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Original Article

Applicability of Lipid Ratios in the Prediction of Atherogenic Risks of Women on Combined Oral Contraceptives in North-Central Nigeria

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Abstract

Background: Combined Oral Contraceptive (COC) pill is associated with atherogenic and cardiovascular changes. Some service providers use individual lipid parameters to assess these changes unlike objective calculation using standard formulae. Objective: To determine and compare the atherogenic changes in women on COCs using six lipid ratios; coronary heart disease risk ratio, atherogenic index of plasma, atherogenic co-efficient, Cholesterol index, Castelli risk index I, and Castelli risk index II. **Materials and Methods:** A prospective, comparative study among new acceptors of contraceptives at four family planning clinics in Ilorin, North-Central Nigeria. Participants were categorized into COCs acceptors (group I, n=120) and acceptors of non-hormonal contraceptives (group II, n=120). Participants were followed up with serial lipid profiles at 0, 3 and 6 months after uptake. Atherogenic risks were calculated using six standard formulae; statistical analysis was with SPSS version 21.0 and Analysis of variance (ANOVA) was used to compare the differences of more than two means, Bonferroni Post Hoc test was used to test for specific significance within the group and p-value <0.05 was considered significant. **Results:** A total of 225 participants (111 COC users, 114 non-COC users) aged 19 to 48 years completed the study. Serum levels of Low-Density Lipoprotein showed a statistically significant rise among the COC users over the study period (p=0.038), especially between the third and sixth months. The lipid ratios were statistically increased using all six methods despite apparently normal lipid parameters. **Conclusion:** Atherogenic changes may occur in the presence of apparently normal lipid parameters among COC users; therefore, serial lipid ratio using standard method formulae is recommended.

Keywords: *Atherogenic ratio, atherogenic risk, combined oral contraceptive, lipid parameters, lipid ratio, standard formula*

Introduction

Contraceptives have improved the lives of women and their families globally and combined oral contraceptive (COC) is one of the most commonly used and effective contraceptive methods worldwide.[1] Acceptability and uptake of COC varies across regions, but the reported prevalence in Nigeria ranges from 3.74% to 25%.[2,3] COCs suppress ovulation by the maintenance of constant negative feedback on the anterior pituitary and hypothalamus there by preventing mid-cycle luteinizing hormone surge.[4] The progestogen component acts on the cervical mucus, making it thick and impervious to spermatozoa as well as impeding implantation.[4] Extensive use of COCs by females through their reproductive lives has raised concerns about the effects on changes in lipid metabolism with a potential for an increased risk of cardiovascular disease which is one of the leading causes of adult mortality.[5] Over the years, Sub-Sahara Africa has been contending with associated morbidity and mortality from preventable infectious diseases; in recent years, noncommunicable diseases such as atherosclerosis and coronary heart disease (CHD) have been reported to be on the increase in this region.[6] Therefore, it is pertinent to evaluate the lipid and cardiovascular changes relative to COC use among these women since COCs are widely available and can be procured without a prescription. It has been postulated that ratios of commonly-measured parameters such as lipids and lipoproteins may be acceptable in identifying individuals at risk of cardiovascular diseases, but evidence

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suggests that atherogenic ratios perform better than individual lipid parameters in predicting cardiovascular risks.[7,8] Lipid ratios such as the Atherogenic Index of Plasma (AIP), Atherogenic Coefficient (AC), CHD-Risk Ratio (CHD-RR), Cholesterol index (CHOLindex), and Castelli Risk Indices (CRI) I and II serve as quick, simple, and objective alternatives for identifying individuals at risk, especially when the conventional lipid parameters like total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) appear normal.[8-14] This may decrease the complexity of the assessment and increase the efficacy of identifying those at risk of cardiovascular disease. However, research on the clinical usefulness of lipid ratios to identify individuals with cardiovascular risks and metabolic syndrome is limited in Sub-Saharan Africa.[15] Therefore, this study aimed to determine the atherogenic risks of women on COCs using six of the available standard lipid ratios among COC users compared to non-COC users.

