

Cerebral vein thrombosis in women using short course oral contraceptive consumption

Payam Sasannejad¹ M.D., Ali Mellat Ardekani² M.D., Arash Velayati¹ M.D., Ali Shoeibi¹ M.D., Morteza Saeidi¹ M.D., Mohsen Foroughipour¹ M.D., Mahmoud Reza Azarpazhooh¹ M.D.

¹ Department of Neurology, Ghaem Medical Center, Mashhad University of Medical Sciences, Mashhad, Iran.

² Department of Neurology, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Corresponding Author:

Ali Mellat Ardekani and Mahmoud Reza Azarpazhooh contributed equally to this work.

Ali Mellat Ardekani, Department of Neurology, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Email: ali_mellat@ssu.ac.ir

Tel/Fax: (+98) 3518224001

Mahmoud Reza Azarpazhooh, Department of Neurology, Ghaem Medical Center, Mashhad University of Medical Sciences, Mashhad, Iran.

Email: r_azarpazhooh@yahoo.com
azarpazhoohmr@mums.ac.ir

Tel/Fax: (+98) 5118429828

Received: 5 February 2011

Revised: 6 August 2011

Accepted: 21 January 2012

Abstract

Background: Muslim women tend to postpone their menstrual period using short course oral contraceptives (OC) during Ramadan, Muslims fasting month. Recently, many cases of stroke, particularly cerebral vein thrombosis (CVT), have been reported in Ramadan.

Objective: This work studies the incidence of CVT and its relation to Ramadan.

Materials and Methods: This is a cohort study conducted from October 2006 to October 2009 and included 4 consecutive Ramadan's. All patients with definite diagnosis of CVT who were referred to the neurology department of Ghaem Hospital, Mashhad, Iran in this four-year period were included in the study.

Results: During the study period, 70 cases with CVT (11 males and 59 females) were recruited. Twenty five cases were admitted during Ramadan months which was significantly higher than all the other 32 months ($p=1.9 \times 10^{-7}$). The higher frequency of females (6 times more) among CVT cases probed by investigating possible risk factors and short term OC consumption was revealed as the major risk factor ($p=0.00071$).

Conclusion: Higher incidence of CVT in females during Ramadan suggests the presence of specific risk factors in this group. Our study revealed that short-term use of OCs may be a major risk factor for CVT.

Key words: Cerebral vein thrombosis, Oral contraceptives, Menstruation, Ramadan.

Introduction

The view on contraception and birth control varies among different countries, due to religion and cultural, socioeconomic and educational factors (1). Oral contraceptives (OC) consumption is one of the most widely used methods of birth control.

Currently, more than 100 million women use OC worldwide (2). Despite the high levels of OC use in the United States, Europe, Latin America, and the Caribbean, the popularity of OC across Asian countries has remained relatively low (3). The use of contraception dates back to many years ago in Islamic countries. Rhazes and Avicenna, the most famous Persian scientists in the 9th and 10th

century, listed many birth control substances in their books "The Canon of Medicine" and "Al-Hawi". Although, among Muslims, there is still some reluctance to use contraception, the fertility rate has decreased and contraceptive usage has increased in Islamic countries (4-9). Religious and cultural factors have also had a great influence on the pattern of OC usage.

For instance, as Islamic law prohibits women from participating in some Islamic ceremonies during the menstrual period, Muslim women tend to use oral contraception as a tool to postpone menstruation. These prohibitions include entering the holy places in Mecca and Medina in Hajj ceremony or in Muslim mosques and also fasting in the Islamic month of Ramadan, the ninth and the

holiest month of the Islamic calendar which is marked by praying and fasting. There are several reports about adverse vascular complications of short-term OC consumption during Hajj Ceremony and also a few studies about cerebral vein thrombosis (CVT) among Iranian Muslims during Ramadan (10).

We have previously shown a higher incidence of CVT among OC consumers during Ramadan (11). However, to further investigate the relation between short-term OC consumption and CVT in Ramadan, this study presents the result of an additional investigation on a larger group of OC consumers.

