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ASSESSMENT OF HUMAN ESTROGEN AND LIPID PROFILE OF WOMEN WITH INFERTILITY IN KANO METROPOLIS

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ABSTRACT

Infertility is a health condition associated with hormonal disorders and dyslipidemia leading to psychological, physical, mental, spiritual and medical detriments to patients among others. The aim of this study was to assess estrogen and lipid profile among patients with infertility in Kano metropolis. A total of 50 infertile female patients and 50 apparently healthy controls were used for the study, with age range between $18-45$ years. Blood sample was collected from the participants. lipid profile was measured by enzymatic spectrophotometric method, precipitation enzymatic method for high density lipoprotein cholesterol (HDL-C), Estrogen was determined using quantitative enzyme linked immunosorbent assay technique and BMI was calculated using the weight and height of the subjects using standard techniques. SPSS software package version 20 was used for analysis of data. This study reveals that, the higher frequency of primary and secondary infertility was observed in age group between 19-28years with the frequency of 24 and 2, also on age range of between 39-48 years in secondary infertility. The lower frequency of primary and secondary infertility was observed in age group between the range of 39 – 48 and 9-28 years with the frequency of 5 and 1 respectively. The higher frequencies of 62% was observed in BMI of 18- 24.9 kg/m^2.The mean value of Weight, BMI and TG were significantly (p =0.00) higher in patients group compared with controls. While E2, TC and LDL-C were significantly (p =0.00) lower in patients group compared with controls. No significant correlation (p>0.05) correlation was established between serum E2 with BMI, TC, HDL-C and LDL-C respectively. Result of our study suggested increased BMI, dyslipidemia and decreased estrogen are associated with infertility. Therefore, patients with this condition may be recommended for BMI, lipid profile and E2 hormonal assay, this may serve as an important parameter for reducing the complication in this group of patients.

***Keywords**: human estrogen, lipid profile, women, infertility, BMI*

INTRODUCTION

Infertility has been a global problem of public health importance both in Nigeria and many part of Africa, especially sub-Saharan region (Akinloye and Truter, 2011). This is not only because of the high prevalence of infertility between the couples but also due to its important social effect on the couples and their family. In Africa, children are fabric of the society, without which no meaningful social and economic progress could be considered worthwhile (Anokye *et al.,* 2017).

Infertility in women is fundamentally the inability to conceive a baby after 12 months of contraceptive-free intercourse (Cooper *et al*., 2010) or infertility is defined as the inability to conceive naturally after one year of regular unprotected intercourse or copulation, most at times infertility is seen in some degree of sub-fertility in which 1 in 7 couples need specialist help to conceive. Sub-fertility can be either primary or secondary (Guranath *et al.,* 2011). Primary subfertility is a delay for a couple who have had no previous pregnancies for either a year or more and secondary subfertility is a delay for a couple who have conceived previously for more than a year or more without the use of any method of family planning, although the pregnancy may not have been successful for example, miscarriage, and ectopic pregnancy (Taylor, 2003).

Estrogen is a hormone that plays various roles in the body. The other important but less powerful estrogens are *estrone* and *estriol*. Estrogens affect the growth, differentiation and function of diverse target tissues throughout the body not just those involved in the reproductive process (McArthur *et al.*, 2010).

Lipid is a macro biomolecule that is soluble in polar solvent, a non-polar solvent are typical hydrocarbons used to dissolve naturally occurring hydrocarbons and they do not dissolve in water, they include fatty acids, waxes sterols, fat soluble vitamins, monoglycerides, diglycerides, triglycerides and phospholipids (IUPAC, 2000).

Dyslipidaemia could also affect estrogen due to their strong relationship and subsequently affect infertile women (Randolph *et al.,* 2001). Moreover, estrogen also contributed in the regulation of lipoprotein lipase and lipoprotein lipase is responsible for hydrolyzing TG to chylomicrons and VLDL. Therefore, estrogen decrease during menopause could cause dysregulation of lipoprotein lipase (Chatterjee *et al*., 2011).

Aim

The aim of the study is to assess serum lipid profile and estrogen in infertile women in Kano metropolis.

