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MATERNAL-FETAL MEDICINE

Prevalence, risk factors and pregnancy outcomes of women with vascular brain lesions in pregnancy

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Abstract

Background Vascular brain lesions (VBL) occur in up to 4.0% of the general population. With the increasing availability and use of sophisticated imaging techniques, there are more patients being diagnosed with asymptomatic intracranial AVMs and cavernous hemangiomas.

Objectives Here we evaluate the association between VBL in pregnancy and the maternal and fetal outcomes.

Study design The study cohort was identified by isolating all pregnancies from the nationwide inpatient sample (NIS), from the healthcare cost and utilization project (HCUP) over a five-year period. Within this cohort, cases with an arteriovenous malformation (AVM) or cerebral vascular malformations (CVM) were identified and their prevalence was calculated. Baseline demographic characteristics were compared and the odds ratios for various complications and outcomes were calculated.

Results Amongst 4,012,396 deliveries, VBL were identified in 214 cases: a prevalence of 5.33 cases per 100,000 deliveries. Majority of VBL cases were identified in women between 25 and 35 years of age, but the proportion of women aged 35 and older was greater amongst those patients with VBL. 74% of cases were of Caucasian race and more cases with VBL had a private insurance payer (62.1%). Seizure disorders were present in 63.6% of the cases with VBL. Whilst VBL are not associated with unfavorable obstetrical complications, they are more likely to be delivered by caesarean section (CS) − 79% of VBL cases were delivered by CS compared to 33% of the patients without VBL (OR 7.03 CI 95% 4.98–9.92). Instrumental delivery was performed in 10.3% of the vaginal deliveries for index cases. Index cases were less prone to fetal growth restriction. VBL accounted for 8.4% of 166 cases of intracranial bleeding occurring during the antepartum period within the entire pregnant population.

Conclusions Presence of VBL does not appear to carry additional risk to mother or fetus during pregnancy

Keywords Vascular brain lesions · Cerebral arteriovenous malformations · Cavernous hemangioma · Pregnancy

Introduction

Cerebral vascular malformations occur in 0.1–4.0% of the general population, developmental venous anomalies and capillary telangiectasia are usually benign, while cavernous malformations and arteriovenous malformations have a greater tendency toward neurologic sequelae [1].

Cerebral arteriovenous malformations (AVM) are uncommon, occurring in approximately 1–10 persons per 10,000 of the asymptomatic population [2, 3]. Cavernous hemangiomas (CVM) are more common, occurring in 40 people per 10,000 of the general population and represent around 1% of all intracranial vascular lesions [4–6]. The natural history of asymptomatic cerebral AVMs remains poorly understood as many may remain undiagnosed and only present with the development of symptoms or complications: for example,

The Study was done at McGill university, Montreal, Canada. The corresponding author has changed institution after completing the study.

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intracranial hemorrhage, seizures, headaches, and long-term disability [7, 8]. It is thought that the physiological changes in the cardiovascular system that occur during pregnancy might influence the likelihood for AVM hemorrhage in pregnancy [9].

Uncertainty also remains regarding the natural history of cavernous hemangiomas in pregnancy. Recent data contradicts the previously held hypothesis that these lesions may both increase in size and be at greater risk for bleeding in pregnancy as a consequence of the elevated hormone levels [10, 11].

With the increasing availability and use of sophisticated imaging techniques, there are more patients being diagnosed with asymptomatic intracranial AVMs and cavernous hemangiomas [7, 12]. Several studies have evaluated the risk of AVM rupture during pregnancy however the conclusions have been contradictory [13, 14]. Due to a dearth of data, the impact of these lesions on pregnancy management and outcomes remains ill-defined.

The purpose of our study is to evaluate the association between vascular brain lesions in pregnancy and the maternal and fetal outcomes in a large population-based database and endeavours to shed some light on this uncertainty.

Methods

The nationwide inpatient sample (NIS), from the healthcare cost and utilization project (HCUP) of the agency for healthcare research and quality (AHRQ) was examined for all pregnancy-related discharge codes inclusive in the years 2008 to 2012. The NIS represents the largest all-payer inpatient healthcare database, containing discharge data for more than 1000 hospitals, which represents a 20% stratified sample of community hospitals. Each hospital discharge represents a subject in the dataset with information recorded for demographic, non-clinical and clinical elements.

The study cohort was identified by isolating from the dataset of all pregnancies. All pregnancy-related discharges were identified by applying the International Classification of Diseases, 9th Revision ICD-9 codes (ICD-9 codes 630–648) or delivery codes (ICD-9 codes 74 for caesarean delivery and 72, 73, 75, v27, or 650–659 for vaginal delivery). Postpartum admissions constituted discharge records that contained a postpartum diagnosis (ICD-9 codes 670–677) and that did not also include a delivery code. We identified antenatal (pre-delivery) admissions by isolating from the pregnancy-related cases those without a delivery or postpartum code.

