Experimental and clinical studies

Pregnancy and the Risk of Hemorrhage from Cerebral Arteriovenous Malformations

Jonathan C. Horton, M.D., Ph.D., Wiley A. Chanters, M.D., Susan I. Lyons, R.N., Raymond D. Adams, M.D., and Raymond N. Kjellberg, M.D.

Department of Neurology and Neurosurgery (JCH, SLL, RDA, RNE), Massachusetts General Hospital, Boston, Massachusetts, and Department of Computer Medicine (WFC), George Washington University, Washington, District of Columbia

We conducted a retrospective analysis of 451 women with an arteriovenous malformation (AVM) of the brain to determine whether pregnancy is a risk factor for cerebral hemorrhage. A total of 540 pregnancies occurred among our patient population, resulting in 438 live births and 102 abortions. There were 17 pregnancies complicated by a cerebral hemorrhage. The hemorrhage rate during pregnancy for women with an unruptured AVM was 0.035 ± 0.005 per person-year. The hemorrhage rate for nonpregnant women of childbearing age with an unruptured AVM was 0.01 ± 0.002 per person-year. Pregnancy did not increase significantly the rate of first cerebral hemorrhage from an AVM (P = 0.35). We found that women with an AVM face a 3.5% risk of hemorrhage during pregnancy. Pregnancy is not a risk factor for hemorrhage in women without a previous hemorrhage. This conclusion assumes no selection bias exists in our study population; a bias would be introduced if the risk of fatal outcome were a hemorrhage were greater in pregnant women than in nonpregnant women. (Neurosurgery 27:867–872, 1990)

Key words: Cerebral arteriovenous malformation, Cerebral hemorrhage, Pregnancy, Proton beam therapy

Congenital arteriovenous malformations (AVMs) of the brain affect approximately 0.14% of the American population or about 350,000 individuals (5, 9, 23). The exact prevalence is uncertain because the number of persons harboring asymptomatic lesions is unknown. AVMs can often result from many years, until they present clinically with headaches, seizures, neurologic deficits, or hemorrhages (1). Of these diverse manifestations, the hemorrhage is the most frequent and dangerous.

For women of childbearing age with cerebral AVM, one of the most important questions is whether pregnancy increases the risk of an intracranial hemorrhage. Numerous case reports and clinical series have documented the occurrence of hemorrhages from an AVM during pregnancy (2, 4, 6, 7, 10, 12, 20, 28), suggesting that pregnancy is a risk factor for hemorrhage. In one large study, Robinson et al. (23) found that pregnancy carries an 81% risk of hemorrhage. This report has been cited widely in the neurologic literature (21, 26, 27), and some physicians routinely warn women with an AVM to avoid pregnancy. Other investigators have expressed doubt that pregnancy increases the incidence of hemorrhage from a cerebral AVM (24, 29, 31).

Over the past decade, almost a thousand patients with an AVM of the brain have been referred for treatment with proton beam radiation at the Massachusetts General Hospital (17). A considerable number of women among this patient population have borne children in the course of, and hemorrhages during pregnancy have been rather infrequent. We therefore undertook this retrospective study to reexamine the risk of hemorrhage from a cerebral AVM during pregnancy.

METHODS

A total of 451 women received proton beam therapy between January 1977 and June 1986. On hospital admission, a detailed medical history was obtained from each patient. Each patient also received a comprehensive neurologic evaluation. In every case, the existence of an AVM was confirmed by cerebral arteriography performed at the Massachusetts General Hospital a few days before treatment. In 1986, a two-page questionnaire was mailed to all surviving women aged 18 years or older, inquiring about details of their neurologic and obstetrical history. In particular, each patient was asked the exact dates and circumstances of each intracranial hemorrhage, dates and outcome of each pregnancy, and whether a hemorrhage had occurred either during or after any pregnancy.

Of 390 questionnaires sent, direct replies were received from 343 patients. The hospital medical record of each patient was reviewed and corroborated with information reported in the questionnaire. In the event of any discrepancy, the patient was contacted by telephone for clarification. There were 47 patients who never responded to the questionnaire or to subsequent follow-up inquiries. In addition, 10 women had died of a cerebral hemorrhage since undergoing proton beam treatment. One patient had died of hepatic carcinoma.

