Parity and Risk of Subarachnoid Hemorrhage in Women
A Nested Case-Control Study Based on National Swedish Registries

David Gaist, MD, PhD; Lars Pedersen, MSc; Sven Cnattingius, MD, PhD; Henrik Toft Sørensen, MD, PhD

Background and Purpose—Subarachnoid hemorrhage (SAH) is the only type of stroke with female predominance, suggesting that reproductive factors may play a role in the etiology. We conducted a population-based study to examine the influence of parity on the risk of SAH in women.

Methods—We linked data from 3 national Swedish registries to identify first-ever hospitalizations for SAH in a cohort of women followed up since first childbirth during 1973–1997. Within this cohort, we conducted a nested case-control study and estimated the odds ratio (OR) and 95% CI of SAH by parity adjusted for age, calendar period, and length of follow-up. Information on smoking habits before the subject’s first childbirth was available in a subset of the data (women with first births during 1982–1997).

Results—Of the 887 cases identified, 70% had suffered from SAH ≥5 years after giving birth to their last child. The OR declined with increasing parity (1 child: reference; 2: OR=0.83 [95% CI, 0.70 to 0.99]; 3: OR=0.72 [95% CI, 0.58 to 0.91]; 4: OR=0.72 [95% CI, 0.48 to 1.08]; ≥5: OR=0.67 [95% CI, 0.32 to 1.41]). Adjusting for daily cigarette consumption before first childbirth in the subsample in which this information was available reduced but did not eliminate the association of the disorder with parity.

Conclusions—Parity may confer a moderate long-term protective effect on the risk of SAH. The biological mechanism underlying this association is currently unknown. (Stroke. 2004;35:28-33.)

Key Words: cigarette smoking ■ epidemiology ■ parity ■ stroke ■ subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) is caused, in 85% of cases, by a ruptured aneurysm. The disorder primarily affects individuals aged <60 years, carries a high morbidity and mortality rate, and is the only type of stroke that afflicts women more than men.1,2 The gender gap may provide clues about the pathology of this disorder.3 Efforts to explain the female susceptibility to SAH have hitherto focused mainly on exogenous factors (use of oral contraceptive and hormone replacement therapy) and endogenous hormonal (mainly menopausal) factors.4,4 The influence of reproductive factors such as parity has received relatively little attention. Three studies examining the associations of parity and gravidity with stroke did not provide separate estimates for SAH.6–8 Two recently published case-control studies with well-characterized cases of SAH yielded conflicting results concerning parity,9,10 possibly because of limitations of methodology and sample size.

To investigate further the effect of parity on SAH, we performed the present nationwide population-based study in which we followed a large cohort of parous women for SAH through registries with decades of national coverage.

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Subjects and Methods

Registry Data
The present case-control study, nested within a population-based cohort, was based on data from 3 nationwide Swedish registries: the Inpatient Register, Birth Register, and Cause of Death Register. The coverage of the Inpatient Register of in-hospital admissions in Sweden increased over time, from 60% in 1973 at the time the registry was founded, to 80% in 1980, and to >99% since 1987.11 Discharge diagnoses are recorded according to the International Classification of Diseases, Eighth Revision (ICD-8) (1969–1986), International Classification of Diseases, Ninth Revision (ICD-9) (1987–1996), and International Classification of Diseases, Tenth Revision (ICD-10) (since 1997). Recorded data include the dates of admission and discharge, up to 6 discharge diagnoses (8 discharge diagnoses in 1997), and up to 6 codes for surgical procedures performed (12 codes in 1997).11

The Birth Register covers >99% of all deliveries in Sweden.12 Since 1982, the Birth Register also includes data on the mother’s daily consumption of tobacco (none, 1 to 9 cigarettes daily, and ≥10 cigarettes daily), which was recorded at the time of the women’s first visit to the antenatal clinic.
The Cause of Death Register, which has been computerized since 1961, includes person-specific information about date and cause of death of all deaths in Sweden. Information from these registers was linked by means of the unique, national registration number assigned to each resident in Sweden. All Swedish residents have access to tax-supported medical care.

