

## Does low dose contraceptive pills increase stroke rate? A cross sectional study in North-West Iran

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### ABSTRACT

**Objectives:** Several reports concern the relationship between low dose oral contraceptive pills (OCP) and the occurrence of strokes. The present study investigates this relationship in childbearing stroke women admitted to university referral hospitals in North-West Iran.

**Methodology:** One hundred seventy eight female patients between 15 and 44 years of age who were admitted to two referral University Hospitals in a six years period were evaluated in this descriptive-analytical study. Data concerning the use of OCP and other risk factors were recorded. The OCP usage data were compared between the patients and the matched normal population.

**Results:** The average age of the patients was 35.5±7.4 years. Seventy three patients were admitted with arterial stroke, 15 patients had cardioembolic origin, 39 patients with venous stroke and 46 patients with hemorrhagic stroke, 45.2%, 20%, 59% and 30.4% of them used OCP respectively. Approximately 26.3% of the matched female population of childbearing age used OCP and there was a significant correlation between venous stroke ( $P<0.0001$ ) and atherothrombotic stroke ( $P<0.0001$ ) with OCP usage. Migraine was the only risk factor that significantly correlated with OCP consumption and stroke. In addition, the data concerning OCP use in the stroke patients, without any other risk factors (32/71: 45%), demonstrated a significant difference comparing the matched population ( $P<0.0001$ ).

**Conclusion:** OCP usage increases the risk of venous and atherothrombotic stroke in North-West of Iran, particularly in those individuals who suffer concurrent migraine.

**KEY WORDS:** Stroke, Oral Contraceptive Pills, Childbearing women, Risk factors, Migraine.

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### INTRODUCTION

The female population not only carries a higher burden of stroke during their lifespan, it also accounts for the majority of stroke deaths.<sup>1,2</sup> Overall incidence of first time strokes is 5.5 per 100 000 women years and they have a higher lifetime risk of stroke than men (1 in 5 vs. 1 in 6), a statistic that is influenced in part by the longer life expectancy in women.<sup>3,4</sup>

New data, however, indicate that the incidence in women in the mid-life years might be increasing.<sup>5</sup> Stroke in the young women is associated with an

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additional set of risk factors and etiologies.<sup>6</sup> The causes of stroke in them are in a wide range such as hematologic disorders, substance abuse, trauma, dissections, oral contraceptive use, pregnancy and postpartum states, and migraine.<sup>7</sup>

OCP is the preferred method of contraception and it has been estimated that over 100 million women worldwide are on oral contraceptive pills (OCP) because of their ease of use and proven efficacy.<sup>8,9</sup>

The pharmacological use of estrogen exerts influence on the circulating levels of markers of vascular tonus, and inflammation, as well as prothrombotic, and fibrinolytic markers, but the impact of these changes on the atherosclerotic disease is still uncertain.<sup>10</sup> OCP increases stroke risk in young women, and this risk is proportional to the hormonal dose. The dose of estrogen is most directly related to stroke risk, although progesterone-only formulations are also correlated with a slightly increased risk of stroke.<sup>8</sup> Several studies have demonstrated a strong correlation between the consumption of OCP containing more than 50 mg ethinyl estradiol and the risk of stroke. No significant relationship has been documented between the consumption of OCP containing <50 mg ethinyl estradiol in non-smoking individuals and the risk of ischemic or hemorrhagic stroke, although the relationship between low-dose OCP with stroke has been more difficult to prove in patients without other risk factors.<sup>9,11,12</sup>

In view of the high rate of OCP consumption and the possibility that this could increase the risk of stroke in women and because no previous studies exist evaluating the relationship between stroke and OCs in young women in that region, this study was designed to investigate the relationship between use of LD OCP and the incidence of stroke in women of North-West of Iran.

## METHODOLOGY

**Subjects:** We conducted a cross-sectional descriptive-analytical study of women aged between 15 and 44 years, hospitalized in the neurology wards of two referral university-affiliated hospitals in Tabriz city (Imam Hospital and Razi Hospital) from the beginning of 2002 until the beginning of 2008 and diagnosed with ischemic or hemorrhagic stroke. Data concerning place of residence (urban or rural), OCP use & duration of it, vascular risk factors, and migraine history were obtained from their admission files and if necessary via phone call.