No questionnaires were mailed to patients less than 18 years of age; there were 50 patients in this category. Therefore, in a total of 108 (47 + 10 + 1 + 50) cases, we obtained the obstetric and neurologic history from the hospital medical record, without the benefit of direct communication with the patients.
patient. If the medical record was incomplete, we contacted referring physicians or outside hospitals for further details. In some instances, we obtained information from family mem-
bers, relatives, or acquaintances. By this approach, it was possible eventually to compile a complete hemorrhage record and obstetrical history for all 451 patients up to the date of 
proton beam treatment.
For each patient, events up to the date of proton beam therapy were included in our analysis. This study assumes that an AVM is a congenital lesion, present before actual diagnosis. All hemorrhages and pregnancies that occurred after proton beam therapy were excluded. Therefore, this study examines the risk of hemorrhage during pregnancy for an untreated AVM only.
A cerebral hemorrhage associated with pregnancy was de-
fined as occurring any time during a 1-year period. This 1-
year period consisted of 40 weeks of gestation, beginning from the last menstrual period, plus an additional 12-week post-
partum interval. A postpartum interval was included because the anatomical and physiological changes induced by preg-
nancy do not resolve immediately after delivery. Although traditionally the puerperium is regarded as a 6-week period, we designated a 12-week postpartum period to maximize the possibility of detecting any prolonged or delayed effects of pregnancy.
Many pregnancies terminated prematurely in either a sponta-
nous or planned abortion. Abortions occurred on the average at 11.8 ± 3.7 weeks of gestation. Since 11.8 weeks represent 0.3 (1.1/3.40) gestational weeks of the duration of a full-term pregnancy, all aborted pregnancies were weighted accordingly. A hemorrhage associated with these interrupted pregnancies was defined as occurring any time during gesta-
tion or during a proportionate postabortion period. For ex-
ample, if an abortion occurred at 20 weeks, a 6-week posta-
borption period was designated.
Two women gave birth to twins, and one woman had triplets. These three cases of multiple births were counted as single live births.

Statistical analysis
The data are expressed as means ± standard deviation. For all patient categories, hemorrhage rates and confidence inter-
vals were determined by application of the person-years method described by Kahn (14). The means were compared by employing the t test for population proportions (10).

RESULTS
The data for our study population are summarized in Table 1. The mean age at the time of diagnosis of an AVM was 27.5 ± 12.9 years. On average, 4.1 years elapsed between the diagnosis and subsequent proton beam therapy. The age distribution of all patients at the time of diagnosis (fig. 1) indicates that an AVM is most likely to present clinically with a hemorrhage during the prime childbearing years.

The 451 women in the study lived from birth to the date of proton beam therapy for a combined total of 14,235 person-
years. There were 459 hemorrhages among the entire popu-
lation, yielding an overall rate of hemorrhage of 0.032 (459/ 
14,235) per person-year. Hemorrhages occurred in 273 of the 451 patients (60.5%). Therefore, an average of 1.7 hemor-
rhages (459/273) occurred in each woman with a history of hemorrhage.

Pregnancies occurred among 238 women, representing 52% (238/451) of the study population. There were 540 pregnan-
cies, resulting in 438 live births and 102 abortions. The summed duration of these pregnancies was equivalent to 468.0 person-years (438 ± 102.0). Hemorrhages occurred during 17 pregnancies. Therefore, the hemorrhage rate during pregnancy was 0.036 per person-year (17/468.0). This figure is close to the overall hemorrhage rate of 0.032 per person-
year calculated above for all patients.

Of the 17 cerebral hemorrhages that took place during pregnancy, 14 occurred during gestation, whereas 2 occurred during the 12-week postpartum period. One hemorrhage oc-
curred 7 days after an elective abortion performed at 12 weeks of gestation. The hemorrhages did not show a tendency to cluster during any particular trimester of pregnancy (fig. 2).

Of the 14 pregnancies complicated by a cerebral hemor-
rhage during gestation, 3 resulted in an abortion and 11 resulted in healthy, full-term infants. One baby was born by vaginal delivery and 10 were born by cesarean section. Four of the mothers have permanent neurological deficits; the remaining 10 mothers have recovered completely.