Study Population
We identified a cohort comprising all women with a record of a first childbirth in the Birth Register from January 1973 through December 1997, a total of 1,082,658 primiparous women. Information on any subsequent births was also retrieved from the Birth Register. The dates of death for deceased women were available through previous linkage of the Birth Register with the Cause of Death Register, but only for subjects giving birth in 1987–1997. Data on admissions to hospitals in Sweden were retrieved from the Inpatient Register from the earliest date available (1973) and until 1997.

Women entered the cohort at the time of their first childbirth and were followed up until 1 of the following events occurred: a first-ever admission for SAH, death, or end of the study period (December 31, 1997), whichever came first.

Definition of Cases and Controls
For a nested case-control study within the cohort, cases were defined as women with a discharge diagnosis of SAH (ICD-8 or ICD-9: 430; ICD-10: I60) at any time during follow-up. The date of first admission for SAH was considered the index date.

Excluded from the study were the following: (1) women who had an Inpatient Register diagnosis of SAH dated before their first childbirth; (2) cases with concurrent diagnoses of potential nonaneurysmal causes of SAH on their index admission (ie, trauma, arteriovenous malformation, or cerebral neoplasm) (n=39); (3) cases with any registered diagnoses of a number of rare disorders reported to predispose to SAH (eg, polycystic kidney disease, Ehlers-Danlos disorder, congenital heart disease) (n=3); and (4) cases of SAH that arose during the puerperium (up to 6 weeks after delivery) (n=23), since this is a period with excess risk of not only ischemic stroke and intracerebral hemorrhage but probably also SAH because of short-term postpartum changes in hemodynamics, coagulation, or vessel walls.

For each case, we identified all women in the cohort who were still at risk on the index date of the case, were of the same age as the case (year of birth), and had been followed up for the same length of time (year and month of first childbirth). As with the cases, controls were ineligible if identified within 6 weeks of their latest childbirth. We randomly selected 10 eligible controls for each case. Fewer than 10 controls were matched in 7.7% of cases, but only 1.1% of case-control sets included fewer than 5 controls.

Validity of Discharge Diagnoses
Since we did not have access to hospital records, we relied on the validity of the registry diagnosis of SAH. In a previous Danish study in a highly comparable setting, a neurologist with access to medical records validated the inpatient registry diagnosis of SAH (ICD-8 and ICD-10 codes) according to strict predefined criteria. The degree of misclassification was found to be <20%. Among the validated cases in that study, 25 had also received codes for operative procedures for aneurysms, all of whom were classified as definite cases of aneurysmal SAH (D. Gaist, MD, PhD, unpublished data, 2000). Guided by these findings, we identified all cases in the present study with a diagnostic code for SAH who had also received a code for an aneurysm operation at any admission within 21 days of the index admission. The 21-day time limit allowed for transfers between departments. We termed this subsample the aneurysmal surgery group.

Definition of Parity and Potential Confounders
Parity was defined as the number of children recorded in the last childbirth record of each woman registered during follow-up, ie, before the index date. Parity was classified into 5 groups: 1 child (reference group), 2, 3, 4, and ≥5 children. Multiple births (eg, twins, triplets) contributed to parity with the number of children born. The time gap between last recorded delivery and date of index date was also determined (<1 year, 1 to 4 years, 5 to 9 years, ≥10 years).

Women with any cesarean deliveries were identified because this mode of delivery might be a proxy for pregnancies with problematic conditions that carry a high short-term risk of SAH. Women with multiple births, who might have been exposed to exogenous hormone stimulation, were likewise identified.

Statistical Analyses
We used conditional logistic regression analysis to estimate odds ratios (ORs) and 95% CI of SAH by parity. With the matched design, these ORs took into account age at index date, follow-up period, and calendar date. Cesarean delivery and multiple births were not included in the conditional logistic regression since they changed the crude OR for parity by <10%. In nested case-control studies, the OR is an unbiased estimate of the relative risk.

To further minimize issues of bias, confounding, and censoring, we repeated the analyses in 2 subgroups: the aneurysmal surgery group and women aged ≥40 years at the time of diagnosis.