Use of low dose OCP (< 50 mg ethinyl estradiol) is most popular in the society studied; therefore the

data in the present study concerns LD OCP usage. Data concerning the rate of OCP consumption among urban and rural populations were obtained from local health centers (21% and 29% of urban and rural populations of North-West Iran in the same group of age with this study). Ethical committee of Tabriz University of Medical Sciences has been approved this study.

Data are expressed as mean  $\pm$  standard deviation. Statistical analysis was performed by SPSS for Windows software using independent t-tests and chi-square tests. As the rates of OCP consumptions differ between urban and rural populations (21% versus 29%, respectively), urban and rural patients were separately analyzed to outline the potential risk of stroke among OCP consumers. A *P* value less than 0.05 was considered statistically significant.

## RESULTS

During the study period, 178 women aged between 15 and 45 years and diagnosed with stroke were hospitalized (mean age  $35.55 \pm 7.40$  years). Urban patients accounted for 85 cases (mean age  $34.49 \pm 7.62$  years) while 93 cases were rural patients (mean age  $36.69 \pm 7.07$  years).

Seventy-eight patients (43.8%) had a history of OCP use (39 urban and 39 rural cases). The mean duration of OCP use was  $3.80 \pm 5.93$  years and there was no significant relation between the incidence of stroke and the duration of OCP usage (*P* = 0.645). The type of stroke, the prevalence of stroke subtypes and the percentage of patients with each type of stroke that were using OCP is presented in Fig.1. Eighteen out of 38 urban patients suffering arterial stroke had used LD OCP and this was significantly different from the urban population in which 21% of individuals had used LD OCP (*P*=0.000). Of 21 cases of venous stroke, 12 patients had used LD OCP, and this was a significant difference in comparison to the urban population (*P*=0.000). Of 18 cases of hemorrhagic stroke, seven patients had used LD OCP, but there was no significant difference from the urban population (*p*=0.062).

Among the rural patients, 15 suffering arterial stroke had used OCP (42.85%), which was not significantly different from the percentage of individuals using OCP in the matched rural population (*P*=0.072). In terms of venous stroke, ten patients had used OCP (58.8%), which was significant compared with the matched rural population (*P*=0.007). Seven patients suffering hemorrhagic stroke used OCP and this was not significantly different from the incidence in the

