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Alterations in Lipid Profile and Indices of Atherogenicity among Infertile Women Seeking Conception by Assisted Reproductive Technology

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Abstract

Female infertility is common all over the world and lipid disorders are suggested to play a role. This study aimed to evaluate the plasma lipid profile and indices of atherogenicity among infertile women attending assisted reproductive technology clinics. Serum lipid profile (total cholesterol, triglycerides, low- density lipoprotein cholesterol, high- density lipoprotein cholesterol, and calculated indices of atherogenicity were determined in 140 infertile women and 50 healthy age-matched women of proven fertility. The lipid profile was assayed by the spectrophotometric method using reagents supplied by Randox Laboratories, Crumlin, Antrim, UK. The means values of measured parameters were compared between cases and controls by unpaired Students-test. The results showed that age ($p<0.001$), total cholesterol, triglycerides, low-density lipoprotein, AIP, some cardiac risk ratios, and atherogenic coefficients were significantly higher ($p<0.001$) while high-density cholesterol was significantly lower ($p<0.001$) among infertile women than control subjects. The difference in the mean body mass index between the cases and controls was not significant. The calculated indices of atherogenicity except high density/low-density ratio were significantly higher among infertile women seeking assisted reproductive technology for conception than control subjects. The higher indices of atherogenicity among this group of subjects might predispose them to cardiovascular diseases. Therefore, routine evaluation of lipid profile and indices of atherogenicity is suggested.

Keywords: Female, Fertilization, Infertility, Lipids, Reproductive techniques

Introduction

The need to identify risk factors and serum markers of atherosclerosis in the process of early detection and prediction of risk for cardiovascular diseases (CVD) is gaining increasing attention. Mathematical models are used to calculate how much atherogenic low-density lipoprotein cholesterol (LDL-c) is driving the progression of atherosclerosis (1). Cardiac risk ratio (CRR) is the ratio of total cholesterol value to high-density lipoprotein cholesterol (HDL-c) value (2,3), atherogenic coefficient (AC) is calculated by subtracting the value of HDL-c from total cholesterol, all divided by HDL-c value while Atherogenic index of plasma (AIP) is defined as logarithm [log] of the ratio of plasma concentration of triglycerides to HDL-C and is strongly correlated with CVD risks (4). However, the information in the literature that has examined the association between indices of atherogenicity and infertility in women seeking pregnancy via assisted reproductive technology is scanty (5). Indices of atherogenicity are said to be critical indices that better predict cardiovascular risk than values of lipid profile parameters (6, 7).

Female infertility is common all over the world with couples experiencing significant financial and emotional burdens. Even though several factors are implicated in infertility (8), lipid disorders are suggested to play a role. Some authors have reported that fertility potential among couples with abnormal lipids was lower with a fecundability Odds ratio (FOR) and high total cholesterol in both males and females (9). Infertile women seeking conception by assisted fertilization technology may be at increased risk of cardiovascular disease because they are administered with exogenous gonadotropins. Ovulation induction by exogenous gonadotropins is some of the commonest causes of lipoprotein modifications (10). Individualized gonadotropin dosage to reduce adverse effects of excessive ovarian response or poor response has been advocated (11). Also, derangement in lipid concentrations can impact negatively on the basic function that requires cholesterol.

Hence dyslipidemia may be a major determinant in the progression of infertility (12). Some authors have reported

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that in human in-vitro, abnormal maternal serum lipid profile was associated with poorer oocyte quality, ovarian function, and embryo development (12). This is an indication of a potential reduction in fertility (13). The incidence of dyslipidemia among infertile subjects is on the increase all over the world. Many of its possible causes are not associated with hormonal imbalance but, hyperlipidemia can be linked to various hormonal diseases such as diabetes, polycystic ovary syndrome, and metabolic syndrome. Besides the clinical symptoms of cardiovascular disease, dyslipidemia and the associated syndromes have also been associated with infertility (14, 15).

Atherosclerotic disease is a chronic and degenerative process that begins slowly probably during infancy. It is a disease with a wide range of clinical manifestation which may be asymptomatic or may eventually manifest as cardiovascular disease. The inflammatory process and the accompanying oxidative stress contribute to the mechanisms of the development of atherosclerosis (16). The incidence of atherosclerosis may differ according to the stage of the disease, individual patient race, age, sex, and environmental factors (16). A study has shown that Nigerians seemed to have an unfavorable risk profile for CVD which was not obvious using simple lipid profile parameters (17). This study aimed to determine the lipid profile and indices of atherogenicity among infertile women seeking assisted reproductive technology.

