

# Oral Contraceptive Consumption And Cerebral Venous Thrombosis In Mashhad, Iran

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## Abstract

**Background:** Causes of Cerebral Venous Thrombosis (CVT) varies around the world. Oral Contraceptive (OCP) are among the most frequent causes of CVT. **Methods:** Consecutive patients admitted with CVT in Ghaem hospital, Mashhad during 2005-2008 were prospectively investigated. Diagnosis of CVT was made by corresponding results of MRI, and MRV or conventional angiography. All of the patients had a complete medical history, physical examination and underwent a standard battery of diagnostic investigations by stroke neurologists.

**Results:** 62 patients (51 females, 11 males) with mean age 32.3 ranged 18-62 years were admitted with CVT. OCP consumption was found as risk factor in 56.8% of females with CVT. This group of females have been used LD and HD types of OCP in 97% and 3% respectively. 41% of females with CVT; (21/51) have been on short term OCP consumption. In this later group of females, Ramadan and Hadj religious months were the reason of using short term OCP in 86% and 5% respectively. **Conclusion:** Short term OCP consumption is the most common cause of CVT in Iranian women. Programs for public awareness should be conducted for reducing use of OCP in short term periods during Ramadan and Hadj months.

## INTRODUCTION

For a long time, cerebral venous thrombosis (CVT) was considered a rare disease confirmed by autopsy and associated with poor prognosis. In recent decades, the outlook for CVT has been dramatically improved by the advent of Magnetic Resonance Imaging (MRI) and MR Venography leading to earlier diagnosis<sup>1</sup>.

Numerous conditions, both intracranial and extracranial, have been implicated to cause CVT. When the thrombosis arises without an obvious cause, an extensive and early workup is needed because the underlying disease may require treatment in its own right<sup>1</sup>. Even after full investigations, in 20% - 25% of cases, the cause remains uncertain<sup>2</sup>. A diagnosis of idiopathic CVT should be made with caution, because other features of an underlying disease may only become evident on follow-up and after repeated investigations<sup>1</sup>. Distribution of etiology of CVT varies around the world, e.g. Behcet disease accounted for about 25% of all CVT in Saudi Arabia<sup>3</sup>. Puerperium remains a frequent cause of CVT, particularly in developing countries,

which have more frequent prenatal infections and dehydration<sup>4</sup>. Among drugs that have been associated with the occurrence of CVT, Oral Contraceptives (OCP) are by far the most common<sup>1</sup>. This etiologic study investigates the causes of CVT in East of Iran.

## MATERIALS AND METHODS

Consecutive patients with definite diagnosis of CVT admitted in Ghaem hospital, Mashhad during 2005- 2008 enrolled in a prospective observational study. Diagnosis of CVT was made by stroke neurologists. Confirmation of CVT is by corresponding both MRI and MRV. Thrombosis should be observed in T<sub>1</sub> and T<sub>2</sub> sequences of MRI with loss of signal void in the corresponding T<sub>2</sub> sequence of the related sinus<sup>5</sup>. Detection of cut off point or filling defect in the related sinus in MRV is necessary for confirmation of CVT diagnosis by MRI technology<sup>5,6</sup>. Patients with high suspicion of CVT and absence of both MRI, MRV clues of CVT underwent conventional angiography for detection of sinus filling defect<sup>5,6</sup>. Medical history included, history of deep venous thrombosis and repeated abortion in the patients

and their first degree relatives. Information about recent head trauma, dehydration, fasting, pregnancy and its trimester, puerperium, mastoiditis, sinusitis and recently administered drugs were taken by the patients or their first degree relatives<sup>7</sup>. Detailed history of OCP consumption, its duration and type of OCP based on the estradiol component were taken<sup>7</sup>. Short term OCP consumption defined as using OCP in recent 3 months<sup>7</sup>. Postpartum period defined as 3 months after delivery<sup>7</sup>. Patients with fever or evidence of sinusitis or mastoiditis in the medical history or physical examination had special sinus or mastoid imaging done<sup>8</sup>. Brain tumors and metastasis were ruled out by MRI. Blood chemistry, complete blood count, ESR and coagulation profile including Antithrombin III, proteins C, S and factor 5 Lyden were investigated in the patients<sup>8</sup>. Vasculitis profile including anticardiolipin, antiphospholipid antibodies, ANA, Anti-DNAs and HLA B27 were requested in the patients<sup>8</sup>. ENT, Infectious disease and Rheumatology consultations were performed in the patients. The research was approved by ethics committee of Ghaem hospital. A signed informed consent was taken by the patients or their first degree relatives.

