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Original Article

Does Oral Contraceptive Use Increase the Risk of Future Cardiovascular Events? Results from the Isfahan Cohort Study

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ABSTRACT

Background: Oral contraceptives (OCP) have been previously reported to be a risk factor for venous thromboembolism and pulmonary embolism. However, their effects on cardiovascular disease (CVD) and stroke are still controversial. In this study, we aimed to clarify whether there is an increased risk of future CVD in women with a history of OCP use.

Methods: This cohort study was conducted between 2001 and 2011 in a group of women ≥35 years of age. The participants were divided into 2 groups: with a history of OCP use and without a history of OCP use. A questionnaire containing demographic data, history of OCP use, and other risk factors of CVD was completed by the participants. Body mass index, hypertension, and blood biochemistry markers (including fasting plasma glucose, total cholesterol, triglyceride, high-density lipoprotein, and low-density lipoprotein) were determined at the beginning of the study. Stroke, myocardial infarction (MI), sudden cardiac death, and total CVD were assessed during the study. Finally, all the gathered data were analyzed using SPSS, version 15. The chi-square test and the independent *t*-test were used to compare the groups. The Cox regression model was utilized to evaluate the association between CVD event and OCP use.

Results: Out of 3,254 women aged ≥35 years in this study, totally 1,391 (42.7%) individuals had a history of OCP use and 1,863 (57.3%) women had no history of OCP use. There were differences between the groups (OCP users and nonusers) in terms of age (P≤0.001), hypertension (P≤0.001), and waist circumference (P=0.009), whereas there were no differences as regards diabetes mellitus (P=0.353), fasting plasma glucose (P=0.177), and dyslipidemia (P=0.368). None of the events, comprising MI (HR: 0.514 [0.288–0.919]), stroke (HR: 0.803 [0.501–1.287]), sudden cardiac death (HR: 0.39 [0.156–0.97]), and CVD events (HR: 0.802 [0.642–1.003]), showed a significant relationship between the event and OCP use in the comparison between the OCP users and nonusers. Even after adjusting for the demographic data and risk factors, the same results were obtained.

Conclusions: In contrast to previous studies, our data revealed no increased risk of future stroke and CVD events, consisting of MI, stroke, and sudden cardiac death, due to a history of OCP use. A historyof OCP use for a longer period of time compared with a shorter period of time showed no difference concerning the prevalence of future CVD. ***(Iranian Heart Journal 2016; 17(1): 29-37)***

Keywords: Oral contraceptives ■ Myocardial infarction ■ Stroke■ sudden cardiac death ■ Cardiovascular disease

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Cardiovascular disease (CVD) is the most important cause of morbidity and mortality in both developed and developing countries, with a rising pattern of occurrence.[1] Over 17 million people die annually of CVD-related disorders, with the bulk of the mortalities occurring in countries with low-to-intermediate incomes.[2] Thus, there is a world-wide concern to find suitable ways for the control and management of CVD. Previously suggested risk factors for the occurrence of CVD are diabetes, hypercholesterolemia, hypertension (HTN), smoking, obesity, alcohol abuse, decreased physical activity, poor dietary behaviors, use of oral contraception (OCP), familial history of CVD, and male sex.[1,3,4] OCP use has been widespread since these medications were first introduced about half a century ago in order to decrease unintended pregnancies by blocking ovulation and implantation.[5,6] It has been previously reported that the use of anti-androgens and estrogen is associated with a higher risk of pulmonary embolism and venous thromboembolism.[7] Nonetheless, the data are still inconclusive as to whether or not OCP use is associated with a higher risk of CVD development. Although there are some studies showing no robust association between OCP use and CVD,[8-11] we cannot disregard other investigations that have found an increased risk of CVD among OCP users.[12-14] There are also data from multiple studies demonstrating an increased risk of ischemic stroke related to OCP administration.[15] It has been reported that the risk of ischemic stroke is higher in OCP-using women, with the risk being even greater if OCP use is accompanied by other risk factors such as smoking and HTN.[15,16] An increased occurrence of CVD and stroke in older age may stem from the accumulative presence of known risk factors of both CVD and stroke in the elderly (including HTN, diabetes, smoking, and hypercholesterolemia).[17,18]
The present population-based cohort study was conducted to clarify whether there is an increased risk of future CVD, cerebrovascular accidents, and sudden cardiac death in women with a history of OCP use in comparison with those with no history of OCP use.

