level in the female HIV exposed seronegatives was significantly higher compared to the male control (p=0.000) whereas there was significantly lower estradiol levels in the male HIV positive individuals when compared to the female control, female HIV seropositive and female exposed HIV seronegative individuals respectively (p=0.000). Furthermore, there was significantly lower estradiol levels in the male HIV exposed seronegative individuals when compared to the female control, female HIV seropositive and female exposed HIV seronegative individuals respectively (p=0.000????). See table 3.

Table 1: Serum FSH, LH, Testosterone, progesterone and Estradiol Levels in the HIV Serodiscordant couples (mean±SD)

Parameter	Control (n=40)	HIV serodiscordantcouples (n=40)	t-value	p-value
FSH (IU/mL)	10.62±4.19	7.84±7.39	2.073	0.042*
LH(IU/mL)	8.07±1.33	7.79±5.51	0.313	0.756
Testosterone(ng/mL)	4.30±3.68	3.86±3.07	0.575	0.567
Progesterone(ng/mL)	0.46±0.43	0.36±0.38	1.164	0.248
Estradiol(ng/mL)	83.70±75.73	65.66±84.75	1.004	0.319

*Statistically significant at $p<0.05$.

Table 2: Gender comparison of serum FSH, LH, Testosterone, progesterone and Estradiol Levels in the HIV Serodiscordant couples (mean±SD)

Parameter	Female control (n=20)	Male control (n=20)	Female HIV discordant group (n=20)	Male HIV discordant group (n=20)	f-value	p-value
FSH(IU/mL)	9.87±1.08	11.37±5.80	7.00±2.29	8.67±10.27	1.883	0.140
LH(IU/mL)	8.89±1.29	7.25±0.75	7.20±2.10	8.38±7.56	0.886	0.452
Testosterone(ng/mL)	0.71±0.12	7.88±0.81[a]	1.77±2.87[b]	5.95±1.41[a,b,c]	84.865	0.000*
Progesterone(ng/mL)	0.60±0.47	0.33±0.34	0.48±0.46	0.23±0.24[a]	3.425	0.021*
Estradiol (ng/mL)	158.15±10.19	9.26±0.37[a]	109.30±94.51[a,b]	22.03±42.46[a,b,c]	37.439	0.000*

*Statistically significant at $p<0.05$. Marks show large variation.

Key:

a=compared with female control

b= compared with male control

c= compared with female HIV positive

Comment [WU7]: Variations in values are large, it causes data analysis error. It is recommended to use a different statistical analysis.

Comment [WU8]: I stopped to review here

Comment [WU9]: In humble opinion.
The works report is important but: before submitted this document again, please.
1.Please recheck your data. The values presented here. The values have a lot of variation.
2.It seems that the data is not normal. Data should be test for normality and then, be evaluate by other types of statistics analyses.
3.Then, it is recommended review and rewrite the document.

Table3: Hormone profile levels in the participant groups studied (mean±SD)

Parameter	Female control (n=20)	male control (n=20)	Female positives (n=16)	Female negatives (n=4)	male positives (n=16)	male negatives (n=4)	f-value	p-value
FSH(IU/mL)	9.87±1.08	11.37±5.80	7.06±2.49	6.75±1.42	4.88±0.92	9.62±11.34	1.527	0.192
LH(IU/mL)	8.89±1.29	7.25±0.75	7.70±1.77	5.18±2.34	5.30±0.89	9.15±8.31	1.426	0.225
Testosterone (ng/mL)	0.71±0.12	7.88±0.81[a]	2.11±3.13[b]	0.43±0.05[b]	5.28±0.86[a,c,d]	6.12±1.49[a,b,c,d]	53.309	0.000*
Progesterone (ng/mL)	0.60±0.47	0.33±0.34	0.46±0.46	0.56±0.51	0.23±0.24[a,b,c,d]	0.21±0.23[e]	3.425	0.021*
Estradiol (ng/mL)	158.15±10.19	9.26±0.37[a]	106.03±106.10[b]	122.38±1.18[b]	3.88±0.78[a,c,d]	26.57±46.62[a,c,d]	22.323	0.000*

Key:

a=compared with female control

b= compared with male control

c= compared with female HIV positive

d= compared with female HIV negative

e= compared with male HIV positive

DISCUSSION

Human immunodeficiency virus (HIV) is a significant topic of public health debate at the moment, with more complex concerns emerging among HIV serodiscordant couples.Given the foregoing, the current study examined the levels of sex hormones in the serodiscordant couples in Jos, Nigeria.

