OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article **Physiology**

Effect of Combined Oral Contraceptive on Lipid Profile Level and Cardiovascular Risk

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DOI: 10.36348/sjmps.2023.v09i05.006 | **Received:** 18.03.2023 | **Accepted:** 29.04.2023 | **Published:** 20.05.2023

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Abstract

Background: Combined oral contraceptive pills are an effective and widely used method for contraception. Combined oral contraceptives have been shown to alter lipid profiles among various population groups with different patterns of dyslipidemia and cardiovascular risk. ***Objectives:*** The study aimed at determining the lipid profile pattern and cardiovascular risk among combined oral contraceptive users. ***Methods:*** This cross-sectional analytical study was conducted in the Department of Physiology, Rajshahi Medical College, from January 2018 to December. 2018. The study group was made of 100 women. (mean age 24.1 ± 5 years), who took combined oral contraceptive pills (30 mg ethinyl estradiol, 150 mg Levonorgestrel) for a period ranging from 1-60 months, while 100 age-matched women with regular mentruation with no history of hormonal use within the last six months before the investigation were used as controls. Fasting blood samples from all study subjects were collected and analyzed for lipid profile [Total cholesterol (TC), High-Density Lipoprotein- cholesterol (HDL-c), Low-Density Lipoprotein- cholesterol (LDL-c) and Triglyceride (TG)] using standard calorimetric Techniques. ***Results:*** Combined oral contraceptive use was associated with increased levels of total cholesterol ($p \leq 0.001$), Low-density lipoprotein cholesterol ($p \leq 0.001$), triglyceride ($p \leq 0.001$), as well as decreased high-density lipoprotein cholesterol (HDL-c) ($p = .408$) in comparison to controls. ***Conclusion:*** Combined oral contraceptive use is associated with alteration in lipid profile, particularly increases total cholesterol triglyceride, LDL and decreased HDL-c. These changes carry a potential risk in the development of cardiovascular disease. Evaluating the most effective and safest contraceptive methods is important to avoid the potential risk of developing cardiovascular disease.

Keywords: Combined oral contraceptive pills, Dyslipidemia, Lipid profile.

INTRODUCTION

Population explosion is one of the important issues worldwide, specifically in a developing country like Bangladesh. Contraceptives are devices, techniques and methods used to prevent conception, thereby causing a population explosion. The contraception method is used worldwide for over-birth control or unwanted pregnancies [1]. To avoid unwanted pregnancy, users should take combined oral contraceptives that consist of the steroid hormone estrogens in combination with a progestogen [2].

The use of contraceptives is beneficial but also has some side effects too. The widespread use of hormonal contraceptives provides an opportunity for assessing the influence of estrogen and progesterone on various biochemical parameters analysis, including HDL-C, LDL-C, TC and TAG among users. Oral contraceptives are involved in many diseases, such as myocardial infarction and carcinogenicity [3, 4]. An increase in the risk for ischemic stroke in women taking oral contraceptives has been reported. Other studies showed that oral contraceptives also increase the risk of venous or arterial thromboembolism [5]. The extent of the effects of oral oestrogen on venous

thromboembolism has been speculated to be greater due to the first pass of this hormone through the liver, as there is evidence that plasma concentration of many coagulation and inflammation proteins synthesized by the liver are affected more intensely by oral oestrogens employed as hormonal replacement therapy [6].

Arterial disease is a collective term used for manifestations of cardiovascular disease in the coronary and systemic arteries. It is caused by atherosclerosis, a chronic low-grade inflammatory process of the arterial wall leading to the formation of atheromatous plaques, which eventually may either result in (Partial) occlusion of the affected artery (as in Myocardial infarction) or get ruptured disseminate and embolisedown stream arterial branches (as in ischemic stroke). Elevated blood levels of lipids are probably the most important biochemical risk factor for atherosclerosis. The concept of atherosclerosis as a process related mostly to lipid metabolism has now changed to view atherosclerosis as a chronic inflammatory response induced mainly by LDL deposition in the arterial wall. The present study attempt was designed to determine the effect of OCP on some biological parameter changes and its implication in many diseases.

