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Effects of Human Immunodeficiency Virus Infection and Antiretroviral Therapy on Ovarian Reserve and Invitro Fertilisation Success

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ABSTRACT

Objectives: *To study the relationship between HIV infection, antiretroviral therapy and CD4 lymphocyte counts on the ovarian reserve.*

Design: *A retrospective cohort study.*

Setting: *The study was conducted at a fertility centre in Johannesburg.*

Patients: *The study group comprised of HIV positive patients undergoing IVF treatment. The control groups were HIV negative patients who were also undergoing IVF treatment. The study group was further subdivided into patients on ARV treatment and those who were not on treatment.*

Interventions: *Comparisons were made between the study and control groups and between the two arms of the study group with regards to outcome measures.*

Main Outcome Measures: *1) Ovarian reserve using anti-műllerian hormone (AMH) levels and antral follicle count (AFC) as biomarkers, and 2) pregnancy outcomes.*

Results*: A total of 79 study patients underwent IVF treatment; 75 achieved embryo transfer and 21 pregnancies were obtained. Of the patients who achieved pregnancy, only one had a CD4 count < 200. Of the 21 patients who achieved pregnancy, 9 were not on prior ARV treatment and 12 were on ARV treatment. The HIV seropositive group had statistically lower AMH levels when compared with the expected age related AMH levels ($p = 0.011$). Comparing the two arms in the study group, treatment with ARV therapy was also noted to statistically affect AMH levels ($p = 0.045$). Significantly fewer pregnancies were noted in the HIV positive group (28% vs 34.5%) and there were more pregnancies amongst those on ARV treatment compared with those who were not on treatment, but this was not statistically significant (57% vs 43%).*

Conclusion: *The mechanism by which HIV infection influences AMH and ovarian reserve remains speculative. In our study we demonstrated that HIV infection has a negative effect on ovarian reserve and the fact that the majority of those who conceived had a CD4 >200 suggests that CD4 counts may influence conception.*

Keywords

HIV infection, Antiretroviral therapy, Ovarian reserves, CD4 count.

Introduction

The prevalence of HIV infection in Sub-Saharan Africa remains a significant health burden. According to Statistics South Africa-July 2017, approximately 18% of the reproductive aged population in South Africa is HIV positive. Looking at females alone, this percentage is as high as 21%. Of these, only 56% of adults are on antiretroviral treatment [1].

A substantial number of these couples present for assisted reproductive technology for either infertility related problems or for assistance with safe conception; that being to prevent vertical transmission to the baby, or horizontal transmission in the sero-discordant couple or HIV super-infection in the HIV concordant couple.

The effects of antiretroviral (ARV) therapy and the primary human immunodeficiency virus (HIV) infection on the ovarian reserve remain unknown and much controversy still exists in the literature. Some studies show no effect, [2] while others show that HIV reduces ovarian reserve resulting in premature menopause. It is also unknown if this effect is secondary to the primary viral infection, in which case the early introduction of antiretrovirals will be beneficial or whether this is as a result of confounders, such as pelvic inflammatory disease and genital tract tuberculosis, to which HIV positive patients are more susceptible. Yalamanchi et al. proposed that the HIV infection poses a threat to the reproductive system either directly or indirectly [3]. However, either way ovulatory functions in HIV positive individuals are usually compromised. It has also been suggested that ARV therapy may cause mitochondrial depletion in oocytes and hence affect pregnancy [4]. There are many studies which have demonstrated a positive association between CD4 counts and AMH levels [5-7].

It is well known that a higher probability of conception (natural or assisted) exists for women below the age of 35 when compared to women who are over the age of 35, whilst women who are 45 years and older have the least chances of achieving a positive pregnancy [8].

Notwithstanding this age related decline in infertility, Imai et al, has shown that HIV infected women tend to lose their ovarian function earlier in life when compared to HIV negative women [9]. An estimated 25% to 40% lower fertility potential has been observed in HIV infected women who were not ARV therapy recipients [10].

Objectives

Very few trials have been conducted to look at the effects of ARV therapy, CD4 lymphocytes counts and the primary viral infection on the ovarian reserve and reproductive functioning, as a whole.

The primary objective of this study was to evaluate the effects of HIV infection on the ovarian reserve by using anti-műllerian hormone (AMH) levels and antral follicle counts (AFC) as biomarkers. The secondary objectives were to evaluate the effects of antiretroviral therapy on the ovarian reserve and to investigate the relationship between viral load and CD4 lymphocyte counts and the ovarian reserve.

