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Frequency and outcome of cerebral venous thrombosis attributed to oral contraceptive pills

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Abstract

Background: Oral contraceptive (OCP) use is a significant risk factor for cerebral venous thrombosis (CVT). There is limited research on its association with CVT development in Islamic countries. Therefore, our study aimed to assess the risk of different OCPs in developing CVT and their prognosis. *Methods:* This is an observational retrospective single-center cohort study that included CVT patients between March 2018 and March 2021. All CVT participants were registered in the organized registry system (CVT registry code: 9001013381) at the Neurology Research Center of Shiraz University of Medical Science. Univariate analysis and multivariable binary logistic regression modeling were applied to determine the associated factors leading to poor outcome. *Results:* A total of 204 patients (139 women, 65 men) were enrolled in the study. Seventy-four females (53.25% of total female patients) used OCPs, with second-generation OCPs being the most commonly used type (70%). OCP consumption was associated with a lower mortality rate (P=0.004, aOR=11.732) and a better 3-month follow-up outcome (p=0.001, aOR=9.882) than their female counterparts who did not use OCPs. The duration and generation of OCPs did not affect the follow-up outcome (P=0.148, P=0.428, respectively) or mortality (P=0.555, P=0.569, respectively). In multivariable analysis, the use of OCPs was a predictor of a favorable 3-month follow-up outcome in females (aOR =4.423, 95% CI: 0.423-46.248).
Conclusion: These results suggest that OCPs may have a positive impact on the prognosis of CVT in women. However, further research is required to understand the underlying mechanisms and validate these findings.

Keywords: Venous thrombosis; Cerebral venous sinus thrombosis; Oral Contraceptive; Prognosis; Risk factors

INTRODUCTION

Cerebral venous thrombosis (CVT) is a type of cerebrovascular disease that predominantly affects women.[1,2] In Iran, a study reported an annual incidence of 19.9 per 1,000,000 in women and 5.1 per 1,000,000 in men.[3] This gender difference may be attributed to specific risk factors such as the use of oral contraceptives (OCPs), pregnancy,

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and the postpartum period.[4,5] Some studies have indicated that CVT associated with these gender-specific risk factors has a more favorable prognosis compared to cases occurring in men.[4,6]

Oral contraceptives are widely recognized as a risk factor for thromboembolic events, including CVT.[7,8] The risk of thrombosis is higher with higher concentrations of estrogens or with OCPs containing third-generation progestogens (gestodene and desogestrel, drospirenone, and cyproterone). However, OCPs containing levonorgestrel and the lowest effective dose of ethinylestradiol (30 μg) carry a lower risk.[7,9-11] Additionally, the risk of thrombosis is elevated during the first 6-12 months after initiating OCP use.[10]

Despite the well-established association between OCPs and the development of CVT, there is limited literature available on this topic in non-Western countries, particularly in Islamic countries. Given the widespread use of OCPs among young women, the occurrence of CVT in this population can have significant implications for their well-being. Therefore, the aim of this study is to assess the role of different generations of OCPs as predisposing factors for CVT and evaluate their prognoses in Iran, a low-to-middle-income Islamic country.

METHODS

Patients' registry and definition

This retrospective cohort study was conducted at Namazee Hospital, a leading referral center for stroke in Shiraz. The study included adult patients who were admitted to the hospital with a diagnosis of CVT between March 21st, 2018, and March 20th, 2021. The Neurology Research Center of Shiraz University of Medical Science developed a registry system, coded by the Iran Ministry of Health (registry code: 9001013381), where all adult patients with confirmed CVT were registered.

The diagnosis of CVT was established based on clinical symptoms and radiological evidence observed in brain Computed Tomography (CT), CT-venography, Magnetic Resonance Imaging (MRI), and MR-venography. To identify relevant medical records, we used the 10th version of the International Classification of Diseases (ICD-10) and searched for primary diagnostic codes such as G08 (Intracranial and intraspinal phlebitis and thrombophlebitis), O87.3 (Cerebral venous thrombosis in the puerperium), O22.5 (Cerebral venous thrombosis in pregnancy), I63.6 (Cerebral infarction due to cerebral venous thrombosis, nonpyogenic), I67.6 (Nonpyogenic thrombosis of the intracranial venous system), and I61.9 (Nontraumatic intracerebral hemorrhage, unspecified). Patients who were misdiagnosed were excluded after evaluation by expert Neurologists. Additionally, patients with uncertain diagnoses, incomplete data, and those with a concurrent diagnosis of Coronavirus disease 2019 (COVID-19) were excluded due to potential associations with higher mortality.