Of the 438 live births among the entire study population, 375 occurred by vaginal delivery and 63 by cesarean section. None of the hemorrhages occurred during labor, vaginal delivery, or cesarean section.

After the diagnosis of a cerebral AVM, 126 patients sought medical advice concerning the risk of pregnancy. Instructions to avoid pregnancy were given to 101 patients, 42 of whom were advised to undergo sterilization. A total of 36 women subsequently underwent sterilization. There were 20 thera-
peutic abortions performed because of the risk of hemorrhage posed by an AVM.
FIG. 2. Week of occurrence for each case of an intracerebral hemorrhage associated with pregnancy. The point enclosed by a box denotes a hemorrhage that occurred 1 week after an elective abortion.

Calculation of rate of first hemorrhage during pregnancy:
Of the 238 women who became pregnant, 141 (58.6%) experienced a cerebral hemorrhage before the date of their protein beam therapy. Most hemorrhages occurred after pregnancy for two principal reasons. First, for most patients, a cerebral hemorrhage was the signal event that led directly to the diagnosis of an AVM and subsequent protein beam treatment. Pregnancy was unlikely to occur during the rather short interval of 4 years that averaged between diagnosis and protein beam treatment. Second, after a hemorrhage many women decided it was unsafe to have children or postponed childbearing until after treatment. Thus, the mere occurrence of a hemorrhage diminished the likelihood of a subsequent pregnancy.

A number of studies have reported that after a first hemorrhage, the risk of a second cerebral hemorrhage is increased (8, 11). Therefore, the small group of women in our population with a history of a previous hemorrhage probably faced an increased risk of hemorrhage during pregnancy. These patients may constitute a higher risk subgroup compared with the majority of patients—216 of the 238 women—with no history of a cerebral hemorrhage. We decided therefore to calculate separately the rate of first hemorrhage during pregnancy for these women with an unruptured AVM. These 216 patients accounted for 409 live births and 83 abortions. The duration of their pregnancies was equivalent to 433.9 person-years (409 + 83 × 0.3). Of the 17 hemorrhages associated with pregnancy, 15 occurred in women with no history of a hemorrhage before pregnancy. The hemorrhage rate during pregnancy from an unruptured AVM was therefore 0.035 per person-year (15/433.9) ± 0.005 (95% confidence interval, 0.024–0.045).

The rate of first cerebral hemorrhage in pregnant women was then compared with the rate of first hemorrhage in nonpregnant women of childbearing age. The distribution of ages at the time of pregnancy for all women in the study is graphed in Figure 3. All pregnancies occurred between ages 15 and 41 years. Therefore, we calculated the rate of first hemorrhage in nonpregnant women for the interval from age 15 to 41 years only. The rate was determined by simply calculating the rate of first hemorrhage for all women within this age bracket, excluding 1-year period for any pregnancies and excluding any hemorrhages associated with pregnancy. The rate was 0.031 ± 0.002 hemorrhages per person-year (95% confidence interval, 0.028–0.034). This figure was compared with the rate of first cerebral hemorrhage for pregnant women, 0.035 ± 0.005 (confidence interval, 0.024–0.045), and no significant difference was present (P = 0.35). The power (1 − β) to detect a twofold difference in rates at a 5% level would be 0.93.

FIG. 3. Distribution of patient ages at the time of pregnancy. For each 2-year group, the number of pregnancies terminating in an abortion is indicated.

DISCUSSION
Previous reports have stressed that the risk of hemorrhage from an AVM depends on the age of the patient (19, 20). The age distribution of patients at the first occurrence of a hemorrhage (Fig. 1) is consistent with this observation. The risk of a hemorrhage from an AVM appears lowest during childhood and the early teenage years, and then rises for the prime childbearing period. We cannot explain this aspect of the natural history of AVMs. Our data do not support the conclusion that pregnancy contributes to the increased risk of a hemorrhage that accompanies the childbearing years. The rates of first hemorrhage for pregnant women and nonpregnant women during the childbearing period are comparable.