Materials and Methods

This was a prospective, comparative study conducted between August 30, 2017 and June 30, 2018 at four major family planning clinics comprising three secondary facilities and one tertiary facility in Ilorin, North-Central Nigeria. These facilities are Ajikobi Cottage Hospital, Adewole Cottage Hospital, State Specialist Hospital, and University of Ilorin Teaching Hospital.

The study participants were consenting new acceptors of contraceptives at the study sites during the study period and categorized into those who commenced COC (COC users; Group I) and those who commenced nonhormonal methods for example barrier, nonhormone impregnated intrauterine device and sterilization (non-COC users; Group II). The inclusion criteria for the study were age 15–50 years and no history of hormonal contraceptive use for a minimum of 6 months before recruitment. Women on contraceptives before the study period, those who commenced other hormonal contraceptive methods except COC and other noncontraceptive users were excluded from the study. The COC used for the study was Microgynon® ED Fe which contains ethinyl estradiol (30 µg) and levonorgestrel (150 µg) produced by Bayer Pharma, Germany.

Sample size determination and sampling method

The minimum sample size was determined by the formula for comparative study.[16]

$$N = \frac{2z^2pq}{d^2}$$

The prevalence of COC use in the study area was 3.74%,[2] allowing for 10% attrition, a minimum sample size of 240 was calculated; therefore, 120 participants were recruited for each study group. To eliminate bias, the sample size was divided into proportions for each study site based on the monthly family planning clinic attendance to give a 13% (University of Ilorin Teaching Hospital), 38% (State Specialist Hospital), 29% (Adewole Cottage Hospital), and 20% (Ajikobi Cottage Hospital) of the total sample size, respectively. A purposive sampling method was used for recruitment and eligible participants were recruited after counseling about the study followed by written informed consent.

Sample collection and processing

Fasting blood samples were collected between 8 am and 10 am at recruitment, 3 and 6 months into the study, from all participants and analyzed for TC, TG, HDL-cholesterol, and LDL-cholesterol (LDL-C). The samples were analyzed at the chemical pathology laboratory of the University of Ilorin Teaching Hospital, Ilorin, Nigeria. Blood samples were collected from the veins on the forearms and allowed to stand for 1 h to enable clotting and retraction. They were then spun in a bench-top centrifuge at 3,000 revolutions per minute for 3 min.

Biochemical assays

Serum TC was determined using MAPADA® Spectrophotometer (Shanghai Mapada, 2012) which measured the absorbance of the colour complex. This was used to calculate the concentration. Commercially-prepared TC kits and TG SL kits (Agappe Diagnostics India) were used for the analysis of cholesterol and TGs, respectively, while combi HDL/LDL kit was used for HDL and LDL analysis. Quality control of the equipment, reagents, analytical method, and analytes was validated using a commercially prepared control kit for lipid profiles of two randomly selected samples from each batch of the samples analyzed.

Atherogenic ratios

The atherogenic ratios were calculated using the formulae as stated below:

a. CHD-RR:[12] HDL/TC
b. AIP:[13] log (TG/HDL)
c. AC:[14] TC-HDL/HDL
d. Chol index:[9] LDL-HDL (or LDL-HDL + 1/5TG if TG >4.516 mmolL^{-1})
e. Castelli risk index (CRI) I: TC/HDL
f. CRI II:[10,11] LDL/HDL

Data analysis

Data analysis was performed using SPSS version 21.0 (IBM, Armonk, NY, USA); Chi-square and *t*-tests were calculated. Repeated measure analysis of variance was used to compare the differences of more than two means across the two groups, Bonferroni *post hoc* test was used to test for specific significance within the group, and $P < 0.05$ was considered statistically significant.

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Ethical consideration

The study complied with institutional and national guidelines on ethical standards in human studies. Ethical approval was obtained from the Ethical Review Committee of the University of Ilorin Teaching Hospital, Ilorin, Nigeria (Approval number: ERC PAN/2016/02/2498), and written informed consent was obtained from each participant at recruitment into the study.