MATERIALS AND METHODS

Study Area

The study was carried at several hospitals within Kano metropolis.

Study Design

The study is a Hospital-based prospective cross-sectional study.

Study Population

The participants were divided into two groups: Comprising of test subjects (Group A) and control subjects (Group B). Test subjects were infertile women while control groups include apparently healthy women

(Fertile). Detailed information about the study wasgiven to the clients and consent to participate was soughted before patient sample and data was taken with the assistance of the gynecologist.

Sample Size Determination

The sample size was obtainedusing the formula for the calculation of minimum sample size used in a study involving human subjects/patients, which is:

$$n = \frac{z^2 p(1-p)}{d^2}$$

Where

n = sample size

z = statistic for level of confidence at 90% = 1.64,

p = prevalence = 4% (Abiodun *et al*., 2007).

d = allowable error 5% = (0.05)

Therefore, sample size (n) will be calculated as follows;

$$n = \frac{1.64^2 \times 0.04\ (1-0.04)}{0.05^2}$$

$$= 41$$

Therefore$n = 41$ samples

Control= 41 samples

Total samples = 82 samples

Sampling Technique

Simple random sampling technique was employed for this study.

Ethical Consideration

Ethical clearance to conduct the research was obtained from the ethical committee of Kano State Ministry of Health (Ethical Approval Number: NHREC/17/03/2018). The consents were sought from participants before administration of questionnaires as attached in Appendix IV. All study was carried out in accordance with the Declaration of Helsinki.

Inclusion Criteria

1. Infertile women within the ages of 18-45 years, who consented to be enrolled in the study.
2. Apparently healthy fertile women between 18-45 years was use as control.

Exclusion Criteria

1. Patients with a history of hysterectomy
2. Patients on contraceptives

Sample Collection, Processing and Preservation

About 5ml of venous blood sample was collected aseptically from the ante-cubital vein of each participant using sterile syringe with the vacutainer tube containing gel and clot activator. The sample was allowed to clot, retracted and then centrifuged at 3500rpm for 5minutes. The separated serum was then transferred into labeled serum containers and stored at -20°C until ready for assay.

Equipment

The following equipment was used for the study: Electronic 90-1HospibrandUSA Superior Quality Equipment, UV-VISIBLE Spectrophotometer: Weigh Scale, Height Scale, Tourniquet, Test Tube Rack, Timer, Calculator, Magnet separator, Multimix Major, Luckam, Serial No. 424, Model No MF, Pipettes, (100uL-1000uL) and Disposable tips from Eppendorf Gmbt, Itamurge 65, fed Rep. Germany, Water Bath TT420 Multi-purpose use Techmel and Tehmel USA.

Anthropometric Measurements

The subject's height wasmeasured using a portable stadiometer and measure to the nearest meter. Each individual stood erect without shoes and with all head covering removed. The weight of the subjects was

measured by a portable standard weighing machine and measure to the first decimal function of kilograms. Individual weight was obtained with the usual outdoor clothes but without shoes. All heavy objects (bunch of keys, bangles, wrist watches and mobile phones among others was removed from the subjects. Body mass index (BMI) was calculated using the formula BMI= weight (kg)/height^2 (m)^2 and classified underweight (BMI<18), normal (BMI 18 - 24.9), overweight (BMI 25 - 29.9), obesity (BMI 30-39.9) and morbid obesity (BMI > 40).

{BMI = weight (Kg)/ height (m^2)}

Laboratory Assay Methods

Serum levels of Total Cholesterol (TC), Triglyceride (TG), and High-Density Lipoprotein (HDL) was determined using assay kits from Randox Manual RX Monza, while that of Estrogen (E2) was from ACCU BIND Inc. USA Enzyme Immunoassay Test Kit.

Total Cholesterol Assay

Serum total cholesterol was assayed according to the technique.

Procedure

All reagent and samples wasbrought to room temperature. Clean test tubes were placed in a rack as test, standard, control and blank respectively, one (1.0ml) of working total cholesterol reagent was dispensed into each test tube. Ten (10µl) of sample, standard, control and were dispensed respectively. The tubes were then mixed and incubated in a water bath for 10-15minutes. The absorbance of the standard and the samples was measured spectrophotometrically at 546 nm after blanking with reagent blank.