We adjusted for the effect of smoking in the subset of data that included this information, ie, women with first births during 1982–1997. Subjects from this subset with missing information on smoking (4% of cases and controls) were included in the reference group because a separate analysis indicated that the OR of SAH in the group with missing information (OR=1.07) was highly comparable with that of the reference group (OR=1.0).

Trends in ORs over parity were tested by means of the χ² for trend test. The data were analyzed with the use of the SAS version 8.02 statistical package (SAS Institute Inc).

Results
After application of the exclusion criteria, a total of 887 cases of SAH were identified, matched to 8512 controls. The median age of cases at the time of diagnosis was 38.1 years (range, 17.7 to 62.1 years), and they had been followed up for a median of 12.9 years.

Most cases suffered from SAH >1 year after their last registered childbirth (93%); in 70% of cases, ≥5 years had elapsed (Table 1). Twin births were equally frequent in cases and controls, but cesarean deliveries were more frequent among cases. The parity of cases was less than that of controls (Table 1).

The OR of SAH declined with increasing parity (1 child: reference; 2: OR=0.83 [95% CI, 0.70 to 0.99]; 3: OR=0.72 [95% CI, 0.58 to 0.91]; 4: OR=0.72 [95% CI, 0.48 to 1.08]; ≥5: OR=0.67 [95% CI, 0.32 to 1.41]) (χ² for trend: 8.2, P=0.004). The point estimates were not materially different in the restricted samples, but, probably because of the lower number of cases, parity was no longer significantly associated with risk of subarachnoidal bleeding (Table 2).

We separately analyzed the subset of cases with first births in 1982–1997 in which information was available on smoking habits at the time of the first visit to the antenatal clinic. Cases belonging to this subset were considerably younger (median age at diagnosis, 33.3 years [range, 19.9 to 55.7 years]) and had been followed up for a shorter period (median follow-up, 7.1 years). The distribution of parity in cases and controls in the subset is presented in Table 3. Adjusting for the effect of smoking in the subset reduced but did not eliminate the association with parity in all strata (Table 3). Daily cigarette
smoking recorded before first childbirth was clearly linked in a dose-response fashion to later-life relative risk of SAH (0 cigarettes: reference; 1 to 9 cigarettes: OR=2.31 [95% CI, 1.65 to 3.24]; ≥10 cigarettes: OR=3.68 [95% CI, 2.58 to 5.24]). This relation was even more pronounced in the subcohort with cases from the aneurysmal surgery group (0 cigarettes daily: reference; 1 to 9 cigarettes: OR=3.24 [95% CI, 1.80 to 5.80]; ≥10 cigarettes: OR=4.39 [95% CI, 2.25 to 8.59]).

**Discussion**

In this large, population-based study, we found that high parity was associated with a moderately reduced risk of SAH in women several years after their last childbirth. Controlling for smoking habits before first childbirth in a subset of the data in which this information was available somewhat reduced but did not eliminate the association.

The relation between childbearing and SAH has received little attention. Three studies ⁶–⁸ have focused on the risk of stroke in general or of ischemic stroke and found moderately elevated risks linked to gravidity and parity. Only 1 of these studies⁸ considered intracerebral hemorrhage. While it found a 2-fold to 3-fold increase in risk for parous compared with nulliparous women, the study comprised only 33 cases, and the CIs were wide.

Two recently published studies⁹,¹⁰ focused on the relation between childbearing and the risk of a first-ever SAH. In a


<table>
<thead>
<tr>
<th>Parity (no. of childbirths)</th>
<th>Cases, n (%)</th>
<th>Control, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>310 (35.0)</td>
<td>2524 (30.0)</td>
</tr>
<tr>
<td>2</td>
<td>396 (44.6)</td>
<td>3928 (46.2)</td>
</tr>
<tr>
<td>3</td>
<td>142 (16.0)</td>
<td>1625 (19.1)</td>
</tr>
<tr>
<td>4</td>
<td>31 (3.5)</td>
<td>340 (4.0)</td>
</tr>
<tr>
<td>5+</td>
<td>8 (0.9)</td>
<td>95 (1.1)</td>
</tr>
</tbody>
</table>