Materials and methods

In a cohort study, from October 2006 to October 2009, including 4 consecutive Ramadans, all cases with diagnosis of CVT were registered and entered to the study. The study was conducted in the Neurology Department of Ghaem Hospital, Mashhad, Iran which is the main referral center of neurology in the Northeast of Iran. The description of case registry and evaluation is explained in details in our previous publication (11).

In brief, CVT was diagnosed based on the clinical presentations and neuro imaging findings. Patients were evaluated for several CVT risk factors such as past or family history of venous thrombosis, hypercoagulopathy state, collagen vascular disorders, infectious disorders, complicated otitis, cancer, past history of trauma, drug abuse and history of migraine, as well as history of short and long-term consumption of OC and the type of OC based on the estradiol component.

Statistical analysis

The incidence of CVT during the Ramadan months in comparison with other months was analyzed by regression studies using SPSS version 11.5 (SPSS Inc, Chicago, IL, USA)

statistical software. Chi-squared was used to investigate CVT relation to OC consumption. One-tailed *t*-test was applied to analyze demographic data with *p*-value less than 0.05 considered as statistically significant. This study was approved by the Ethic Committee of Mashhad University of Medical Sciences.

Results

During the study period, 70 cases (11 males and 59 females) with definite diagnosis of CVT entered the study. All patients had BMI below 29. Among these cases, 25 (24 females, 1 male) were admitted in Ramadan and 45 (35 females, 10 males) were admitted in months other than Ramadan. Regression analysis revealed that the incidence of CVT in Ramadan was 4.96 additional cases (95% CI: 3.37-6.43, $p=0.000117$) comparing to all the reminding 32 months which calculated to be 1.09 cases per month (95% CI: 0.58-1.60) (Figure 1).

Statistical analysis of demographic data addressed OC consumption as the only risk factor with statistical significance (Table I). Excluding male patients from the analyses, 19 out of 24 female CVT cases in Ramadans had a history of short term OC consumption. In contrast, the OC consumption was found in 12 out of 35 female CVT cases discovered in non-Ramadan months ($p=0.00071$). Among the OC consumers in Ramadan, 17 cases used LD and 2 had a history of HD consumption.

Surprisingly, no other risk factors were detected in this group. We also did not detect any risk factor in the 5 non OC consumers in this group. In contrast, among the CVT cases detected in non-Ramadan months, 12 cases consumed OC and 18 had other risk factors for CVT such as hyper coagulopathy state due to factor V Leiden (3 cases), systemic lupus erythematosus (2 cases), complicated otitis and mastoiditis (2 cases), pregnancy (4 cases), a history of recent (within 6 months)

caesarian section (4 cases), and severe dehydration, history of oral corticosteroid use and esteradiol injection after severe uterine bleeding (each in 1 case) (Table I).

The superior sagittal sinus either with or without involvement of lateral sinuses was the most common site for CVT (Table II). Table II shows the clinical characteristics of women

with CVT in Ramadan and non-Ramadan in which seizure as a symptom of CVT was observed more frequently in Ramadan group ($p=0.006$) as well as ischemic venous infarcts ($p=0.017$) (Table II). Overall, 6 patients died in the hospital and 6 were discharged with significant disability (Modified Rankin scale ≥ 3).

Table I. Demographic data of patients with cerebral vein thrombosis

Demographics	Female (N= 59)	Male (N= 11)
Age: Mean± standard deviation (years)	34 ± 7	36 ± 5
Risk factor		
Short course OCP	23	-
Long course OCP	8	-
Hypercoaguability states	3	1
Mastoiditis	2	4
Pregnancy	4	-
Cesarean section	4	-
Systemic lupus erythematosus	2	-
Other risk factors	1	3
No apparent risk	12	3
Site of CVT		
Superior sagittal sinus	39	6
Right lateral sinus	22	6
Left lateral sinus	9	2

OCP: Oral contraceptive pill.
CVT: Cerebral vein thrombosis.