Results

A total of 240 women were recruited but 225 comprising 111 COC users and 114 non-COC users completed the study and were included in the analysis.

Table 1 shows that the mean age for both groups was similar. Among the teenage participants, 4 (3.6%) and 6 (5.3%) were users and non-COC users, respectively. Only 1 (0.9%) COC user and 19 (16.7%) non-COC users were nulliparous while most of the COC users 110 (99.1) and non-COC users 95 (83.3) had at least one parous experience. There was a significant difference in the parity between the two groups ($P < 0.001$). The majority of participants 217 (96.4) had formal education while 8 (3.6) had none. Most participants were manual or nonmanual workers (101; 44.9%) and three women each from both groups were unskilled. Largely, 100 (90.1%) COC users and 80 (70.2%) non-COC users were married. In all, 63.1% of COC users and 75.4% of nonusers had previous contraceptive experience; this was a statistically significant difference between the two groups ($P = 0.044$).

Table 2 shows the serial comparison of levels of serum TC, TG, HDL, LDL, and six atherogenic ratios for COC users and non-COC users. Using individual parameters in the lipid profile, the mean LDL value among the COC users showed a significant increase over the study period ($P = 0.038$) while non-COC users experienced an initial decrease, then

Table 1: Sociodemographic characteristics of participants

Variables	COC users (*n*=111), *n* (%)	Non-COC users (*n*=114), *n* (%)	*t*-test	*P*
Age (years), mean±SD	32.81±7.22	33.61±8.22		
≤20	4 (3.6)	6 (5.3)	0.656	0.985
21-25	20 (8.0)	22 (19.3)		
26-30	28 (25.2)	27 (23.7)		
31-35	24 (21.6)	22 (19.3)		
36-40	20 (18.0)	22 (19.3)		
>40	15 (13.5)	15 (13.2)		
Parity				
0	1 (0.9)	19 (16.7)	26.947	<0.001
1-2	40 (36.0)	20 (17.5)		
3-4	52 (46.8)	44 (38.6)		
≥4	18 (16.2)	31 (27.2)		
Formal education status				
None	3 (2.7)	1 (0.9)	11.339	0.010
Primary	31 (27.9)	54 (47.4)		
Secondary	48 (43.2)	30 (26.3)		
Tertiary	29 (26.1)	29 (25.4)		
Marital status				
Single	1 (0.9)	21 (18.4)	20.901	<0.001
Married	100 (90.1)	80 (70.2)		
Divorced	9 (8.1)	11 (9.6)		
Widowed	1 (0.9)	2 (1.7)		
Occupation				
Unskilled	3 (2.7)	3 (2.6)	6.905	0.075
Manual/nonmanual	50 (45.0)	51 (44.7)		
Intermediate skilled	18 (16.2)	33 (28.9)		
Professional	40 (36.0)	27 (23.7)		
Income (Naira)				
≤30,000	30 (27.0)	40 (35.1)	1.706	0.426
31,000-100,000	60 (54.1)	55 (48.2)		
>100,000	21 (18.9)	19 (16.7)		
Previous contraceptive use				
Yes	70 (63.1)	86 (75.4)	4.051	0.044
No	41 (36.9)	28 (24.6)		

SD: Standard deviation, COC: Combined oral contraceptive

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Table 2: Comparison of serial serum lipid profiles and atherogenic ratios of combined oral contraceptive users and nonusers