METHODS

This cohort research study was done in the setting of the Isfahan Cohort Study (ICS) by the grants of Isfahan University of Medical Sciences from 2001 to 2011.[19] The participants were healthy women aged ≥35 years. Insufficient data and inaccessibility to the participants during the study period were the exclusion criteria. All the participants were primarily informed about the study's goal, process, and protocols before they signed a written informed consent.
At the first stage, a questionnaire was used to obtain information about demographic data, history of hormone replacement therapy, history of OCP use (which could be consumed at any age even before 35 years), duration of OCP use (it may be used years before the initiation of the study), smoking, HTN, diabetes, age at menarche, number of pregnancies, number of abortions, age at first pregnancy, age at menopause, and CVD. Waist circumference was also measured, and according to the recommendation of the

International Diabetes Federation, central obesity was defined as waist circumference ≥80 cm for women.[20,21] Body mass index (BMI) was defined as the body mass divided by the square of the body height, and scores of 19–24.9 kg/m^2, 25–29.9 kg/m^2, and 30 kg/m^2 or more were considered normal, overweight, and obesity, respectively. Fasting plasma glucose (FPG) was measured using standardized and calibrated instruments, and the patients were considered to have diabetes mellitus if they fulfilled the following diagnostic criteria: FPG≥126 mg/dL or 2-hour postprandial plasma glucose ≥200 mg/dL or patients with symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose ≥200 mg/dL.[22,23] Systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg or the use of antihypertensive agents was defined as HTN.[24] All the participants' levels of cholesterol, triglyceride, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured, and the values were categorized regarding the following definitions: hypercholesterolemia as total cholesterol ≥200 mg/dL, hypertriglyceridemia as triglyceride ≥150, high LDL as LDL≥130, and low HDL as HDL<50.[25]

On the basis of the participants' medical records and history, the diagnosis of MI was confirmed when at least 2 of the following criteria were fulfilled: 1) presence of chest pain for at least 15 minutes, 2) presence of new developed Q waves in at least 2 out of the 12 ECG leads, and 3) elevated laboratory markers.[26] A definite diagnosis of stroke was also made by a neurologist as determined by magnetic resonance imaging or computed tomography scan.

Follow-up surveys were carried out every 2 years to determine CVD, stroke, and sudden cardiac death by inquiring the participants about any hospital admission.

Subsequently, the participants were divided into 2 large groups of OCP users and nonusers. Data analysis was done regarding new-onset CVD during the study period. The occurrence of stroke or sudden cardiac death was also determined in a similar way. In order to omit study bias and find the exact effects of OCP on the above-mentioned disorders, we adjusted the participants in both groups in terms of their demographic data and other risk factors. Accordingly, there were 5 models of adjustment: 1) adjusted with the demographic data, 2) adjusted with the demographic data and HTN, 3) adjusted with the demographic data and waist circumference, 4) adjusted with the demographic data and hormone replacement therapy, and 5) adjusted with the demographic data, waist circumference, diabetes, and HTN.

All the gathered data were analyzed using SPSS, version 15 (SPSS Inc., Chicago, Illinois, USA). The continuous and categorical data are described as means ± SDs and absolute numbers (percentages). The independent *t*-test and the chi-square test were used to compare the groups. The association between the 2 groups was assessed using the Cox regression models. A P value <0.05 was considered statistically significant.