Triglyceride Assay

Triglyceride was assayed according to the technique.

Procedure

All reagent and samples was brought to room temperature. Clean test tubes were placed in a rack as test, standard, control and blank respectively, one (1.0ml) of working triglyceride reagent was dispensed into each test tube and ten (10µl) of sample, standard, control and blank was dispensed respectively. The tubes were then mixed and incubated in a water bath for 10-15minutes. The absorbance of the standard and the samples were measured spectrophotometrically at 546 nm after blanking with reagent blank.

High Density Lipoprotein-Cholesterol Assay

High density lipoprotein-cholesterol wasassayed according to the technique.

Procedure

Precipitation method

All reagents were brought to room temperature, into labeled precipitate test tubes, 200µl of sample, control and standard was dispensed into the respective tubes.In to label precipitate test tubes, 500µl of working mono-precipitant reagent was dispensed into Sample, control and standard tube respectively. The tubes were left to stand for 10 minutes at room temperature. Then was centrifuged at minimum of 4000 r.p.m for 10 minutes. The supernatant will be collected carefully.

Spectrophotometric method

All reagent and samples was brought to room temperature. A well clean test tube was place in a rack as test, standard,

control and blank respectively,one (1.0ml) of working total cholesterol reagent was dispensed into each test tube. Fifty (50µl) of supernatant will be dispense into sample tube, 50µl of standard, control and distill water blank were dispensed respectively. The tubes were then mixed and incubated in a water bath for 10-20 minute at room temperature. The absorbance of the standard and the samples was measured spectrophometrically at 546 nm after blanking with reagent blank.

Estimation of Serum Low Density Lipoprotein-Cholesterol

Serum low density lipoprotein-cholesterol wasenumerated according to the formula described by Friedewald *et al*. (1972).

LDL-C (mmol/l) = Total cholesterol-[HDL+ (triglyceride/2.2)]

Measurement of Serum Estrogen (E2)

The serum Estrogen (E2) was assayed using ELISA Product of ACCU BIND Inc. USA, technique.

Procedure

The desired number of coated well in the holder was secured. A data sheet with samples identification was made, 50µL of standard, samples, and controls was dispensed into appropriate wells. It will thoroughly mix for 10 seconds, and then 100µLof enzyme conjugate reagent was dispensed into each well. It will be thoroughly mixed for 30 seconds. It was then incubated at room temperature for 60 minutes. The incubation mixture was mixed by flicking plate contents into a waste container. The microtiter wells were rinse and flick 3 times with 350µl washing buffer. The wells were stroked sharply onto absorbent paper to remove residual water droplets. One hundred (100µL) TMB solutions were dispensed into each well and Incubate at room temperature in the dark for 15 minutes without shaking. Fifty (50µL) of stop solution was then added to each well to stop the reaction.

Statistical Analysis

The collected data was analyzed using Statistical Package of Social Science (SPSS) version 20.The mean and standard deviation was computed and results was expressed as a mean ± SD. Students t-test was used to compare differences between means. Correlation was performed by Pearson's Correlation Coefficient, Statistical Significance will be set at $p < 0.05$.Result was presented in figures and tables.

RESULTS

Figure 1 shows distribution of patients according to age groups. A total of 45 patients had primary infertility and 5 had secondary infertility out of the total infertile patients. The higher frequency of primary infertility was observed in Age group between 19-28years with the frequency of 24 and lowest frequency was observed in age group between 29-30years with frequency of 16. In secondary infertility, the higher frequency of 2 was observed in between age group of between 19-28 and 39-48 respectively. However, the lower frequency of 1 was observed between age ranges of 29-38.

Table 1 revealed the distribution of BMI in patients and controls. In both patients and controls the highest frequency of BMI was observed in normal with the percentage

frequency of 62% and 82% respectively and the lowest frequency of BMI was observed in moderate obesity with percentage frequency of 6% and 2% in patients and controls respectively.