Within this cohort of pregnancies, cases with an AVM or CVM were identified using ICD-9 codes for AVM (747.81) and CVM (228.02); the control group was comprised of the remaining pregnant women without an AVM or CVM coded diagnosis. A list of the additional diagnostic and procedural codes that were examined during this study is presented in supplementary Table 1.

Due to the nature of this retrospective study it is not possible to determine wether the ICD-9 codes for AVM and CVM were given either in the current admission for delivery or before. The evaluation of the outcomes of pregnancy with VBL is relevant, base on whether the diagnosis was done during pregnancy or before.

The MUHC-REB has determined that research using anonymized data obtained from the HCUP database does not require any further REB review.

Statistical analysis

The prevalence of vascular brain lesions (VBL) was calculated with the denominator being all delivered pregnancies during the study period and reported as cases per 100,000 deliveries. Baseline demographic characteristics were compared using the Chi-Square or Fishers exact tests, as the appropriate. To calculate the odds ratios (OD) for various complications and outcomes, a logistic regression model with a 95% confidence interval (CI) was used for each of the observed outcomes or complications. Furthermore, this model was adjusted for maternal baseline characteristics.

Results

During the study period (2008–2012), we identified a total of 4,012,396 deliveries in the HCUP-NIS dataset. Vascular brain lesions (VBL) were identified in 214 cases that recorded a delivery during the same admission. This represents the prevalence of the vascular brain lesions of 5.33 cases per 100,000 deliveries. AVM and CVM were identified in 135 (63.1%) and 79 (36.9%) cases, respectively.

Examination of the baseline demographic characteristics is presented in Table 1. The majority of VBL were identified in women between 25 and 35 years of age, but the proportion of women aged 35 and older was greater amongst those patients with VBL. 74% of cases were of Caucasian race and more cases with VBL had a private insurance payer (62.1%). Seizure disorders were present in 63.6% of the cases with VBL. We examined obstetrical complications among pregnant women with VBL (Table 2). It does not appear that VBL are associated with unfavorable obstetrical complications. However, cases with VBL are more likely to be delivered by caesarean section (CS) regardless of the nature of their previous delivery. 79% of VBL cases were delivered by CS compared to 33% of the patients without VBL (OR 7.03 CI 95% 4.98–9.92). Additionally, instrumental delivery was performed in 10.3% of the vaginal deliveries among the index cases. The need for non-operative maternal

Table 1 Demographics of vascular brain lesions (VBL) in pregnancy at the time of delivery

Demographics	VBL *N* (%) *N* = 214	No VBL *N* (%) *N* = 4,012,182	*P* value
Age (years)			***
< 25	51 (23.8)	1,322,080 (33.0)	
25–34	122 (57.0)	2,108,078 (52.5)	
> 35	41 (19.2)	582,024 (14.5)	
Race			***
Caucasian	159 (74.3)	2,347,224 (58.5)	
Black	10 (4.7)	493,263 (12.3)	
Other	45 (21.0)	1,171,695 (19.2)	
Income (annual USD)			**
< 38,999	43 (20.1)	1,066,996 (26.6)	
39,000–47,999	50 (23.4)	994,506 (24.8)	
48,000–62,999	59 (27.6)	1,057,219 (26.4)	
> 63,000	62 (29.0)	893,461 (22.3)	
Primary payer			***
Medicaid	57 (26.6)	1,741,846 (43.5)	
Private insurance	133 (62.1)	1,998,386 (49.9)	
Other*	24 (11.2)	271,950 (6.6)	
Smoking	19 (8.9)	258,866 (6.5)	n.s.
Seizure disorders	136 (63.6)	3,816 (0.1)	***
Previous C-section	45 (21.0)	661,802 (16.5)	**

Chronic hypertension, pregestational diabetes were examined however cases were below the reporting for NIH-HCUP

*Others include Medicare, self pay and other payers

n.s. not significance $P > 0.05$

**$P < 0.05$

***$P < 0.01$

mechanical ventilation does not appear to be increased in cases with VBL. Fetal complications did not appear to be increased, interestingly fetal growth restriction (FGR) was less prevalent in the index cases, however, due to the small number of cases we cannot report this data [as per HCUP regulations]. Maternal death was a rare occurrence and, therefore, similarly we cannot report these data. There was a total of 166 cases of intracranial bleeding during the antepartum period from all causes within the entire pregnant population; VBL were associated with 8.4% of these bleeding cases.