## RESULTS

Sixty two patients (51 females, 11 males) with mean age 32.3 ranged 18-62 years were admitted with CVT. Table 1 represents etiologies of CVT in our patients. Multiple causes were found in 29% of the patients. OCP consumption was found as risk factor in 56.8% of females (29/51) with CVT. This group of females have been used LD (35µg ethynil estradiol and 0/3 µg nervogesterone) and HD (50 µg ethynil estradiol and 0/5 µg nervogestrone) types of OCP in 97% and 3% respectively. Short period (less than 3 months) of OCP consumption was found in 41.2% of females (21/51). Short period consumption was found in 72.4% of females with CVT who have taken OCP; (21/29). 95.2% of this later group of patients used LD; 20LD and 1HD respectively. Among females with short term OCP consumption, Ramadan and Hadj religious months were the reason of using short term OCP in 85.7% (18/21) and 4.8% (1/21) respectively. Distribution of CVT in Ramadan is significantly higher than other months in the females;  $X^2 = 14.7$ ,  $p = 0.001$ . Among 29 females who have been on OCP; dehydration, hypercoagulable state and both of these conditions were found in 44.8% (13/29), 10.3%(3/29) and 6.9%(2/29) respectively. Fasting in Ramadan consisted the reason of dehydration in 88.9% (16/18). Hypercoagulable state was associated with other risk factors in 55.5%; ( 5/9).

63.6% of our males with CVT had uncertain etiology despite complete diagnostic investigations.

## Figure 1

Table1: Etiologies of cerebral venous thrombosis in 62 Iranian patients.

Etiology	Females (51)	Males (11)	Both genders (62)
Oral Copntraceptives	29-56.8%	—	29-46.8%
Dehydration	17-33.3%	1-9.1%	18-29%
Hypercoagulable state	7-13.7%	2-18.2%	9-13.8%
Postpartum	2-3.9%	—	2-3.2%
Pregnancy	3-5.9%	—	3-4.8%
Other Drugs	2-3.9%	—	2-3.2%
Otitis	1-1.9%	1-9.1%	2-3.2%
Meningioma	1-1.9%	—	1-1.6%
Lupus Erythematus	1-1.9%	—	1-1.6%
Multiple	18-35.3%	—	18-29%
Uncertain	8-15.7%	7-63.6%	15-24.2%

## DISCUSSION

It is well stablished that incidence of septic CVT has been greatly reduced since the introduction of antibiotics<sup>9</sup>. Puerperal CVT was reported to be responsible for 25% of maternal deaths in India and to complicate 4.5 of 1000 obstetrical admissions<sup>10</sup>. In a Mexican study<sup>4</sup>, the puerperal state caused 60% of all CVT, whereas in western Europe and north America puerperal and pregnant states to gether account for 5% to 20% of all CVT<sup>11,12</sup>. In developed countries, the role of OCP is more important<sup>1,9</sup>. 82.2 % of our CVT were seen in females and OCP was the causing factor in 56.8% of these females. OCP consumption constituted 43% of CVT etiologies and found in 51% of females with CVT in Tabriz, north western Iran<sup>13</sup>. In a French study of 134 CVT patients, OCP was the only etiologic factor in 10% of the cases, however OCP use was also associated with other conditions such as systemic Lupus or Behcet disease in another 10%<sup>11</sup>. Congenital thrombophilia or hypercoagulable states accounts for up to 10% of CVT causes<sup>9</sup>. The detection of congenital thrombophilia should be systematic in CVT since it potentiates the risk of venous thrombosis associated with other conditions, including OCP or puerperium<sup>9,14</sup>. The use of OCP in carriers of thrombophilic abnormality extensively increases the risk of CVT (Ods Ratio: 149)<sup>15</sup>

. De Bruijin reported a 30-fold increased risk of CVT in women with a combination of thrombophilic abnormalities and use of OCP, as compared to women without either risk factor<sup>16</sup>. Increased levels of coagulation factors 7,8, 10, fibrinogen and prothrombin has been found in women using

OCP, this findings are more pronounced in women on OCP containing desogestrol<sup>17</sup>. LD is the usual type of OCP in Iranian drug market. Short term LD-OCP has an extremely important role in development of CVT in Iranian women. Since menstrual period prohibits Muslim women of entering holy places during Hadj customs and disallows their fasting in Ramadan. Thus they use short term OCP for a month in order to postpone menstruation and performing religious duties. At the other side dehydration during fasting in Ramadan facilitates development of CVT in females who are on short period OCP consumption. This concept highlights the need for public awareness of this important complication of OCP in muslim women especially during Ramadan month.

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