Anthropometric indices of patients and control group were shown in table 2. The mean values of BMI in patients (23.75 ± 3.70 kg/m^2) and that of the control (21.46 ± 2.79kg/m^2)and weight of patient (67.64 ± 9.48 kg) and that of the control (60.68 ± 6.23 kg) were statistically significantly higher ($p<0.05$) in patient group than in the control group, where there is no statistical significant ($p>0.05$) in height between patients (1.69 ± 0.05 m) and the control group (1.69 ± 0.06) with p-value of (0.75).

Table 3 shows the estrogen and lipid profile in patients and control. The mean values of estrogen (154.87 ± 57.04pg/mL), LDL (2.22 ± 0.78 mmol/L) and total cholesterol (3.20 ± 0.64 mmol/L) were significantly lower ($p<0.05$) in patients than in control with estrogen (206.50 ± 93.76pg/mL), LDL (3.43 ± 1.31 mmol/L) and total cholesterol (4.40 ± 1.32 mmol/L), where triglyceride was statistically lower ($p>0.05$) higher in patients (0.74 ± 0.61 mmol/L) when compared with controls (0.54 ± 0.31 mmol/L) but no any statistical difference in HDL observed between patients (0.68 ± 0.23 mmol/L) and that of the control (0.74 ± 0.27 mmol/L).

Correlation of estrogen and lipid profile of patients is shown in table 4. There is no statistical significant ($p>0.05$) correlation between estrogen and triglyceride ($p = 0.61$), HDL-C ($p = 0.54$), LDL-C ($p = 0.72$) and total cholesterol ($p = 0.74$) in the patient. There was a negative correlation between estrogen with HDL-C ($r = -0.09$) and a positive correlation with triglyceride ($r = 0.07$), LDL-C ($r = 0.05$) and total cholesterol ($r = 0.05$).

Table 5 shows the relationship between estrogen with BMI in patients and controls. There is no any statistical significant ($p>0.05$) correlation between estrogen and BMI in both patients ($p = 0.31$) and controls ($p = 0.90$). There was a negative correlation between estrogen and BMI in the patients ($r = -0.15$) and a positive correlation was observed between estrogen and BMI in the controls ($r = 0.02$).