The functional outcome of patients at discharge and at the three-month follow-up was assessed using the modified Rankin Scale (mRS) score. A poor outcome was defined as an mRS score greater than 2 at discharge and the three-month follow-up.

We recorded various predisposing risk factors, including infections, hypercoagulable states (e.g., hyperhomocysteinemia, Protein C and S deficiency), rheumatologic and hematologic diseases, pregnancy, puerperium, medications (particularly oral contraceptives), dehydration (e.g., fasting), malignancy, mechanical risk factors, and miscellaneous factors.

In this study, our variables of interest included the generation and duration of use of oral contraceptives (OCPs) as well as the fasting state.

Statistical analysis

Data analysis was conducted using IBM SPSS Statistics for Windows, Version 16.0 (IBM Corp., Armonk, NY). A significance level of $P < 0.05$ was considered statistically significant.

For quantitative variables that did not follow a normal distribution, the median with interquartile range (IQR) was used to represent the data. Qualitative variables were presented as frequencies and relative frequencies (%). To compare the age of CVT patients and the duration of OCP consumption among different groups, the Mann-Whitney and Kruskal-Wallis tests were employed. The Chi-square test or Fisher's exact test, as appropriate, were used to compare independent variables such as demographic characteristics and predisposing risk factors.

Univariate analyses were performed to examine the relationships between various potential prognostic factors (e.g., age, thrombosis of the deep venous system, intracranial hemorrhage, mental status disturbance, comatose state on admission, OCP consumption, duration and category of OCP use, pregnancy or puerperium,

rheumatologic disease, hematologic disease, hypercoagulable state, infection, dehydration, mechanical risk factors, malignancy, presentation symptoms, smoking history, history of drug abuse, residential area, and admission during Ramadan) and the 3-month follow-up outcome in female patients. Subsequently, a multivariable binary logistic regression analysis using a backward elimination approach was conducted to identify independent predictors of a poor follow-up outcome. The input variables included those that showed an association with poor follow-up outcome in the univariate analyses at a significance level of $P < 0.3$. The goodness of fit of the model was assessed using the Hosmer-Lemeshow test, with a P-value greater than 0.2 indicating a reliable fit. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) are reported.

Study protocol approval

Study protocol approval was obtained from the institutional review board and the Ethics Committee of Shiraz University of Medical Sciences (SUMS) (IR.SUMS.MED.REC.1400.478).

RESULTS

Demographics

Table 1 provides information on the types of OCPs and other hormonal medications used by our patients, including their progesterone and estrogen contents.

Seven patients were excluded from the study due to concomitant COVID-19 infection, and an additional five patients were excluded due to missing data. Ultimately, a total of 204 eligible

Table 1: The OCPs used by patients and their contents

		Estrogen	Progestin	Number of patients
Second generation	Contraceptive-LD	0.03 mg Ethinyl estradiol	0.15 mg Levonorgestrel	50(67.6%)
	Contraceptive-HD	0.05 mg Ethinyl estradiol	0.25 mg Levonorgestrel	2(2.7%)
Third generation	Contraceptive-DE	0.03 mg Ethinyl estradiol	0.15 mg desogestrel	1(1.4%)
Fourth generation	Cyproterone compound	0.035 mg Ethinyl estradiol	2 mg cyproterone acetate	13(17.6%)
	Yasmin	0.03 mg Ethinyl estradiol	3 mg drospirenone	4(5.4%)
	Yaz	0.02 mg Ethinyl estradiol	3 mg drospirenone	1(1.4%)
	Medroxyprogesterone 10 mg	-	10 mg Medroxyprogesterone acetate	1(1.4%)
	Emergency Contraceptive	-	1.5 mg Levonorgestrel	5(6.8%)
	Premarin	0.625 mg conjugated estrogen	-	1(1.4%)

patients with CVT were included in the analysis. Among them, there were 65 male patients and 139 female patients, resulting in a female-to-male ratio of 2.14:1. The median age of male patients (39 [31.5, 50.5]) and female patients (41 [32, 45]) did not differ significantly (P = 0.722). Among the female patients, 74 of them had used oral contraceptives (OCPs) prior to the occurrence of CVT. Other clinical characteristics of the patients can be found in Table 2.

Predisposing risk factors

The largest etiological group of CVT patients consisted of 97 women (representing 69.7% of females and 47.5% of all patients) with gender-specific risk factors, including pregnancy, puerperium (25 patients), and OCPs consumption (74 patients). A comparison of the predisposing risk factors is presented in Table 3. A comparison of the predisposing risk factors is illustrated in Table 3.

