Parity and risk of death from subarachnoid hemorrhage in women: Evidence from a cohort in Taiwan

Abstract—The authors examined the relationship in women between age at first birth, parity, and subarachnoid hemorrhage mortality. They followed each woman from the time of her first birth and linked vital status with a mortality database. The risk was increased by 8% for each additional year of mother's age at first birth. The relative risk was 0.63 for women who had borne two children and 0.62 for women with three or more births.

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Subarachnoid hemorrhage (SAH) is the only type of stroke that occurs more often in women than in men, for reasons that are poorly understood.[1]

Hypertension, cigarette smoking, and alcohol drinking are risk factors for SAH.[2] These risk factors, however, are more common in men than in women, so the excess of SAH in women is not related to these factors.

Hormonal factors, including oral contraceptive (OC) use[2] and hormone replacement therapy (HRT),[2] have been suggested as possible explanations for the female susceptibility to SAH. However, study results have not been consistent.

To date, there are limited data regarding the relationship between childbearing and SAH.[3-5] One study reported no relationship between parity and SAH[3]; a second study reported that there was an increase in the risk for SAH in women who had given birth to more than one child when compared with nulliparous women, but the association failed to reach significance[4]; and a third study reported a decreasing trend between the risk of SAH and increasing parity.[5]

We studied a cohort of women who experienced a first and singleton childbirth between January 1, 1978, and December 31, 1987, to further explore the relationship between parity and the risk of death from SAH.

Methods. It is the responsibility of the parents or the family to register infant births within 15 days. The registration form, which requests information on maternal age, education, parity, date of delivery, infant gender, and birth weight, is completed by the physician attending the delivery. The Birth Registration System, which is managed by the Department of Interior, has released computerized data on live births since 1978. Because most deliveries take place in either a hospital or a clinic and it is mandatory to register all live births at local household registration offices, the birth registration data are considered complete, reliable, and accurate.

The study cohort consisted of all women with a record of a first and singleton childbirth in the Birth Register between January 1, 1978, and December 31, 1987. Information on subsequent births was also retrieved from the Birth Register. Each woman has her own personal identification number, which was used to track the women from the time of their first birth to December 31, 2003. Their vital status was ascertained by linking records with the mortality database, identifying the date of any deaths occurring in this cohort.

The person-years of follow-up for each woman were calculated from the date of first birth to the date of death or December 31, 2003. Death rates were calculated by dividing the number of deaths from SAH by the number of person-years of follow-up. Cox proportional hazard regression models were used to estimate the relative risks (RRs) of death from SAH associated with parity (the number of children recorded in the last birth record of each woman registered during follow-up). SAH death is defined according to the ICD-9 (Code 430). The adjustment variables in the final model included age at first birth and parity. Analyses were performed using the SAS package. Values of $p < 0.05$ (two sided) were considered significant.

Results. Altogether, 1,292,462 primiparous women with complete information were included in the analysis (table). A total of 27,402,995.5 person-years were observed. There were 189 SAH deaths, yielding a mortality rate of 0.69 cases per 100,000 person-years. No significant effects of marital status, years of schooling, and birthplace on risk of SAH deaths were found (data not shown). After adjustment for age at first birth, the RRs for SAH death were 0.63 (95% CI = 0.42-0.94) for women who had borne two children and 0.62 (95% CI 0.41 to 0.94) for women with three or more births, when compared with women who had borne one child. The RR was 1.08 (95% CI 1.04 to 1.12) for each additional year of mother's age at first birth after adjustment for parity.

Discussion. We used a prospective study to examine the relationship between parity and the risk of death from SAH. Previous studies all used case–control designs.[3-5]

The results of previous studies concerning the association between parity and risk of SAH have been inconclusive.[3-5] Our study findings are in agreement with the results of a large population-based case–control study.[5] Other case–control studies[3,4] have found no significant association between parity and SAH. Our data, like the previous study with a positive result,[5] take into account the effect of the num-

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Table *Relative risk of death from SAH by age at first birth and parity*

Variable	No. of subjects	Follow-up person-years	No. of death from SAH	Mortality rate (per 100,000 person-years)	Crude RR (95% CI)	Multivariate-adjusted RR* (95% CI)
Age at recruitment (1st birth)						
≤25	859,942	18,528,113.08	102	0.55	1.00	—
26–30	372,895	7,687,356.67	70	0.91	1.78 (1.31–2.41)	—
>30	59,625	1,187,525.75	17	1.43	2.96 (1.77–4.96)	—
Continuous	1,292,462	27,402,995.50	189	0.69	1.10 (1.06–1.14)	1.08 (1.04–1.12)
Parity						
1	157,207	3,262,010.42	39	1.20	1.00	1.00
2	564,727	11,809,326.92	77	0.65	0.54 (0.37–0.80)	0.63 (0.42–0.94)
3+	570,528	12,331,658.17	73	0.59	0.47 (0.32–0.69)	0.62 (0.41–0.94)

* Mutually adjusted.

SAH = subarachnoid hemorrhage; RR = relative risk.

ber of children on the risk of SAH. In other studies, however, 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 SAH.[5]

We found that the risk of death from SAH increases with age at first birth. The reasons are unknown, but they may relate to long-lasting hormonal changes including lower sex hormone–binding globulin (SHBG) levels and higher total estrogen levels. Lower levels of SHBG have been suggested to be associated with decreased serum levels of estradiol bound to SHBG, and with lower bioavailability, resulting in atherogenic changes and hypertension[6] and possibly in increases in the risk of SAH.

The mechanism by which increased parity may confer protection against future development of SAH in women remains unknown. 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.[7] In contrast, nulliparity has been associated with increased estradiol levels. Estrogens lead to increased blood pressure[7] and therefore may increase the risk of SAH.

Mortality data rather than data on inpatient cases were used in this study; however, the mortality of a disease is a function of its incidence and fatality rate. Lack of verification of the diagnosis of SAH may include many patients with intracerebral hemorrhage (ICH). ICH occurs twice as often as SAH,[8] and distinction between these two types of hemorrhage without CT scanning or MRI is erroneous in approximately 20% of patients.[9] The proportion of patients in whom the diagnosis is confirmed by CT or MRI is not available in this study. However, there is no reason to believe that the misclassification of SAH deaths might have occurred differentially by parity, and therefore, this factor was unlikely to account for the association we observed.

Cigarette smoking, alcohol drinking, and hypertension have been documented as risk factors for SAH.[2] The prevalence rates of cigarette smoking and alcohol drinking are low (approximately 5%) in Taiwanese women.[10] Given these low prevalences, the association between parity and SAH deaths in our study is unlikely to be affected remarkably by these behaviors. There is no information available on hypertension for individual study subjects, and thus it could not be adjusted for directly in the analysis. However, there is no reason to believe that there would be any correlation between hypertension and parity.

Hormonal factors including OC use and HRT have been used to explain the female susceptibility to SAH, but we were unable to adjust for these two factors in the current study because of the lack of available data. Because OC use and HRT are uncommon in Taiwan compared with Western countries, the confounding effect resulting from these two factors should be small, if they existed at all.

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