



Investigation of the Relationship between Myocardial Infarction, Angina Pectoris, and Venous Thrombosis and Some Risk Factors in the Women Suffering from Cardiovascular Diseases with a History of Contraceptive Pills Consumption

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ARTICLE INFO

Article Type:
 Research Article

Article History:
 Received: 30 Dec 2014
 Revised: 24 Aug 2015
 Accepted: 19 Sep 2015

Keywords:
 Cardiovascular Diseases
 Myocardial Infarction
 Thrombosis

ABSTRACT

Background: Cardiovascular diseases have various etiologies. Previous studies have come to contradictory results regarding the effects of Oral Contraceptive Pills (OCPs) on the risk of myocardial infarction, angina pectoris, and venous thrombosis. Thus, further investigation is required in this area.

Objectives: This study aimed to determine the relationship between cardiovascular diseases and some risk factors in the women with a history of contraceptive pills consumption.

Patients and Methods: The present case-control study was conducted on 317 women with cardiovascular diseases (myocardial infarction, angina pectoris, and deep venous thrombosis) selected through simple purposive sampling from CCU, ICU, post-ICU, and neurology departments of Nemazee, Faghihi, and Al-Zahra heart hospitals. Also, 371 controls were selected among 20 – 60 year-old women without cardiac diseases. The data were collected through questionnaires, interviewing the patients and their first-degree relatives, and the patients' medical records. The main variables studied in both groups included the history of OCPs consumption, weight gain, blood sugar level, and hypertension. Then, the data were analyzed using chi-square test, correlation coefficient, and odds ratio. Besides, $P < 0.05$ was considered to be statistically significant.

Results: The mean age of the study population was 49.2 ± 13.4 years. Besides, 10.6%, 4%, and 2.7% of the women had used OCPs for 6 - 10, 11 - 15, and more than 16 years, respectively. There were no significant differences between the two groups in terms of history of using OCPs (47.3% vs. 51.5%, $P = 0.8$). In addition, no significant relationship was observed between consumption of OCPs and incidence of myocardial infarction ($P = 0.202$), angina pectoris ($P = 0.260$), and thrombosis ($P = 0.389$). However, a significant difference was found between the two groups regarding the frequency of hyperlipidemia, hyperglycemia, and hypertension ($P < 0.001$).

Conclusions: The results showed no significant association between the use of OCPs and cardiovascular diseases. Nevertheless, other risk factors of cardiovascular diseases were higher among the patients with a history of contraceptive pills consumption.

► Implication for health policy/practice/research/medical education:

Given that the frequency of myocardial infarction, angina pectoris, and venous thrombosis is higher among contraceptive pills consumers compared to non-consumers, health providers have to assess mothers' risk factors of cardiovascular diseases at each visit.

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1. Background

Oral Contraceptive Pills (OCPs) were introduced over 40 years ago and are now the most common birth control

method with the pregnancy rate of 0.1%. These pills have various advantages, including protection against cancers, reduction of menstrual irregularities, and reduction of unwanted pregnancies (1). Nowadays, in order to decrease the risk of OCPs, the pills containing less than 50 µg ethinylestradiol are being used (2-4). In fact, doses of estrogen and progesterone have been decreased and the new formulation only includes progesterone, which is utilized for reduction of androgenic side effects (5). To date, wrong assumptions exist regarding the safety of hormonal contraception. Moreover, cardiovascular side effects and embolic risks have not been eliminated either before (6, 7) or after menopause (7, 8). Thus, physicians should provide women with the information about both advantages and risks of contraception (9). Denmark Heart Center has reported a low risk of thrombotic stroke and myocardial infarction due to consumption of OCPs containing 20 µg ethinylestradiol (0.9-1.7). However, the risk increased to 1.3 - 2.3 with consumption of OCPs containing 40 µg ethinylestradiol. Overall, contradictory results have been obtained concerning the risk of venous thromboembolism, myocardial infarction, and thrombotic stroke due to consumption of OCPs (10).

In a systematic meta-analysis, Chan et al. investigated 20 studies and showed that the risk of stroke as the result of OCPs was only related to thrombotic but not hemorrhagic stroke (11). Furthermore, another study indicated that consumption of OCPs increased the risk of stroke in migraine sufferers, irrespective of other risk factors (12). One other study revealed that consumption of OCPs in white women was accompanied by an increase in the risk of cardiovascular diseases, insulin resistance, glucose intolerance, and high triglyceride levels (13). Combined OCPs have also been reported to increase the risk of thromboembolic events and cardiovascular disorders, particularly among the obese women who smoke cigarettes or have a family history of cardiovascular diseases (14). Moreover, it has been stated that using OCPs leads to occurrence of diabetes, blood clots, hypertension, and thrombosis (15).