RESULTS

Out of the 3,254 women (age ≥35 y), who participated in the present study, a total of 1,391 (42.7%) individuals were OCP users and 1,863 (57.3%) were nonusers. According to Table 1, there were differences between the groups (OCP users and nonusers) vis-à-vis age (P≤0.001), educational level (P≤0.001), HTN (P≤0.001), waist circumference (P=0.009), and number of pregnancies (P≤0.001), whereas there were no differences in regard to occupational status (P=0.665), residency (urban vs. rural) (P=0.455), diabetes mellitus (P=0.353), FPG (P=0.177), dyslipidemia (P=0.368), smoking (P=0.548), age at menarche (P=0.391), number of abortions (P=0.287), age at first pregnancy (P=0.158), and age at menopause (P=0.127).

Data were available on the duration of OCP consumption for 1,355 women (not all the

study participants), with a mean number of 62.98 months of consumption. The median of OCP use was 4 years; and by setting up this number as the cutoff point, the data showed that there were 47 (8.7%) CVD events in the women with OCP use <4 years and 77 (12.6%) CVD events in the women with OCP use ≥4 years; the difference was statistically significant (P=0.034). Comparison between the women with OCP use >4 years and those with OCP use <4 years revealed an HR of total CVD events of 1.485 (95% CI: 1.033 to 2.134).

Table 2 depicts the adjusted HR of CVD events in the women with OCP use >4 years and those with OCP use <4 years. Table 3 reveals that although there was a difference between the groups regarding sudden cardiac death, no similar differences were found in terms of MI, stroke, and total CVD events at 10 years' follow-up.

As is seen in Table 4, none of the events—comprising MI, stroke, sudden cardiac death, and CVD—showed a significant HR in the comparison between the OCP users and nonusers, even after adjusting the demographic data and other risk factors.

Table 1. Demographic and clinical data of the study populations

	OCP+ (N=1391)	OCP- (N=1863)	P value
Demographic data			
Age(mean, SD)	47.65(9.3)	52.39(12.2)	.000
Educational level			.000
Illiterate, n (%)	539(38.7)	980(52.6)	
Primary school, n (%)	560(40.3)	540(29)	
More than primary school, n (%)	292(21)	343(18.9)	
Occupational status			.665
Housekeeper, n (%)	1322(95)	1767(94.8)	
Employed, n (%)	69(4.9)	96(5.1)	
Residency			.455
Urban, n (%)	1041(72.9)	1336(71.7)	
Rural, n (%)	377(27.1)	527(28.3)	
Cardiovascular risk factors			
Diabetes mellitus n (%)	144(10.4)	212(11.4)	.353
FPG (mg/dL)	88.1(31.2)	89.6(33.1)	.177
HTN, n (%)	401(28.8)	656(35.2)	.000
SBP(mm Hg)	120.51(20.8)	123.25(22)	.000
DBP(mm Hg)	78.43(12)	78.95(12.1)	.226
Dyslipidemia, n (%)	1283(92.2)	1702(91.4)	.368
Total cholesterol (mg/dL)	218.3(51.6)	220.9(53)	.161
TG (mg/dL)	189(101)	188.2(99.1)	.832
HDL (mg/dL)	47.9(10.2)	48.5(10.6)	.081
LDL (mg/dL)	132.5(42)	134.6(43.9)	.169
Smoking n (%)	51(3.7)	61(3.3)	.548
Waist circumference (cm)	97.1(12.3)	95.5(13)	.009
BMI (kg/m^2)			.209
Normal (19–24.9)	384(27.6)	567(30.4)	
Overweight (25–29.9)	571(41)	741(39.8)	
Obese (≥30)	436(31.3)	555(29.8)	
Obstetric characteristics			
Age at menarche (mean, SD)	13.8(1.4)	13.7(1.5)	.391
Pregnancy (number)			.000
0	6 (0.4)	61(3.3)	
1-5	618(44.9)	397(21.3)	
>5	767(55.1)	1405(75.4)	
Abortion (number)			.287
0	771(55.4)	988(53)	
1–5	591(42.4)	776(41.6)	
>5	29(2)	99(5.3)	
First pregnancy (age)	17.9(3.0)	18.1(3.6)	.158
Menopause (age)	46.12	46.63	.127