Variable	Mean±SD			ANOVA	*P*
	0 month	3 months	6 months		
TC (mmolL^{-1})					
COC users	3.66±1.57	3.68±1.57	3.71±1.57	0.029	0.972
Non-COC users	3.65±1.52	3.67±1.51	3.67±1.50	0.007	0.993
TG (mmolL^{-1})					
COC users	1.26±0.48	1.31±0.47	1.37±0.47	1.503	0.224
Non-COC users	1.39±0.55	1.39±0.54	1.40±0.56	0.013	0.988
HDL (mmolL^{-1})					
COC users	1.38±0.41	1.34±0.40	1.33±0.40	0.462	0.630
Non-COC users	1.45±0.44	1.48±0.48	1.42±0.47	0.477	0.621
LDL (mmolL^{-1})					
COC users	2.41±0.82^{a}	2.58±0.82^{a}	2.69±0.81^{b}	3.312	0.038
Non-COC users	2.39±0.86	2.55±0.77	2.31±0.77	0.853	0.427
AIP					
COC users	−0.07±0.22^{a}	0.06±0.22^{a}	−0.02±0.22^{b}	62.264	<0.001
Non-COC users	−0.02±0.19	−0.02±0.19	−0.02±0.19	0.500	0.608
CRI I					
COC users	2.75±1.39^{ab}	2.73±1.39^{a}	2.89±1.51^{b}	20.398	<0.001
Non-COC users	2.77±1.25	2.75±1.20	2.73±1.24	1.701	0.187
CRI II					
COC users	1.76±0.79^{ab}	1.58±0.49a	1.70±0.52^{b}	55.679	<0.001
Non-COC users	1.86±0.55	1.87±0.53	1.85±0.53	1.069	0.347
AC					
COC users	1.75±1.39^{ab}	1.73±1.39a	1.89±1.51^{b}	20.398	<0.001
Non-COC users	1.77±1.25	1.75±1.20	1.73±1.24	1.701	0.187
CHOL index					
COC users	0.93±0.88^{ab}	0.76±0.65^{a}	0.88±0.65^{b}	105.635	<0.001
Non-COC users	1.12±0.66	1.14±0.65	1.12±0.66	0.941	0.393
CHD RR					
COC users	0.48±0.29^{ab}	0.49±0.30^{a}	0.47±0.28^{b}	29.210	<0.001
Non-COC users	0.43±0.22	0.44±0.23	0.44±0.23	2.299	0.105

Using the Bonferroni *Post hoc* test, mean values with different alphabets (a and b) indicates significant difference while values with at least one similar alphabet are not significantly difference. SD: Standard deviation, ANOVA: Analysis of variance, TC: Total cholesterol, TG: Triglycerides, HDL: High density lipoprotein, LDL: Low density lipoprotein, AIP: Atherogenic index of plasma, AC: Atherogenic coefficient, CHD-RR: Coronary heart disease risk ratio, CHOL index: Cholesterol index, CRI-I: Castelli risk index I; CRI-II: Castelli risk index II, COC: Combined oral contraceptive

a rise which was not significant (P = 0.427). There was a significant rise in LDL among the COC users over the 6 months (P = 0.038) and this increase was more marked between the third and 6th month as shown with the *Post hoc* test (a and b). However, the serial mean values for TC, TG, and HDL among COC users and non-COC users were not statistically significant. In general, using individual lipid profile parameters suggests that only LDL showed a significant rise among COC users, while other parameters were apparently within the normal range.

In the comparison of the AIP, CRI I and II, AC, CHOL index, and CHD-RR in COC users and nonusers, all show statistically significant serial rise among COC users (P < 0.001). There were no significant serial changes in AIP (P = 0.608), Castelli I (P = 0.187), Castelli II (P = 0.347), AC (P = 0.187), CHOLindex (P = 0.393), and CHD-RR (P = 0.105) among the non-COC users and the period of significant changes are highlighted using Bonferroni *post hoc* test as shown in Table 2. In general, the use of the six objective formulae showed a significant atherogenic risk for COC users despite values that were within the reference range.