Age at index date*, years

| <30 | 139 (15.7) | 1359 (15.9) |
| 30–34 | 169 (19.1) | 1687 (19.8) |
| 35–39 | 224 (25.3) | 2206 (25.9) |
| 40–44 | 191 (21.5) | 1887 (22.2) |
| 45+ | 164 (18.5) | 1373 (16.1) |

Time since last birth†, years

| <1 | 60 (6.8) | 457 (6.3) |
| 1–4 | 207 (23.3) | 2212 (26.0) |
| 5–9 | 240 (27.1) | 2303 (27.1) |
| 10+ | 380 (42.8) | 3436 (40.7) |

Year of index date*, 1991–1997

| 1991–1997 | 585 (65.9) | 5642 (66.3) |

Had operation for aneurysm‡

| None | 281 (31.7) | NA |

Ever multiple births

| 12 (1.4) | 136 (1.6) |

Ever Caesarean delivery

| 185 (20.9) | 1299 (15.3) |


<table>
<thead>
<tr>
<th>Parity</th>
<th>All Women</th>
<th>Aged ≥40 Years on Index Date</th>
<th>Aneurysmal Operation*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>OR (95% CI)†</td>
<td>Cases</td>
</tr>
<tr>
<td>1</td>
<td>310</td>
<td>Reference</td>
<td>126</td>
</tr>
<tr>
<td>2</td>
<td>396</td>
<td>0.83 (0.70–0.99)</td>
<td>155</td>
</tr>
<tr>
<td>3</td>
<td>142</td>
<td>0.72 (0.58–0.91)</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>0.72 (0.48–1.08)</td>
<td>10</td>
</tr>
<tr>
<td>5+</td>
<td>8</td>
<td>0.67 (0.32–1.41)</td>
<td>4</td>
</tr>
</tbody>
</table>

*Restriction criterion only applicable to cases. Only cases with codes for operation at aneurysm at any admission within 21 days of index date included.

†OR (95% CI) indicates odds ratio (95% confidence interval). Odds ratio adjusted for index date, at index date, and length of follow-up.

**TABLE 3. Relative Risk Estimate of Subarachnoid Hemorrhage by Parity and Smoking Habits Prior to First Childbirth**

<table>
<thead>
<tr>
<th>Parity</th>
<th>Cases</th>
<th>Controls</th>
<th>Adjusted* OR (95% CI)†</th>
<th>Full-model† OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>103</td>
<td>851</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>2</td>
<td>108</td>
<td>1096</td>
<td>0.77 (0.55–1.07)</td>
<td>3.62 (0.62–1.24)</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>321</td>
<td>0.69 (0.43–1.14)</td>
<td>0.82 (0.50–1.35)</td>
</tr>
<tr>
<td>4+</td>
<td>4</td>
<td>75</td>
<td>0.40 (0.14–1.15)</td>
<td>0.45 (0.16–1.32)</td>
</tr>
</tbody>
</table>

Smoking cigarettes daily‡

| None | 130 | 1754 | Reference | Reference |
| 1–9  | 59  | 376  | 2.31 (1.65–3.24) | 2.27 (1.62–3.19) |
| 10+  | 55  | 214  | 3.68 (2.58–5.24) | 3.63 (2.54–5.18) |

Only women with first childbirth in Sweden in 1982–1997 are included.

*Adjusted OR: odds ratio adjusted for index date, age at index date, and length of follow-up.

†Full-model OR: odds ratio adjusted for index date, age at index date, length of follow-up, smoking, and parity.