FPG, Fasting plasma glucose; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; TG, Triglyceride; HDL, High-density lipoprotein; LDL, Low-density lipoprotein

Table 2. Hazard ratio of CVD events in the women with OCP use >4 years in comparison to the women with OCP use <4 years

	Myocardial Infarction (fatal and nonfatal)	Stroke (fatal and nonfatal)	Sudden Cardiac Death	Cardiovascular Events
Crude hazard ratio (95% CI) P value	1.152 0.429-3.094 0.779	1.597 0.737-3.460 0.235	0.896 0.181-4.441 0.893	1.485 1.033-2.134 0.33
Model 1 hazard ratio (95% CI) P value	0.992 0.367-2.682 0.988	1.505 0.690-3.281 0.304	Not adjusted	1.308 0.908-1.884 0.150
Model 2 hazard ratio (95% CI) P value	0.937 0.345-2.54 0.898	1.424 0.652-3.109 0.375	Not adjusted	1.262 0.875-1.819 0.212
Model 3 hazard ratio (95% CI) P value	0.972 0.359-2.632 0.955	1.488 0.681-3.250 0.319	Not adjusted	1.287 0.893-1.856 0.176
Model 4 hazard ratio (95% CI) P value	0.962 0.353-2.622 0.940	1.403 0.624-3.068 0.396	Not adjusted	1.252 0.867-1.806 0.230
Model 5 hazard ratio (95% CI) P value	Not adjusted	1.509 0.692-3.292 0.301	Not adjusted	1.303 0.904-1.878 0.155

Model 1: adjusted with demographic data
Model 2: adjusted with demographic data and hypertension
Model 3: adjusted with demographic data and waist circumference
Model 4: adjusted with demographic data, hypertension, diabetes mellitus, and waist circumference
Model 5: adjusted with demographic data and hormone replacement therapy

Table 3. Events during 10 years of follow-up

	OCP+	OCP-	P value
MI (fatal and nonfatal), n (%)	16(1.4)	40(2.5)	.360
Stroke (fatal and nonfatal), n (%)	28(2.4)	45(2.8)	.490
Sudden cardiac death, n (%)	6(0.5)	29(1.2)	.046
Total cardiovascular events	125(10.6)	201(12.5)	.125

MI, Myocardial infarction; OCP, Oral contraceptives

Table 4. Hazard ratio of cardiovascular disease events in the oral contraceptive users compared with that in the nonusers

	Myocardial Infarction (fatal and nonfatal)	Stroke (fatal and nonfatal)	Sudden Cardiac Death	Cardiovascular Events
Crude hazard ratio (95% CI) P value	.514 (.288-.919) .025	.803 (.501-1.287) .362	.390 (.156-.970) .043	.802 (.642-1.003) .053
Model 1 hazard ratio (95% CI) P value	.750 (.410-1.372) .351	1.056 (.645-1.730) .829	.940 (.351-2.514) .901	1.147 (.907-1.452) .252
Model 2 hazard ratio (95% CI) P value	.734 (.401-1.341) .314	1.043 (.637-1.706) .868	.921 (.345-2.459) .870	1.133 (.896-1.432) .299
Model 3 hazard ratio (95% CI) P value	.790 (.404-1.354) .328	1.024 (.625-1.677) .926	.955 (.357-2.560) .928	1.122 (.887-1.420) .337
Model 4 hazard ratio (95% CI) P value	0.754 0.411-1.382 0.361	1.071 0.653-1.757 0.786	0.965 0.359-2.594 0.943	1.150 0.909-1.457 0.245
Model 5 hazard ratio (95% CI) P value	.891 (.512-1.548) .682	1.005 (.625-1.617) .983	.876 (.331-2.321) .790	1.157 (.923-1.449) .206
Model 6 hazard ratio (95% CI) P value	0.730 0.399-1.334 0.306	1.011 0.619-1.655 0.962	0.947 0.354-2.533 0.913	1.118 0.884-1.414 0.351

