

Atherogenic and Cardiovascular Risks of Women on Combined Oral Contraceptives: A Comparative Study

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ABSTRACT

Background: Although combined oral contraceptive (COC) is commonly used in sub-Saharan Africa, data on its cardiovascular disease risk remains scanty. The study aimed to determine serial serum lipid profiles and cardiovascular disease risks among COC-users. **Methods:** This is a prospective, comparative multicentered study conducted at four health facilities in Nigeria. Participants were new users of contraceptives; 120 each of women initiating COCs (group I) and those initiating other forms of nonhormonal contraceptives (group II) were recruited and monitored over a 6-month period. Serial lipid profile, blood pressure, and atherogenic risk for cardiovascular diseases were measured at recruitment (start) and scheduled follow-up clinic visits at 3 months and 6 months for all participants. Statistical analysis was performed with SPSS (version 21.0) and P value < 0.05 was considered significant. **Results:** In all, 225 participants (111 COC-users, 114 nonCOC-users) that completed the study were aged 18 to 49 years. There was a statistically significant increase in the diastolic blood pressure ($P = 0.001$), Low Density Lipoprotein- Cholesterol ($P = 0.038$) and higher atherogenic risk ($P = 0.001$) among COC-users compared to nonCOC-users. The serial total serum cholesterol, triglyceride, High Density Lipoprotein, systolic blood pressure, and body mass index were higher among COC-users but were not statistically significant compared to nonCOC-users. **Conclusion:** Alterations in lipid profile and increased short-term atherogenic risk for cardiovascular disease were reported among the COC-users in this study. Serial lipid profile and atherogenic risk assessment for cardiovascular diseases are recommended for monitoring of COC-users.

KEYWORDS: Atherogenic risk, cardiovascular risk, combined oral contraceptive, family planning, hormonal contraceptive

INTRODUCTION

Fertility regulation through contraception is a cardinal component of reproductive health services; combined oral contraceptive (COC) is a commonly used contraceptive method with a prevalence of 3.74^[1]–25%.^[2] COC acts by preventing ovulation subsequent to luteinizing hormone (LH) and follicle stimulating hormone (FSH) level suppression, abolition of the mid-cycle LH surge and diminution of endogenous steroid levels.^[3]

Reports in the last two decades have shown an association between hormonal contraceptives and cardiovascular diseases.^[3,4] Dyslipidemia, which is a common feature with COC use, has been associated with coronary heart diseases.^[5] However, atherogenic risks calculated from standard lipid ratios have been

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shown to be a more reliable predictor for coronary heart disease risks over individual lipid parameters.^[6] Also, the estrogen/progestogen combination in COC were reported to exert unpredictable effects on lipid metabolism by affecting a variety of metabolic factors modulated by the type of estrogen/progestogen combination.^[7]

Although cardiovascular morbidities and mortalities are fewer in sub-Sahara Africa compared to high-income countries, the current trend of globalization and adoption of western habits in the population leading to increasing deaths from noncommunicable diseases including cardiovascular disease, warrant efforts to further evaluate the effect on women using COC in these countries. Currently, data on atherogenic changes and cardiovascular risks especially using Atherogenic Index of Plasma (AIP) in women on COC in sub-Sahara Africa are negligible and still a subject of debate, thereby necessitating further studies. Atherogenic index is calculated as $\log_{10}(\text{TG}/\text{HDL})$ and is a widely acceptable and very sensitive index for predicting cardiovascular risks across the globe. In sub-Sahara Africa, COC is one of the contraceptives that are decentralized and obtainable over the counter; thus, physical and biochemical assessments before its initiation as well as regular hospital follow-up visits are not mandatory. The decentralization of COC is a strategy to encourage uptake and reduce the high maternal morbidity and mortality from complications of unsafe abortions. Therefore, this study is aimed at assessing the lipid and cardiovascular changes as well as the atherogenic risk for cardiovascular diseases among women using COC.

MATERIALS AND METHODS

This was a prospective, comparative multicentered study involving four major family planning clinics (one tertiary and three secondary health facilities) in Ilorin, North Central Nigeria conducted between August 30, 2017 and June 30, 2018. These facilities were University of Ilorin Teaching Hospital, State Specialist Hospital, Adewole Cottage Hospital, and Ajikobi Cottage Hospital and were selected because they cut across the three Local Government Areas in Ilorin (South, East, and West).