Deep venous thrombosis, which occurs due to orthopedic surgeries in 50% and general surgeries in 25% of the cases, is usually accompanied by mortality and morbidity. According to some researches, the risk factors of thrombosis include older ages, obesity, history of thrombosis, varicose veins, OCPs consumption, malignancies, and general anesthesia. However, the aforementioned risks were not associated with hormotherapy during menopause, sex, race, smoking, and blood group (16).

2. Objectives

Considering the fact that contraception methods can cause a change in the risk factors of thromboembolic disorders and a limited number of studies have been conducted in this regard, the present study aims to investigate the relationship between the frequency of venous thrombosis, angina pectoris, and myocardial infarction and some risk factors in the women with the history of OCPs consumption in the selected hospitals of Shiraz University of Medical Sciences in 2006 - 2008.

3. Patients and Methods

3.1. Study Design

This case-control study was performed from June 2007 to the end of November 2008 at Nemazee, Faghihi, and Al-Zahra heart hospitals, Shiraz, Iran. The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences (No. 86 - 3509) and written informed consents were obtained from all the participants after providing them with an explanation about the study design and objectives.

3.2. Participants

In this study, 317 women with cardiovascular diseases (myocardial infarction, angina pectoris, and deep venous thrombosis) were selected through simple purposive sampling from CCU, ICU, post-ICU, and neurology departments of Namazi, Faghihi, and Al-Zahra heart hospitals where the aforementioned diseases are diagnosed by cardiology and nephrology specialists. Besides, 371 women between 20 and 60 years old were selected from general surgery, neurology, and urology departments of the same hospitals through simple purposive sampling as the control group. These departments were selected because hospitalized patients are examined regarding cardiovascular diseases before surgery. Therefore, to ensure that the risk of cardiovascular disease in the control group, patients' records and cardiologists' consultation were reviewed.

3.3. Data Extraction

The inclusion criterion of the study was diagnosis of cardiovascular diseases in the case group and absence of these diseases in the control group. On the other hand, the exclusion criteria of the study were having a history of myocardial infarction before OCPs consumption, pregnancy 6 months before the incidence of myocardial infarction, early menopause, oophorectomy, ovarian cancer, and breast cancer.

The data were collected through interviews using a demographic information questionnaire as well as questions regarding the risk factors of cardiovascular diseases, such as hyperlipidemia, hyperglycemia, hypertension, and method of contraception (OCPs or other methods). Then, the participants' height and weight were measured with minimum cover and without shoes with the accuracy of 1 cm and 100 gr, respectively. In order to eliminate individual error, all the measurements were performed by two individuals. Besides, the information was gathered by interviewing the patients and their first-degree relatives as well as by using their medical records.

3.4. Statistical Analysis

All the statistical analyses were performed using the SPSS statistical software, version 16.0 (SPSS Inc., Chicago, IL, USA). The values were expressed as mean ± Standard Deviation (SD) and percentages. Chi-square test (or Fisher's exact test if required) was used for comparison of the categorical variables. Besides, Pearson's correlation coefficient was used to assess the correlation between the quantitative variables and odds ratio. $P < 0.05$ was considered to be statistically significant.

4. Results

The mean age of the study women was 56.21 ± 11.91 years in the case group and 43.10 ± 11.63 years in the control group. The most frequent age group was 31 - 60 years (75.8%) and the rate of illiteracy was 34.6% in both groups. The frequency of demographic variables in the study population has been presented in Table 1.

According to the study results, 47.3% of the patients with cardiovascular diseases and 51.5% of those in the control group had consumed contraceptive pills; however, the difference between the two groups was not statistically significant ($P = 0.276$) (Table 2). Furthermore, 49.6% of the study subjects used OCPs, 21.2% did not use any contraception methods, and the rest used other methods of contraception. Among the OCPs consumers, 10.6% and 4% had used the pills for 6 - 10 and 11 - 15 years, respectively. Additionally, 2.7% of the subjects had used OCPs for more than 16 years.

The results showed no significant relationships between consumption of OCPs and the incidence of myocardial infarction ($P = 0.202$), angina pectoris ($P = 0.260$), and thrombosis ($P = 0.389$) (Table 3).