Materials and Methods

This is a cross-sectional study of women seeking conception via Assisted Reproductive Technology. The subjects comprised of 140 infertile women aged 36.8±0.35, body mass index 24.8±0.01, and 50 healthy women of proven fertility and aged 30.0±0.02, body mass index 24.03±0.01 who served as controls.

Inclusion criteria

All healthy women attending an ART clinic seeking pregnancy by ART. Apparently healthy Women between the ages of 25-45 without menses (anovulatory) and other histories of infertility and not on contraceptives were enrolled.

Exclusion criteria

Those Women < 45 who are still menstruating and are on contraceptives and those above 45 years were excluded.

Ethical Consideration

The protocol of the study was reviewed and approved by the Health Research ethics committee of the Lagos State Ministry of Health, Lagos State, Nigeria (Reference HM 1208/255 dated 23rd June 2018). Informed consent was sought from the participant to indicate voluntary participation in this study.

Sample Size Determination

The sample size (N) was calculated using sample size determination formula for health studies (18) and a 10% prevalence of female infertility in Nigeria (19). Therefore a minimum of 140 samples and 50 controls were recruited for the study.

Sample Collection

Under strict aseptic precautions, 5mL of fasting venous blood was obtained from each of the participants into a lithium heparin bottle. Blood samples were collected at baseline coinciding with Days 2-4 of women menstrual cycles and before ovarian stimulation and administration gonadotropins. Samples were centrifuged at a speed of 3000rpm for 5 minutes and plasma was separated. The plasma recovered was transferred to a fresh tube for determination of lipid profile.

Sample Analysis

Triglyceride, total cholesterol, and HDL-c were determined by the spectrophotometric method using reagents kits supplied by Randox Laboratories, Crumlin, Antrim, UK. Indices of atherogenicity were calculated as indicated in the introduction section and LDL-c was calculated using Friedewald et al. (20) formula.

Statistical Analysis

All data analysis was performed using SPSS. 21.0 Software (SPSS, Chicago, IL). Continuous variables were expressed as means ±standard deviation and analyzed using the independent Student t-test. A p-value of less than 0.05 was considered to be statistically significant.

Results

A total of 190 women were recruited in the study. This comprised of 140 infertile women seeking assisted reproductive technology and 50 healthy women of proven fertility as controls. Table 1 describes the demographic characteristics of the study population. The mean ages of the study population were significantly higher ($p<0.001$) than control subjects. There was no significant difference in the means body mass index (BMI) and the age of onset of menstruation (Menarche) between the cases and controls. Table 2 shows the pattern of lipid profile and indices of atherogenicity among the study population compared with controls. The mean HDL-c level was significantly lower ($p<0.001$) among the infertile women than the fertile controls. On the other hand, total cholesterol, triglyceride, LDL-c, VLDL-c, AIP, cardiac risk ratios except for HDL-c/LDL-c ratio, and AC were significantly higher ($p<0.001$) among infertile women than control subjects.

Discussion

Female infertility is a social menace and has an economic, social, and psychological impact on the individual, and the society. Infertile women seeking conception by assisted reproductive techniques are treated with recombinant follicle-stimulating hormone to stimulate their ovaries to produce oocytes as well as human chorionic gonadotropins (hCG). These exogenous hormones have been reported to increase lipid concentrations. It is very important to know the lipid profile levels and indices of

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Table 1: Demographic characteristics of study population

Variables	Infertile women (n=140)	Controls (n=50)
Age(years)	35.9±0.35	30.0±0.01
Body mass index(Kg/m^3)	24.8±0.5	24.03±0.2
Menarche (Years)	13.1±1.0	13.0±0.2
Irregular menstruation	40(28.6%)	0(0%)
Gynecological surgery	50(35.7%)	03(06%)
Physical activity	120(85.7)	32(64%)
Cigarette smoking	02(1.4)	0(0%)
Alcohol Consumption	10(7.1%)	15(30%)

Table 2: Comparison of Lipid profile parameters and atherogenic indices between infertile and fertile women

Parameters	Infertile Women (n=140)	Fertile Women (n=50)	P Value
Triglycerides(mmol/L)	1.72±0.02	1.60±0.07	0.001
Total Cholesterol(mmol/L)	5.70±0.01	5.46±0.02	0.001
HDL-c(mmol/L)	0.89±0.02	1.16±0.02	0.001
LDL-c(mmol/L)	3.90±0.02	3.60±0.02	0.001
VLDL-c(mmol/L)	082±0.02	0.73±0.02	0.001
AIP	0.52±0.001	0.29±0.001	0.001
Cardiac Risk Ratios			
TC/HDL-c	6.38±0.04	4.69±0.03	0.001
LDL-c/HDL-c	4.35±0.05	3.11±0.04	0.001
HDL-c/LDL-c	0.22±0.06	0.32±0.04	0.5
AC	5.39±0.06	3.72±0.04	0.001

HDL-c=High Density Lipoprotein cholesterol; LDL-c= Low-Density Lipoprotein cholesterol; VLDL-c=Very Low-Density Lipoprotein cholesterol; AIP=atherogenic index of plasma lipid; atherogenic coefficient

atherogenicity to predict cardiovascular risk and fecundity potential.