Materials and Methods

This was a retrospective cohort study. Ethics approval to conduct this study was sought from and granted by the institutional review board of Durban University of Technology. The study was conducted at a fertility centre in Johannesburg. The patients involved in the study were between the ages of 24 and 39 years that being the age recognized as the reproductive age group. Data was obtained and analysed retrospectively. The study group consisted of HIV positive females undergoing IVF treatment and the control groups were HIV negative patients undergoing IVF treatment. The study group was further subdivided into patients on ARV treatment and those who were not. Comparisons were made between the two groups with regards to ovarian reserve and pregnancy outcomes. Comparisons were also made between the two arms of the study group looking at the effects of CD4 counts and viral loads on the outcome measures.

Results

We had a total number of 82 study patients who underwent IVF treatment; however 3 of these cases were abandoned due to a poor ovarian response to treatment. Of the remaining 79 patients, 75 achieved embryo transfer. There were 21 pregnancies. All those who achieved pregnancy with the exception of one had a CD4 count > 200. Of the 21 patients, 9(43%) were not on prior ARV treatment and 12 (57%) were on ARV treatment. The mean age of the population group was 34 years and the mean AMH was 2.78ng/ml with a normal mean expected antral follicle count of 9-16 follicles.

A one sample t-test was run to compare the AMH levels of HIV positive women to their expected levels relative to their age. Table 1 shows expected age related anti-műllerian hormone values and the frequency of patients in our study with the same age. Using the expected AMH value and the actual AMH value, the AMH relative difference was calculated. On this basis, if HIV positive women exhibited the same AMH level as HIV negative women, the relative difference would be zero. This was tested through another one sample t-test and we found that the HIV seropositive group had statistically lower AMH levels than expected for age when compared with the “control” HIV seronegative group (p-value 0.011) with the AMH level in HIV positive women being on average -0.7348, lower than what is expected.

As depicted in the [Figure 1], we note from our study that only about 28% of the study population had a normal AMH concentration, while 49% showed lower AMH levels than normal. This suggests that patients who are HIV positive may have an accelerated decline in AMH concentrations.

Approximately 51% of the study population (regardless of treatment) had low antral follicle counts, and approximately 44% had normal antral follicle counts. It can be inferred from both these results (AMH and AFC), that the ovarian reserve of HIV positive patients is lower than expected.

The two arms in the study group were compared using an independent t-test. A Levene’s test for homoescadicity revealed that the two arms were heteroescadistic. We found that there was a significant difference between the two groups in terms of AMH levels ($p = 0.045$) and those on treatment with ARV therapy had results that were closer to the AMH levels expected of their age

group. The average difference for women on treatment and AMH levels for their age was -0.4384 while the average difference for women not on treatment was -1.3731.

A total of 48 patients had undetectable viral loads, taken as a viral load of <100 copies/ml. The remaining 34 patients had detectable viral loads. [Figure 2] is a box and whisker plot showing the viral load variations amongst those patients with detectable levels of HIV viral load >100 copies/ml.

Age (y)	Age expected AMH (ng/ml)	Frequency	Percent (%)	Valid percent (%)	Cumulative percent (%)
39	1.73	14	17.1	17.1	17.1
38	1.95	4	4.9	4.9	22.0
37	2.16	10	12.2	12.2	34.1
36	2.37	8	9.8	9.8	43.9
35	2.58	8	9.8	9.8	53.7
34	2.78	11	13.4	13.4	67.1
33	3.02	4	4.9	4.9	72.0
32	3.25	4	4.9	4.9	76.8
31	3.47	6	7.3	7.3	84.1
30	3.70	3	3.7	3.7	87.8
29	3.82	1	1.2	1.2	89.0
28	3.94	3	3.7	3.7	92.7
27	3.99	1	1.2	1.2	93.9
26	4.02	2	2.4	2.4	96.3
25	4.05	1	1.2	1.2	97.5
24	4.07	2	2.4	2.4	100
	Total	N=82	100.1	100.1	

Table 1: Correlation of age and expected age related AMH values, with the frequency in each group and cumulative percent.

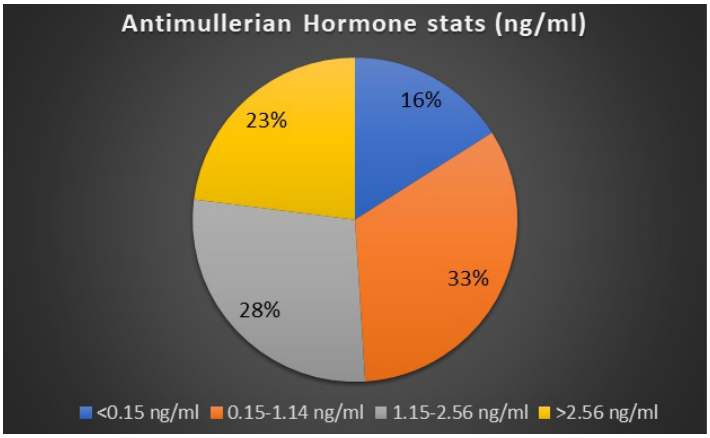

Figure 1: Anti-műllerian hormone range groups and percentage in the study population.

