Menstrual and Reproductive Factors for Subarachnoid Hemorrhage Risk in Women
A Case-Control Study in Nagoya, Japan

Kazushi Okamoto, MD; Rokuro Horisawa; Takashi Kawamura, MD; Akihiko Asai, MD; Masataka Ogino, MD; Takuya Takagi, MD; Yoshiyuki Ohno, MD

Background and Purpose—We sought to examine the relationship between menstrual and reproductive factors and the risk of subarachnoid hemorrhage (SAH), using a case-control study.

Methods—Cases consisted of a consecutive series of 124 women patients with first spontaneous SAH aged 30 to 79 years and confirmed aneurysm(s) by angiography and/or CT scan. Hospital and community controls subjects were identified, matched to each case by age (±2 years).

Results—Increased SAH risk was associated with (1) earlier age at menarche (adjusted odds ratio [OR]=3.24 for age <13 years compared with age ≥13 years; 95% CI, 1.25 to 4.03) and (2) nulligravidity (adjusted OR=4.23; 95% CI, 1.05 to 7.56). No significant association of SAH risk was found with regularity of menstrual cycle, age at pregnancy, age at first birth, and number of births. The greatest risk was for the combined effect of nulligravidity and earlier menarche (<13 years) (adjusted OR=6.37; 95% CI, 1.12 to 36.2).

Conclusions—The combined effect of several variables related to menstrual and reproductive history may exert a greater influence on risk of SAH compared with a single menstrual or reproductive variable. (Stroke. 2001;32:2841-2844.)

Key Words: case-control studies ■ pregnancy ■ subarachnoid hemorrhage ■ women

Unlike other types of stroke, subarachnoid hemorrhage (SAH) occurs more often in women than in men,1-3 with a peak incidence between 40 and 60 years of age.4 Several epidemiological studies have examined the risk factors for SAH, primarily focusing on hypertension,4-8 smoking habits,4,7,9,10 and alcohol use.6,9-11 In women it was reported that hormone-related factors are in part associated with the occurrence of SAH.12,13 Previous studies have demonstrated that oral contraceptive use was significantly associated with an increased risk of SAH.4,9,12-16 However, few studies have examined the relationship between menstrual and reproductive factors and SAH.12,13 According to Park et al,17 early menarche was reported to be associated with an increased SAH risk. Longstreth et al12 reported that a state of estrogen deficiency was associated with decreased risk. In recent years, Qureshi et al11 reported that the risk of intracerebral hemorrhage was 3-fold higher in women who had ever been pregnant than in nulligravida women. We conducted a case-control study to explore the association between menstrual and reproductive factors and the risk of SAH, using a relatively large number of newly diagnosed patients.

Subjects and Methods
The study was performed from April 1992 to March 1997 at 2 medical hospitals located in Nagoya, Aichi Prefecture, Japan (Nagoya Daini Red Cross Hospital and Nagoya City Higashi Municipal Hospital). We recruited all consecutive SAH patients admitted during this period. SAH was diagnosed by aneurysmal bleeding pattern on CT, with the additional condition that the presence of 1 or more aneurysms was confirmed by cerebral angiography. Patients with other causes of SAH were not eligible as cases in this study.

Case subjects included were women aged 30 to 79 years and those who experienced the first spontaneous onset of SAH. We excluded SAH patients aged ≥80 years because of the difficulty in obtaining matched control subjects for them. We also excluded patients aged <30 years because of the possibly of different etiologies.7 We selected 2 control groups who had no past history of SAH, matched to each cases by age (±2 years) and sex: one control group (hospital control) was selected from patients with gastrointestinal disease treated at the same hospital as the cases, and another control group (community control) was selected by random sampling of subjects living in the same district as the cases. Among SAH patients, eligible cases were 75% of all admitted SAH patients, while the recruitment rate of eligible hospital controls was approximately 5% of all admitted gastrointestinal patients; for community controls it was difficult to obtain the recruitment rate because all community controls were not always chosen in the same area.