Table 2: Demographic criteria and clinical characteristics of CVT patients

			Males (n=65)	**OCP attributed females (n=74)**	**Non-OCP-attributed females (n=65)**	**p-value**
Age (median, IQR)			39[31.5,50.5]	39[32,44]	42[32.5,47.5]	0.259
Residence		Urban	57(87.7 %)	59(79.7%)	56(86.2%)	0.386
		Rural	8(12.3%)	15(20.3%)	9(13.8%)	
Previous CVT			3(4.6%)	0(0%)	1(1.5%)	0.094
Previous DVT or PTE			4(6.2%)	1(1.4%)	6(9.2%)	0.083
Family history of CVT			5(7.5%)	4(6%)	2(2.9%)	0.448
Family history of DVT or PTE			5(7.5%)	5(7.5%)	4(5.7%)	0.893
Recurrence of CVT			1(1.9%)	1(1.7%)	0	0.472
Presentation syndrome	Focal neurological deficit		21(32.3%)	18(24.3%)	13(20%)	0.190
	Increased ICP syndrome		11(16.9%)	20(27%)	10(15.4%)	
	Isolated headache		20(30.8%)	27(36.5%)	22(33.8%)	
	Encephalopathy syndrome		12(18.5%)	8(10.8%)	19(29.2%)	
	Unspecified		1(1.5%)	1(1.4%)	1(1.5%)	
Mode of onset		Acute	39(60.9%)	44(59.5%)	42(66.7%)	0.463
		Subacute	15(23.4%)	24(32.4%)	15(23.8%)	
		Chronic	10(15.6%)	6(8.1%)	6(9.5%)	
Sinus involvement		Mainly superficial	57(87.7%)	58(78.4%)	56(86.2%)	0.273
		Mainly deep	8(12.3%)	16(21.6%)	9(13.8%)	
Intracranial hemorrhage			22(33.8%)	31(41.9%)	29(44.6%)	0.426
Mental status disturbance on admission			25(38.5%)	24(32.4%)	26(40%)	0.616
Comatose state on admission (GCS<9)			2(3.1%)	2(2.7%)	5(7.7%)	0.322
Ramadan-month admission			5(7.7%)	13(17.6%)	6(9.2%)	0.147
In-hospital mortality rate			4(6.2%)	1(1.4%)	9(13.8%)	0.011*
Outcome at discharge#		Favorable	40(65.6%)	55(75.3%)	37(59.7%)	0.145
		Poor	21(34.4%)	18(24.7%)	25(40.3%)	
Outcome at 3-month follow-up#		Favorable	50(82%)	68(97.1%)	49(79%)	0.004*
		Poor	11(18%)	2(2.9%)	13(21%)	

#mRS >2 is defined as a poor outcome on discharge and 3-month follow-up.

Table 3: Predisposing risk factors

	Males (n=65)	OCP attributed females (n=74)	Non-OCP-attributed females (n=65)	p-value
Infection	10(15.4%)	2(2.7%)	10(15.4%)	0.019*
Hypercoagulable state	9(13.8%)	3(4.1%)	2(3.1%)	0.034*
Pregnancy or Puerperium	-	3(4.1%)	22(33.8%)	0.000*
Hematology	4(6.2%)	2(2.7%)	5(7.7%)	0.378
Rheumatology	5(7.7%)	3(4.1%)	3(4.6%)	0.618
Not-OCP Medications	8(12.3%)	3(4.1%)	5(7.7%)	0.195
Malignancy	4(6.2%)	0(0%)	10(15.4%)	0.000*
Mechanical	12(18.5%)	1(1.4%)	4(6.2%)	0.001*
Dehydration (fasting, etc)	3(4.6%)	9(12.2%)	5(7.7%)	0.268
Miscellaneous	4(6.2%)	0(0%)	3(4.6%)	0.037*
Unknown	22(33.8%)	0(0%)	11(16.9%)	0.000*

32 (15.6 %) patients had more than one risk factor.

Oral contraceptives

Among all female patients, OCP use was the most common predisposing factor for CVT, observed in 74 women (53.2% of all female patients). Among these OCP users, three patients (4.1%) had an underlying hypercoagulable state, and three others (4.1%) had an underlying rheumatologic disease in addition to OCP usage. Two patients (2.7%) used OCPs during pregnancy or the puerperium period unknowingly. Among the patients with OCP-related CVT, one patient (1.4%) had a previous history of CVT/DVT, and nine patients (13.5%) had a family history of CVT/DVT, which might have served as a warning for OCP usage according to the UK Medical Eligibility Criteria (UKMEC) categories 2-4.[12] Overall, 57 patients (77% of OCP-attributed patients) had no other identified cause for CVT except OCPs, despite comprehensive screening for infection, hematological, and rheumatological conditions.

