The Risk of Aneurysmal Subarachnoid Hemorrhage During Pregnancy, Delivery, and the Puerperium in the Utrecht Population

Case-Crossover Study and Standardized Incidence Ratio Estimation

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Background and Purpose—It is unclear whether the risk of aneurysmal subarachnoid hemorrhage (aSAH) is increased during pregnancy, labor, and the puerperium. We compared the risk of aSAH during this period with the risk outside this period.

Methods—We included women with aSAH between 18 and 42 years of age (n=244) from our prospectively collected database of patients with subarachnoid hemorrhage treated in the University Medical Center Utrecht, the provincial referral center, between January 1987 and April 2006. We estimated the relative risk of aSAH during pregnancy, delivery, or the puerperium by a case-crossover design and calculated a standardized incidence ratio, dividing the observed number of patients with aSAH during pregnancy, delivery, or puerperium by the expected number based on the incidence in the general population of women of the same age during the study period.

Results—Of the 244 women, 4 were pregnant, 3 in the puerperium and none in labor. The relative risk of aSAH during pregnancy, delivery, or the puerperium was 0.4 (95% CI, 0.2 to 0.9). Based on the number of women aged 18 to 42 years within the catchment area of our hospital and the number of pregnancies within the study period, the expected number of patients with aSAH during pregnancy, delivery, or the puerperium was 12, resulting in a standardized incidence ratio of 0.6 (95% CI, 0.2 to 1.1).

Conclusions—The risk of aSAH is not increased during pregnancy, labor, and the puerperium. There is no need to advise against pregnancy in women with an increased risk of subarachnoid hemorrhage and no evidence to advise against vaginal delivery in such women. (Stroke. 2009;40:000-000.)

Key Words: aneurysms ■ epidemiology ■ postpartum ■ pregnancy ■ SAH

Aneurysmal subarachnoid hemorrhage (aSAH) during pregnancy, delivery, and the puerperium is a serious condition for the mother and the unborn child. The reported maternal case-fatality from aSAH during pregnancy or the puerperium is comparable with the 50% case-fatality of subarachnoid hemorrhage (SAH) in general.1,2 The fetal case-fatality is approximately 17%.2 Maternal mortality in the Western world is approximately 10 per 100 000 deliveries.3,4 Because the number of direct deaths (those related to complications directly related to the pregnant state) has fallen strikingly over the past decades, death from indirect causes has become increasingly important.1,5,6 SAH may account for up to one of 10 of all maternal deaths in pregnant women and up to one of 4 maternal deaths from indirect causes.3

The reported frequency of SAH in pregnant women and during the puerperium ranges from 8 to 31 per 100 000 deliveries.7-11 The incidence of aSAH for women in general is 11.5 per 100 000 person-years and increases with age.12 It remains unclear whether the risk of aSAH is increased during the period of pregnancy, delivery, and the puerperium. Some have suggested that the risk of SAH during pregnancy, delivery, or the puerperium is higher than outside this period,13-16 whereas others concluded that rupture of an aneurysm is not more common during pregnancy than at other times.16 An increased tendency of aSAH with advancing gestational age has been suggested and related to the hemodynamic changes that occur during the course of pregnancy.2,4,17

The purpose of this study was to assess whether the risk of aSAH is increased during pregnancy, delivery, or the puerperium in comparison with the time that women are not pregnant, in delivery, or in the puerperium.
Methods
We estimated the relative risk of aSAH during pregnancy, delivery, or the puerperium by means of the case-crossover design and by calculating a standardized ratio for the incidence of aSAH (observed number of patients with aSAH during pregnancy, delivery, or the puerperium/expected number of patients with aSAH during pregnancy, delivery, or the puerperium). Women were selected from a prospectively collected database of 2231 patients with SAH referred to the University Medical Center Utrecht, The Netherlands, between January 1987 and April 2006. The University Medical Center Utrecht functions as the referral center for all patients with SAH in the region of approximately the province of Utrecht.