METHODOLOGY

This cross-sectional analytical study was conducted in the Department of Physiology and Biochemistry. Rajshahi Medical College and Hospital between the period of January 2018 to December 2018. 100 healthy married women aged 20 – 45 years who took combined oral contraceptive pills were enrolled in the study group. The pills used in this study were sukhi containing 30 mg ethinyl estradiol and 150 mg levonorgestrel (second generation). Study subjects were selected by systemic sampling technique from Model family planning clinic, Gynae Outdoor, Rajshahi Medical College Hospital. 100 apparently healthy women who were non oral contraceptive user were included as a control group. After careful matching of age, BMI and lifestyle factors, the women (user and non-user) were classified into & groups according to their age. The user group was also categorized into 5 groups according to their duration of using these pills. A clear influence was noted on the fasting biochemical parameters of the lipid profile. The protocol of this study was approved by the Ethical Review Committee (ERC) of Rajshahi Medical College.

Collection, Processing and Analysis of Blood Samples:

All the subjects were free from diabetes, cardiac vascular disease and other systemic diseases. Before the recruitment aim, the benefit and procedures of the study were explained and informed written consent from each subject was taken. Physical examinations of all subjects were done. BMI was calculated by dividing the weight in kg with height in M2 at the first visit Fasting blood sample was collected after 8 hours of fasting by vene puncture taking all aseptic precautions. 6 ml of collected blood was immediately transferred into a sterile test tube without anticoagulant. Then serum samples were obtained by centrifugation at 3000 rpm for 20 minutes. The separated serum was stored at 2-50 c for over 24 hours. Serum levels of total cholesterol, Triglyceride and HDL were estimated by enzymatic methods using semi-automated analysis, and LDL was calculated using the Friedewaled equation (LDL = cholesterol – (TG ÷ 5 + HDL).

Data Processing and Statistical Analysis:

Statistical Package for Social Science (SPSS) Computer software was used for data analysis. Results of the analysis were expressed as mean ± standard deviation and frequency with percentage. The statistical analysis was done by student's t-test, chi-square test and ANOVA t-test. A probability value less than 0.05 was considered a significant value.

RESULT

A total number of 200 apparently healthy people (100 ocp users and 100 non-ocp users) were selected in this study. Among the study subjects, mean (± SD) age (years), weight (Kg), height (cm) and body mass index [BMI (kg/m)] of the ocp users were 33.02 ± 8.00 years, 61.55 ± 8.5 kg, 158.46 ± 6.4 cm and 24.00 ± 3.61 kg / m and that of non-ocp users were 33.07 ± 7.96 years 59.78 ± 8.54 kg, 157.46 ± 4.71 cm and 24.25 ± 3.63 kg / m. There was no statistically significant difference between the two groups regarding age (p > 0.5). Regarding BMI, out of 100 users, 38 (38.0%) had normal BMI, 30(52.6%) were overweight, and 32 (74.4%) were obese. On the other hand, out of non-users, women 62(51.2%) had normal BMI, 27 (47.4%) were overweight, and 11 (50. 0%) were obese (Table-1)

Table- 1 General characteristic of the oral contraceptive users and non-users (n-200)

Parameters	OCP users	Non-OCP users	*P*-value
Age (years)	33.02 ± 8.00	33.07 ± 7.96	0.965
Weight (kg)	61.55 ± 8.54	59.78 ± 8.54	0.145
Height (meters)	158.45 ± 6.47	157.00 ± 4.71	0.070
Body mass index	24.40 ± 3.61	24.25 ± 3.63	0.774

Table 2 shows the distribution of cardiovascular parameters among the study groups. It was observed that the mean (± SD) pulse rate of ocp users (78.23 ± 3.65 beats/min) was comparatively higher than that of non-ocp users (77.41 ± 5.03 beats/min). The mean (± SD) systolic blood pressure of

the ocp users was significantly higher than non-ocp users (121.65 ± 10.87 mm Hg versus 113.45 ± 11.36 mm Hg, p=0.001), while mean (± SD) diastolic blood pressure of the ocp users was significantly higher than non-ocp users (79.65 ± 8.94 mm Hg versus 74.75 ± 7.85 mm Hg, p = 0.001).

Table-2 Distribution of cardiovascular parameters of the study groups.

Variable	OCP users ± SD	Non-OCP users ± SD	*P*-value
Pulse (beats/min)	78.23 ± 3.65	77.41 ± 5.03	0.482
Systolic BP (mmHg)	121.65 ± 10.87	113.45 ± 11.36	<0.001s
Diastolic BP (mmHg)	79.65 ± 8.94	74.15 ± 7.85	<0.001s

