Evaluation the Relationship between Oral Contraceptives Containing Drospirenone with Dyslipidemia and Risk of Cardiovascular Diseases among Women in Al-kut City

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Abstract

Chronic and prolong use of oral contraceptives (OCs) may lead to appearance of undesirable effects in women who used these drugs. There are many types of contraceptives, some contain estrogen and the other contain progesterone, or combination of them in the same drug. This work was performed in a population of adult females to study the relationship between the chronic use of OCs with dyslipidemia and the threat of cardiac diseases. A total 163 volunteers were participated in this study, and, their aged between 21-42 years old. In addition, all women were free of heart disease, dyslipidemia and any hormonal disturbance according to their health records. They were categorized into three differnt groups, the control group included 52 unmarried women and does not use any OCs, group A: included 57 women took OCs (combination pill estrogen and progestin) for less than 6 months, and group B contained 54 women used OCs for more than one year. We meassued lipid profile, and blood indices of cardiovascular disease, like Creatine Kinase-MB (CK-MB), insulin, Lactate Dehydrogenase (LDH) albumin, leptin and HbA1c test. In addition, we determined the coronary risk index, atherogenic Coefficient, and an atherogenic index . Our results recorded a significant increase in total cholesterol, LDL, coronary risk index (TC/HDL), LDH and HbA1c in group2 compared to compared to control group. Furthermore, our data demonstrated no clear differences in Triglyceride, leptin hormone, TG, HDL, insulin, albumin and CK-MB in group2 compared to control. Moreover, the data indicated a significant elevation in the concentration of leptin hormone, LDH, HbA1c, TC, TG, LDL, coronary risk index , atherogenic Coefficient and Atherogenic index, and significant decline in HDL and albumin in group B compared with control group. Therefore, we concluded that oral contraceptive could deter the lipid profile status and some enzyme related to the cardiovascular system. These alterations convey a possible risk for the development of cardiac diseases. Routine screeing of lipid tests would be measured in women used OCs for long periods to avoid any potential risk of cardiac diseases.

Key words: *oral contraceptive, lipid profile, cardiovascular disease, leptin, CK-MB.*

Introduction

Oral contraceptives (OCs) are female exogenous hormones that are used either to control birth, regulate pregnancy and to treat other medical conditions, such as poly cystic ovaries, menopause, hyperandrogenism and menstrual cramps [(1,2)]. Most of these OCs containing one or both synthetic forms of female hormones (estrogen and progesterone), which are naturally synthesized by a woman's body [(3)]. These combined OCs pills act by inhibiting the roles of follicle stimulating hormone (FSH) and luteinizing hormone (LH), thus decrease the metabolic action of ovary, subsequently inhibiting the ovulation [(4)]. The prolonged use of oral contraceptives induce different side effects with women, which are

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associated with cardiovascular disease, diabetes mellitus and growth hormone disturbance [5, 6]. Several studies revealed that hormonal contraceptive increase LDL and TG by increasing the synthesis of apolipoprotein B-100 [7]. In addition, oral and hormonal contraceptives may also increase the chance to develop different cancers (breast or liver), cardiovascular diseases and serious blood diseases [8]. Lipid parameters are highly associated with CVD like HDL-C or Total Cholesterol / HDL-C and consider as suitable predictors to monitor and determine who is in risk for the CVD [8].

The main goal of current project to study the off-target effect for prolonged use of combined OCs in lipid profile status, leptin and insulin, and some predictors related with heart damage in two groups of volunteers, after 6 months and one year of oral contraceptive use.

Material and Methods

Study subjects and design

This study included 163 adult women who volunteered for this study after their consent. Their ages were between 21 and 42 years. The women who have heart disease, liver disease, dyslipidemia, diabetes mellitus, and any hormonal disturbance, according to their health reports were excluded from study. This study performed according to approved protocol by the Ethical Committee in the Institute of Endocrinology and an informed printed consent was obtained from each woman. The volunteers were classified into three main groups. The control group involved 52 adult unmarried women who did not use oral contraceptives. The second group A included 57 adult married women who used combined oral contraceptives contain containing Drospirenone, Ethinyl Estradio for 6 months only. The third group B included 54 women used OCs pills for one year. About five ml of blood was collect to measure all theses tests.

Biochemical analysis

The Total cholesterol (TC), High density lipoprotein cholesterol (HDL-C), Low density lipoprotein cholesterol (LDL-C), Triglycerides (TG), Very low density lipoprotein cholesterol VLDL-C, Lactate Dehydrogenase (LDH), CK=MB: Creatine kinase isoenzyme of heart muscle ,and albumin were determined in serum by using automated chemical clinical analyzer from FUJIFILM, Japan. While, leptin and insulin hormones were measured by using standard leptin and insulin ELISA kits. (Elabscience, china). Quantitative determination of glycated hemoglobin (HbA1c) was measured in EDTA tube contained blood samples by using NycoCard reader II, Norway. Atherogenic indices estimated according to: Coronary Risk Index = TC/HDL-C [9]. Atherogenic Coefficient =TC HDL-C/HDL-C [10], and Atherogenic Index = Log (TG/HDL-C) [11].