Model 1: adjusted with demographic data
Model 2: adjusted with demographic data and hypertension
Model 3: adjusted with demographic data and waist circumference
Model 4: adjusted with demographic data and hormone replacement therapy
Model 5: adjusted with demographic data, hypertension, diabetes mellitus, and waist circumference
Model 6: adjusted with demographic data, hypertension, diabetes mellitus, waist circumference, and hormone replacement therapy

DISCUSSION

Drospirenone/ethinyl estradiol pills, norelgestromin/ethinyl patches, and etonogestrel-ethinyl estradiol vaginal rings have been 3 well-known forms of contraceptive agents since their first introduction.[27] The use of the oral form of contraceptive agents known as "OCP" is associated with an increased risk of venous thromboembolism and breast and liver malignancies and plays a protective role in colorectal, ovarian, and endometrial cancers.[28] Jick et al.[29] found that stroke and MI were rare in young women who used contraceptive agents. Regarding their findings, no increased risk of stroke or MI was found in the users of norgestimate-containing OCP compared with the users of contraceptive patches. In our study, the main goal was to evaluate whether OCP could increase the risk of future CVD events, including MI and sudden cardiac death. We recruited a large number of women in a long-period, cohort survey and assessed them in terms of CVD and stroke events.

A study on women aged <50 years with OCP use revealed that although OCP could be a risk factor for developing MI—in the absence of other risk factors—there was only a limited rise in death by MI.[30] Likewise, our data showed no increased risk of MI in the OCP users compared with the nonusers. Moreover, the women with OCP use >4 years were at a higher risk of CVD in the presence of other predisposing factors than those with OCP use <4 years. It may, therefore, be concluded that the longer use of OCP is a risk factor for CVD progression.

Regarding the numeral score, we found no increased risk of MI among our OCP users. By contrast, a study by Tanis et al.[31] showed that the use of second-generation OCP was a greater predisposing factor for MI than the use of third-generation OCP. The authors also found that use of any type of OCP as whole in comparison with non OCP use had an OR=2, meaning that there was an increased risk of MI in the setting of OCP use. Data of a multicenter study revealed a high risk of MI incidence correlated with the use of second-generation OCP compared with the use of third-generation OCP.[32]

Stroke was another entity we evaluated in our study participants. According to our findings, there was no increased risk of stroke associated with OCP use. A study by Petitti et al.[33] revealed that low-estrogen OCP was not associated with an increased risk of stroke. In contrast to our data, a recent published meta-analysis of observational studies showed an increased risk of first-ever ischemic stroke in OCP users.[34] The authors of another meta-analysis found that the risk of ischemic stroke was increased by the use of OCP and even low-estrogen agents had a hazardous influence on stroke progression.[15]

Our metabolic assessment of the study participants revealed no significant differences regarding total cholesterol, triglyceride, LDL-C, HDL-C, and FPG between the OCP users and nonusers. A study on healthy African-American women who consumed low-dose OCP showed that OCP use was able to elevate insulin resistance, glucose intolerance, and triglyceride. In addition, in that study, total cholesterol, LDL, and FPG did not show differences between the low-dose OCP users and the control group.[6]

A recent systematic review and meta-analysis revealed that the use of combined OCP was associated with an increased OR of venous thromboembolism (not evaluated in our study) and ischemic stroke (contrary to our findings); however, the authors reported no increased risk of hemorrhagic stroke or MI (similar to our findings).[35] Lack of information about the type of OCP used by the participants and the type of stroke (ischemic vs. hemorrhagic) can be considered as the limitation of our study.

In conclusion, contrary to the findings of previous studies, our data revealed no increased risk of future stroke and CVD

events—comprising MI, stroke, and sudden cardiac death—by a history of OCP use. A history of OCP use for a longer period of time compared with a shorter period of time showed no difference as regards the incidence of future CVD events.

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