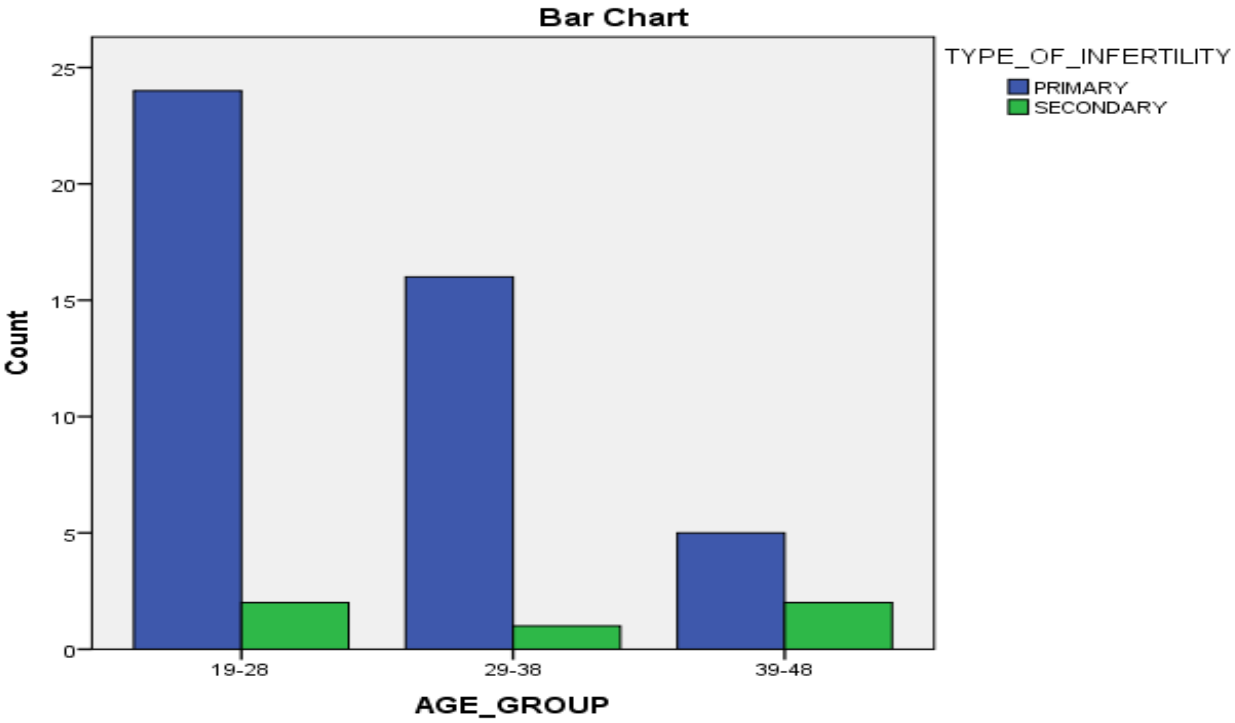

Figure 1: Distribution of patients according to age group

Table 1: Distribution of BMI Category in participants

BMI Category	BMI (kg/m^2)	patients [n, (%)]	control [n, (%)]	p-value
Underweight	<18	1 (2)	3 (6)	0.04*
Normal	18-24.9	31 (62)	41 (82)	
Overweight	25-29.9	15 (30)	5 (10)	
Moderate Obesity	30-39.9	3 (6)	1 (2)	
Morbid obesity	>40	0 (0)	0 (0)	
Total		50 (100)	50 (100)	

*BMI= Body Mass Index; n= Number; %=percentage;p≤ 0.05 (significant of t-test) for patient Vs Control for Analysis **

Table 2: Anthropometric indices(Mean±SD) inpatients and controls

Parameter	n	Patients	Controls	t-value	p-value
Height(m)	50	1.69 ± 0.05	1.69 ± 0.06	-0.335	0.74
Weight(kg)		67.64 ± 9.48	60.68 ± 6.23	4.336	0.00*
BMI(kg/m^2)		23.75 ± 3.70	21.46 ± 2.79	3.491	0.00*

*p≤ 0.05 (significant of t-test) for patient Vs Control for Analysis *; BMI= Body Mass Index;n= Number.*

Table 3: Estrogen and Lipid profile (Mean±SD) in infertilepatients and controls

Parameters	Patients n=50	Controls n=50	t value	p-value
E2(pg/mL)	154.87 ± 57.04	206.50 ± 93.76	- 3.33	0.00*
TC(mmol/L)	3.20 ± 0.64	4.40 ± 0.32	-5.58	0.00*
HDL-C(mmol/L)	0.68 ± 0.23	0.74 ± 0.27	-1.02	0.31
TG(mmol/L)	0.74 ± 0.61	0.54 ± 0.31	2.14	0.00*
LDL-C(mmol/L)	2.22 ± 0.78	3.43 ± 1.31	-5.58	0.00*

*p≤ 0.05 (significant of t-test) for patient Vs Control for Analysis *; n=Number of Subject; E2= Estrogen; TG=Triglyceride;T.C=Total cholesterol; HDL-C= High Density Lipoprotein Cholesterol; LDL-C= Low Density Lipoprotein Cholesterol.*

Table 4: Correlation between Estrogen hormone and lipid profile in infertile patients

Variable	R	CI (95%)	p-value
Estrogen & TC	0.05	3.02 – 3.40	0.74
Estrogen & HDL-C	– 0.09	0.62 – 0.75	0.54
Estrogen & TG	0.07	0.57 – 0.92	0.61
Estrogen & LDL-C	0.05	2.00 – 2.50	0.72

*r=Pearson correlation coefficient; CI=Confidence interval; p≤ 0.05 (significant of t-test) for patient Vs Control for Analysis *; TG=Triglyceride; TC=Total cholesterol; HDL-C= High Density Lipoprotein Cholesterol; LDL-C= Low Density Lipoprotein Cholesterol.*

Table 5: Correlation between Estrogen hormone and body mass index in patients and controls

Variables	R	CI (95%)	p-value
Infertile patients			
Estrogen hormone	– 0.15	20.67 – 22.26	0.31
BMI			
Healthy control			
Estrogen hormone	0.02	22.70 – 24.81	0.90

BMI

*r=Pearson correlation coefficient; CI=Confidence interval; p≤ 0.05 (significant of t-test) for patient Vs Control for Analysis *; BMI=Body Mass Index.*

Discussion

Female infertility has been a global problem. It is a social menace in our society. It has economic, social and psychological impact on the individual, and our society at large. In Africa, female infertility produces social consequences for African women and these consequences are particularly profound for women as compared to men, regardless of the cause of infertility (Inhorn *et al*., 2002).