The diagnosis of SAH was based on the presence of extravasated blood in the basal cisterns on CT scan or, in patients without SAH on CT scan, on xanthochromia of the cerebrospinal fluid in the presence of an aneurysm. Presence of an aneurysm was confirmed by means of CT angiography, MR angiography, or catheter angiography. Patients with an aneurysmal pattern of hemorrhage on CT in whom CT angiography, MR angiography, or angiography had not been performed because death was imminent were not excluded. For the present analysis, we included all women with an aSAH between 18 and 42 years of age (n=244), because in the general population, 99% of pregnancies occur in women in this age range.

Case records were reviewed for occurrence of SAH during pregnancy, delivery, or the puerperium. The puerperial period was defined as the period of 6 weeks after delivery. In patients with aSAH during pregnancy, delivery, or the puerperium, we retrieved information on maternal age, gestational age, or number of days into the puerperium at the time of aSAH, location of the aneurysm, mode of delivery, treatment of the aneurysm, and maternal and fetal outcome. Maternal outcome was categorized according to the 5-point Glasgow Outcome Scale: death (1), persistent vegetative state (2), severe disability (3), moderate disability (4), and good recovery (5).18 Of all 244 women with aSAH in the absence of pregnancy, delivery, or the puerperium, we retrieved information on the number of children born before the aSAH in a subgroup of 88 patients who had the aSAH between January 1987 and December 1996 and who were interviewed in depth on risk factors for SAH, including number of pregnancies before the SAH. We considered this cohort representative for the whole cohort of 244 patients and extrapolated the number of pregnancies in these 88 patients to the 149 included patients for whom no detailed history on the number of children born before the SAH was available.

To calculate the standardized ratio of the incidence of aSAH during pregnancy, delivery, or the puerperium, this incidence was compared with the overall incidence of aSAH in women aged 18 to 42 years. The expected number of women with an aSAH during pregnancy, delivery, or the puerperium in the province of Utrecht, the catchment area of the University Medical Center Utrecht, was calculated with data from the Statline data bank of Statistics Netherlands (http://statline.cbs.nl/StatWeb/?LA=en). We used the reported number of women aged between 18 and 42 years of age in the province of Utrecht and the number of childbirths in the midyear of the study period (1996). We extrapolated these numbers to the entire study period from 1987 through 2006 to determine the total number of women-years and the total number of childbirths during the total study period. With the number of women-years and the total number of 244 women aged 18 to 42 years admitted with aSAH during the study period, we calculated the observed incidence of aSAH in this age group. From the total number of children born during the study period, we calculated the total number of years of pregnancy and puerperium during the study period. From the observed incidence of aSAH and the total number of pregnancy years, we calculated the expected number of aSAHs during pregnancy within the study period.

Data Analysis
In the case-crossover study design, the risk for each case of having an aSAH while pregnant or in the puerperium was compared with the risk of having an aSAH outside this period for this individual patient.19,20 For the time at risk during pregnancy and the puerperium, we assumed a period totaling 9 months. We excluded the first 6 weeks of the pregnancy because the hemodynamic changes in relation to pregnancy are less prominent during this time than in the subsequent months and inclusion of these first 6 weeks of pregnancy could potentially result in an underestimation of the effects of pregnancy on the risk of aSAH. In a sensitivity analysis, we also assessed the risk of aSAH during pregnancy, delivery, and the puerperium with a risk period of 3 months instead of 9 months.

For each patient, the first 18 years of age were subtracted from the person-time at risk because in this period, the exposure to pregnancy is extremely small in The Netherlands. To compare the person-time at risk during the 9-month period from gestational Week 7 until Week 6 of the puerperium, we expressed the time at risk of a patient in “9-month periods” by multiplying the number of years by 129. For example, the person-time at risk for a woman of 30 years was calculated as (30−18)×129 equals 16 “9-month periods.” To assess the effect of a possible overestimation of the number of pregnancies by extrapolating the number of pregnancies in 88 patients with a detailed history to the other 149 patients who had an aSAH outside the period of pregnancy, delivery, and the puerperium, we performed a sensitivity analysis in which we assumed the number of pregnancies to be only half of the number observed in the 88 patients who were interviewed in detail.

The standardized ratio of the number of patients with aSAH during pregnancy, delivery, or the puerperium between 18 and 42 years of age in the period from 1987 through 2006 in the province of Utrecht was calculated by dividing the observed number of patients with aSAH during pregnancy, delivery, or the puerperium by the expected number of patients in this age range during this time period.