Discussion

VBL are uncommon and for patients with such lesions who become pregnant there are concerns as to whether these might pose an increased risk of morbidity for the mother or impact upon the prognosis of their pregnancy [1]. Pereira et al. emphasized the increased maternal and fetal mortality when the lesions are first diagnosed in pregnancy and the lack of knowledge regarding the exact mechanism responsible for the interaction of pregnancy [15]. The objectives of this study were to examine a large population-based cohort to evaluate the prevalence of diagnosed AVM and CVM in pregnancy over time and to determine if there are any associations with obstetrical outcomes and maternal complications during pregnancy.

From the examined dataset, it appears that a diagnosis of VBL is more likely if the primary payer is a private insurance provider; this might contribute to the apparent higher prevalence of the diagnosis in Caucasian women. We cannot report on possible associations with chronic medical complications due to the small number of patients (lying below

Table 2 Pregnancy outcomes in patients with vascular brain lesions (VBL) at the time of delivery

Finding	VBL *N* = 214 (%)	No VBL *N* = 4,012,182 (%)	Crude OR (95% CI)	aOR* (95% CI)	*P* value
Pregnancy related hypertension	23 (10.7)	303,597 (7.6)	1.47 (0.95–2.28)	1.24 (0.80–1.93)	0.336
Pre-labor membrane rupture	12 (5.6)	200,212 (5.0)	1.13 (0.63–2.02)	0.88 (0.48–1.55)	0.668
Induction of labor	21 (9.8)	801,464 (20.0)	0.44 (0.28–0.68)	0.37 (0.23–0.58)	< 0.0001
Chorioamnionitis	Δ	72,675 (1.8)	0.51 (0.13–2.10)	0.42 (0.10–1.71)	0.229
Instrumental delivery	22 (10.3)	260,757 (6.5)	1.65 (1.06–2.56)	1.2 (00.81–1.98)	0.300
Cesarean section	169 (79.0)	1,330,414 (33.2)	7.57 (5.44–10.51)	7.03 (4.98–9.92)	< 0.0001
Postpartum hemorrhage	Δ	107,965 (2.7)	0.51 (0.16–1.60)	0.32 (0.11–1.16)	0.074
Mechanical ventilation	Δ	2,484 (0.1)	15.22 (3.78–61.32)	2.58 (0.63–11.10)	0.201
Preterm birth	15 (7.0)	289,497 (7.2)	0.97 (0.57–1.64)	0.67 (0.40–1.14)	0.136
Fetal growth restriction	Δ	90,466 (2.3)	0.61 (0.19–1.92)	0.31 (0.10–0.97)	0.044
Stillbirth	Δ	24,789 (0.6)	2.29 (0.73–7.15)	2.04 (0.63–6.55)	0.231
Fetal anomalies	Δ	30,351 (0.8)	0.61 (0.08–4.3)	0.20 (0.02–1.50)	0.105

Δ As per NIS-HCUP privacy protection regulations of NIS-HCUP subjects, cells equal to or less than 10 are not allowed to be reported

*Adjusted for maternal age, race, income, epilepsy and previous cesarean section

the NIH-HCUP limit for reporting) however, there was no difference in the smoking status between the groups. Seizure disorders are clearly evident in the VBL group and likely related to the lesions' presence. In our cohort, there was a significant reduction in the rate of fetal growth restriction (FGR) in the cases of VBL. There were no increases in other obstetrical complications in the VBL cases compared to controls. However, there was higher risk for delivery by CS and, probably consequential to this, a reduced likelihood for induction of labour (IOL). With respect to maternal complications, there was no increased risk for mechanical ventilation and although the trend suggested an increased risk of postpartum hemorrhage, this did not reach significance.

Prevalence data suggest that up to 0.5% of the population might have an AVM [7, 16, 17], but in series reporting autopsy findings, the rate increases to 1%. Some data indicate estimates for the occurrence of symptomatic lesions at 0.94 per 100,000 persons years [18]. AVM is the leading cause of non-traumatic intracerebral hemorrhage in people under 35 years of age [19]. CVM are the second most frequent vascular lesion in the CNS [20] with a prevalence ranging from 0.4% to 0.6% of the population [21] with an prevalence of 0.15–0.56 per 100,000 persons per year [22]. In our study, the combined prevalence of AVM and CVM was much lower. This might be because overall, pregnant women represent a younger and healthier population than those reported in prior studies that have reported prevalence or because our numbers reflect only previously diagnosed women who sought medical care or those who were diagnosed due to symptoms. In women developing symptoms in pregnancy, there may be a tendency to avoid imaging for those with milder symptoms, which might lead to a delay or failure of recognition of these conditions. Jamieson and coleuges reviewed the literature and concluded that a new-onset headache or new-onset neurologic symptoms necessitate imaging, contrast administration should be avoided in pregnancy if possible [23].