Table II. Clinical characteristics of women with CVT during study

Characteristics	Ramadan (n=24)	Non Ramadan (n=35)	p-value
Clinical features			
Seizure	17	12	0.006
Focal neurologic deficit	14	13	0.131
Imaging			
Ischemic venous infarct	14	20	0.017
Paranchymal hemorrhage	7	13	0.52
Subarachnoid hemorrhage	5	5	0.50
Morbidity	3	3	1
Mortality	2	4	1

CVT: Cerebral vein thrombosis.
Chi-square test.

Month	2006	2007	2008	2009
1		2	0	0
2		0	2	1
3		0	0	1
4		1	2	1
5		2	2	0
6		1	3	0
7		1	4	0
8		1	0	1
9	2	10	7	5
10	1	0	2	
11	1	0	0	
12	1	2	3	

Figure 1. Distribution of CVT cases among females during study period. The order of the months is according to Arabic calendar, "Ramadan" is the ninth month of the calendar.

Discussion

Oral contraceptives are associated with several major side effects including cardiovascular, cerebro vascular, and peripheral vascular disorders (12-16). Although several studies have investigated the safety and possible side effects of long-term OC consumption, short-term OC consumption requires more investigation (10). Venous thrombosis (both deep vein and cerebral vein thrombosis) are known side effects of OC consumption that might stem from a genetic susceptibility for hyper coagulopathic disorders (17-21). However, the safety and the real mechanism of vascular events, particularly in newer generation of OC, is still a matter of debate.

Our study aimed to investigate the relation between short-term OC consumption and CVT in Ramadan. This study clearly showed almost a five-fold increase in the incidence of CVT in Ramadan, in the presence of no other detectable risk factor other than OC consumption. Although we could not find any known predisposing factor in these patients, it seems that other predisposing factors in

Ramadan such as fasting, dehydration, and stress may facilitate contraceptive side effects on vasculature and exacerbate thrombotic events associated with them. Presence of a genetic susceptibility factor might also be related to this high incidence of CVT in short term OC users.

We observed that CVT cases in Ramadan were in more severe conditions in terms of clinical presentations and outcome. As shown in table II, seizures and ischemic infarcts with neurologic sequels were more common in Ramadan group. This observation may have similar implications for practice. In order to reduce the mortality and morbidity of CVT among OC consumers during Ramadan preventive modalities need to be taken into consideration. Patients should be advised to have adequate hydration. They should also be monitored for any possible pre-thrombotic risk factors including infections, connective tissue diseases, malignancies and other known hyper coagulability states. Some studies reported that underlying factors could be identified in up to 80% of patients (22).

In fact, the slow progression of thrombosis in the brain venous system gives the

physician an opportunity to detect and treat the disease in early stages, when the morbidity can remain minimal. Physicians should be aware of early symptoms of CVT. Arguably, even a simple headache, for instance, in an OC consumer referring to ER or clinic in Ramadan can be a red flag of an evolving CVT.

Conclusion

In conclusion, the short-term OC consumption may lead to serious vascular disorders such as CVT even in the absence of other known hyper coagulability conditions. This study suggests that the side effects of short term OC use may outweigh its benefits and thus, should be prescribed with utmost caution.

Acknowledgments

This work was supported by a grant (#87632) from Mashhad University of Medical Sciences, Mashhad, Iran.