Statistical Analysis

The one-way analysis of variance (ANOVA) was applied to check the mean differences of all three groups. The results were presented as mean ± standard deviation to define the differences among group at $*P<0.05$, $**P<0.01$, and $***P<0.001$ levels

Results

In order to study the association between oral contraceptivein taking and dyslipidemia in women, we measured the levels of TC, TG, LDL-V, VLDL and HDL-C. Our results demonstrated a significant elevation in TC, TG, (LDL-C and VLDL data not shown), and a significant decline ($P<0.01$) of HDL-C level in women (group B) that used oral contraceptive pills for one year compared with the control group. Wheases, the data from group (A) did not show any significant difference in TG, and HDL-C when compared to the control as shown **Figure 1. A-C**.

Moreover, consistent with the lipid profile status, our data demonstrated a sigficant increase in coronary risk index and atherogenic coefficient and lactate dehydrogenase values in women were used combined oral contraceptives for 6 and 12 months only as shown in **Figure 2. A-C**. Furthermore, our results showed no significant alterations in the level of creatine kinase-MB (CK-MB) (data not shown) in women used OCs for 6 and 12 months compared to the control groups.

Furthermore, the data demonstrated no significant differences in mean value of insulin and a significant differences in glycated hemoglobin (HbA1c) in women used oral contraceptive for 6 and 12 months respectively compared to the control group **.**In addition, our results exhibited an important differences in leptin, and albumin

concentrations in group B only, and a clear differences among group A and B as (data not shown). Collectively , the results, confirm a significant difference in some criteria when comparing the results of women who used oral contraceptives for one year compared to those used for 6 months.

Discussion

Contraceptives have been used to prevent ovulation and prevent sperm penetration into the ovum ([12]. The data from our study demonstrated that OCs caused a clear alteration in lipid profile and cause dyslipidemia especially when using contraceptives for very long periods (Figure1). Our results are similar with several other studies that demonstrated the combined OCs correlated with disturbance of lipid profile subsequently induce dyslipidemia [13] .

Next, our data indicated there were a significant elevation in serum TC, LDL, TG and decrease of HDL in women used combined OCs as compared with control. Thus, Chonic use of the control birth pills containing estrogen may stimulate liver lipogenesis, which in turn increase of TG and LDL concentration [14,15]. In addition, use of estrogens is associated with stimulating hepatic synthesis of triglycerides and impair of hepatic lipase expression, resulting in increased serum levels of triglycerides [16].

Moreover, OCs containing progestin decreased HDL concentration by increase the activity of lipase enzyme in liver ,which accelerated the elimination of HDL [17]. Despite of the benefit of the estrogen in the protection of endothelial, oral combined contraceptives that contain progesterone, could decrease the HDL-C's concentration in plasma [18]. In addition, increase the concertation of VLDL in women used OCs could be ascribed to the estrogen hormone's effect, that can enhance the secretion of VLDL in the liver [19].

The results of the present study also demonstrated that oral contraceptive increase the cardiovascular risk indices (TC/HDLC) and (TC/HDLC) as shown in **Figure 2**. Many report revealed that increase in the concentrations of TC LDL-C, and the reduction of HDL-C enhance cardiac diseases biomarkers ,which are the major risk factors for cardiovascular diseases [20]. One study clarified that increase the lipid profile in women used oral contraceptive lead to increased risk of coronary arterial disease and atherogenesis [21].

Our data also showed a sigficant increase in the concentration of LDH and this was similar to the onother study that revealed that oral contraceptive caused significant increase of blood serum enzyme including LDH and exert DNA damage [22]. Therfreroe, Lactate dehydrogenase enzyme (LDH) could be the most important indicator to diagnosis the myocardial infarction or heart attack.

Next, our results exhibited a significant increase in glycated hemoglobin in oral contraceptives users in comparison to non-user women. HbA1c produces of non-enzymatic glycolysis, which is re-measured every 3 months reflecting the average glucose in previous weeks [23]. in addition, Our study showed normal fasting insulin level, and increased HbA1c that are indicative of glucose and insulin resistance. Also, HbA1c was associated, excessive triglycerides, decline of HDL-cholesterol and directly related to the occurrence of atherosclerosis [24].

Serum albumin concentration decreased significantly after one year of oral contraceptive use compared to the control group. Also, pills containing estrogen induce glomerular hyperfilteration and increase albumin excretion, because of greater tubular load of albumin that lead to decrease of serum albumin concentration [25].