Data analysis revealed that mean (± SD) serum cholesterol (TC), serum triglyceride (TG) and serum low-density lipoprotein cholesterol (LDL-C) levels were significantly higher among ocp users compared to non ocp users (236.3 ± 26.57 mg/dl, 166.35 ± 44.25 mg/ dl, 163.43=26.10mg/dl versus 199.43 ± 41.65 mg/dl 126.24 ± 31 mg/dl 135.46 ± 39.07 mg/dl $p<0.001$). On the other hand ocp users had significantly lower level of mean serum high-density lipoprotein cholesterol (HDL-C) than non-users (41.80 ± 3.33 mg/dl versus 42.18 ± 3.14 mg/dl , $p> 0.408$) Table – 3

Table – 3: Distribution of the fasting lipid profile among study groups(N=200)

Lipid profile (mg/dL)	OCP users (n=100)	Non-users	*P*-value
Total cholesterol	236.3 ± 26.57	199.43 ± 41.65	<0.001s
S. triglyceride	166.38 ± 44.25	126.24 ± 31.24	<0.001s
S. LDL-C	163.43 ± 26.10	135.46 ± 39.07	<0.001s
S. HDL-C	41.80 ± 33	42.18 ± 3.14	0.408 NS

The test significance was calculated using unpaired t-test, s= significant Ocp users women were categorized into five groups according to their duration of use, i-e 1- 12 months, 13-24 months, 25-36 months. Significant increases in total cholesterol LDL-C and triglycerides were noted in combined oral contraceptive users of > 1 year duration. However, in ocp users, S. HDL-C were not significantly increasing with the duration of use ($P > 0.632$)

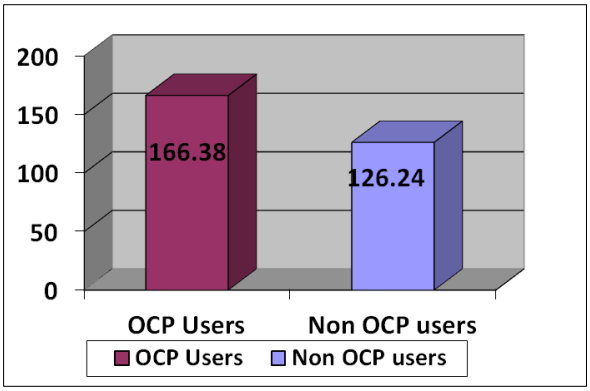

Figure-I: Fasting serum cholesterol concentration between oral contraceptive users and non-users

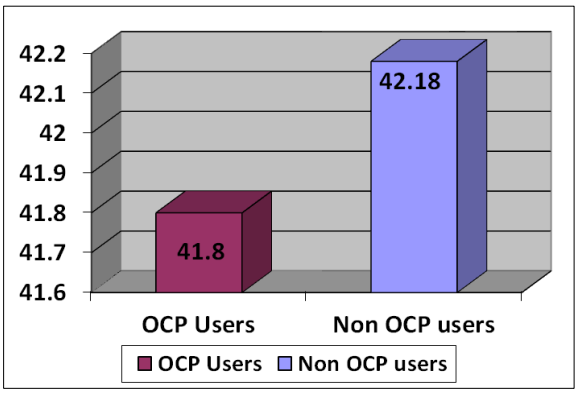

Figure-II: Fasting serum triglycerides concentration between oral contraceptive users and non-users

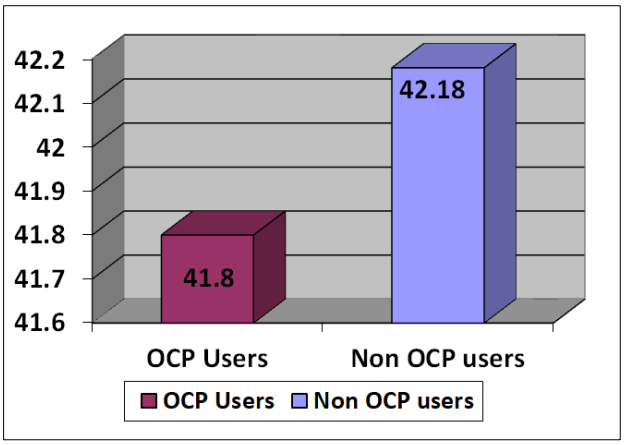

Figure-III: Fasting serum HDL-C concentration between oral contraceptive users and non-users