References

- Galazios G, Tsikouras P, Liberis V, Koutlaki N, Vlachos G, Teichmann AT, et al. Attitudes towards contraception in three different populations. *Clin Exp Obstet Gynecol* 2008; 35: 22-26.
- Mosher WD, Martinez GM, Chandra A, Abma JC, Willson SJ. Use of contraception and use of family planning services in the United States: 1982-2002. *Adv Data* 2004; 10: 1-36.
- Lee J, Jezewski MA. Attitudes toward oral contraceptive use among women of reproductive age: a systematic review. *ANS Adv Nurs Sci* 2007; 30: 85-103.
- Srikanthan A, Reid RL. Religious and cultural influences on contraception. *J Obstet Gynaecol Can* 2008; 30: 129-137.
- Sueyoshi S, Al-Khozahe HO, Ohtsuka R. Effects of reproduction norms on contraception practice among Muslim women in Amman, Jordan. *Eur J Contracept Reprod Health Care* 2006; 11: 138-145.
- Hogan D, Biratu B. Social identity and community effects on contraceptive use and intentions in southern Ethiopia. *Stud Fam Plann* 2004; 35: 79-90.
- Kridli SA, Newton SE. Jordanian married Muslim women's intentions to use oral contraceptives. *Int Nurs Rev* 2005; 52: 109-114.
- Comerasamy H, Read B, Francis C, Cullings S, Gordon H. The acceptability and use of contraception: A prospective study of Somalian women's attitudes. *J Obstet Gynaecol* 2003; 23: 412-415.
- Cebeci Save D, Erbaydar T, Kalaca S, Harmanci H, Cali S, Karavus M. Resistance against contraception or medical contraceptive methods: a qualitative study on women and men in Istanbul. *Eur J Contracept Reprod Health Care* 2004; 9: 94-101.
- Azarpazhooh MR, Rafi S, Etemadi MM, Khadem N, Fazlinejad A. The relation between short-term oral contraceptive consumption and cerebrovascular, cardiovascular disorders in Iranian women attending Hajj. *Saudi Med J* 2008; 29: 1024-1027.
- Saidee M, Froghipoor M, Sasannejad P, Mellat Ardakani A, Azarpazhooh MR. The relation between short course oral contraceptive consumption and cerebral vein thrombosis in Ramadan. *Iran J Neurol* 2008; 7: 260-265.
- Farmer RDT, Preston TD. The risk of venous thromboembolism associated with low oestrogen oral contraceptives. *J Obstet Gynaecol* 1995; 15: 195-200.
- WHO collaborative study of cardiovascular disease and steroid hormone contraception. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet* 1995; 346: 1575-1582.
- Spitzer WO, Lewis MA, Heinemann LAJ, Thorogood M, MacRae KD. On behalf of transnational research group on oral contraceptives and the health of young women. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. *BMJ* 1996; 312: 83-88.
- Scoditti U, Buccino GP, Pini M, Pattacini C, Mancina D. Risk of acute cerebrovascular events related to low oestrogen oral contraceptive treatment. *Ital J Neurol Sci* 1998; 19: 15-19.
- Siritho S, Thrift AG, McNeil JJ, You RX, Davis SM, Donnan GA, et al. Risk of ischemic stroke among users of the oral contraceptive pill: The Melbourne Risk Factor Study (MERFS) Group. *Stroke* 2003; 34: 1575-1580.
- Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. *Lancet* 1994; 344: 1453-1457.
- Wysokinska EM, Wysokinski WE, Brown RD, Karnicki K, Gosk-Beirska I, Grill D, et al. Thrombophilia differences in cerebral venous sinus and lower extremity deep venous thrombosis. *Neurology* 2008; 70: 627-633.

19. Hillier CE, Collins PW, Bowen DJ, Bowley S, Wiles CM. Inherited prothrombotic risk factors and cerebral venous thrombosis. *QJM* 1998; 91: 677-680.
20. de Bruijn SF, Stam J, Koopman MM, Vandenbroucke JP. Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users who are carriers of hereditary prothrombotic conditions. *BMJ* 1998; 316: 589-592.
21. Dentali F, Crowther M, Ageno W. Thrombophilic abnormalities, oral contraceptive, and risk of cerebral vein thrombosis: a meta-analysis. *Blood* 2006; 107: 2766-2773.
22. Bousser MG, Russell RR. *Cerebral Venous Thrombosis*. London: WB Saunders, 1997.