Participants were women who presented at the family planning clinics for contraception. The inclusion criteria for COC-users were consent for initiation of COC without history of hormonal contraceptive use for a minimum of 6 months prior to recruitment; whereas nonCOC-users were women commencing nonhormonal contraceptives (barrier, nonhormone-impregnated intrauterine device, and sterilization) and have not used hormonal contraceptive for a minimum of 6 months prior to recruitment. The COC used for

the study was Microgynon ED Fe, (Bayer Pharma, Germany), which contains ethinyl estradiol (30 µg) and levonorgestrel (150 µg).

The minimum sample size was determined by the formula for comparison of groups.^[8]

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

where Prevalence of combined oral contraceptive usage in the study area is 3.74%^[1] and allowing for 10% attrition, a minimum of 120 women each were recruited in each of the user and the nonCOC-user group giving a total sample size of 240. To have a proportionate sampling from four centers, the average numbers of women on contraception seen monthly were used to determine the percentage each center makes out of the total sample size and women from University of Ilorin Teaching Hospital made 13% of total sample size, 38% from State specialist Hospital, 29% from Adewole Cottage Hospital, and 20% from Ajikobi Cottage Hospital.

However, a total of 225 women, comprising 111 users and 114 non-users completed the study and were included in the analysis. A total of nine users, comprising five participants who changed to other forms of contraception and four others who were lost to follow-up, were eliminated from the study. Similarly, six non-users, comprising four participants who were lost to follow-up and two participants who became pregnant, were equally removed from this study.

The sampling method was purposive sampling, and eligible subjects who gave their consent were recruited at the study sites after client education followed by an informed written consent. Thereafter, all participants had their anthropometric measurements taken by measuring height and weight to calculate the body mass index (BMI) ($\text{weight [kg]} / (\text{height [m]})^2$) as well as serial systolic and diastolic blood pressure measurements at recruitment (start), 3 months and 6 months after. Height (to nearest 0.1 cm) was recorded with subjects barefooted using a portable stadiometer. Weight was measured (to nearest 0.1 kg) using a ZT-120 weighing scale (Med-Lab Scientific Co. England) whereas blood pressure measurement was with mercury sphygmomanometer. Two measurements of the blood pressure with not more than 10 mmHg difference were performed; blood pressure, height, and weight measurements were taken by trained research assistants recruited for the study.

Fasting blood samples were collected (between 8 am and 10 am) at recruitment, 3 months and 6 months of study from all participants and analyzed

for total cholesterol, triglycerides, high density lipoprotein- cholesterol (HDL-C), and low-density lipoprotein- cholesterol (LDL-C) levels. The samples were analyzed at the chemical pathology laboratory of the University of Ilorin Teaching Hospital, Ilorin, Nigeria. Blood samples were collected from a vein on the forearm and allowed to stand for 1 hour to enable clotting and retraction. They were then spun in a bench top centrifuge at 3000 revolutions per minute for 3 minutes. The determination of the serum cholesterol involved using MAPADA® Spectrophotometer (Shanghai Mapada, 2012) to determine the absorbance of the colour complex, which was used to calculate the concentration. Commercially prepared (Agappe Diagnostics India) total cholesterol kits and triglyceride SL kit were used for analysis of cholesterol and triglycerides, respectively whereas combi HDL/LDL kit was used for HDL and LDL analysis. The AIP of each participant was calculated as logarithm to base 10 of triglyceride and HDL-C ratio^[9] of the participants at 3 months and 6 months. Quality control of the analysis was achieved by using commercially prepared control kit for lipid profile on two randomly selected samples from each batch of the samples analyzed.

Data analysis was performed using SPSS version 21.0 (IBM, Armonk, NY, USA); Chi-square and *t*-test were calculated, $P < 0.05$ was statistically significant.

The study complied with institutional and national guideline on ethical standards in human studies. A written informed consent was obtained from all participants whereas ethical approval was obtained from the Ethical Review Committee of the University of Ilorin Teaching Hospital, Ilorin, Nigeria before commencement of the study (Approval number: ERC PAN/2016/02/2498).