Moreover, a significant difference was observed between

the case and control groups with respect to blood sugar level (32.2% vs. 12.4%), blood lipids (47.6% vs. 19.1%), and hypertension (57.1% vs. 15.4%) ($P < 0.001$) (Table 4). The odds ratios for blood sugar level, blood lipids, and hypertension were estimated as 1.99 (1.263 - 3.146), 1.95 (1.296 - 2.293), and 3.817 (2.560 - 5.693), respectively (Table 5).

The study findings showed no statistically significant difference between the case and the control group with regard to exercise (walking) ($P = 0.6$) and Body Mass Index (BMI) ($P = 0.12$). However, a significant difference observed between the two groups concerning the consumption of salt ($P < 0.001$).

5. Discussion

Cardiovascular diseases are the leading cause of death in many countries and are rapidly increasing in developing countries. These diseases are considered to be a major health and social problem in East Mediterranean and Middle Eastern countries, including Iran (17, 18).

The findings of the present study revealed no significant relationship between cardiovascular disorders and consumption of OCPs ($P = 0.8$). Up to now, various studies have been conducted on this issue with contradictory results.

Table 1. The Frequency of Demographic Variables in the Study Population

Variable	Case	Control	P value
Age (year), n (%)			
30 ≤	5 (1.8)	55 (14.9)	< 0.001
31 - 60	228 (71.9)	293 (79.2)	
61 ≥	84 (26.5)	23 (5.9)	
Total	317 (100)	371 (100)	
Gravidity, n (%)			
5 ≤	102 (32.3)	255 (68.7)	< 0.001
5 - 10	160 (50.6)	102 (27.5)	
11 ≥	54 (17.1)	14 (3.8)	
Total	316 (100)	371 (100)	

Table 2. The Relationship between Cardiovascular Diseases and the Contraception Method in the Study Population

Variables Groups	Using Contraceptive Pills, n (%)	Using Other Contraceptive Methods (%)	Total	P value
Case	150 (47.3)	167 (52.7)	317 (100)	0.276
Control	191 (51.5)	180 (48.5)	371 (100)	
Total	341 (49.6)	374 (50.4)	688 (100)	

Table 3. The Relationship between Myocardial Infarction, Angina Pectoris, and Venous Thrombosis and Using Contraceptive Pills and Other Contraception Methods in the Study Population

Variable	Using of Contraceptive Pills, n (%)	Using of Other Contraception Methods, n (%)	Total	P value
Myocardial infarction, n (%)				
Yes	50 (45.5)	60 (54.5)	110 (100)	0.202
No	291 (50.3)	287 (49.7)	578 (100)	
Total	341 (49.6)	347 (50.4)	688 (100)	
Angina pectoris, n (%)				
Yes	85 (24.9)	95 (27.4)	180 (26.2)	0.260
No	256 (75.1)	252 (72.6)	508 (73.8)	
Total	341 (100)	347 (100)	688 (100)	
Thrombosis, n (%)				
Yes	17 (45.9)	20 (54.1)	37 (100)	0.389
No	324 (49.8)	327 (49.6)	651 (100)	
Total	347 (50.4)	341 (49.6)	688 (100)	

Table 4. Comparison of the Two Groups Regarding Blood Lipid Level, Hyperglycemia, and Hypertension

Variable	Patient (with Cardiac Disease)	Control (without Cardiac Disease)	Total	P value
Blood sugar, n(%)				
Elevate	105(33.2)	46(12.4)	151(22)	< 0.001
Normal	212(66.8)	325(87.9)	536(78)	
Total	317(100)	371(100)	688(100)	
Blood lipid, n(%)				
Elevate	151(47.6)	71(19.1)	222(32.3)	< 0.001
Normal	166(52.4)	300(80.9)	466(67.7)	
Total	317(100)	371(100)	688(100)	
Hypertension, n(%)				
Elevate	181(57.1)	57(15.4)	238(34.6)	< 0.001
Normal	136(42.9)	314(84.6)	450(65.4)	
Total	317(100)	371(100)	688(100)	

Table 5. The Rate of Odds Ratios of the Many Variables in the Study Population

Variables	Odds Ratio
Age	
≥ 60	7.9(2.619 - 23.918)
30 - 60	2.6(1.450 - 4.496)
Gravidity	
5 - 10	3.4(1.661 - 6.982)
> 10	1.7(0.84 - 3.476)
Blood lipid level	1.95(1.296 - 2.935)
Blood sugar level	1.99(1.263 - 3.146)
Hypertension	3.81(2.560 - 5.693)