Discussion

Over the study period, there were significant changes in the atherogenic risks of women on COCs which was determined by using standard formulae in the face of seemingly normal lipid profiles except LDL. Utilization of COCs is associated with changes in serum lipid profiles hence, the need to determine the atherogenicity of women who are taking these drugs as this may predispose them to arteriosclerosis, myocardial infarction, and stroke.[17]

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However, it has been shown that the determination of the atherogenic risk of women on COCs using lipid ratios is better than using individual lipid parameters.[9,12,17] Many studies have reported cardiovascular and atherogenic changes among CCOC users but only a few used multiple lipid ratios to assess the extent of these risks.[17]

Despite all the lipid parameters remaining within normal limits during the study period, LDL levels increased significantly among COC users ($P = 0.038$). This increase, though marginal, may explain the reason why second-generation COCs are known to be proatherogenic and this was similar to the findings from a Nigerian study where a statistically significant increase in LDL-C was reported within 13–24 months of COC use ($P = 0.005$).[17]

Generally, normal levels of TC, TG, and HDL as seen in this study connotes low atherogenic risk, but the relationship between COC use and changes in serum lipid profile has led to further evaluation of the cardiovascular risk and its predisposition to coronary artery disease and stroke.[17] This study reported a statistically significant increase in all lipid ratios in COC users ($P < 0.001$) and this showed that the use of COCs was associated with short-term atherogenic risks. Available evidence suggests that lipid ratios are better predictors of atherogenic risk than individual lipid parameters.[6-8,13] The findings from this study agree with this observation because most of the conventional lipid parameters were not significantly changed during the study period, but the lipid ratios predicted the existence of atherogenic risks even in the presence of seemingly normal individual lipid parameters. A similar finding was reported in the Czech republic where AIP increased with short-term usage of hormonal contraceptives even when other lipid ratios remained unchanged and individual lipid parameters were within normal range.[18] AIP is being employed by Medical experts across the globe as it strongly predicts atherosclerosis and serves as a diagnostic alternative and for treatment monitoring.[19] Studies have demonstrated the relevance of CRI I and II in the prediction and management of cardiovascular diseases; there is a strong association between CRI-I with coronary plaque formation.[5,20] Furthermore, Oyelola.[21] in Nigeria and Asare *et al*.[22] in Ghana reported an increase in CRR-I and CRR-II among women on COCs compared to the nonusers but these were contrary to the findings from a study in South-Eastern Nigeria where these ratios were significantly lower among COC group.[23] However, a study done among blacks, whites, and Hispanics reported no difference in CRI-II between COC users and nonusers but the methodology was quite different as current smokers and alcoholics were not excluded and three different races were included.[24] The CRI-I, AC, CRII, CHOL Index, and AIP predicted a significantly higher prevalence of predisposition to cardiovascular risks among semi-urban dwellers in Nigeria with CRI-I showing the highest prevalence among the female population. This shows that there are varying reports regarding the effects of COC usage on the atherogenicity of women despite studies emanating from similar sub-regions. The relatively new CHOL Index has been shown to have a significant relation with coronary artery disease and is consequently used reliably to predict cardiovascular risks.[9] Like other atherogenic ratios, this study reported a significant increase in the CHOL Index and its likely association with dyslipidemia.

The implication of using standard lipid ratios as against conventional lipid parameters in the prediction of atherogenic risk is that cardiovascular changes appeared to be more pronounced and would be detected early with the reduction in morbidity and mortality.[8] Therefore, lipid profiles within the normal range do not exclude the risk of cardiovascular diseases.[8,13] It is important to incorporate routine atherogenic screening using lipid ratios before initiation and during follow-up of women on COCs. This would be advantageous in the early identification of high-risk women and prompt referral to the appropriate clinics, thereby reducing the burden of an already-increasing population of apparently undiagnosed cardiovascular patients.

Conclusion

The study documented short-term changes in atherogenic ratios among COC users over the study period. We recommend serial assessment and monitoring of the atherogenic risk of this group, especially in the face of apparently normal conventional lipid parameters. Clinicians should be encouraged to adopt the use of different lipid ratios for early detection and in the follow-up of patients at risk of atherogenic diseases.

Strength and limitations

The study contributed to the limited available information in Sub-Saharan Africa on the relationship between short-term COC use and atherogenic risks while the serial assessment of rarely used lipid ratios provides a proper channel for a more robust and objective analysis though a long-term evaluation would be desirable.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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