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Data Collection
SAH patients and their matched controls were interviewed by 2 investigators (K.O. and R.H.). We asked cases to recall their lifestyle during the 5 years before the onset of SAH, and we asked controls to recall their lifestyle before the interview, using a structured questionnaire specifically designed for the case-control study. The questionnaire included information on sex, age, educational level, medical history, family history, smoking habits, and menstrual and reproductive history. Questions on menstrual and reproductive history included menstrual status and regularity, age at menarche, total number of pregnancies and live births, age at first pregnancy and first birth, and oral contraceptive use. SAH patients were interviewed within 1 month after their admission, and the 2 control groups were interviewed within 2 weeks after completion of the case subject interviews. SAH patients and hospital controls were interviewed at a hospital, and community controls were interviewed at their homes.

Hypertension was considered present when subjects had been diagnosed with hypertension before the survey. Smoking status was ascertained in relation to number of cigarettes smoked per day during the 5 years before the survey (onset of SAH/interview), and subjects were categorized as current smokers (smoking at least 1 cigarette per day), ex-smokers (not smoking for at least 1 year before the survey), and never smokers. Educational level was classified into 3 categories (less than high school, high school, college or more).

When the patients were unable to provide any information about their lifestyle and history because of early death or impaired conditions, proxies (mainly spouses) were interviewed. Whenever possible, a standardized in-person interview was conducted for the patients and for their 2 matched controls. When this was not possible, a proxy interview was performed.

Institutional ethics committees in each of the 2 study hospitals approved the protocol before commencement. All participants provided informed consent, including next of kin for case subjects who were severely ill, unconscious, or dead and including proxy respondents for control subjects, after verbal explanation of the study protocol was provided.

Odds ratio (ORs) and 95% CIs were estimated by the use of a multiple unconditional logistic regression model in which potential confounders (age at diagnosis, past episode of hypertension, smoking status, educational level) were controlled.18 Smoking status was classified as current smokers or nonsmokers (including ex-smokers). Age at menarche (<13 years, ≥13 years), total number of pregnancies (nulligravidity, ≥1), total number of live births (nulliparity, ≥1), age at first pregnancy (<26 years, ≥26 years), and age at first birth (<27 years, ≥27 years) were categorized into dichotomous levels. The results were unaltered when analyzed with the use of 2 controls separately or in combination, and therefore we have described the findings obtained with the use of 2 controls.

Results
A total of 124 consecutive female SAH patients and 248 matched controls were identified in the study period (mean age, 60.0 ± 10.0 years and 60.3 ± 10.5 years, respectively).

Table 1 shows selected background characteristics of patients and controls. Proxy interviews accounted for 29.0% in all groups. SAH patients had significantly higher proportions of hypertensive subjects (P=0.0000) and current smokers (P=0.00002). SAH patients were more educated than each of the 2 controls (P=0.02). All analyses were performed with combined hospital and community controls because no significant differences in demographic characteristics between the 2 controls were observed.

The associations of menstrual and reproductive history with SAH are shown in Table 2. An increased SAH risk was associated with earlier age at menarche (adjusted OR=3.24 for age <13 years compared with age ≥13 years; 95% CI, 1.25 to 4.03), nulligravidity (adjusted OR=4.23; 95% CI, 1.05 to 7.56), and age at first pregnancy (adjusted OR=1.45; 95% CI, 0.91 to 2.33). No significant association with increased risk was found with regularity of menstrual cycle or age at first pregnancy, although we found a seemingly higher risk associated with older age at first birth (adjusted OR=1.45; 95% CI, 0.91 to 2.33). The SAH risk was
TABLE 3. Adjusted ORs* for SAH by Age at Menarche

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at menarche</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;13 y</td>
<td>34.7</td>
<td>26.2</td>
<td>3.24 (1.25–4.03)</td>
</tr>
<tr>
<td>≥13 y</td>
<td>63.3</td>
<td>47.5</td>
<td>1.00</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>72.9</td>
<td>77.9</td>
<td>1.00</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>27.1</td>
<td>22.1</td>
<td>0.67 (0.36–1.23)</td>
</tr>
<tr>
<td>Menstrual cycle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>73.7</td>
<td>70.9</td>
<td>1.00</td>
</tr>
<tr>
<td>Irregular</td>
<td>26.3</td>
<td>29.1</td>
<td>0.84 (0.48–1.48)</td>
</tr>
<tr>
<td>Age at first pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;26 y</td>
<td>56.1</td>
<td>69.8</td>
<td>1.00</td>
</tr>
<tr>
<td>≥26 y</td>
<td>43.9</td>
<td>30.2</td>
<td>1.78 (1.13–2.80)</td>
</tr>
<tr>
<td>Age at first birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;26 y</td>
<td>49.0</td>
<td>58.8</td>
<td>1.00</td>
</tr>
<tr>
<td>≥26 y</td>
<td>51.0</td>
<td>41.2</td>
<td>1.45 (0.91–2.33)</td>
</tr>
<tr>
<td>Gravidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11.6</td>
<td>2.6</td>
<td>4.23 (1.05–17.56)</td>
</tr>
<tr>
<td>≥1</td>
<td>88.4</td>
<td>97.4</td>
<td>1.00</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13.4</td>
<td>3.5</td>
<td>1.82 (0.76–17.5)</td>
</tr>
<tr>
<td>≥1</td>
<td>86.6</td>
<td>96.5</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Values are percentages unless indicated otherwise.
*Adjusted OR is obtained from multivariate analysis adjusted for age, hypertension, smoking habits, and educational level.