The risk of first hemorrhage for pregnant women with an unruptured AVM is 3.5%. The risk of first hemorrhage for nonpregnant women of childbearing age is not significantly less.

For this study, pregnancy was defined as a 1-year period comprised of 40 gestational weeks and 12 postpartum weeks. Because gestation represents only 0.73 of a 1-year period, the risk of a hemorrhage occurring during gestation is only 2.7% (0.77 × 3.5%). This figure is important in weighing the threat that a maternal cerebral hemorrhage poses to the fetus.

Our figure of a 3.5% risk of first hemorrhage during pregnancy appears extremely low when compared with the 87% risk of hemorrhage reported by Robinson et al. (25). This discrepancy can be explained by reviewing their study. They identified a total of 23 patients from a large referral population in whom the diagnosis of an AVM was associated with pregnancy. In 21 of 24 patients, a subarachnoid hemorrhage was the first clinical manifestation. The authors concluded that pregnancy carries an 87% (21/24) likelihood of a hemorrhage from an AVM. The correct interpretation is that when an AVM becomes clinically evident in association with pregnancy, a hemorrhage will be the first manifestation in 87% of cases.

Among our population, symptoms leading to the diagnosis of an AVM developed during pregnancy in 28 patients. In 17 of these patients, a cerebral hemorrhage was the initial event. Thus, a hemorrhage was the first manifestation of an AVM.
in 61% of our pregnant patients. Our data are compatible with those of Robesson et al. (25) in suggesting that most cases of AVMs discovered during pregnancy will present with a cerebral hemorrhage.

Cerebral hemorrhages occurred fairly evenly throughout gestation and the postpartum period among our 17 patients who died during pregnancy. No particular interval of preg-
nancy appeared to be the most dangerous. Hemorrhages were not concentrated during Weeks 15 to 20 or Weeks 20 to 24, as reported by other investigators (25, 28). The scattered distribution of hemorrhages during pregnancy shown in Fig-
ure 2 supports indirectly the conclusion that pregnancy does not increase the risk of a hemorrhage.

Most obstetricians advocate a cesarean section for pregnant women with a cerebral AVM. The uterine contractions of labor and the Valsalva maneuvers of vaginal delivery are accompanied by dramatic, transient increases in blood pres-
sure, cardiac output, and cerebral blood flow (16, 22). It is possible, however, that these abrupt fluctuations may largely offset each other, resulting in only minor changes in transmural pressure across the fragile vascular channels of an AVM (12). In this study, most babies were born by normal, spontaneous vaginal delivery, simply because both the obste-
trician and the patient were unaware of the existence of the AVM during pregnancy. There were 375 vaginal deliveries, and none was complicated by a cerebral hemorrhage. It is not surprising that no hemorrhages occurred during parturition. If the overall risk of a hemorrhage during pregnancy is 3.5%, and labor and delivery constitute less than 0.3% of the total duration of pregnancy, the risk of a hemorrhage during labor or delivery is exceedingly low; however, a hemorrhage from an AVM during parturition has been reported in the medical literature (18). It is unknown whether the risk of hemorrhage can be reduced by performing a cesarean section. Until further evidence is available to address this point, the obstetrician must depend on clinical judgment to decide the best method of delivery.

Study limitations

Our findings cannot be applied to predict the risk of a hemorrhage during pregnancy for women with a history of a previous hemorrhage. This study included only 20 women who became pregnant after a previous hemorrhage (8 of these women were pregnant both before and after their first hem-
orrhage). They accounted for 48 pregnancies, resulting in 29 live births and 19 abortions. Two of the pregnancies were complicated by a hemorrhage. Therefore, the rate of cerebral hemorrhage for these women was 0.058 (2/35.7) per person-
year, but this figure is based on too small a sample to draw any firm conclusions. Our clinical impression is that a first hemorrhage, the risk of subsequent hemorrhage is in-
creased, as suggested by other investigators (6, 11). Our ob-
servations at the time of hemorrhage were consistent with this, because of the risk of a subsequent hemorrhage is more likely to be reported for proton beam treatment. Patients with a history of hemorrhages from AVMs should recognize that the risk of a recurrent hemorrhage is probably increased, and therefore that the risk of a hemor-
rhage is increased.