Results
Of the 244 women with aSAH between the ages of 18 and 42 years, 4 were pregnant and 3 were in the puerperium. Of the 4 women with SAH during pregnancy, one had the aSAH in the first trimester, one in the second trimester, and 2 in the third trimester. None of the cases of aSAH occurred during delivery. Patient characteristics, location of the aneurysm, mode of delivery, treatment, and maternal and fetal outcome are summarized in the Table. In only one patient, the aneurysm was occluded before delivery; in 4 patients, the aneurysm was treated after delivery or induced termination of the pregnancy. Two patients died as a result of the aSAH before the aneurysm could be treated. Two of the 7 children died.

Risk of Aneurysmal Subarachnoid Hemorrhage During Pregnancy, Delivery, or the Puerperium Estimated by the Case-Crossover Method
The relative risk of aSAH during pregnancy, delivery, or the puerperium was 0.4 (95% CI, 0.2 to 0.9) compared with the risk of aSAH not during pregnancy, delivery, or the puerperium. In the sensitivity analyses, the relative risk for the assumption of a risk time of 3 months instead of 9 months for each pregnancy was 1.3 (95% CI, 0.6 to 2.8) and for the assumption of 50% less pregnancies in the women who had their aSAH outside the time of pregnancy and were not interviewed in person, the relative risk was 0.6 (0.3 to 1.3).

Standardized Incidence Ratio Estimation of the Risk of Aneurysmal Subarachnoid Hemorrhage During Pregnancy, Delivery, and the Puerperium
The number of women between the ages of 18 and 42 years in the catchment area of the University Medical Center...
Utrecht was 218 481 in Year 1996. For the study period of 19.3 years, this adds up to 4 216 683 (218 481×19.3) person-years at risk. We observed aSAH in 244 women between 18 and 42 years of age, resulting in an incidence of 5.8 per 100 000 person-years (244/[4 216 683/100 000]), which is comparable with the reported incidence of SAH in women in this age range.12 With an average number of births per year in the province of Utrecht of 14 818 during the study period, the relative risk estimates in this age range.12 With an average number of births per year in the province of Utrecht of 14 818 during the study period, the total number of births during the study period was 285 987, resulting in 214 490 person-years at risk (285 987×9/12). Based on an incidence of 5.8 per 100 000 person-years, the expected number of patients with aSAH during pregnancy or the puerperium in the period January 1987 to April 2006 in the catchment area of the University Medical Center Utrecht was 12 (214 490/100 000)×5.8). In fact, 7 patients with aSAH during pregnancy, delivery, or the puerperium were admitted, resulting in a standardized incidence ratio of aSAH during pregnancy, delivery, or the puerperium of 0.6 (95% CI, 0.2 to 1.1).

**Discussion**

We did not find an increased risk of aSAH during pregnancy, delivery, and the puerperium and we found no instances of aSAH during delivery. The results were similar in the case-crossover analysis using the time of pregnancy, delivery, and the puerperium as a trigger and the comparison between expected and observed numbers of aSAH during pregnancy, delivery, or the puerperium. The relative risk estimates in both analyses were comparable.

A case-crossover design can be used if the exposure is intermittent, the effect on risk is immediate and transient, and the outcome is abrupt.19 The onset of aSAH is abrupt, and therefore aSAH is a valid outcome in a case-crossover study. To our knowledge, the period of pregnancy, delivery, and the puerperium has not been used before as a trigger in a case-crossover study. Exposure to pregnancy, delivery, and the puerperium is intermittent, which is a prerequisite, but the duration is longer than that of most other triggers used in case-crossover studies. Because the start and the end of this period can be clearly delineated, and because the effect is transient, the period of pregnancy, delivery, and the puerperium is in our view a valid trigger in a case-crossover study.

