

The relation between short-term oral contraceptive consumption and cerebrovascular, cardiovascular disorders in Iranian women attending Hajj

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ABSTRACT

الأهداف: من أجل تقييم طيف المضاعفات الوعائية المحتملة نتيجة لاستهلاك موانع الحمل (OC) عبر الفم على المدى القصير.

الطريقة: في هذه الدراسة الكتائبية، تم تقييم حاجات إيرانيات من مقاطعة رازاف- خوراسان - إيران، تحت عمر 50 واللواتي سيؤدين فريضة الحج في عام 2005م. تمت مراجعة نتائج الفحص السريري لهن، عوامل الخطر الوعائية واستهلاك موانع الحمل (OC) عبر الفم قبل الحج لجميع الحاجات. تمت متابعة حالتهم على ضوء احتمال الإصابة بمضاعفات وعائية خلال الحج وفي العام التالي.

النتائج: شملت الدراسة 896 امرأة، وأجريت المتابعة الكاملة لـ 642 منهن. أظهرت النتيجة إن 782 (87.3%) من الحاجات استعملن موانع الحمل (OC) عبر الفم. تعرضت واحدة منهن لتجلط في الوريد الدماغي، وأصيبت واحدة أخرى باحتشاء في عضلة القلب، وتعرضت أخرى لتجلط في الأوعية العميقة. تعرضت 18 حالة (2.8%) لارتفاع عارض في ضغط الدم. وتعرضت 10 حالات (1.5%) لاشتداد ألم الشقيقة. لم تكن العلاقة بين الإصابة بمضاعفات وعائية واستهلاك موانع الحمل (OC) عبر الفم ملحوظة إحصائياً في هذه الدراسة ($p=0.365$).

خاتمة: على الرغم من تحليل المضاعفات الوعائية لاستهلاك موانع الحمل (OC) عبر الفم على المدى الطويل، وتم إثباتها في العديد من الدراسات، فقد ركزت قليل من الدراسات على آثار استهلاك موانع الحمل (OC) عبر الفم على الجهاز الوعائي على المدى القصير. وهنا يبدو أن استخدام موانع الحمل (OC) عبر الفم قد ينتج عنه مضاعفات وعائية على المدى القصير، لذلك فإنه يوصى بإجراء المزيد من الدراسات مع عينات أكثر من أجل تحديد أمان ومضاعفات ذلك.

Objectives: To evaluate the spectrum of probable vascular complications due to short-term oral contraceptives (OC) consumption.

Methods: In this cohort study, selected Iranian female pilgrims from Razavi-Khorasan, Iran province <50 years old, attending Hajj in 2005 were evaluated. We reviewed their physical examinations, vascular risk factors and OC consumption before Hajj. Pilgrims were followed-up in terms of developing possible vascular complications during Hajj and the following year.

Results: This study included 896 individuals and completed follow-up was performed for 642. The results showed that 782 (87.3%) of pilgrims used OC. One person developed cerebral vein thrombosis, one myocardial infarction, and one deep vein thrombosis. Eighteen patients (2.8%) experienced transient hypertension. Ten patients (1.5%) had migraine exacerbations. The relationship between developed definite vascular complications and OC consumption was not statistically significant in this study ($p=0.365$).

Conclusion: Although vascular complications of long-term OC consumption have been analyzed and proved in several studies, few studies have determined short-term OC consumption effects on the vascular system. It seems that even short-term usage of OC may result in vascular complications, thus further studies with more samples is recommended to determine its safety and complications.