A second study limitation is that our calculation of the rate of first hemorrhage, for both pregnant and nonpregnant women, overestimates the true rate among the general popu-
lation. The precise number of individuals in the general population with cerebral AVMs is unknown, and our knowledge of the exact prevalence of asymptomatic AVMs and the risk of hemorrhages from asymptomatic AVMs is impossible to determine the true rate of hemorrhage in the
general population. An ideal study would identify an asymptom-
omatic group of patients and follow their natural history prospectively. There is no practical way to identify sizable numbers of individuals with occult AVMs. However, nonhemorrhages of untreated individuals might be expected. Consequently, this study was retrospective, based on patients who have come to medical attention because of symptoms from their AVMs and who are likely to be most representative of individuals seeking advice from a practicing physician. Our cohort is not in one important way: all the patients were referred for proton beam therapy. Usually, proton beam therapy is reserved for a minority of patients with lesions that are less amenable to surgical resection, either because of their large size or difficult anatomical location. The clinical profile of our patient population, reflected in terms of the age at diagnosis, percentage of patients experi-
encing a hemorrhage, and average yearly rate of hemorrhage, is similar to a patient population reviewed by a major surgical referral center (11). Beauchamp as patients referred for proton beam therapy represents a selected subgroup of all patients with cerebral AVMs, our findings should be interpreted cau-
siously.

Our study assumes that the risk of a fatal outcome after a hemorrhage is the same in pregnant women and nonpregnant women. About 10% of patients died after a first hemorrhage (13). If deaths were more likely to occur in pregnant women than in nonpregnant women, women who hemorrhaged dur-
ing pregnancy would be underrepresented in our study pop-
ulation, because they would survive in relatively smaller numbers to receive proton beam therapy. No direct information is available comparing the hemorrhage fatality rates from AVMs in pregnant women and nonpregnant women. Our conclusions are limited by this potential source of bias.

Some incidental data are provided by the Minneapolis Maternal Mortality Study on the rate of fatal hemorrhages occurring during pregnancy. From 1950 to 1973, there were 37 maternal deaths from hemorrhage among 1,763,824 pregnancies in Minnesota (3). Autopsies revealed a bony aneurysm in 25 cases and an AVM in 4 cases. If autopsies had been performed in all 37 cases, AVMs would have been expected in 5 cases. If the prevalence of AVMs is 0.0014, and the hemorrhage rate during pregnancy is 0.035, among 1,763,824 pregnancies, a total of 66 hemorrhages from AVMs would be anticipated. Assuming a fatality of 10%, about 1 or 9 maternal deaths would occur. This prediction is close to the total of 5 deaths recorded in the Minneapolis Maternal Mortal-
ity Study, providing some confidence in our figure for the rate of a hemorrhage during pregnancy.

SUMMARY

Women with AVMs of the brain harbor a lesion that may hemorrhage at any time, with a potentially lethal outcome. Faced with this danger, some women decide not to have children under any circumstances. Many women, how-
ever, consider the possibility of having children and desire a quantitative assessment of the risk of a hemorrhage during pregnancy. We found that the risk of a hemorrhage during pregnancy was 3.5% for patients with untreated AVMs. The risk of a hemorrhage is not significantly increased by pregnancy, since nonpregnant women of comparable age face the same annual risk of a hemorrhage. This conclusion is an important clinical guideline for the treatment of a cerebro-
bral hemorrhage. Women with a history of a previous cerebral hemorrhage likely face an increased risk (5.8%) of a hemorrhage during any subsequent pregnancy. In view of our findings,
the risk of a hemorrhage from AVMs during pregnancy may be considerably less than previously thought. We think that it is not unreasonable for women with AVMs to contemplate pregnancy, and that abortions and sterilizations should not be advocated on a routine basis.