RESULTS

A total of 225 women, comprising 111 COC-users and 114 nonCOC-users completed the study and were included in the analysis. Table 1 shows that the age range was 18–49 years for both groups; four (3.6%) COC-users and six (5.3%) nonCOC-users were teenagers. One (0.9%) COC-user and 19 (16.7%) nonCOC-users were nulliparous whereas 78 (70.3%) COC-users and 57 (50.0%) nonCOC-users were multiparous (para 2 to 4). Tertiary education predominates (87; 38.7%) followed by secondary education (80; 35.6%), most participants

Table 1: Socio-demographic variables of participants

Variable	COC-users <i>n</i> =111 (%)	Non-users <i>n</i> =114 (%)	Total <i>N</i> =225 (%)
Age Group (years)			
≤20	4 (3.6)	6 (5.3)	10 (4.4)
21-30	48 (43.2)	49 (43.0)	97 (43.1)
31-40	44 (39.6)	44 (38.6)	88 (39.1)
> 40	15 (13.5)	15 (13.2)	30 (13.3)
Mean±SD	31.88±6.87	32.89±8.70	
Range	20-49	17-49	
Parity			
0	1 (0.9)	19 (16.7)	20 (8.9)
1	4 (3.6)	7 (6.1)	11 (4.9)
2-4	78 (70.3)	57 (50.0)	135 (60.0)
≥5	28 (25.2)	31 (37.2)	59 (26.2)
Educational Status			
None	3 (2.7)	1 (0.9)	4 (1.8)
Primary	31 (27.9)	23 (20.2)	54 (24.0)
Secondary	48 (43.2)	32 (28.1)	80 (35.6)
Tertiary	29 (26.1)	58 (50.9)	87 (38.7)
Marital Status			
Single	1 (0.9)	21 (18.4)	22 (9.8)
Married	110 (99.1)	93 (81.6)	203 (90.2)
Occupation			
Housewives	0 (0.0)	3 (2.6)	3 (1.3)
Traders	53 (47.7)	51 (44.7)	104 (46.2)
Civil Servants	14 (12.6)	27 (23.7)	41 (18.2)
Students	4 (3.6)	18 (15.8)	22 (9.8)
Artisans	40 (36.0)	15 (13.2)	55 (24.4)

Table 2.1: Comparison of serial serum lipid profile, BMI, blood pressure, and atherogenic risks of COC-users and non-users at 0 month

Variable	Mean±SD	<i>t</i>	<i>P</i>
TC (mmolL ⁻¹)			
COC-users	3.67±1.57	0.072	0.943
Non-users	3.65±1.52		
TG (mmolL ⁻¹)			
COC-users	1.26±0.48	-1.890	0.060
Non-users	1.39±0.55		
HDL (mmolL ⁻¹)			
COC-users	1.45±0.44	1.030	0.304
Non-users	1.39±0.40		
LDL (mmolL ⁻¹)			
COC-users	2.38±0.87	-1.175	0.241
Non-users	2.51±0.82		
SBP (mmHg)			
COC-users	114.91±6.20	0.842	0.468
Non-users	114.87±7.12		
DBP (mmHg)			
COC-users	68.20±9.17	0.105	0.916
Non-users	68.07±9.11		
BMI (kgm ⁻²)			
COC-users	23.42±4.36	-2.929	0.004
Non-users	25.19±4.70		
Atherogenic Index			
COC-users	-0.07±0.22	-1.826	0.069
Non-users	-0.02±0.19		

t: Independent Samples T test, Atherogenic Index=log (TG/HDL)

Table 2.2: Comparison of serial serum lipid profile, BMI, blood pressure, and atherogenic risks of COC-users and non-users at 3 months

Variable	Mean±SD	<i>t</i>	<i>P</i>
TC (mmolL ⁻¹)			
COC-users	3.71±1.57	-0.216	0.829
Non-users	3.67±1.50		
TG (mmolL ⁻¹)			
COC-users	1.37±0.47	0.457	0.648
Non-users	1.40±0.56		
HDL (mmolL ⁻¹)			
COC-users	1.42±0.47	-0.326	0.745
Non-users	1.40±0.40		
LDL (mmolL ⁻¹)			
COC-users	2.31±0.77	2.106	0.036
Non-users	2.53±0.82		
SBP (mmHg)			
COC-users	114.68±8.72	0.928	0.354
Non-users	115.61±6.10		
DBP (mmHg)			
COC-users	74.13±7.56	-0.731	0.465
Non-users	73.42±6.89		
BMI (kgm ⁻²)			
COC-users	23.60±4.42	-2.684	0.008
Non-users	25.23±4.68		
Atherogenic Index			
COC-users	-0.20±0.22	-8.034	<0.001
Non-users	-0.02±0.19		

t: Independent Samples T test, Atherogenic Index=log (TG/HDL)

were traders (104; 46.2%) with comparative percentage in both groups (53[47.7%] vs. 51[44.7%]). COC use was commoner among Artisans (36.0% vs. 13.2%) whereas 110 (99.1%) COC-users and 93 (81.6%) nonCOC-users were married.