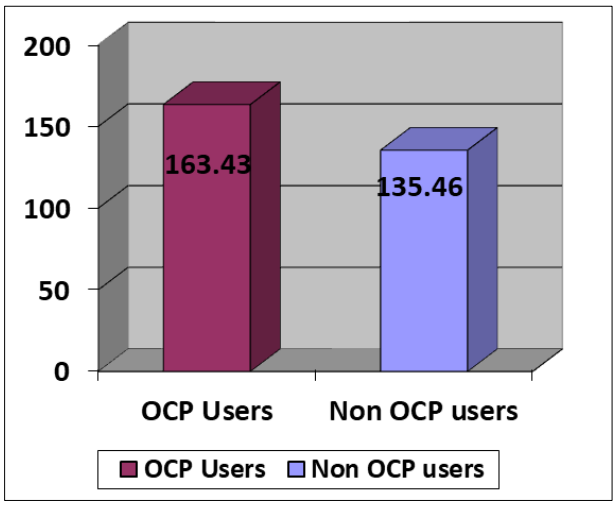

Figure IV: Fasting serum LDL-C concentration between oral contraceptive users and non-users

DISCUSSION

Combined oral contraceptives (COCs) are widely used as an effective and reliable method for preventing conception and for other important non-contraceptive reasons. The evidence of combined oral contraceptives (COCs) impact on some biochemical markers related to cardiovascular disease, diabetes, systemic high blood pressure, inflammatory disease, stroke, cancer etc., is inconclusive, contradictory and limited by methodological inconsistencies. So this study aims to investigate the possibility of an association between the OCP and biomarker levels alteration and identify, collate and critically appraise studies accessing the influence of hormonal contraceptives on these disease's spectrum.

In our study, the serum cholesterol level was significantly higher in oral contraceptive users compared to non-oral contraceptive users. This finding is compatible with Emokpae MA *et al.* [7], Wynn *et al.* [8], Hassan EE *et al.* [9]. There was an increase in total cholesterol due to the increase in β-lipoprotein cholesterol. The elevation of serum cholesterol level may be due to the effect of estrogen as it increases liver lipogenesis. Serum total cholesterol level is a major indicator of the risk of coronary heart disease. For every 1% increase in the total serum cholesterol level, a 2% increase in the incidence of coronary heart disease is found [10].

On the other hand, J.A. Abdel. Barry [11], and Esrobar-Moreal H [12] have observed that serum total cholesterol level was not significantly different between the groups nor changed with age or length of contraceptive use. A possible explanation of these different results could be the regulation of serum cholesterol, which is affected by its rate of synthesis, LDL receptor activity, or its ability to be converted into bile acid. Therefore, using low-dose combined oral contraceptives might have a negligible effect on cholesterol homeostasis. The use of oral contraceptive pills may increase the risk of cardiovascular disease by increasing the levels of triglycerides [13, 14, 9,11].

This is mainly due to the effect of estrogen as it increases liver lipogenesis, which results in elevated levels of triglycerides (TG) rather than decreased clearance. It has been suggested that the TG changes are due to the induction by estrogens of hepatic microsomal enzymes that limits the rate of TG

synthesis. The status of elevated serum triglyceride level may be an independent predictor of coronary heart disease as ethinyl estradiol increases hepatic secretion of triglyceride-rich lipoprotein [15].

In this study, the effects of second-generation COCs on lipid metabolism were examined. We have found HDL-C levels decreased in the levonorgestrel group, which can be due to second-generation progestins with androgenic activity and dominant progestin can lead to adverse effects and make the lipid profile unfavourable, which is one of the key metabolic changes that can be linked to an increase in the incidence and severity of cardiovascular disease, particularly ischemic heart disease.

This study has found significantly increased LDL-cholesterol levels with the duration of oral contraceptive use. This finding is compatible with [16, 17, 18, 19, 1]. In the liver, triglyceride synthesis is enhanced by estrogen and inhibited by androgen, and these triglycerides are partly brought into circulation as low-density lipoproteins. A high level of low-density lipoproteins is an independent risk factor for coronary heart disease in both men and women [15]. The excessive influx of LDL cholesterol by way of the "Scavenger pathway" may result in the deposition of cholesterol in arterial walls and atheroma formation.

One of the strengths of this study is that we have included only healthy adult married women in our study after careful matching of age, BMI and lifestyle factors. This study suggests that oral contraceptive users clearly show OCP's marked effects on serum CRP and lipid profiles. High level of serum lipid and CRP invites many problems to contraceptive users, i.e. cardiovascular risk by increased cholesterol levels. One of the weaknesses of our study is that the long-term effects were not taken into account in the present study. The full impact of oral contraceptives on cardiovascular risk factors may not be fully concluded from the short duration of studies done so far. Finally, further data are necessary for possible quantitative interactions between OC use, other coronary risk factors and MI.

CONCLUSION

Combined oral contraceptives have been shown to alter lipid profile among oral contraceptive users in Rajshahi city with different patterns of dyslipidemia and cardiovascular risk.

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