Discussion

To the best of our knowledge, this is the first case-control study that has comprehensively examined the relationship between menstrual and reproductive factors and the risk of SAH. We found that earlier age at menarche and nulligravidity, when combined, were strongly associated with an increased risk of SAH.

In this study we used self-report and retrospectively recalled data of reproductive history in both SAH patients and controls; according to Peganini-Hill et al, reproductive histories appeared to be reported with a considerably high degree of validity.

Consistent with previous studies, age at menarche was significantly inversely associated with SAH risk, even after adjustment for suggestive and conventional risk factors for SAH. Little information is available regarding the relationship between reproductive factors and SAH risk. We found that lower gravidity or parity and older age at first pregnancy were significantly associated with an increased risk, although there was no significant association with age at first birth. It has been suggested that the protective effect of higher parity may be related to the higher progesterone levels during pregnancy, resulting in a better balance between progesterone and estrogens during this period. In contrast, early menarche and nulliparity were reported to be associated with increased estradiol levels. Estrogens lead to elevated blood pressure and make the blood vessels less stiff. It is further reported that early menarche and nulligravidity were associated with decreased sex hormone–binding globulin levels. Lower levels of sex hormone–binding globulin were suggested to be associated with decreased serum levels of estradiol bound to sex hormone–binding globulin, with lower bioavailability and then increased androgenicity, resulting in atherogenic changes and/or hypertension. These findings appear to be the most likely explanation for our results: levels of estrogen with bioavailability, not the total amount of estrogen level, may be related to an increased SAH risk.

There are several limitations of this study. First, the hospital-based case-control study used in this study is prone to selection bias. Almost all patients with severe and acute medical conditions are admitted to Nagoya City Higashi Municipal Hospital in the eastern area or Nagoya Daini Red Cross Hospital in the southern area. In addition, community controls were also randomly selected among people living in the same area as the SAH patients. Accordingly, the effects of selection bias, if any, seem small. However, the generalizability of our results is considerably limited by the patients’ age (30 to 79 years) in this study. Second, no significant differences in distribution of potential confounders were observed between hospital and community controls, suggesting that information bias was not large in this study. Third, in this study information was provided by proxy respondents in...
approximately one third of the cases (for subjects who had died or were too seriously impaired).

As previously reported,29 however, proxy respondents provided acceptable information for family history of SAH, hypertension, smoking, and drinking, and according to Longstreth et al.,30 partner agreement regarding reproductive history was sufficiently high. The associations observed between reproductive history and SAH risk in this report were altered after the data were reanalyzed with the exclusion of data obtained from proxy respondents (not shown). Finally, in this study some variables analyzed were based on small numbers of cases and controls. It is possible that our results may be somewhat overestimated. However, a significant increased risk for age at menarche or gravidity remained after the cutoff point changed from 0 versus ≥1 to 0.1 versus ≥2. It seems unlikely that the observed associations were entirely due to small numbers of cases and controls, suggesting that earlier age at menarche or lower number of pregnancies may influence increased risk of SAH.

Two strengths of the present investigation warrant mention. First, all SAH patients in this study were newly diagnosed, and we included live and deceased subjects to avoid the distorting effect of survival bias. Second, bias due to disease misclassification is also unlikely because all the patients recruited were those with aneurysmal SAH diagnosed by cerebral angiography and CT, and control subjects with possible SAH events were not included.

In summary, our study clearly suggests that hormonal, metabolic, or other effects of menstrual and reproductive history may exert an influence on SAH risk.

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References

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