Tables 2.1-2.3 shows the pattern of changes observed in the cardiovascular parameters from baseline through 3 months and then 6 months

Table 3 shows a serial increase in the diastolic blood pressure for COC-users compared to an initial increase followed by a decrease for nonCOC-users over the study period but the difference was statistically significant among the COC-users ($P = 0.001$). There was a statistically significant increase in the mean LDL-C value among COC-users ($P = 0.038$) whereas nonCOC-users experienced an initial decrease followed by a rise, but the increase was not significant ($P = 0.427$). In addition, the AIP shows a statistically significant serial rise among COC-users ($P = 0.004$) compared to the nonCOC-users ($P = 1.000$) despite all participants in this study being in low-risk categories. The pattern of the serial levels of serum total cholesterol, triglyceride, HDL, systolic blood pressure, and BMI show some

Table 2.3: Comparison of serial serum lipid profile, BMI, blood pressure, and atherogenic risks of COC-users and non-users at 6 months

Variable	Mean±SD	<i>t</i>	<i>P</i>
TC (mmolL ⁻¹)			
COC-users	3.68±1.57	-0.040	0.968
Non-users	3.67±1.51		
TG (mmolL ⁻¹)			
COC-users	1.31±0.47	1.078	0.282
Non-users	1.39±0.54		
HDL (mmolL ⁻¹)			
COC-users	1.48±0.48	-1.551	0.122
Non-users	1.39±0.40		
LDL (mmolL ⁻¹)			
COC-users	2.24±0.77	2.709	0.007
Non-users	2.53±0.81		
SBP (mmHg)			
COC-users	112.52±9.19	3.025	0.003
Non-users	115.61±5.80		
DBP (mmHg)			
COC-users	71.17±7.48	2.127	0.035
Non-users	73.11±6.18		
BMI (kgm ⁻²)			
COC-users	23.51±4.40	-2.786	0.006
Non-users	25.20±4.69		
Atherogenic Risk			
COC-users	1.58±0.49	4.250	<0.001
Non-users	1.87±1.58		
Atherogenic Index			
COC-users	-0.06±0.22	-2.922	0.004
Non-users	-0.02±0.19		

t: Independent Samples T test, Atherogenic Index=log (TG/HDL)

variations that were not statistically significant among the COC-users and nonCOC-users.

DISCUSSION

A total of 225 participants comprising 111 COC-users and 114 nonCOC-users completed the study in a 6-month period. The participants were aged 18–49 years; majority were married with tertiary education. There was a statistically significant serial increase in the diastolic blood pressure and mean LDL-C for COC-users whereas nonCOC-users experienced an initial decrease followed by an increase, which was not significant. The AIP shows a statistically significant serial rise among COC-users compared to nonCOC-users. Although there were variations in the pattern of the serial levels of serum total cholesterol, triglyceride, HDL, systolic blood pressure and BMI, these were not statistically significant among the COC-users and nonCOC-users.

The age range of participants in the study is similar to previous reports of low contraceptive uptake among teenagers (4.4%) restating the poor contraceptive use by

Table 3: Comparison of serial serum lipid profile, BMI, blood pressure, and atherogenic risks of COC-users and non-users

Variable	0 month Mean±SD	3 months Mean±SD	6 months Mean±SD	ANOVA	P
TC (mmolL ⁻¹)					
COC-users	3.66±1.57	3.68±1.57	3.71±1.57	0.029	0.972
Non-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-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-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	2.58±0.82	2.69±0.81	3.312	0.038
Non-users	2.39±0.86	2.25±0.77	2.31±0.77	0.853	0.427
SBP (mmHg)					
COC-users	111.80±9.55	112.52±9.19	114.68±8.72	2.972	0.053
Non-users	115.53±11.68	115.61±5.80	115.61±6.10	0.004	0.996
DBP (mmHg)					
COC-users	68.20±9.17	71.17±7.48	74.13±7.56	14.846	0.001
Non-users	68.07±9.19	70.11±6.18	69.42±6.89	18.133	0.116
BMI (kgm ⁻²)					
COC-users	23.42±4.36	23.51±4.40	23.60±4.42	0.047	0.954
Non-users	25.19±4.70	25.20±4.69	25.23±4.68	0.002	0.998
AIP					
COC-users	-0.07±0.22	-0.06±0.23	-0.02±0.22	5.581	0.004
Non-users	-0.02±0.19	-0.02±0.20	-0.02±0.19	0.000	1.000