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Soon after oral contraceptives (OC) came to market vascular conditions, mainly strokes were reported around the world. Since then several researchers have investigated the incidence of stroke in OC consumers.^{1,2} Most of the researchers believed that there is noteworthy but slight increase of stroke incidence among women consuming OC.² The exact mechanism of stroke however has remained unknown. Nowadays, it is proved that OC acts in many different ways. They affect the circulating level of coagulating factors, and apparently produce a hyper-coagulant state.³⁻⁵ The increase in blood pressure is another possible effect of OC which may result in stroke.⁶⁻⁸ Oral contraceptives can also change the lipid profile which may lead to atherosclerosis.⁹ Some researches also suggest that certain genetic disorders such as factor V Leiden deficiency could increase stroke susceptibility among OC consumers.¹⁰⁻¹² It is shown that the presence of other vascular risk factors such as hypertension, smoking, hyperlipidemia, diabetes and migraine, can dramatically increase the risk of vascular complications due to OC.¹² Migraine has also been suggested to increase the chance of stroke, and this risk may grow in OC consumers.¹³ Other major vascular complications of OC include myocardial infarction (MI) and deep vein thrombosis (DVT).¹⁴ Some earlier epidemiologic studies presented 4-8 times increase in risk of DVT in OC consumers. This risk declined to 3 times by lowering the estrogen level of these tablets, yet DVT is still considered the major complication of OC.¹⁵ Many studies have shown a higher risk of MI in OC consumers particularly those >35 with other vascular risk factors mainly smoking.¹⁶ So far, most of the studies into OC have assessed the safety of the long-term OC consumption. However, there is a tendency in Muslim women to postpone their menstrual period by means of short-term OC consumption during Ramadan as well as Hajj ceremony. Therefore, assessing the safety of short-term OC consumption is important in the Muslim community. This study was assigned to evaluate the probable vascular complications or safety of short-term OC consumption.

Methods. Iranian pilgrims usually attend Hajj ceremony in groups of 100-200 patients called Caravans which are attended by a general practitioner (GP). In year 2005, we randomly selected 12 Caravans from Razavi-Khorasan, Iran province, which together included 896 women <50 years old and entered them into a cohort study. This study was conducted in Neurology Department in Ghaem Hospital, Mashhad, Iran and approved by the Ethics Committee of Mashhad University of Medical Science. Subjects voluntarily participated in 3 phases of our study as follows: in the initial phase, the GPs checked all subjects for any vascular

risk factors prior to the ceremony. The demographic data was collected by means of questionnaires which inquired data on age, vascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, smoking, and history of vascular disorders in family. Previous use of OC, history of migraine and history of past vascular conditions in subjects and their families were also taken into account. In the second phase, during Hajj, we assigned GPs to examine each individual thoroughly for probable vascular disorders, particularly for any signs, and symptoms of stroke, MI, DVT, hypertension or migraine exacerbation. One cardiologist supervised the study in Saudi Arabia. Pilgrims were divided into 2 groups according to the OC consumption. The common OCs in Iran are classified based on the estrogen level to the commercial name of low dose (LD) (35µg ethinyl estradiol and 0.3 µg norgestrel) and high dose (HD) (50µg ethinyl estradiol and 0.5µg norgestrel). In the final phase, we managed to follow up 642 patients (71.6%) for one year after they returned to Iran through monthly physical examinations and phone calls. Each subject underwent further diagnostic evaluations if any signs of vascular disorders showed up.

The relationship between short-term OC consumption and cerebral, cardiac, and peripheral vascular conditions in OC consumers and non-consumers were analyzed using Statistical Package for Social Science (SPSS) version 11.5. The *p* value was calculated using Chi-square and Fisher exact test and *p*<0.05 was considered as significant.

Results. Throughout the first and second phases of our study, we managed to evaluate 896 subjects and 642 patients (71.6%) were followed up for another year. Table 1 shows the prevalence of risk factors among all subjects (n=896). Among the 896 pilgrims, 782 individuals (87.3%) had used OC during the ceremony. As shown in Table 1, 49 individuals were used to consuming OC and 733 individuals had used OC for the first time during this Hajj. Six hundred fifty-three individuals (72.9%) had used LD, and 105 individuals (11.7%) HD, and 24 subjects (2.7%) had used other forms of contraceptives. Most of the subjects (655/733, 89.3%) was using the OC for at least 29 consecutive days and none of them longer than 2 months. During the follow up period the following vascular conditions were detected. One patient developed cerebral vein thrombus, one MI

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and one DVT. We could not find any prior vascular risk factors in these patients except the subject with MI who had a history of hypertension. Eighteen patients (2.8%) suffered from transient hypertension during the ceremony and a few months after which were resolved in further follow up in all subjects. Ten patients (1.5%) out of 49 cases with history of migraine had migraine exacerbations. Although 7 cases (1%) were suspected of vascular complications, they did not agree to further evaluation and the condition remained undetermined (Table 2). All the cases with definite vascular conditions and transient hypertension were older than 35 years. No vascular disorder was detected among the 114 remaining subjects who had not used OC. One case in this group had migraine exacerbation.