In this study, plasma concentrations of triglycerides, total cholesterol, LDL-c, VLDL-c, and the indices of atherogenicity except for HDL-c/LDL-c ratio were significantly higher while HDL-c was significantly lower among infertile women than controls.

The observed results are consistent with previous studies (8, 10, 12). Wang et al. (12) evaluated lipid profile levels in infertile women and associated their levels with oocyte and embryo qualities. The authors reported that the quality of embryo may be associated with lipid abnormalities in infertile females. They observed a negative association of embryo quality with triglycerides, total cholesterol, and LDL-c levels. The level of HDL-c correlated positively with embryo quality (12). The important role of HDL cholesterol in the process of mammalian female reproduction has been aptly demonstrated in knockout (SR-BI KO) female mice. The experimental study showed that a high incidence of exencephaly with female bias in embryos lacking SR-BI as associated with abnormal HDL metabolism (21). Besides, it was reported that HDL-c exhibit a vital cytoprotective effect on oocytes and surrounding granulosa cells (22). The study by Wang et al (12) is an indication that an adequate level of HDL-c is required for the development of oocytes to the embryo. This protective effect of HDL-c may be attributed to the delivery of cholesterol to corpus luteum as a substrate for the biosynthesis of progesterone by both HDL-c and LDL-c (23).

The increasing incidence of the negative effect of raised body mass index (BMI) on IVF outcomes has been reported (24, 25). In this study, there was no significant difference in the means of BMI between infertile women and control subjects. However, BMI was reported to be negatively associated with the number of normally fertilized oocytes, cleavage embryos, and good quality embryos. It was reported that high BMI may adversely influence the pregnancy rate of IVF in subjects with endometriosis (12).

The biologic mechanism by which lipids and lipoproteins affect successful reproduction is the role lipids play in ovarian steroidogenesis (8, 23). Others have suggested that the dysregulation of insulin which disrupts ovarian function may be implicated (26). A 50% increased risk of myocardial infarction or coronary heart disease was reported among women with menstrual irregularities in comparison with those who had normal cycles from the ages of 20 to 35 years (27). The results show that infertile females have significantly higher triglycerides compared to control. Some authors reported that high triglycerides levels are found in both obese and non-obese women suffering from infertility (28). High serum levels of total cholesterol and LDL-c in infertile women is an indication disproportionate steroidogenesis that may be taking place and this could be the reason for infertility. This agrees with a study that observed that women with different causes of infertility had increased total cholesterol levels (29).

It was suggested that lipid may be used as a marker of fertility. In the United States of America, it was recommended that adults over the age of 20 years undergo lipid profile screening every 5 years as this will enable the identification of reduced fecundity (30). Although cholesterol is a precursor of steroid hormones, a high level

of it can cause infertility in females (31). Abnormality of LDL-c had not been consistently reported in some cases of infertility. Even those with normal LDL-c levels had shown increase VLDL-c relative to the control group (32). A significantly higher index of atherogenicity was observed among infertile women when compared with the fertile group. This implies that infertile women have a higher risk of developing cardiovascular diseases than the fertile group. This is particularly important because Black Africans are known to have lower lipid levels than Caucasians (33). Therefore, the use of lipid levels to diagnose cardiovascular diseases in Africans may be misleading. Glew et al. (17) reported that they were able to differentiate patients with stroke from normal individuals via the use of cardiac risk ratios. The need to identify prospective women seeking intervention via assisted reproductive technology who are at risk of CVD cannot be overemphasized.

Conclusion

Plasma triglyceride, total cholesterol, LDL-c, and indices of atherogenicity (except HDL-c/LDL-c ratio) were significantly higher while HDL-c was significantly lower among infertile women seeking conception via assisted reproduction. It is suggested that this group of women may benefit from periodic lipid profiles and indices of atherogenicity determination for fertility potential and/or CVD risk assessments.

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Conflicts of interest

The authors declare that there is no conflicts of interest.

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