

Oral contraceptive misuse as a risk factor for cerebral venous and sinus thrombosis

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Background: Consumption of oral contraceptive pills (OCP) is a known risk factor for cerebral venous and sinus thrombosis (CVST) among women. We determined whether misuse of OCP could increase the risk of CVST in women. **Methods:** A case-control study was conducted from 2003 to 2007 on 64 female patients with CVST admitted to Al-Zahra medical center and 232 healthy age-matched female OCP users as controls. Patients and controls were interviewed and misuse of OCP was categorized to taking OCP for self-treatment of dysfunctional uterine bleeding, for family planning without physician consult, or for delaying menstruation in purpose of religious customs or traveling, and taking OCP in high dose during the preceding year. **Results:** Among 64 cases and 232 controls, 30 (46.9 %) and 63 (27.2 %), respectively, had a history of OCP misuse (Odds Ratio = 2.36, 95% Confidence Intervals = 1.33 to 4.18, $P = 0.002$). Also, using cyproterone compound (Diane) was more frequent in the CVST group ($P < 0.001$). Multivariate analysis controlling for age, OCP misuse, type of OCP, and history of coagulopathy showed that OCP misuse ($P < 0.001$) and using Diane as the OCP ($P = 0.006$) were both independently associated with CVST. **Discussion:** OCP misuse can be considered as an additional predisposing factor for CVST among women and partly responsible for larger proportion of female patients with CVST. These findings should alarm the healthcare system to create strategies controlling the inappropriate use of OCP among Iranian women.

Key words: Cerebral venous and sinus thrombosis, misuse, oral contraceptive

INTRODUCTION

Cerebral venous and sinus thrombosis (CVST) has varied manifestations and etiologies, so the diagnosis is usually made with delay and difficulty.^[1-5] CVST is not a rare disorder as previously supposed^[6] and often linked to poor prognosis.^[4] It affects younger age groups with a female: male ratio of 3: 1^[7] and different geographical distribution with a higher incidence in the Asian world.^[6,8]

About 80% of the affected patients have a risk factor for CVST.^[9] The risk of CVST is increased by factors that cause hypercoagulability state or venous stasis such as surgery, trauma, prolonged immobilization, pregnancy, postpartum state, and hormonal changes in young adult women.^[10-13] Evidences have shown that using oral contraceptive pills (OCP) is also a strong risk factor for CVST among women.^[14-16]

OCP is the most universal modern method of contraception, followed by female sterilization, in the world.^[17] In our country, the use of OCP has been increased specially in the last two decades and is available to married couples, free of charge, at public

clinics.^[18,19] However, current conceptions displayed that many female patients took these drugs inappropriately without physician or health service approval. Also, many women use OCP for delaying menstruation to perform religious customs such as fasting in Ramadan (the month of fasting) and religious travels. In these cases, OCP are mostly being used in inappropriate time (menstruation cycle) or without physician consultation.^[20] Saidee *et al.* in their study in Mashhad (Iran) evaluated 19 female cases of CVST who had been admitted during one-year period and found that 11 cases were admitted during Ramadan month which seems to be related to no other reason except OCP consumption, though other cofactors such as dehydration should be considered.^[20]

To the best of our knowledge, there is no systematic study evaluating the role of inappropriate use of OCP in increasing the risk of CVST among women. In our previous study, we found that the annual incidence of CVST is increasing in Isfahan,^[19] and also our clinical observation showed that most of the female patients with CVST have had the history of inappropriate use

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of OCP. Therefore, we hypothesized that inappropriate use of OCP, defined as misuse in this study, can increase the risk of CVST among women.