The correlation between AMH and viral load levels were analysed using non-parametric tests corrected for skewness caused by outliers. Parametric and non-parametric tests were used to identify any relation between the AMH concentrations in patients with detectable and undetectable viral loads. With a mean and standard deviation of 1.1938 and 1.88096, respectively, [Figure 3] graphically represents the relative difference of the anti-műllerian hormone concentrations in the population of patients with detectable viral loads.

In patients with detectable viral loads, the scatter plots show a negative linear relation between the viral load levels and the AMH concentration. The higher the viral load, the greater the difference noted between actual and expected AMH level.

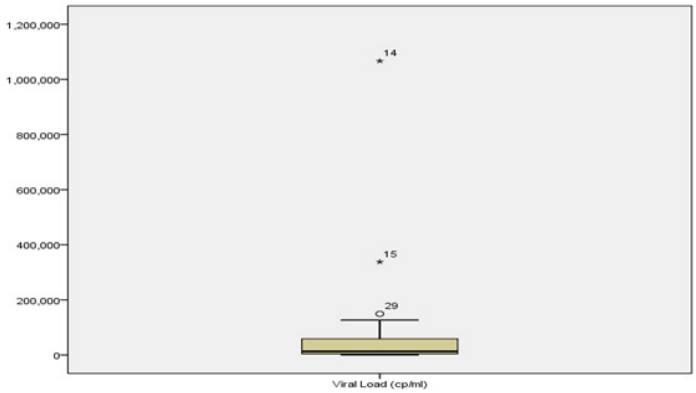

Figure 2: Box and whisker diagram of patients with detectable viral loads (Interquartile range: 55486, 95th percentile: 520181.50).

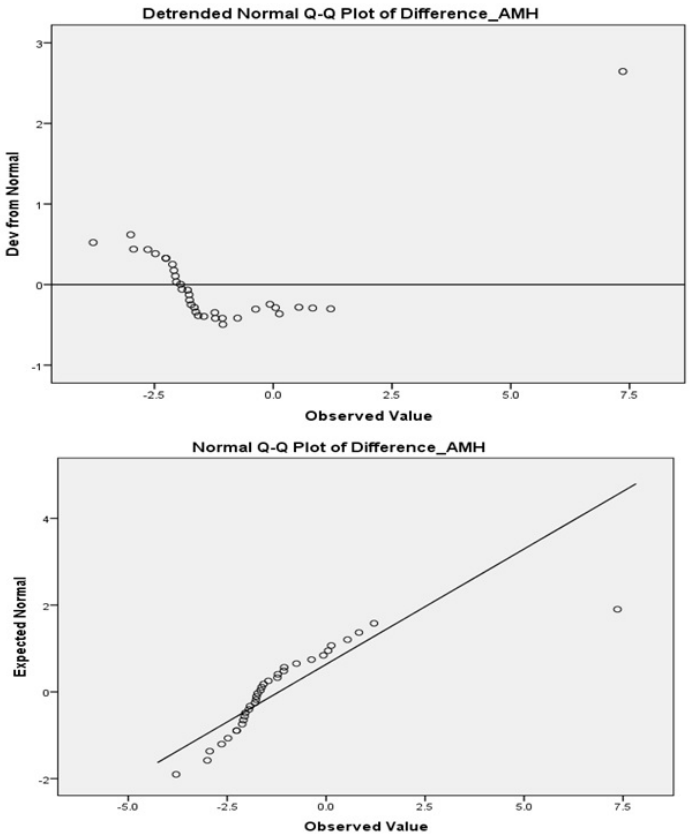

Figure 3: Representation of variable AMH values observed in patients with detectable viral loads (>100 copies/ml).

Most patients had a CD4 cell lymphocyte count of between 350 and 700 (median of 500 and an interquartile range of 300). Figures

4 and 5. From our study, CD4 counts were not found to influence ovarian reserves.

There were significantly fewer pregnancies noted in the HIV positive group (28% vs 34.5%) but of these, there were more pregnancies amongst patients on ARV treatment compared with those who were HIV positive but not on ARV treatment. However this difference was not statistically significant (57% vs 43%). And of those women with HIV who conceived, all with the exception of one had a CD4 count of >200.

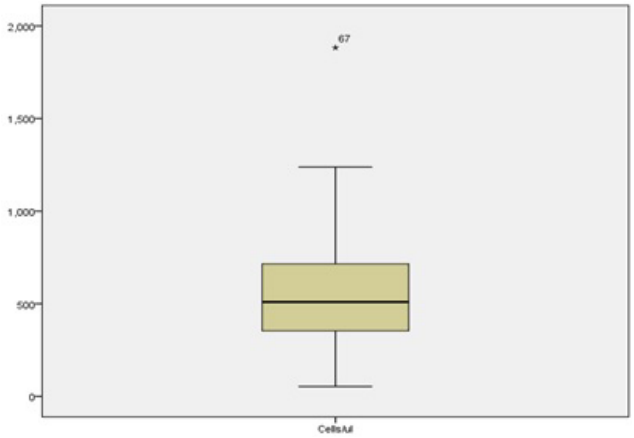

Figure 4: Distribution of the CD4 cells among the population.