‡Smoking habits recorded at first visit to antenatal clinic prior to first childbirth.

smoking recorded before first childbirth was clearly linked in a dose-response fashion to later-life relative risk of SAH (0 cigarettes: reference; 1 to 9 cigarettes: OR=2.31 [95% CI, 1.65 to 3.24]; ≥10 cigarettes: OR=3.68 [95% CI, 2.58 to 5.24]). This relation was even more pronounced in the subcohort with cases from the aneurysmal surgery group (0 cigarettes daily: reference; 1 to 9 cigarettes: OR=3.24 [95% CI, 1.80 to 5.80]; ≥10 cigarettes: OR=4.39 [95% CI, 2.25 to 8.59]).
case-control study involving 268 women with SAH, Mhurchu et al.6 found that parity (≥1 child) was not associated with the disorder (relative risk=0.93 [95% CI, 0.58 to 1.53]). In a smaller study of 124 cases of SAH, Okamoto et al.10 found that nulliparity conferred additional risk in Japanese women (relative risk=1.82 [95% CI, 0.76 to 17.5]). The conflicting results of these 2 studies may be due, at least in part, to methodological limitations. Proxy responses were used in 29% and 65% of cases, and in the study by Mhurchu et al.6 data on parity were missing in 9% of cases but in none of the controls. Furthermore, parous women were compared only with nulliparous women, and nulliparity may reflect an inability to conceive or complete a pregnancy because of health factors with unknown influences on the risk of suffering from a SAH. Possibly as a result of sample size limitations, the effect of the number of children was not explored in either of these studies.

The present population-based study was conducted within a uniformly organized health system with free access to medical care. The use of prospectively collected registry information safeguarded the study against potential bias introduced by recall and proxy-reported data, which may have influenced previous studies.

Nonetheless, this study has several other potential weaknesses. Both our inpatient data and vital status information were incomplete before 1987. The incompleteness of inpatient data may result in misclassification with regard to case status. However, this problem is unlikely to have biased our findings: the rarity of this disorder (≤1 case per 10,000 person-years) makes it highly unlikely that more than an extremely small fraction of controls was affected. The incomplete data on vital status would affect only controls and may have led to an overestimation of the time at risk and hence an underestimate of parity in this group. The direction of this potential bias is therefore conservative, and its magnitude is probably negligible because of the relatively low mortality rates in the age groups studied.

As a result of the short length of follow-up, not all women in our sample will have completed their reproductive history. The effect of this potential lack of information appears to have little impact on our findings, as illustrated by the analyses restricted to women aged ≥40 years at index date, at which point a more complete reproductive history can be assumed. Although the birth register covered births, including stillbirths, it did not include information on abortions. We were therefore unable to explore the possible role of gravidity on the risk of SAH.

Use of an inpatient register to capture cases necessitates that patients are admitted to the hospital and have correctly coded diagnoses. Studies of intensive monitoring of stroke in Sweden have shown that approximately 90% of all cases of SAH are hospitalized.17 Most of our cases occurred during a time period that had wide availability of neuroimaging facilities, a factor known to influence positively the validity of diagnosis.18 Restricting the sample to patients who also had codes for aneurysmal operative procedures yielded results that were highly comparable to the main analysis, indicating that misclassification of diagnosis is not of major concern. Furthermore, we have no reason to believe that the complete-ness or validity of the data on SAH depended on the patient’s reproductive history.

Hypertension and alcohol consumption are recognized risk factors of SAH.2 The association of gravidity with hypertension and systolic blood pressure was examined in a large cross-sectional study in the United States,19 which reported modest associations of increasing gravidity with lower systolic blood pressure and hypertension. A cross-sectional survey of 3576 Norwegian women aged 40 to 42 years found high parity to be correlated with low intake of alcoholic beverages.20 Thus, an important limitation of our study was the lack of data on accepted risk factors for SAH such as hypertension and alcohol abuse as well as more contentious ones (eg, oral contraceptives and hormone replacement therapy).

In the subset of data in which information on cigarette smoking at the time of the first antenatal visit was available, a clear dose-response relationship was established for this known risk factor, which was further enhanced when the sample was restricted to women who had undergone aneurysmal surgery. However, although residual confounding cannot be ruled out, our data indicate that the association between parity and SAH is not due to tobacco consumption since adjusting for this effect did not substantially change the results.

Our findings regarding parity can have only 3 likely explanations. Because of the nature of our study and the relative dearth of information on potential risk factors available, we cannot rule out that the observed associations are due to confounding. The size of the study makes random error a less likely explanation. A final intriguing possibility is that a woman’s reproductive history is causally linked to her risk of SAH.