In addition, the results from our study demonstrated that combined OCs caused significant increase of leptin hormone level as compared with non-users, Leptin is produced mainly from tissue and is equivalent to fat content inside the body [26]. Our interpretation of the high level of leptin in women who have used OCs for beyond than a year may be due to their weight gain, and it is known that the concentration of leptin is associated with body mass index (BMI [27,28]. Our results demonstrated no major alterations in the level of CK-MB among all groups studied. These results is similar with pervious study that illustrated there were no differences in CK-MB in women used oral contraceptive during percutaneous coronary intervention [29,30].

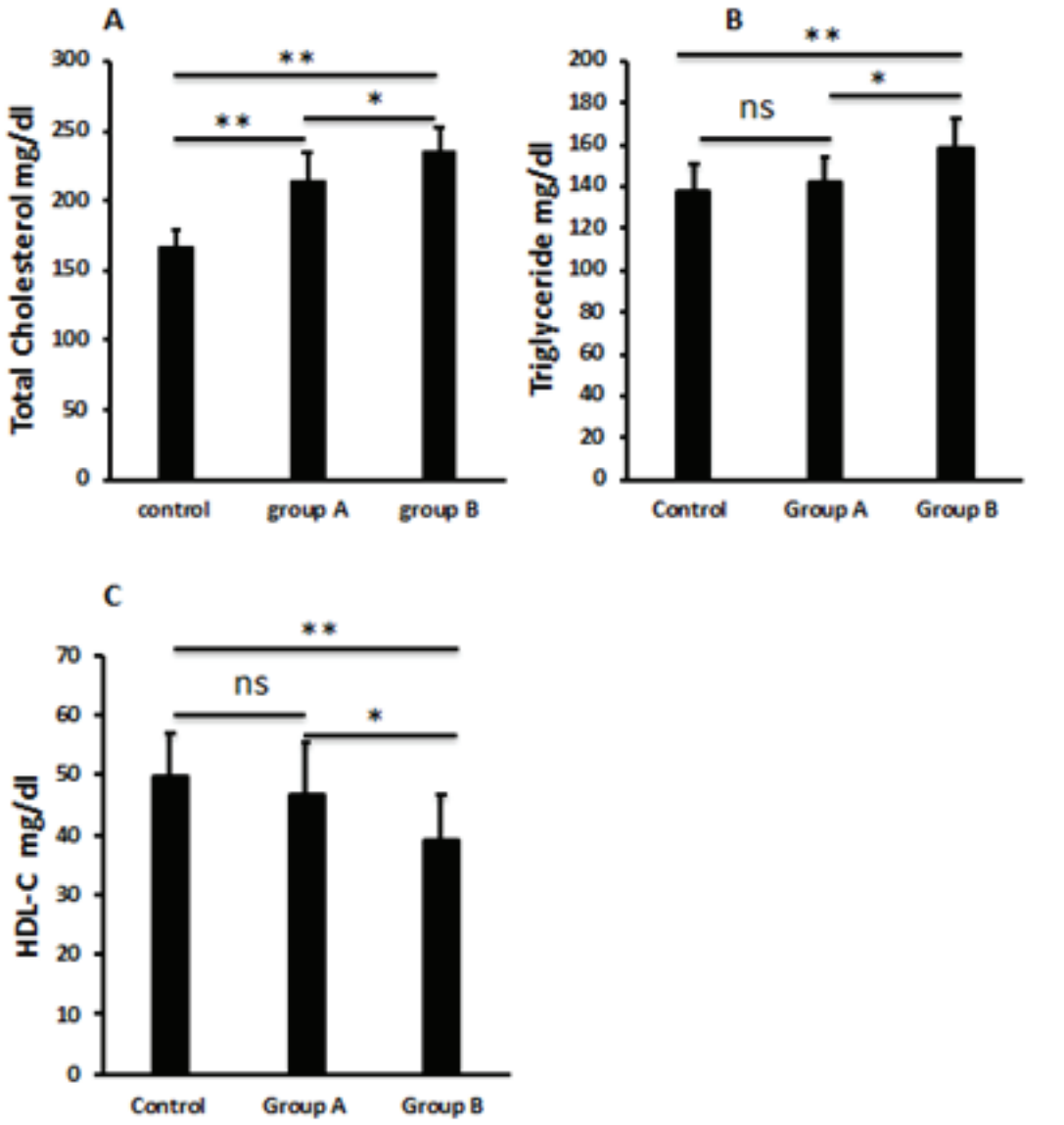

Figure1. Usages of oral contraceptives enhance dyslipidemia in women. A-C represent the level of TC, TG, and HDL-C . The differences in lipid profile concentrations between the control group and two different groups (A and B) using oral contraceptives for 6 and one year respectively. Data represent mean ± SD. P value determined was (ANOVA). *P<0.05 ; **P<0.01; ***P<0.001, and ns as non-significant.