ANOVA: Analysis of Variance; TC=Total cholesterol; TG=Triglycerides; HDL=High Density Lipoprotein; LDL=Low Density Lipoprotein; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; BMI=Body mass index; Atherogenic index of plasma= $\log_{10}(\text{TG}/\text{HDL})$

teenagers in sub-Saharan Africa.^[10,11] The predominance of married women corroborated reports that contraception is embraced primarily within the context of marriage settings in sub-Sahara Africa.^[1,10,11] This remains a concern relative to the plight of the unmarried and their reproductive needs in sub-Saharan Africa. Tertiary and secondary education predominates in this study with only 1.8% having no formal education; as this study was conducted in an urban area (state capital). There was no significant change in BMI similar to a previous report.^[12,13] The observed significant increase in diastolic blood pressure among COC-users in this study may be attributable to previous reports of increased sodium and water retention^[14] or an increase in breakdown of bradykinin, which is a blood pressure lowering agent^[15] reported among COC-users. Wei *et al.*^[16] reported a cumulatively increasing risk of hypertension with the duration of COC use whereas Hyejin and Kisok found a significant dose-response trend between the duration of COC use and the prevalence of hypertension.^[17]

Research reports on the effects of COC on serum total cholesterol changes has varied between a slight but not significant rise,^[18,19] which is similar to this study to

significant increases reported by other researchers.^[13,20] This may be due to the variation in the methodology, as studies which included women with confounding variables (history of smoking, alcohol consumption, and obesity) reported the significant increases.^[13,20] In addition, it appears that the duration of exposure to COC may be relevant as another report indicated significant difference in serum total cholesterol between COC-users and nonCOC-users when the period of evaluation was extended to 12 months of use.^[21]

There was no statistically significant increase in the mean serum triglycerides in both COC-users and nonCOC-users over the 6-month period of this study. A similar study among reproductive age group women exposed to COC who had serial serum lipid profile at 3 months, 6 months and 12 months of use reported no statistically significant increase in triglycerides during the study period.^[21] However, other studies have reported significant findings^[11,22] in the serum lipid profile. There was a significant decrease in the serum HDL-C value among COC-users in a 4-year follow-up study^[21] whereas another study reported an increase in HDL-C level.^[23] In comparison, this study reported a

statistically significant rise in LDL-C level in COC-users and a decrease in the non-user group, which is similar to reports of up to 24 months follow-up evaluation of COC-users.^[21]

The association of COC use with changes in serum lipid profiles has attracted evaluation of the atherogenic risk of the users to determine the predisposition to arteriosclerosis, myocardial infarction and stroke.^[12,23] In this study, there was a statistically significant increase in atherogenic index in COC-users compared to nonCOC-users. This corroborates available evidence, which suggests that lipid ratios and indices are better predictors of atherogenic risks compared to individual lipid parameters.^[6,24,25] This then becomes a more relevant predictor when the total cholesterol and triglyceride levels may not have significantly changed but resulted in an increased atherogenic risk in the individuals as reported in this study. Thus, the AIP predicts the occurrence of cardiovascular risks even in the presence of seemingly normal individual lipid parameters. A similar finding was reported in 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.^[9]

CONCLUSION

The study recorded altered lipid profiles and increased short-term atherogenic risk for cardiovascular risk among users of COC over the study period. We suggest studies to evaluate effects of long-term use of COC on lipid profile and risk for cardiovascular diseases in our population. Meanwhile, COC-users should be offered serial lipid profile and atherogenic risk for cardiovascular diseases as monitoring modalities of their risk for these complications.

Strengths and limitations

The study adds to the limited available information in sub-Saharan Africa on the association between COC and cardiovascular disease risk whereas the serial measurement of parameters provides opportunity for a serial review. However, a longer period of evaluation would have been desirable.

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Conflicts of interest

There are no conflicts of interest.

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