The Effect of Low-dose Combined Oral Contraceptive Pills on Brachial Artery Endothelial Function and Common Carotid Artery Intima–Media Thickness

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Background: Combined oral contraceptives (COCs) are considered for their thrombogenicity and the risk of premature atherosclerosis and the stroke caused by them. The aim of this study was to evaluate the relationship between chronic use of low-dose COCs (ethinyl estradiol 30 mcg + levonorgestrel 150 mcg) and endothelial dysfunction and intima–media thickness. *Methods:* In a cross-sectional study, in 2011-2012, 60 healthy premenopausal women (30 cases of COC consumers and 30 controls as nonconsumers), aged between 25 and 45 years, participated in this study. They were current users for at least a 3-year period. Brachial artery flow-mediated dilatation (FMD) and common carotid artery intima–media thickness (CCA-IMT) were measured for the patients. *Results:* The mean duration of COC consumption was 54.03 ± 27.27 months in the case group. There was a significant FMD% difference between 2 groups of cases and controls: 11 ± 3.53 versus 15.80 ± 9.22 ($P = .01$). In addition, a significant mean CCA-IMT thickness difference was detected: .53 ± .07 versus .44 ± .08 ($P = .00$). However, after multiple regression analysis and adjusting for body mass index (BMI), in COC users, no significant association between COC consumption duration and FMD% and mean CCA-IMT was observed. *Conclusions:* Prolonged used of low-dose COCs may cause changes in both endothelial function (measured by FMD%) and endothelial structure (measured by CCA-IMT). There was a nonsignificant inverse relationship between the duration of COC ingestion and FMD% and a nonsignificant positive relationship with CCA-IMT. Our results are in favor of early atherosclerotic changes in prolonged users of COCs. **Key Words:** Contraceptives—oral—atherosclerosis—carotid intima–media thickness—endothelial function—flow-mediated dilatation—thrombogenesis.

Introduction

Combined oral contraceptives (COCs), introduced over 6 decades ago, are now used by hundreds of millions of woman universally and considered the most popular and effective method of contraception.[1] The hazard of atherosclerotic and thromboembolic complications with the ingestion of hormonal contraceptives is an imperative concern and is relevant for counseling women about their options for contraception.[2]

Thrombogenicity of oral contraceptives particularly estrogen compounds may be attributed to a direct influence of estrogens on the vascular wall and changes in factors that stimulate endothelial dysfunction, and also, changes in coagulation factors.[3]

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It is significant that there is a long latent phase of atherosclerotic progression before symptoms are manifested, and as a consequence, determining arterial function previous to the development of a measurable atherosclerotic plaque in angiography or ultrasonography could have beneficial results for prevention and risk factor classification. Several methods to obtain measures of arterial function and structure have been developed including measurement of endothelial function and arterial compliance (measuring function) and common carotid artery intima–media thickness (CCA-IMT) (measuring structure).

Flow-mediated dilatation (FMD) is a noninvasive method, measured by changes in brachial artery diameter in response to arterial flow changes provoked by a reactive hyperemia.[4] Several clinical and experimental studies propose that endothelial dysfunction could incite atherosclerosis, and resultantly, effective treatment of risk factors may recover endothelial dysfunction.

CCA-IMT, measured by B-mode ultrasound, has been extensively measured for over 2 decades as a substitute for atherosclerosis, and its increment has been linked to increased risk of cerebrovascular and cardiovascular disorders in future and, also, has been suggested as a valuable quantitative indicator of atherosclerosis in monitoring disease progression.[5-7] In healthy adults, CCA-IMT ranges between .25 and 1.5 mm, and values higher than 1.0 mm are regularly considered as abnormal.[7]

Considering the effects of COCs on thrombogenicity, the risk of atherosclerosis and the stroke caused by them, the aim of this study was to evaluate the relationship between chronic use of COCs and endothelial function and intima–media thickness. To study, FMD of brachial artery and IMT of CCA were evaluated by 2-dimensional ultrasonography among healthy young women using low-dose COCs for a significant amount of time (ethinyl estradiol 30 mcg + levonorgestrel 150 mcg) in comparison with control group.

Materials and Methods

In a cross-sectional study, conducted between June 2011 and December 2012, 60 healthy premenopausal women, aged between 25 and 45 years, participated in this study.

To see a 2.0% change in FMD with a power of 80% between 2 groups and standard deviation of 3 (based on the study by Lizarelli et al[8]), 30 subjects were required per group.

In case group, 30 participants were included. The women were current users of a monophasic low-dose COCs (ethinyl estradiol 30 mcg + levonorgestrel 150 mcg) for at least 3 years.

As control group, 30 healthy, age-matched, regularly menstruating women (menstrual cycles between 21 and 35 days with an individual variation of ±3 days) who were not taking any medications and were not using hormonal contraception or maximally taking hormonal contraception for less than 6 months, but not during recent 12 months, were recruited from Shariati hospital staff. In addition, all subjects had normal laboratory tests for blood cholesterol and fasting blood glucose. For detecting hyperlipidemia and diabetes mellitus, providing that the patient had laboratory tests within last 6 months, we relied on the results, but else, we ordered new tests.

Exclusion criteria were use of other routes of hormonal contraception such as hormonal patches, smoking, cardiovascular disease (ischemic heart disease, atrial fibrillation, heart block), hypertension, diabetes mellitus, hypercholesterolemia, alcoholic or drug addiction, having a body mass index (BMI) of 30 kg/m^2 or more, pregnancy, lactation, having a rheumatologic disease, evidences of hyperandrogenism or polycystic ovarian syndrome, menopausal status, and history of oophorectomy.

The study was approved by the ethical committee of the Tehran University of Medical Sciences and the patients signed informed consents before inclusion.

FMD Technique

All examinations were performed after a 15-minute rest in the supine position and in a temperature-controlled room (20°C-23°C) at the Shariati Hospital neurosonology room between 7:00 and 12:00 AM. Initially, systolic blood pressure (SBP) and diastolic blood pressure were measured in the left upper arm using a standard mercury sphygmomanometer after 15 minutes rest in supine position. Afterward, ultrasound examination was carried out using the 5.0-12.0 MHz linear probe of the SonoAce X8 Cardiovascular Ultrasound System (manufacturer in Korea). All arterial pressure measurements and ultrasound exams were performed by the same expert individual in neurosonology who was unaware of the clinical characteristics of the subjects.

Brachial artery FMD in right side was imaged approximately 5-10 cm proximal to the antecubital fossa on the longitudinal plane. Subjects were positioned supine with their right arm supported at heart level at an 80°-90° angle from their chest. A segment with clear near and far intimal interfaces between the lumen and vessel wall was selected. The best quality end-diastolic frame was selected and measurements of the brachial artery diameter from the intima of the far wall to the intima of the near wall were taken (B1). A 5-minute inflation of a pneumatic cuff (50 mm Hg > SBP of the patient) placed around the forearm immediately below the medial epicondyle, followed by a rapid deflation using a standard sphygmomanometer, was performed to induce vasodilation. Sixty seconds after cuff deflation, another scan from the brachial artery was evaluated. New values for the brachial artery diameter (B2) were recorded as before and FMD was calculated as FMD = (B2 − B1)/B1. Change in diameter caused by FMD was calculated as