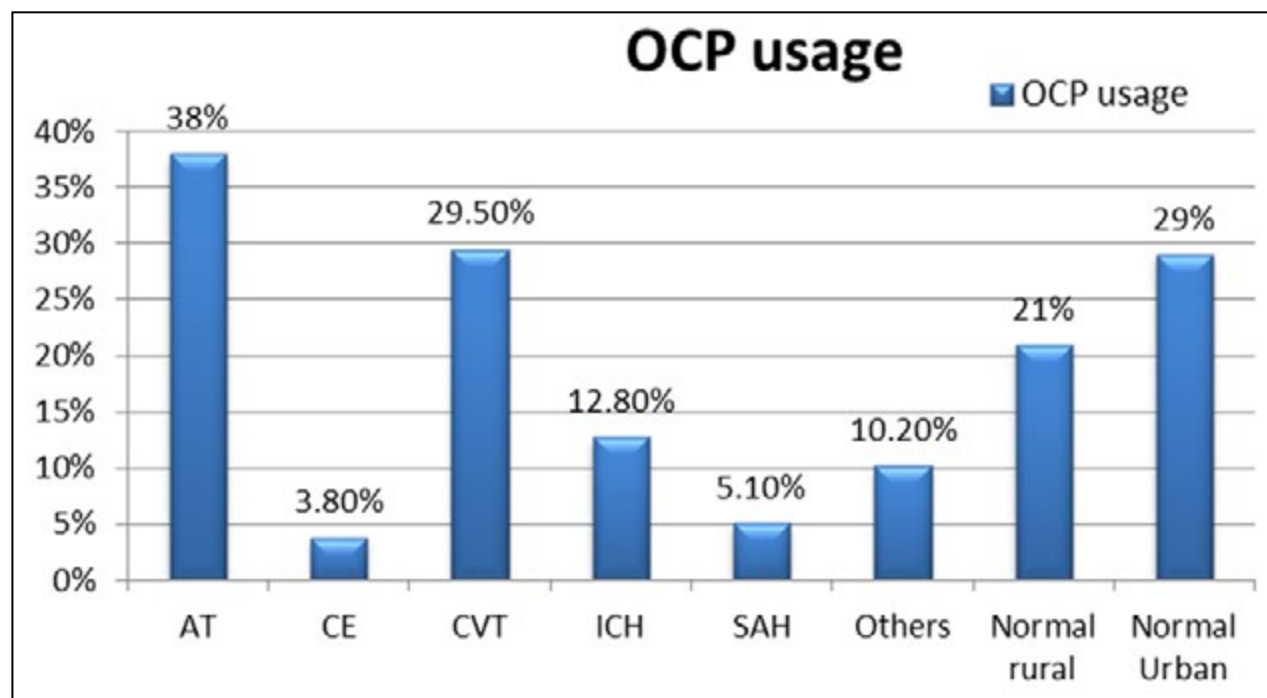


Fig.1: Prevalence of OCP consumption rate in stroke subtypes and matched normal population.

AT: Atherothrombotic; CE: Cardioembolic; CVT: Cerebral Venous Thrombosis; SAH: Sub Arachnoid Hemorrhage.

matched rural population ( $p=0.638$ ). Table-II presents data concerning the effect of other risk factors associated with OCP consumption on the incidence of stroke.

Migraine and simultaneous OCP consumption were significantly associated with the incidence of stroke ( $p=0.037$ ). Combination effects of risk factors and OCP consumption on stroke incidence is shown in Table-I.

Three patients smoked and did not use OCP but some patients presented with multiple risk factors. Seventy one patients with stroke did not have any

others risk factors except LD OCP consumption (32%) but 26.3% of matched rural and urban populations had this risk factor, respectively. ( $p=0.0000$ ). Twenty three of 51 patients with ischemic stroke used OCP, a significant number in comparison with a matched population ( $p=0.003$ ). However, nine patients, out of a total of 20 cases suffering from hemorrhagic stroke, used OCP and this was not significantly different from the matched population ( $p=0.061$ ).

There were significant relationships between OCP consumption and the incidence of arterial atherothrombotic and venous strokes but no significant relationships between OCP consumption and hemorrhagic and arterial embolic strokes.

Table-I: Combination effects of risk factors and OCP consumption on stroke incidence.

Risk factor	No. of Stroke Patients	OCP users	P-value
Pregnancy	19	5	0.09
Diabetes	14	5	0.496
Hypertension	55	19	0.077
Hyperlipidemia	15	8	0.466
Heart disease	13	3	0.168
History of DVT	3	2	0.433
Migraine	31	19	0.037
History of stroke	28	13	0.812
Smoking	3	0	0.119

DVT: Deep vein thrombosis

Table-II: Relationship between OCP consumption and stroke type.

Stroke type	No. of Patients	OCP usage (%)	P-value
Arterial	73	45.2	0.000
Atherothrombotic	58	51.7	0.000
Cardioembolic	15	20	0.579
Venous	39	59	0.000
Hemorrhagic:	46	30.4	0.525
Intracranial hemorrhage	30	33.3	0.395
Subarachnoid hemorrhage	16	25	0.893

Average OCP consumption in the experimental group was 26.3% from 2002 to 2008. (Table-II)

## DISCUSSION

This study investigated the use of LD OCP; and data concerning the use of LD OCP, without taking into account other risk factors, demonstrated that OCP usage in isolation was significantly related to the incidence of stroke in women of a reproductive age. There was a relatively more OCP consumption in patients suffering venous and thrombotic stroke than in a control population.