Twenty-four patients were admitted during Ramadan, including five male patients (7.7%), 13 OCP-attributed female patients (17.6%), and six non-OCP-attributed female patients (P = 0.156). There was no significant difference between male and female patients regarding Ramadan admission (P = 0.252), nor between OCP-attributed females and non-OCP-attributed females in terms of Ramadan admission (P = 0.216). Among the 13 OCP-attributed female patients, nine (12.2% of OCP users) were fasting while taking OCPs. Ramadan admission did not have an impact on the 3-month follow-up outcome among female patients (P = 0.885).

The most commonly used contraceptive in our cohort was Contraceptive-LD (50 patients, 67.6%), followed by cyproterone compound (13 patients, 17.6%). Contraceptive-HD, Contraceptive-DE, Yaz, and Yasmin were used by two (2.7%), one (1.4%), one (1.4%), and four (5.4%) OCP users, respectively. Medroxy progesterone, emergency contraceptive, and Premarin were used by one (1.4%), five (6.8%), and one (1.4%) patient, respectively. Among the OCP users, nine patients used two different categories of OCPs. Regarding the duration of OCP consumption, 29 patients (39.2%) had used OCPs for less than one month, 29 patients (39.2%) had used them for 1-12 months, and 10 patients (13.5%) had used them for more than 12 months (P = 0.005).

Outcomes

During hospitalization, four male patients (6.2%), one OCP-attributed female patient (1.4%), and nine non-OCP-attributed female patients (13.8%) died (P = 0.011). Among the female patients, OCP consumption was associated with a lower rate of in-hospital mortality (P = 0.004, adjusted odds ratio [aOR] = 11.732).

A 3-month follow-up assessment using the modified Rankin Scale (mRS) was available for 193 patients. Among them, a total of 26 patients had a poor 3-month follow-up outcome (P = 0.004), including 11 male patients (18%), two OCP-attributed female patients (2.9%), and 13 non-OCP-attributed female patients (21%).

We compared the mortality rate and the rate of poor outcomes at the 3-month follow-up between second-generation and fourth-generation OCPs, which were the two main categories of OCPs used

in the study. However, no significant associations were found between the OCP category and either mortality rate or poor outcomes at the 3-month follow-up (P = 0.569 and 0.428, respectively). Additionally, the duration of OCP consumption did not have a significant impact on mortality rate or the 3-month follow-up outcome (P = 0.555 and 0.148, respectively).

Based on our univariate analysis, in female patients, a poor 3-month follow-up outcome was associated with older age (P = 0.01), encephalopathy syndrome (P < 0.001), malignancy (P < 0.001), mental status disturbance on admission (P < 0.001), comatose state on admission (P < 0.001), and intracranial hemorrhage (P = 0.002). Furthermore, a favorable follow-up outcome was associated with OCP consumption (P = 0.001, aOR = 9.882) in female patients.

In the multivariable binary logistic regression analysis, consuming OCPs was identified as an independent predictor of a favorable 3-month follow-up outcome (aOR = 4.423, 95% CI: 0.423-46.248). The full model of the multivariable binary logistic regression for predictors of a poor 3-month follow-up outcome is presented in table 4 (Hosmer-Lemeshow test, P = 1.000).

DISCUSSION

In our study, we found that gender-specific risk factors such as pregnancy or puerperium and the use of oral contraceptive pills (OCPs) were the most common predisposing factors for CVT, with OCP consumption being the most prevalent risk factor.

We observed that approximately 14% of patients (1 out of 7) who developed OCP-related CVT could have been prevented if the UK Medical Eligibility Criteria (UKMEC) for prescribing OCPs had been followed. Some of these patients clearly had risk factors that made them more susceptible to venous thromboembolism. Interestingly, the mortality rate was significantly lower in patients whose CVT was attributed to OCP use. Furthermore, during the 3-month follow-up, patients with OCP-related CVT had significantly better outcomes compared to female patients with CVT unrelated to OCP use. It's worth noting that the duration of OCP use and the specific generation of OCPs used did not impact the outcomes or mortality rates during the 3-month follow-up period.