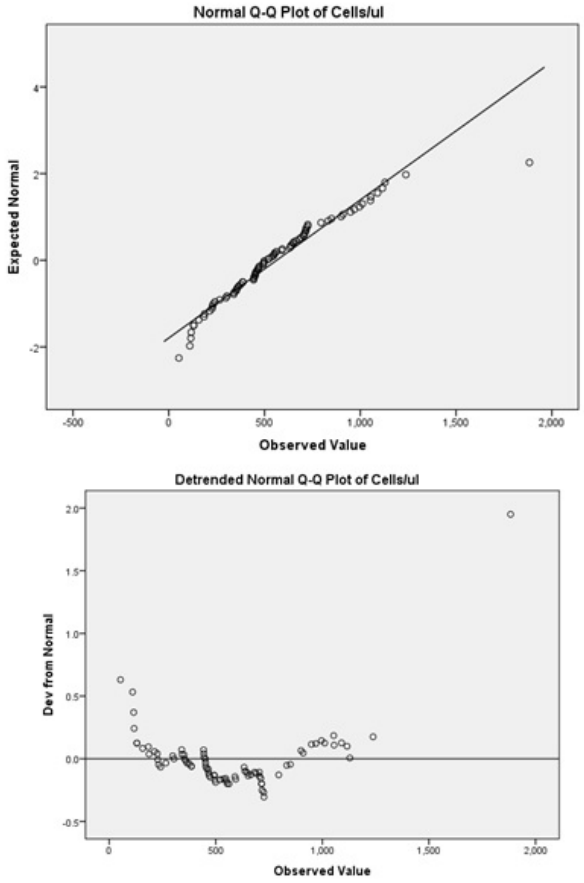

Figure 5: Normal Q-Q plot and detrended normal Q-Q plot of CD4 lymphocyte cells.

Discussion

Statistically, the HIV positive population has a lower AMH compared to AMH values of an age matched population. This biomarker indicates a decreased ovarian reserve which may negatively affect pregnancy outcomes of IVF treatment. Relating to Antral Follicle Counts and independent of ARV treatment, approximately 51% of the HIV positive population had lowers than expected antral follicle counts. Both the lower AMH concentrations and antral follicle counts indicate a diminished ovarian reserve and hence a reduced response to ovarian stimulation in HIV positive patients. Furthermore, in our study, we found that AMH levels were negatively affected by increased viral loads but did not find any association between AMH levels and CD4 counts.

Conclusion

After adjusting for age, the HIV positive population was shown to have a significantly lower AMH than expected. The majority were also found to have lower than expected antral follicle counts. As AMH levels and antral follicle counts are both biomarkers of ovarian reserve, it can be inferred that having HIV decreases a female's fertility potential. In terms of ARV therapy and AMH levels, our results showed a statistically significant difference between those patients who were on the treatment and those who were not. In South Africa, only patients with a CD4 count of < 500 were eligible to start ARV therapy prior to April 2017, and prior to 2015, only patients with a CD4 count of < 350 were eligible. This in part, may account for the fact that our study has failed to show any positive association between the CD4 count and AMH levels, which association has been shown in other such studies. In this regard, it is likely that our study patients may have acquired the virus some time before being exposed to ARV treatment, and the decline in ovarian reserve is largely irreversible.

However interestingly, 95% of the pregnancies achieved were with patients who had CD4 lymphocyte counts of >200 cells/ml. This was irrespective of whether they were on prior ARV treatment or not and suggests that CD4 count may have an effect on conception rates possibly via another mechanism other than by affecting ovarian reserves.

This study adds to the growing pool of research looking at the effects of HIV infection and the treatment thereof on reproductive potential and ovarian reserve. With an increasing number of ART facilities now providing their services to HIV positive patients, this knowledge is important when considering ovarian stimulation protocols and has an effect on IVF outcomes. This will have an impact on the couple's ability to achieve pregnancy both safely and successfully.

Recommendations

From this study we have identified a lower ovarian reserve in females who are HIV seropositive than the HIV seronegative female group of similar age. Furthermore, we concluded that a statistically significant difference exists between the ovarian reserve of HIV seropositive females that are on antiretroviral therapy and those who are not on treatment. Larger studies are

needed in the future which also consider the duration and ARV treatment regimen that the patient is exposed to.

Acknowledgement

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