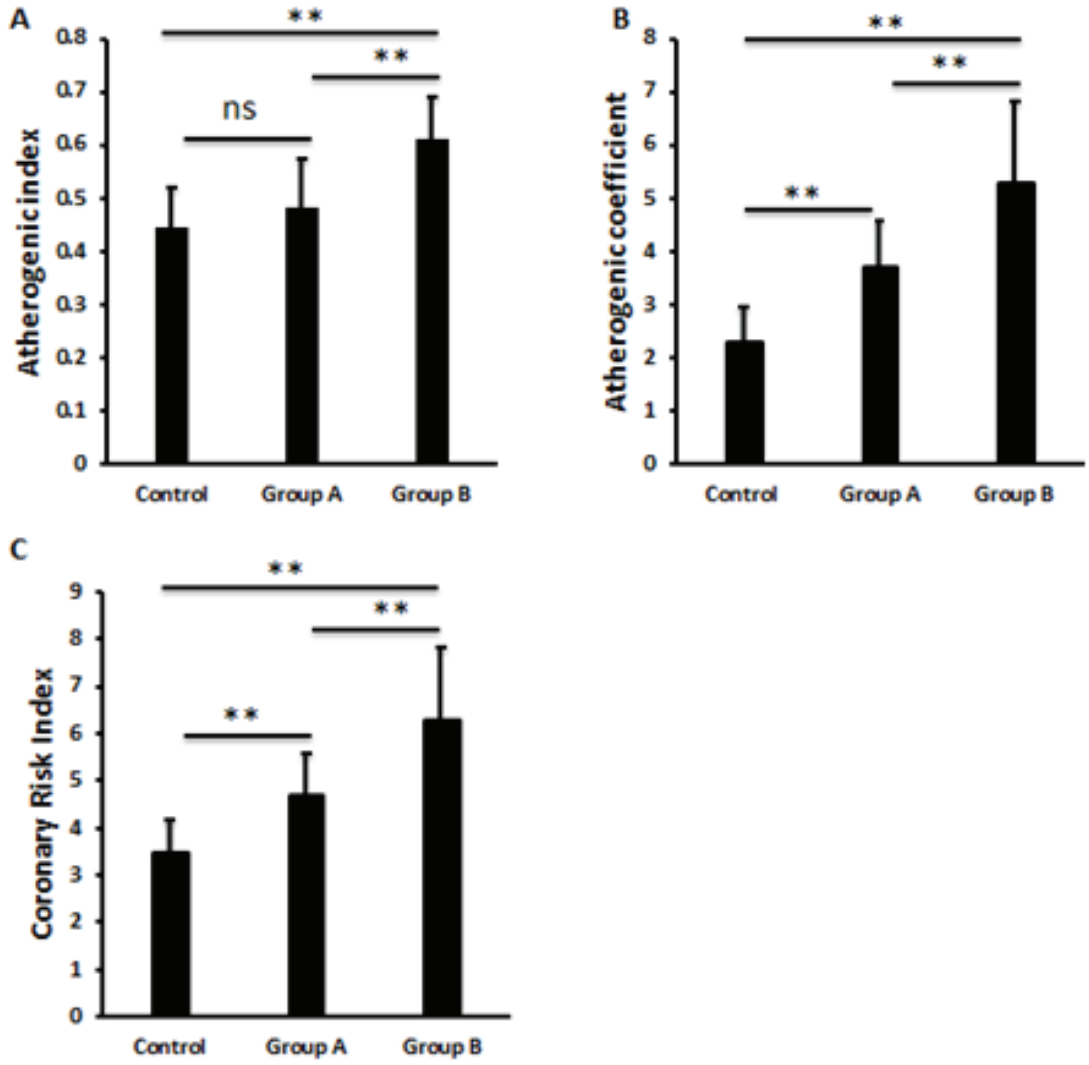

Figure2. Oral Contraceptives promote atherogenic indices and coronary risk index. A-C represent atherogenic indices , atherogenic Coefficient , and coronary risk index,. The differences in atherogenic indices and coronary risk index between the control group and two different groups (A and B) using oral contraceptives for 6 and one year respectively. Data represent mean ± SD. P value determined was (ANOVA). *P<0.05 ; **P<0.01; ***P<0.001, and ns as non-significant.

In conclusions , we have revealed that OCs could deter the lipid profile status and some enzyme related to the cardiovascular system. Therefore, These changes reflect a possible risk fators to induce the incidence of cardiac diseases. Thus, a routine screeing of lipid profiles should be evulated for all women using the OCs for long periods in order to avoid any potential risk of cardiovascular diseases.

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both MOH and MOHSER in Iraq

Conflict of Interest: Non

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