In the study by Gillum, after controlling smoking and blood pressure, the incidence of heart attack was 1.93 folds higher among the OCPs consumers compared to the control group. Moreover, research has indicated that arterial events were found in the OCPs consumers in case they had other risk factors, as well (19). Considering cerebrovascular diseases, a case-control study that was conducted on 234 patients and 324 age-matched individuals as the control group in 2003 showed no significant difference between the consumers of OCPs containing 50 µg or less estrogen and the women who did not use OCPs regarding the risk of ischemic strokes ($P = 0.124$, odds ratio = 1.76, CI = 95%: 3.61 - 0.86). In that study, hypertension, Transient Ischemic Attack (TIA), myocardial infarction, diabetes mellitus, family history of stroke, and smoking more than 20 cigarettes a day were associated with the increased risk of ischemic stroke (20). Overall, a large number of studies have indicated a significant relationship between consumption of OCPs and increase in the risk of cardiovascular diseases. The insignificant relationship in the current study might be due to the sample size and length of OCPs consumption (6 - 10 years in 10.6%, 11 - 15 years in 4%, and over 16 years in 2.7% of the participants).

The findings of the present study revealed no significant relationship between the incidence of myocardial infarction and OCPs consumption. Similarly, Tanis et al. (1990 - 1995) performed a case-control study on 248 women between 18 and 49 years old who had experienced myocardial infarction for the first time and 925 age-matched healthy women. The results indicated that the odds ratio of myocardial infarction was 2 folds (1.5 - 2.8) higher among the OCPs consumers compared to the non-consumers (21). In the research by Chan et al., the risk of stroke due to consumption of OCPs

(0.51 - 1.76) was related to thrombotic but not hemorrhagic stroke. Besides, the incidence of stroke was doubtful in low doses of OCPs (11). In another study, the risk of death within 28 days after the incidence of myocardial infarction was 2.88 folds (1.22 - 6.77) higher among the consumers of OCPs compared to the non-consumers. Besides, this risk was higher among the smokers (22). Spitzer also reported an increase in the risk of myocardial infarction among the consumers of OCPs (23).

In the present study, thrombosis was detected in 7.8% of the study population and it was not associated with consumption of OCPs. Regarding cerebrovascular diseases, Azin et al. investigated the risk factors of cerebral venous sinus thrombosis in 60 patients in Namazi hospital, Shiraz, Iran in 2000 - 2003. In that study, consumption of OCPs was reported to be the main risk factor for these disorders (24). However, Siritho performed a study on 558 patients in 4 hospitals in Melbourne and showed no significant difference between the OCPs consumers and non-consumers concerning the risk of ischemic strokes. On the other hand, hypertension, TIA, myocardial infarction, diabetes mellitus, family history of stroke, and smoking more than 20 cigarettes a day increased the risk of ischemic strokes (20). Another case-control study conducted on 697 cases with stroke in 21 centers in 17 countries (141 countries in Europe and 556 developing countries) showed a 3-fold increase in thrombosis in the OCPs consumers and the important role of hypertension in this increase (25).

In general, consumption of OCPs does not lead to problems in the young women who do not have the risk factors of thrombosis, i.e., obesity, varicose, and diabetes. However, the individuals with these risk factors have an increased risk

of the incidence of thrombosis (26). Several studies have also reported a relationship between OCPs consumption and reproductive cancer (1983) and incidence of venous thrombosis (1995) (27).

In the present study, 60.3% of the participants in the case group and 53.8% of those in the control group were overweight, obese, or very obese, and no significant difference was observed between the two groups in this regard. According to the diet-heart hypothesis, excessive consumption of saturated fats and cholesterol and low intake of polyunsaturated fats increase the serum cholesterol level. This increase leads to formation of atheroma plaques, the accumulation of which results in coronary artery stenosis, eventually leading to myocardial infarction (28). The relationship between nutritional factors and blood lipid levels has been investigated in various studies (28, 29). Low Density Lipoproteins (LDLs) are considered as the first carriers of cholesterol and their blood level is highly correlated to the amount of cholesterol. Also, they are among the risk factors of iatrogenic and cardiovascular diseases (30). Thus, LDLs are definitely associated with cardiovascular diseases and acute, chronic malignancies. Having a diet that is high in saturated fats and cholesterol increases LDL through reduction of the regulation of hepatic LDL receptors (31, 32). The relationship between the increase in blood lipid levels and the incidence of cardiovascular diseases has also been emphasized in other studies (33, 34).