Existing data suggest that there is neither a difference in the prevalence between genders [18, 21, 22] nor an increased risk of haemorrhage in women with an AVM [7]. Therefore, the lower prevalence we observed is unlikely to be attributable to the fact that we report prevalence in a female only population.

According to the literature, cerebral AVM are usually found in young adults between the ages of 20 and 40 [24] but in a population-based study the mean age at diagnosis was 40 years [18]. In our study, the diagnosis of VBL also appeared to be related with increasing age.

The increased prevalence in the private insured patients might reflect better access to diagnostic testing and overall medical care.

Seizures characterize a frequent presentation of VBL [25] and are the most common symptom in CVM [22]. Although there is often a tendency to avoid imaging during pregnancy, there should be a low threshold for undertaking neuro-imaging when investigating seizures in pregnancy, particularly if unrelated to conditions such as eclampsia,this is supported by our data reporting the significant incidence of seizures in pregnant women with VBL.

There is conflicting evidence on whether pregnancy is associated with increased risk of intracranial haemorrhage in CVM [22] but recent papers tend to agree that there is no evidence for increased rupture of AVM in pregnancy [2, 24]. In our data, the cases with intracranial bleeding during the delivery admission were too few in number to permit reporting. Therefore, we examined all intracranial bleeding events occurring within our entire pregnancy cohort, and found that 8.4% of them were due to VBL. This is consistent with existing general population data, where structural lesions account for 5–14% of all intracranial haemorrhages [26, 27]. This provides additional data in support of the view that pregnancy per se does not appear to be a risk factor for hemorrhage from a cerebral AVM, either in the antenatal or intrapartum periods [28].

The preferred method of delivery in our cohort during the study period was by CS for the study group; the CS rate was 79% in the VBL group compared to 33% in the control group ($P < 0.0001$). The dataset does not provide us with information regarding the rate of elective CS deliveries, but the significantly lower rate of IOL in the VBL group of 9.8%, compared to 20% in the control group ($p < 0.0001$), might be reflective of a tendency to avoid vaginal delivery. We also found a higher incidence of prior CS in our study group that might contribute to the increased repeat CS rate in the study group.

Nonetheless, there is no clear evidence suggesting that vaginal delivery increases the risk of cerebral haemorrhage from an AVM, or that CS might protect against this. Although there is a relative lack of studies evaluating the mode of delivery in women with an intact AVM [17], one previous study of 64 cases of gestational cerebral cavernous malformation found no increase in the risk of bleeding with vaginal delivery [10]. Furthermore CS showed no advantage with respect to maternal or fetal outcomes when compared to vaginal delivery, in women following an intracranial haemorrhage from either an aneurysm or an AVM [29].

The rate of preterm birth before 37 weeks was not different between the study groups. This not only indicates no increased risk for spontaneous preterm birth but is also consistent with the lack of data indicating a reduced risk of maternal complications with elective preterm birth in such cases.

There was a difference in the rate of FGR between the groups, but the small number of cases prevent us from reporting these data and from controlling the confounders; therefore we are unable to draw any conclusions,

or speculate upon the possible reasons for this finding, although the rate of FGR in our control group was also lower than the typically expected rate for FGR in developed countries and this might be contributory [30, 31].

Stillbirth is a rare complication and due to the small numbers, we can not report the results for our study group. However, there were no apparent differences between the groups and the rate of stillbirth in the control group was compatible with previous reports in a general population [32]. Similarly for maternal death, a rare complication of pregnancy [33], the number of cases was too small to allow for any analysis.

The limitations of this study are mostly related to the use of an administrative dataset that does not contain data specifically collected to examine the detail of such cerebral malformations in pregnancy. There is also the possibility that within the study period a woman may have had two pregnancies and, therefore, might be represented more than once in the analysis; however, since the outcomes are unique to each pregnancy there is a value in considering each pregnancy individually.

The strengths of this study are its large sample size. Given the rarity of these conditions, institutional studies will not be able to identify the number of cases required to draw conclusions regarding the outcomes associated with these conditions, whilst the use of a single country dataset also reduces to an extent the variations in diagnostic and procedural approaches that might arise in a multinational multicentre study.

Conclusions

Our findings support the importance of diagnosis of VBL during pregnancy and provide treating physicians with additional information about potential complications during pregnancy whilst also providing data which suggests that allowing the pregnancy to continue up to the term bares no additional risks to the mother or baby, in the absence of additional symptoms or mitigating factors.

Author contributions GSM: literature review, data collection, writing manuscript. MSF: data analysis. RB: manuscript writing.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

Ethical approval The MUHC-REB has decided that research using anonymized data obtained from the HCUP database does not require any further REB review.

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