In this finding, the age group 19-28years has the highest number of women with infertility with percentage frequency of 48%. It is in variance with the findings reported by Abha *et al*. (2008) in England where it was above 35years with percentage frequency of 51.4% and also with findings of Digban *et al*. (2017) who observed highest numbering age group 27-35years.

Current study reveals that, the mean values of BMI were statistically significantly higher ($p<0.05$) in patients and in the controls. Our reports agreed with Oztekin *et al*. (2020) in Europe. Our finding disagreed with the report of Joseph *et al*. (2018) in Ghana. The reason to our finding may be due to the fact that adipose tissue is necessary for reproductive function; the excessive adipose tissue is associated with reproductive disturbances and increase in weight which causes higher incidence of menstrual dysfunction and anovulation (Zeynep *et al*., 2015).

Current study reveals that, the mean value of estrogen hormone was significantly lower ($p<0.05$) in patients than in controls. Our finding agreed with the report of Digban *et al*. (2017) in Niger in Nigeria. This is in variance with the report of Alyaa *et al*. (2021) in Saudi Arabia. The reason to our finding may be as a result of several effects that can interfere with synthesis of estrogen in ovary and peripheral tissue leading to Hypoestrogenism which lead genitourinary effects and increase in vaginal pH (Naumova *et al*., 2018).

In this study, the mean values of low density lipoprotein and total cholesterol were statistically significantly lower ($p<0.05$) in patients than in controls, were triglyceride was significantly higher in patients than the controls, but no any statistical difference in HDL observed. This is in agreement with the report of Mahmood (2009) in Iraqi. An explanation to our finding might be due to dyslipidemia which lead to decrease in synthesis of steroid hormones as cholesterols are the main precursor of these hormones (Marther *et al*., 2000).

In this finding, positive correlation, but non-statistically significant ($p<0.05$) was observed between estrogen and triglyceride, low density lipoprotein and total cholesterol in the patients. This agreed with the report of Ariadi *et al*. (2019) in Indonesia and Malgorzata *et al*. (2018) in Canada. Negative correlation

was observed between estrogen and high density lipoprotein. This is in agreement with the report of Jerzy *et al*. (2006) in Poland. Therefore, decrease in estrogen in infertility cause dysregulation of lipoprotein lipase (Chatterjee *et al.*, 2011).

In the current study, negative correlation but not-statistical significant (p>0.05) was observed between estrogen and high density lipoprotein, low density lipoprotein and total cholesterol in the controls. Positive correlation but not-statistically significant between estrogen and triglyceride was observed in the controls. This is in agreement with the report of Sunni *et al*. (2011). An explanation to this finding might be due to variations in lipoprotein cholesterol levels throughout the menstrual cycle which is associated with change of estrogen level according to the normal phases of the monthly cycle since cholesterol is the precursor of steroid hormones (Knopp *et al.*, 2006).

Current study reveals that, negative correlation but not-statistical significant (p>0.05) was observed between estrogen with BMI in patients. This is in agreement with the report by Oztekin *et al*. (2020). Positive correlation was observed between estrogen and BMI in the controls.

Conclusion

Based on this study's finding, it can be concluded that infertility was more commonly observed in age group of 19-28years. BMI increased in women with infertility. Infertility was associated with decrease estrogen, LDL-C and total cholesterol. Estrogen has a negative correlation with HDL-C and a positive correlation with triglyceride, LDL-C and total cholesterol in infertility. Infertility was associated with negative correlation between estrogen with BMI. Hormone assay should be one of the diagnostic tools in management of infertility among women of childbearing age. Lipid profile test and BMI should be recommended for patients with infertility.

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