Information on the risk of aSAH associated with pregnancy is limited. In contrast to our findings, some previous studies have suggested an increased risk of aSAH during pregnancy, delivery, or the puerperium, but these studies had important methodological weaknesses. One study that suggested an increased likelihood of aSAH during pregnancy considered an aSAH associated with pregnancy if it occurred in the time period from 2 years before until 2 years after the pregnancy.14 In our view, an effect of pregnancy on the risk of aSAH up to 2 years after pregnancy is unlikely and an effect on risk of aSAH up to 2 years before the pregnancy implausible. By including these instances of aSAH, this study has probably overestimated the association of pregnancy and aSAH. Moreover, the diagnosis of SAH was not based on CT, which is another source of overestimation in this study.21 Another study based its conclusion on the high numbers of observed and published patients with SAH during pregnancy, but lacked a proper control group.2 Although we found no instances of aSAH during delivery in our series, such patients have been reported,13,15 but rarely. In a nationwide Swedish study encompassing over 1 000 000 deliveries, 8 instances of SAH were found during delivery.15 In Sweden, the proportion of vaginal deliveries is high (85% in the year 2000) compared with some other Western countries but is comparable to that in The Netherlands.22,23 However, in the Swedish study, the period of delivery was defined as the 2 days before the actual delivery and the day thereafter. It is highly unlikely that the delivery itself increases the risk of SAH in the 2 days before delivery. Moreover, the diagnosis of SAH was based on International Classification of Diseases codes, and during pregnancy and delivery, the proportion of nonaneurysmal causes of SAH is higher than outside this period. For these 2 reasons, the increased risk of aSAH during delivery in that study is likely to be overestimated.

A weak point of our study is that we had detailed information on the number of pregnancies of only one third of the patients. We have, however, no reasons to assume that the number of pregnancies differed between the patients we...
could interview in detail and those we could not interview in detail. If the women we could not interview in detail would have had more pregnancies than those interviewed, the risk estimate would have been even lower than the one we found. Conversely, if the women who were not interviewed would have had fewer pregnancies than those interviewed, the overall time spent in pregnancy would have been smaller with an increased risk estimate as a result. The sensitivity analysis, estimating the number of pregnancies in the women who were not interviewed in person to be half of those found in the women who were, also showed no evidence for an increased risk of aSAH during pregnancy, delivery, or the puerperium. This strengthens our finding that pregnancy, delivery, and the puerperium do not increase the risk of aneurysmal SAH.

In our study, we could not include women with an aSAH who died before reaching the hospital. In general, approximately 12% of patients with SAH die before reaching the hospital.\textsuperscript{24} Autopsy after death of a young person is not routinely performed in The Netherlands, and autopsy of the brain requires separate permission. Because the overall outcome of hospitalized patients with SAH is similar between pregnant and nonpregnant women,\textsuperscript{2} it is unlikely that pregnancy leads to a higher proportion of women who do not reach the hospital alive. Thus, it is unlikely that the absence of an increased risk during pregnancy, delivery, and the puerperium is explained by a large proportion of patients who died before reaching the hospital. Another factor to keep in mind is that we used the province of Utrecht as the catchment area to calculate the expected number of aSAHs, whereas in fact, patients are referred also from outside the province of Utrecht. Thus, the 12 expected patients are probably a slight underestimation, and therefore the incidence ratio is a slight overestimation of the risk of aSAH during pregnancy, delivery, or the puerperium.

A strong point of the study is that we used 2 methods to analyze the risk of aSAH during pregnancy, delivery, or the puerperium and that these 2 different approaches resulted in the same conclusion with similar effect estimates. One of the approaches used estimated expected and actual observed instances of aSAH; the other used data from actual patients with aSAH only, thereby avoiding sources of bias usually encountered in case–control studies.

Our study was not designed to answer the question whether women with a known aneurysm before pregnancy have a higher risk of aSAH during pregnancy, delivery, or the puerperium if the aneurysm is left untreated. Because women who become pregnant are young, the tendency will usually be to treat the aneurysm irrespective of whether a pregnancy is considered. The study does also not answer the question whether one or more pregnancies increase the risk of aSAH later in life. The study does, however, show that the risk of aSAH is not increased during pregnancy, delivery, and the puerperium. Therefore, there is no need to advise against pregnancy and no evidence to advise against vaginal delivery in women with an increased risk of aSAH such as women with a previous episode of aSAH or women with a family history of aSAH.

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Disclosures
None.

References