In conclusion, our population-based data show that increasing parity, at least for women of a relatively young age, may protect against SAH. Our results suggest that reproductive factors and smoking play a role in the etiology of SAH.

References


Editorial Comment

Parity and Risk of Subarachnoid Hemorrhage: An Emerging Association

An individual’s risk of developing subarachnoid hemorrhage (SAH) is influenced by genetic and environmental factors. Emerging data have helped to shape our understanding of such factors, and the present work by Gaist and colleagues provides the most definitive efforts to date concerning the potential (inverse) association of parity and risk of SAH.

SAH possesses a number of unique peculiarities compared with other forms of stroke. Although the incidence of other forms of stroke may be decreasing, that of SAH does not appear to be on the wane. Additionally, an epidemiological sex discrepancy is apparent with SAH (the only form of stroke with a clear preponderance of afflicted women). Female sex also appears to have an association with increased risk of intracranial aneurysm formation and growth. Further characterization of this clear sex discrepancy may prove to have some utility in influencing our conceptualization of SAH and its potential prevention and therapy.

A gender gap in SAH has led a number of groups to examine potential hormonal influences on SAH. Although the risk of SAH (as is the risk of all types of circulatory disorders) appears to be significantly increased around delivery (from 2 days before to 1 day after), the overall influence of parity on the risk of developing SAH had heretofore not been clearly established due, at least in part, to methodological and sample size limitations. The present study by Gaist and colleagues helps to clarify the issue of parity and risk of SAH. Using national Swedish registries and a nested case-control design, the authors demonstrate that parity may provide a modest reduction in the risk of developing SAH. Of those individuals sustaining an episode of SAH, 70% did so 5 years or more after birth of their last child. Additionally, there was a general trend for increasing parity to be associated with correspondingly lower odds ratios. Smoking was once again confirmed as a risk factor for development of SAH.

The present study has a number of significant limitations, however, and the authors provide an earnest discussion of these issues. Despite being the most robust study to date concerning parity and risk of SAH, inadequate power is still apparent as evidenced by the fact that parity was no longer significantly associated with risk of SAH in restricted samples despite the point estimates being similar to those of the overall population studied. The registries themselves have some inherent limitations (missing data, potential misclassification, and no means of corroboration), although the authors cogently address this issue. There also appear to be small differences in certain baseline demographics (such as incidence of cesarean deliveries) between cases and controls. Furthermore, with the available data the authors were not able to control for the distribution of known risk factors for SAH between groups (such as hypertension and alcohol consumption). The follow-up also was not long enough to ensure all women had completed their reproductive history, although separate subgroup analysis of women >40 years of age suggested little potential influence. The above notwithstanding, this was a carefully thought out and overall well-conducted study.

The authors have objectively presented their findings concerning the association of parity with risk of SAH, although many questions remain. Speculation concerning the basis for a potential role of parity in conferring protection against the occurrence of SAH is intriguing. Future study may reveal a biological basis for this association, which, in turn, may contribute to our understanding of the pathogenesis of this disease. Alternatively, consideration of behavioral changes associated with pregnancy and the puerperium may be important. For instance, with a greater proportion of time spent by women in a period in which they may be more health conscious and avoid potential harmful exposures, one could postulate a lower risk of developing a condition dependent on, at least in part, certain environmental influences. Future work concerning the potential influence of parity on outcome may also be revealing. Certain known risk factors such as smoking may have some influence on outcome.
Ultimately, an individual’s risk of developing a given disease is dependent on a combinatorial mechanism, influenced by genetic and environmental factors. Delineation of predictive factors may provide valuable insight into the biology of disease and may also provide impetus for preventative therapeutic measures. Studies such as the present one by Gaist and colleagues represent a significant contribution to the literature concerning potential factors predicting risk of SAH. Although the mechanism by which increased parity may confer protection against future development of SAH in women remains unknown, further study of this emerging association is clearly warranted and explanation of this peculiar gender gap will hopefully culminate in advancement of our understanding of this lingering and devastating disease.

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References
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