For women with a history of a previous hemorrhage, the risk of a second hemorrhage occurring during pregnancy is not known accurately. We estimate that the risk is about 5.8%, but our data are very limited. The risk of a recurrent hemorrhage is about 5% in the year immediately after a first hemorrhage (11). Therefore, if pregnancy is planned, the risk of a recurrent cerebral hemorrhage may be reduced by allowing at least a year to elapse between the hemorrhage and any subsequent pregnancy. If the AVM can be treated by either surgical excision, embolization, or radiation, pregnancy should be deferred until treatment is completed. Pregnancy should be postponed at least 2 years after postradiation beam therapy (17).

ACKNOWLEDGMENTS

We thank Drs. Allan Ropper and Christopher Ogilvy for their critical review of the manuscript.

Received for publication, November 16, 1989; accepted, final form, June 12, 1990.

Research projects: Jonathan C. Horton, M.D., Ph.D., Neuro-Ophthalmology Unit, U-125, University of California, San Francisco, CA 94143-0350.

REFERENCES


COMMENTS

In this important manuscript, the authors present a novel approach to a subject that has been logically difficult for neurosurgeons to address. Utilizing a large pool of patients with intracranial arteriovenous malformations (AVMs) referred for postradiation therapy, the authors noted particular clinical situations that are at odds with much of the existing literature regarding AVMs and pregnancy. First of all, in this series, there was no tendency for hemorrhage to cluster at any particular time or during pregnancy, including labor and delivery. Second, the risk of a first cerebral hemorrhage among women with an intracranial AVM was not increased by pregnancy. Both conclusions follow logically from the data presented. Great caution should be exercised in applying these conclusions, however, particularly the latter, to the general population.

In the data analysis, the authors argue that intracranial AVMs are congenital. Although most investigators would agree with this assumption, it remains unproven, es- pecially for the whole gamut of AVMs. This assumption is particularly important here since the authors have indicated only 41 of the 238 women who became pregnant did so in the years between a proven diagnosis of an AVM and postradiation beam therapy.
It is also worthwhile to note that the definition of duration of pregnancy is somewhat arbitrary. The authors chose 52 weeks but could just as easily have chosen a different duration incorporating 40 weeks of gestation and some pre-pregnancy period. Had they chosen 44 weeks, the risk of a first pregnancy would have been increased to 0.0587% per person-year, and the difference between this and the 0.031% per person-year quoted for nonpregnant patients approaches clinical significance.

As the authors point out, this is a highly selected group of patients with several potential sources of bias. Perhaps the most important of these is that the study group could not include patients with an initial fatal intracranial hemorrhage from their AVMs. In addition, patients whose first hemorrhage was severely disabling would be very unlikely to be referred for proton beam therapy.

Previous data regarding unruptured intracranial AVMs (1) suggest that approximately 25 to 30% of initial ruptures are fatal. If one looks at this particular factor alone, it would suggest that among this group of 273 patients with ruptured AVMs, another 60 or so were eliminated from consideration because their initial hemorrhage was fatal. Even if only 15 of these patients had hemorrhaged during pregnancy, it would nearly double the rate of first cerebral hemorrhage from an AVM during pregnancy, and the conclusions would be much different.

David O. Webers
Rochester, Minnesota

In this paper, the authors address the controversial question of whether the risk of hemorrhage from a cerebral arteriovenous malformation (AVM) is increased by pregnancy. They have examined the pregnancy histories of a large number of patients with AVMs and have convincingly shown that the rate of hemorrhage from these lesions is unchanged by the occurrence of pregnancy and is similar to that described in two large studies (1, 2). The parallelism between the incidence of pregnancy and the age at diagnosis explains why there has been an apparent association between hemorrhages from AVMs and pregnancy. Their data suggest that the association is not a causal one.

As the authors recognize, there is a potential for nonverifiable bias of their results because the fact that all of their patients were referred for proton beam therapy. Since there appears to be an association between the size of an AVM and the likelihood that it will hemorrhage (1, 2), there is the potential for bias in the interpretation of the results. For example, larger AVMs might have been referred selectively for proton beam therapy to the authors' center. If this were the case, the natural history of the group of patients they examined may have been more favorable than that in the population of young women with AVMs as a whole. Until a population-based study of prospectively identified patients with AVMs can be conducted, however, these data probably represent the best that will be available to us to answer this important question.

Ralph G. Dacey, Jr.
St. Louis, Missouri