Various studies have demonstrated the relationship between consuming high dose OCP and an increased incidence of venous and arterial complications such as stroke.<sup>9,12</sup> There was a trend towards an increase in the female: male death from ischemic stroke ratios (but not subarachnoid hemorrhage or intracranial hemorrhage) in the 13 years following OCP availability compared with the 13 years before OCP availability, especially in women aged 15–34 years.<sup>2</sup> However, studies carried out in the United States<sup>13</sup> and Australia<sup>14</sup> has concluded that low dose (LD) OCP usage did not increase the risk of stroke, but in a five-year national case-control study the risk of thromboembolic stroke induced by OCP containing 50, 40-30 and 20 mg ethinyl estradiol and progesterone were reported as 4.5, 1.6, 1.7 and 1 times, respectively.<sup>15</sup>

A pooled analysis<sup>13</sup> of 2 studies from the United States reported that the low-dose (50 µg of ethinyl estradiol) OCP was not associated with stroke. This conclusion is in contrast with the results of two published multinational studies<sup>16,17</sup> that showed an association between low-dose OCPs and stroke. These divergent results have led to a controversy that is amplified further by the results of a meta-analysis<sup>18</sup> that reported a statistically significant association between low-dose OCPs and ischemic stroke.<sup>19</sup> These results are in contrast to previous studies demonstrating that LD OCP consumption did not increase the risk of stroke.<sup>11,13,14,19-21</sup> These differences between the present study and others could be explained by the prevalence of vascular diseases in the Iranian population, early onset of these diseases in the population<sup>22</sup>, drug preparation problems or race related changes.<sup>23</sup>

It is widely accepted that the other risk factors, including smoking and migraine, affect the incidence of stroke in young women. Buusser demonstrated OCP consumption in migraine patients (particularly migraines with aura) increased the risk of ischemic stroke up to three

times.<sup>24</sup> Migraine was the only risk factor studied that demonstrated a significant relationship with the incidence of stroke in combination with OCP consumption. These results are in agreement with a previous study that reported a relationship between OCP consumption and ischemic and hemorrhagic stroke in patients with a history of migraine,<sup>13</sup> and other studies that report the role of migraine in the development of stroke, particularly in association with OCP consumption and smoking.<sup>24-26</sup> Mant and colleagues showed that there is an increased risk of ischemic stroke in women who were heavy smokers and used OCP.<sup>27</sup> In the present study, migraine and simultaneous OCP consumption were significantly associated with the incidence of stroke but there were only three smokers, none of whom used OCP, and therefore there were no data relating to the incidence of stroke, OCP consumption and smoking habits.

Most of studies, including the present one, have demonstrated no relationship between the consumption of OCP and the risk of hemorrhagic stroke or death due to stroke.<sup>13,19</sup> But Li and his colleagues carried out a study in China demonstrated an increasing risk for hemorrhagic stroke in women who used LD OCP for a long time period and this risk continued for some time after the individual no longer consumed OCP.<sup>28</sup>

The most frequent major adverse effect of hormonal contraception is an increased risk of vascular disease i.e. venous thromboembolism<sup>10</sup> but Pymar and his colleague concluded that the risk of venous thromboembolism related to OCP consumption was < 3 in 10,000 women.<sup>29</sup> OCP consumption resulted in arterial and venous ischemic stroke more often than hemorrhagic stroke in our study. The incidence of ischemic stroke was significantly correlated to the consumption of LD OCP in both urban and rural communities. Using LD OCP was related to the incidence of arterial and venous stroke in the urban population but only venous stroke in the rural population. Factors that could contribute to the high incidence of arterial stroke in the urban population include psychological and life stresses, poor nutrition, consuming high cholesterol foods, relative inactivity and lifestyle.

## CONCLUSION

This study demonstrates a significant relationship between high frequency OCP consumption in female patients of reproductive age and the incidence of venous ischemic and atherothrombotic stroke. Furthermore, migraine sufferers who

consume LD OCP are at greater risk for stroke than individuals who have no history of migraines or those presenting with other risk factors. Further studies should be carried out to confirm the results presented herein, taking into account different racial and geographical populations.

### **Limitations of the study:**

The urban population, unlike the rural population, did not obtain LD OCP from specific places such as health centers. They could be referred to drugstore to receive pills, and therefore the percentage of OCP consumption could differ between the populations. This study reviewed referrals to two big university hospitals. Urban patients may be admitted to private hospitals more often than rural patients.

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