In this study,there was no statistically significant difference in the mean serum levels of LH, Testosterone, progesterone, or estradiol between the HIV serodiscordant couples and the control group respectively.However, FSH level in the HIV serodiscordant couples was significantly lower than in the control group.The limited sample size used in the current investigation may have had an impact on these results. Furthermore, given that those who were HIV positive were already getting antiretroviral therapy, starting that treatment may have helped these people have improved levels of these hormones.Antiretroviral therapy has been shown to improve sexual functions in human immunodeficiency virus infected individuals (Yelwa*et al*., 2020). In contrast to the present study, several other studies in HIV infected individuals reported significantly lower testosterone with increased FSH, LH and E_2levels compared to control subjects(Yelwa*et al*., 2020; Ezeugwunne*et al*., 2019).

The mean serum testosterone level in the male HIV discordant group was significantly lower than that in the male control group while the mean serum estradiol level in the male HIV discordant group was significantly higher than that in the male control group. However, the mean serum FSH, LHand progesterone levels were not significantly different when compared between the male HIV discordant groups and the male control groups. This finding is partly consistent with previous studies (Ezeugwunne*et al*., 2012).This suggests that the HIV infection may have encouraged the production of estrogen from testosterone, a process known as the estrogenic effect, which is the cause of the low levels of serum testosterone found in these people.Testosterone is peripherally converted to estrogen by the enzymes aromatase and enolase to produce the estrogenic action.Furthermore, some previous investigations found that the serum levels of the reproductive hormones in HIV seropositive males receiving antiretroviral therapy (ART) and those not receiving ART both significantly decreased when compared to HIV seronegative male control participants (Oluboyo*et al*., 2014) which they attributed to the disturbances in hypothalamic-pituitary-gonadal axis or due to metabolic abnormalities associated with HIV/AIDS and this is partly in keeping with the present results.

In this study, the mean serum testosterone, FSH, LH and progesterone levels were not significantly different when compared between the female HIV serodiscordant group and the female control group respectively while in the female HIV discordant group, the mean serum estradiol level was significantly lower than in the female control group. This is in keeping with the results of some previous studies (Yalamanchi*et al*., 2015). Oluboyo and colleagues had earlier reported no significant differences in the mean serum fertility hormone levels in the HIV infected females than in the control subjects (Oluboyo*et al*., 2014).Furthermore, Ukibe et al. had shown that Progesterone, estradiol, and testosterone levels were significantly lower in HIV-infected women than in controls during the follicular and luteal phases of the menstrual cycle, indicating some degree of hypogonadism in these women that may have some bearing on their ability to reproduce.

The mean serum FSH and LH levels in the study groups did not differ significantly when compared within or across groups. When compared to male controls, the mean serum testosterone level among male HIV seropositives did not differ significantly. The mean serum progesterone level was significantly lower in male HIV seropositives compared to the male control. Also, the male HIV seronegative exposed individuals had mean serum testosterone levels that were significantly lower than those of the male controls.This may imply that male HIV-exposed seronegative partners in discordant relationships may eventually develop hypogonadism if untreated.

CONCLUSION

This study revealed significant alterations in the sex hormone levels in HIV-discordant couples, which is crucial for the desire to boost fertility through early detection and subsequent intervention in these individuals.

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RESEARCH ARTICLE
EMERGING REPRODUCTIVE HORMONES PERTURBATIONS IN HIV POSITIVE FEMALES: A NORTH INDIAN STUDY.
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