In this study, the female-to-male ratio was 2.14:1, with OCP use being the most strongly associated risk factor for developing CVT. Previous large-scale studies have reported female-to-male ratios ranging from 1.4:1 to 2.9:1 in CVT cases.[13-18] The frequency of OCP use as a predisposing factor in female patients across these studies ranged from 12% to 54%. It's well-established that OCPs are a recognized risk factor for CVT, and in reproductive-aged women, the use of OCPs can increase the risk of CVT by about seven times.[19-21] This increased risk is thought to be linked to OCPs' ability to induce a hypercoagulable state.[22] The hemostatic changes caused by OCP use are well-documented, including increased levels of procoagulant factors such as fibrinogen, prothrombin, factors VII, VIII, and X, as well as decreased levels of anticoagulant factors like antithrombin and tissue factor pathway inhibitor (TFPI). Additionally, although there is a slight increase in protein C,

Table 4: Multivariable binary logistic regression, predictors of poor 3-month follow-up outcome

	P-value	aOR	95% CI for aOR	
			lower	upper
Age	0.457	1.032	0.950	1.120
Mental status disturbance on admission	0.019	35.256	1.782	697.580
Encephalopathy syndrome on admission	0.585	2.209	0.129	37.899
Ramadan admission	0.906	0.848	0.054	13.321
OCPs consumption	0.214	0.226	0.022	2.364
OCPs consumption duration	0.713	0.938	0.669	1.316
Pregnancy and puerperium	0.648	0.535	0.036	7.875
Malignancy	0.105	8.709	0.635	119.441
Hypercoagulable state	0.033	65.788	1.401	3089.830

P<0.001, Hosmer-Lemeshow test: P=1.000

there is a concomitant increase in its inhibitors and a significant decrease in protein S, which can contribute to a hypercoagulable state and thrombosis.[10,23-26] It is well-established that the risk of CVT is significantly higher in hypercoagulable women who use OCPs.[27-29]

Among patients whose CVT was attributed to OCP use, second-generation OCPs were the most commonly used type, and the majority of women had used OCPs for less than one year. Overall, the use of OCPs was associated with a favorable outcome. However, the duration of OCP use and the specific category of OCPs did not have an impact on the 3-month follow-up outcome or mortality. Several studies have suggested that OCPs containing levonorgestrel (second generation) have a lower risk of thrombosis compared to OCPs containing drospirenone, cyproterone, desogestrel, and gestodene (third and fourth generation).[7,10,30] Progestin-only contraceptives have been considered safe.[31] However, there have been limited reports linking the use of medroxyprogesterone acetate to the development of CVT.[32] There is a lack of research examining the interaction between the category and duration of OCP use and the outcomes of CVT. Prospective cohort studies are needed to evaluate the risk of OCP-related CVT development and its associated outcomes.

Our study found that female patients whose CVT was attributed to OCP use had a lower mortality rate and better outcomes at the 3-month follow-up compared to female patients whose CVT was not related to OCP use. However, predicting poor outcomes in CVT patients overall remained challenging. In previous large-scale CVT studies, such as the ISCVT and Finnish studies, women had a better prognosis than men.[16,33] Some studies have suggested that this improved prognosis in women may be due to gender-specific risk factors, including OCP use.[4,6] Further research is needed to determine whether the better prognosis in women with CVT is solely due to transient risk factors like pregnancy, puerperium, and OCP use, or if it is related to inherent characteristics associated with being female.

It is important to note that our study was not a population study, so we cannot establish a causal relationship between OCPs (and their different components) and CVT. However, our findings could influence the recommendations for OCP use in our community, emphasizing the importance of adhering to the UKMEC criteria for prescribing OCPs.[12] Additionally, Muslim women should be cautioned about fasting during Ramadan while simultaneously using OCPs. For women who do not have fasting requirements, OCPs can be prescribed as the prognosis for potential CVT cases appears to be favorable.

In our study, we observed that some patients used OCPs to suppress menstruation during the month of Ramadan due to religious reasons. Several studies have suggested that there is an increased incidence of CVT during Ramadan for patients using OCPs. This is likely a result of the combined effect of increased blood viscosity due to dehydration and the prothrombotic state associated with OCP use.[34-36] Therefore, it is important to provide relevant education about the adverse effects of OCPs to fasting Muslim women.

There were limitations to our study. Firstly, it was a retrospective observational study conducted at a single center, and there was no control group to assess the risk of developing CVT. Secondly, the majority of OCP users in our cohort used second-generation OCPs, which may limit the generalizability of the results to other generations of OCPs. To evaluate the risk of developing CVT while using OCPs, large prospective multicenter cohort studies are necessary. Additionally, studies with a more balanced distribution of patients using different generations of OCPs are needed to determine if certain generations are more or less likely to be associated with CVT.

In conclusion, OCP use is a common risk factor for CVT, but the prognosis for OCP-induced CVT is favorable. Further prospective studies are needed to assess whether specific generations of OCPs are more likely to contribute to the development of CVT. Future studies conducted in Islamic countries should also explore the use of OCPs in women for religious reasons.

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DISCLOSURE

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