METHODS

Patients and setting

This case-control study was carried out on consecutive adult female patients referring with CVST to the Al-Zahra University Hospital between 2003 and 2007. Those who were pregnant or in the puerperium, have a recent (one year) miscarriage, and those using injectable progesterone were not included. Control age-matched subjects were recruited consecutively from non-gynecologic medical centers of Isfahan University of Medical Sciences during the same period. Considering the study power as to be 80% and determining the type I error as 0.05, and also setting the minimum expected difference of prevalence between the two groups as 0.38, according to the available data^[19,21] and also assuming 10% for missing probability, the sample size for each group determined to be 100. As we have limitation on the number of CVST cases diagnosed during the study (64 cases), our control group would be 232 women according to sample size formula of case-control studies. The study was approved by the Ethical Committee of Isfahan University of Medical Sciences and all patients signed an informed written consent.

Assessments

CVST was diagnosed, based on accepted definitions, according to conventional angiography, computed tomography venography, and/or magnetic resonance imaging and magnetic resonance venography by two unmasked independent qualified neurologists. Patients underwent a structured interview with a trained general

physician about risk factors of CVST at least 3 to 6 months after discontinuation of anticoagulant drug treatment. All the patients and controls who took OCP were conducted to evaluate the purpose and method of OCP usage. Based on patients' responses, we categorized OCP misuse as taking pills during the last year for at least one of the following purposes:

- To delay menstruation during cultural customs or traveling,
- Higher dose consumption (more than one pill per day for at least 4 consecutive days),
- Self-treatment for dysfunctional uterine bleeding,
- Taking OCP for family planning without physician consultation.

Statistical analysis

The two groups were compared regarding the frequency of OCP misuse and kind of OCP. The analyses were performed by SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA) using Chi-Square or Fishers Exact tests, with calculation of Odds Ratio (OR) and 95% Confidence Intervals (CI 95%), and a $P < 0.05$ indicated a statistically significant difference. Multivariate logistic regression analysis was performed to find independent associations of age, OCP misuse, and kind of OCP with CVST.

RESULTS

We included 64 and 232 patients in the case and control groups, respectively. The mean age of CVST and control group were 34.2 ± 9.5 and 32.7 ± 7.9 years, respectively; $P = 0.203$. Five (7.8%) of the CVST patients had a history of coagulopathy compared with none of the controls ($P < 0.001$) [Table 1].

Table 1: OCP misuse types in two groups

	CVST <i>n</i> = 64	Control <i>n</i> = 232	OR (CI 95%)	<i>P</i>
Age	34.2 ± 9.5	32.7 ± 7.9	-	0.203*
History of coagulopathy	5 (7.8%)	0	-	<0.001**
OCP misuse	30 (46.9%)	63 (27.2%)	2.36 (1.33 to 4.18)	0.002**
For delaying menstruation in religious customs or traveling	19 (29.6%)	12 (5.1%)	7.7 (3.51 to 17.06)	<0.001**
Taking high-dose OCP	3 (4.6%)	0 (0%)	-	0.009**
For dysfunctional uterine bleeding without physician consultation	7 (10.9%)	8 (3.4%)	3.4 (1.19 to 11.30)	0.024**
For family planning without physician consultation	8 (12.5%)	43 (18.5%)	0.17 (0.27 to 1.41)	0.173**
OCP type				
Low dose	48 (75.0%)	163 (70.3%)	1.26 (0.67 to 2.38)	0.282**
High dose	6 (9.4%)	17 (7.3%)	1.30 (0.49 to 3.46)	0.376**
Triphasic	0 (0%)	7 (3%)	-	0.173**
Diane (cyproterone compound)	(12.5%)	2 (0.9%)	16.42 (3.39 to 79.5)	<0.001**
Mini pills	0 (0%)	29 (12.5%)	-	0.001**
Marvelon	0 (0%)	2 (0.9%)	-	0.614**

Data are shown as mean ± SD or number (%).; *Independent Sample t-Test; **Chi-Square or Fisher Exact Test; OCP: Oral contraceptive pills; CVST: Cerebral venous and sinus thrombosis

Thirty (46%) from 64 cases and 63 (27.2%), from 232 control had a history of OCP misuse (OR = 2.36, CI 95% = 1.33 to 4.18, $P = 0.002$). Comparison between the two groups regarding different purposes of OCP use and different types of OCP is shown in Table 1. Using cyproterone compound was more frequent in CVST group ($P < 0.001$) and using mini pills was more frequent in the controls ($P = 0.001$).