The findings of the present study indicated a significant relationship between hypertension and increase in the risk of cardiovascular diseases ($P < 0.0001$). In the same line, Dong et al. carried out a cross-sectional study on 3545 women, 892 of whom consumed OCPs. The results revealed that hypertension was significantly higher among the OCPs consumers. This result remained unchanged even after matching regarding BMI, alcohol consumption, physical activity, and treatment of hypertension. In that study, only consumption of the OCPs containing progesterone was not associated with hypertension (25). Bernardo also conducted a study on menopausal women and showed a 2 – 4 mmHg increase in diastolic blood pressure among the OCPs consumers (25).

In our study, 34.6% of the study participants suffered from hypertension. Besides, the frequency of hypertension in the case group (58.3%) was 3 folds higher than that in the control group. Overall, the prevalence of hypertension in this study was higher compared to other studies reporting the prevalence of hypertension as 11.1 - 23.4% (16, 35, 36).

Several studies have revealed that hypertension results from obesity (almost 77.5% of the participants of these studies were obese). Thus, they have suggested that these individuals could decrease their blood pressure by losing weight (9, 35, 37). In the current study also, 41.9%, 16.1%, and 2.3% of the patients with coronary artery diseases were overweight, obese, and very obese, respectively. These measures were obtained as 33.8%, 19.1%, and 0.9%, respectively in the control group. Overall, 75% of the study subjects were overweight. In order to prevent and deal with cardiovascular diseases, society-based initial prevention is of utmost importance. Physical examination, regulation

of lifestyle, and control of blood pressure and blood lipids have also been emphasized in initial prevention (38).

In the current study, a significant relationship was observed between increase in blood sugar level and risk of cardiovascular diseases ($P < 0.0001$). In the recent decade, death resulting from coronary artery diseases has increased by 23% in diabetic women and decreased by 27% in non-diabetic ones. Moreover, in comparison to diabetic men, diabetic women showed a higher prevalence of hospital mortality and heart failure after myocardial infarction (39).

English physicians conducted a study and, after a 40-year follow-up, indicated smoking as a risk factor for at least 30 important diseases and that quitting smoking led to a reduction in myocardial infarctions (35). Also, reduction of mortality resulting from coronary artery diseases, mean serum cholesterol level, and blood pressure after reduction of smoking has been mentioned in various reports (40, 41).

Based on the reports by World Heart Federation, cardiovascular diseases are among the most serious health problems in women, which have been neglected in all societies. In fact, 6 out of 10 mortalities resulting from cardiovascular diseases can be prevented by increasing the general knowledge about such diseases among women. The most important factors in development of cardiovascular disorders include dyslipidemia, hypertension, smoking, stress, diabetes, obesity (particularly android obesity), inactivity, bad eating habits, and excessive alcohol consumption (42). Lack of physical activity is one of the modifiable risk factors of coronary artery disorders (43). Physical activity showed a reverse relationship with BMI, cholesterol level, LDL level, abdominal circumference, and subcutaneous fats (44). A 5-year study conducted on the women working in the department of health also demonstrated that the risk of coronary artery diseases was 2 folds higher among the women who did not walk regularly compared to those who walked at least one hour a week (45). Considering the positive effect of physical activity on reduction of the risk factors of coronary artery disorders, encouragement of physical activity and exercise is among the most important interventional plans.

5.1. Future Research

Future studies are recommended to compare the risk of heart disease before and after menopause among OCPs consumers.

5.2. Conclusion

The results of the present study showed that the frequency of myocardial infarction, angina pectoris, and venous thrombosis was higher among the consumers of OCPs, however, the difference was not statistically significant.

Moreover, the risk factors of cardiovascular diseases, i.e., hyperglycemia, hyperlipidemia, increase in BMI, and inactivity, were higher in the case group compared to the control subjects. Thus, the risk factors of cardiovascular diseases are recommended to be evaluated when clients refer to health centers in order to receive the contraception instruments. By assessment of the mothers' needs for contraception, evaluation of the risk factors, and provision of accurate consultation, the health staff can increase the

confidence coefficient of safe and effective consumption of OCPs.

Acknowledgements

This article is a part of a Research (Project number: 3509). Researchers appreciate Research and Technology Department of Shiraz University of Medical Sciences for supporting this research and heads of Nemazee and Afghani hospitals for their contribution to the study. The authors would like to thank Dr. Nasrin Shokrpour at Center for Development of Clinical Research of Nemazee Hospital for editorial assistance.

Authors' Contribution

Authors' contribution: Akbarzade and Sharifi prepared the first draft of the manuscript, made critical revisions to the paper, and translated it into English. Najaf Zare performed data analysis.

Financial disclosure

There is no financial disclosure.

Funding/Support

This study was financially supported by the Research Vice-chancellor of Shiraz University of Medical Sciences, Shiraz, Iran.

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