The case of stroke belonged to a 36-year-old lady with a history of 2 weeks of HD consumption, who experienced headache, and showed papillary edema

in neurologic examination. She did not accept to postpone her ceremony and after her return to Iran, she was admitted with right-side hemiparesis and aphasia. Magnetic resonance imaging and magnetic resonance venography studies proved cerebral vein thrombosis (CVT). A thorough investigation, including hypercoagulopathy state, showed no underlying disorders. After 6 months, she was admitted again with severe DVT. Further, studies proved B12 deficiency in this case. During the ceremony one case was admitted in hospital who was complaining from chest pain. Myocardial infarction was determined by a cardiologist and through required tests. Another case showed symptoms of DVT late in the ceremony, and the diagnosis was confirmed when she was admitted to the hospital on her return to Iran.

Comprehensive statistical studies, using the Chi-square and Fisher exact tests, shown that there was no statistically significant relationship between short-term OC consumption and definite vascular conditions, hypertension and migraine exacerbation among our population study.

Table 1 - Distribution of vascular risk factors in the subjects.

Risk Factor	n	(%)
Family history of vascular conditions	81	(9)
Previous OC consumption	49	(5.5)
Migraine	49	(5.5)
Hypertension	46	(5.1)
Hyperlipidemia	34	(3.8)
Diabetes	29	(3.2)
Smoking	14	(1.6)
History of previous vascular disorders*	13	(1.5)
No vascular risk factor	581	(64.8)
Total	896	(100)

* Including cerebral vein thrombosis, transient ischemic attack, myocardial infarction, and deep vein thrombosis. OC - oral contraception

Table 2 - The distribution of developed vascular events in the study population.

Vascular events	n	(%)	P-value
Definite vascular conditions (CVT, MI, DVT)	3	(0.3)	0.365
Transient Hypertension	18	(2)	0.135
Migraine exacerbation	10	(1.1)	0.262
Suspicious vascular event	7	(0.8)	0.287
Undetermined (not followed)	254	(28.4)	-
Healthy	604	(67.4)	-
Total	896	(100)	

CVT - cerebral vein thrombosis, DVT - deep vein thrombosis, MI - myocardial infarction

Discussion. In this research, we studied 733 subjects of Iranian female pilgrims with history of short-term OC consumption. We detected 3 definite vascular conditions among the subjects, 2 of them originated from venous system (CVT and DVT) and one from arterial system. However in the cases with definite vascular complications there were no remarkable risk factors except for the case with MI who had a history of hypertension. Although definite vascular conditions were not significantly different between OC consumers and non-consumers, they are devastating enough to deserve more careful consideration. However, the occurrence of 3 cases in our population is greater than what is expected based on the literature.¹³ Although the exact mechanisms of vascular events in these cases are not yet clearly identified, they seem to be multifactorial. In some studies slight but significant increase in blood pressure was reported after OC consumption.^{17,18} In this study, transient hypertension was merely seen in OC consumers, which disappeared a few months after quitting. Migraine exacerbation was another condition reported mostly in the OC consumers group. Although these findings were not born out by statistics, OC might exacerbate migraine and hypertension and eventually lead to further vascular events. Stress, dehydration, tiredness, and rigors of Hajj ceremony are potential factors that may have a role in development of vascular disorders. The very manner of OC consumption during Hajj, continuous consumption of tablets for more than a month, can also be conducive of vascular conditions. Finally, all the patients were above 35 years and this fact emphasized the high risk of age-related OC vascular

complications in this age group. It seems that even short-term OC consumption in women older than 35 years, also the long-term use, might produce serious vascular disorders.

There are a number of limitations to our study. First, we could not follow up 254 individuals and lose contact with them due to wrong telephone numbers, or addresses or because they were not willing to cooperate. There is a chance that we have underestimated transient hypertension since monitoring blood pressure of all subjects on a daily basis was almost impossible. Finally, we could not recruit an adequate number of the subjects for the control group as there was a great tendency for OC consumption among pilgrims and only 20% had not consumed OC during the ceremony. Despite above limitations, there are factors which empowered our study. First of all, to top of our knowledge, this is the first study to evaluate the safety of short-term OC consumption in the Middle-East. The high number of women who had used OC for the first time in their life is another highlight of our study. Although the result of this study showed no statistically significant increase in vascular conditions due to short-term OC consumption, it cannot fully support its safety either. Since a large number of female Muslims experience this form of OC consumption each year, its possible effects and disabling complications should be considered more seriously. Therefore, further studies with more samples seem to be necessary to determine safety or harmfulness of short-term OC usage and so we strongly recommend collaboration between Muslim communities for thorough investigation of this issue.

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