Considering differences between CVST patients and controls in both the type of OCP and the frequency of misuse and history of coagulopathy, we did a multivariate analysis controlling for age, OCP misuse, type of OCP, and history of coagulopathy. The results showed that OCP misuse ($P < 0.001$) and using Diane as the OCP ($P = 0.006$) were both independently associated with CVST.

DISCUSSION

The aim of the present study was to evaluate OCP misuse as a risk factor for CVST in Iranian women. Given the significant large proportion of OCP misuse among women with CVST (46.9%), OCP misuse can be considered as an additional predisposing factor for CVST and partly responsible for larger proportion of female patients with CVST.^[4] This issue has not been emphasized in other studies; however, the pooled analysis of 17 studies including 263 women with CVST and 2 862 women without CVST showed that the summary OR for developing CVST was 5.59 in women using OCP compared with controls (95% CI 3.95–7.91; $P < 0.001$);^[4] we showed this risk can be two times higher if OCP is taken inappropriately (misuse).

Inappropriate use of OCP without physician prescription is frequent among women of our society, but only few studies are done regarding its adverse effects. In one study in city of Mashhad (Iran), Saidee *et al.* evaluated female cases of CVST who had been admitted during one-year period and found that more than half of the cases (11 of 19) were admitted during the month of Ramadan.^[20] Based on the Islamic principles, there are some restrictions for women in menstrual period which disallows their fasting for the rest of the month and women may use different types of OCP in order to postpone menstruation. According to the results of our study, 29.6% of the CVST cases took OCP without physician prescription in luteal phase for delaying menstruation in religious customs or traveling. It seems that starting OCP before menstruation in luteal phase can increase the risk of thrombosis. Some studies showed that during the luteal phase, the platelet function is increased in comparison with the follicular phase. Significant increases could also be found for fibrinogen and fibrinogen degradation products in the luteal phase, indicating a higher thrombotic activity in the luteal phase. Platelet activation during the luteal phase might be caused

in part by slightly elevated levels of vWF in response to progesterone and estrogen actions.^[22-24] Moreover, in the month of Ramadan, the fasting interval (no drinking and eating) lasts more than 12 hours that can result in at least a mild dehydration. Coexistence of OCP use and dehydration in Ramadan can be the reason for increased susceptibility to CVST.^[25] Also, we found that high-dose consumption of OCP without physician prescription was more frequent in the CVST group. It can be due to increasing estradiol dose of pills that can lead to thrombosis. Alternatively, higher than usual doses of OCP (more than one pill per day for >4 successive days) used by patients traveling for religious customs, to delay menstruation, may have made them more susceptible to CVST.

It appears that female who take OCP for family planning without physician prescription may also have some risk factors of thrombosis such as hereditary coagulopathy, and coexistence of these diseases and OCP use can increase the risk for CVST.^[10,19] However, our study did not show higher risk of CVST in this group of women, which may be related to small sample size of the study.

Other than the method of use, the risk of CVST can be influenced by the type of OCP according to estrogen dose and type of progesterone. In our study, mini-pills (progesterone only pills) did not confer any increased risk of venous thromboembolism compared with Diane that was independently associated with the risk of CVST.

CONCLUSION

With respect to the considerable proportion of OCP misuse among women with CVST, it appears that OCP misuse may be considered as an additional predisposing factor for CVST in Iranian women and partly responsible for larger proportion of female patients with CVST. On the other hand, consumption of OCP without physician prescription, even for family planning, can simply trigger the thrombotic event in female patients who have hereditary coagulopathy. Also, accessibility of OCP as an over-the-counter drug in Iran may result in increased self-treatment with OCP that can itself exacerbate the problem. These are a growing health problem that originates from cultural believes and should alarm the health services to solve this cultural problem observed in Iranian women. Further studies with larger sample size in different populations and also in other cities of Iran can provide more confident data to plan preventive strategies.

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