

The Risk for Future Cerebrovascular Disease in Pregnant Women With Moyamoya Disease: A Nationwide Population-Based Study in South Korea

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Abstract

Background: Physiologic changes during pregnancy affect the development of postpartum cerebrovascular disease (CVD) in women with Moyamoya disease (MMD). Due to the rare prevalence of MMD and large regional variations, large-scale studies on the risk of CVD after delivery have not been conducted. The aim of this study was to evaluate whether women with MMD have an increased risk of CVD after delivery.

Methods: Research data was collected from the National Health Insurance Claims Database of the Health Insurance Review and Assessment Service. Patients delivered in Korea from 2007 to 2014 were enrolled. We classified women as CVD if they were diagnosed with stroke and/or cerebral infarction and/or intracranial hemorrhage and/or subarachnoid hemorrhage between delivery and December 31, 2016. To evaluate adjusted hazard ratio for CVD in women with MMD, we used multivariate Cox proportional hazard regression.

Results: Among 3,611,216 Korean women who had delivery, 382 had Moyamoya disease. When compared to women without MMD, women with MMD had a higher prevalence of pregestational diabetes and chronic hypertension. Also, women with MMD had a significantly higher incidence of cesarean section, pregnancy-induced hypertension, and gestational diabetes mellitus ($p < 0.0001$, < 0.0001 , 0.02 , respectively). Among women with MMD, a total of 246 (64.4%) women developed CVD within the follow-up postpartum period, and 87.8% occurred within 2 years of postpartum. Women with MMD were associated with an increased risk of CVD in later (adjusted HR 108.24; 95% CI, 95.37-122.86) after adjusting for maternal age, parity, pregnancy-induced hypertension, gestational diabetes mellitus, pregestational diabetes, chronic hypertension.

Conclusion: Our study showed that the incidence of CVD after delivery was higher in women with MMD. Therefore, we have to have more cautions of women with MMD and provide long-term postpartum surveillance

Background

Moyamoya, which is named in Japanese, is a non-inflammatory vasculopathy diagnosed through the detection of a haze on an angiogram. [1, 2] [3] Moyamoya presents as a variety of clinical symptoms; in children, ischemic changes and seizures are the main symptoms, while in adults, cerebral hemorrhage is the main symptom [1] [4, 5]. The prevalence of Moyamoya is regionally different, and the prevalence rate of Moyamoya is higher in Korea and Japan compared to that in other countries.[1] In Korea, the prevalence of Moyamoya disease 16.1 cases per 100,000 people in 2011 and the incidence was 2.3 cases per 10,000 people from 2007 to 2011. [1, 6] It is more common in women than in men[2, 3, 7, 8], at a ratio of 1.8:1[9], and its prevalence is higher in children and in the second and third quarters of life.[1] As it is common among women of childbearing age[2, 8], special care is required in the management of Moyamoya in women before and after pregnancy.

During pregnancy, estrogen and progesterone increase vasodilation, and the renin-angiotensin-aldosterone system also becomes more active.[10] [11] [12] Together, these physiological changes increase cerebral blood flow. Pregnancy is further accompanied by hemodynamic changes such as an increase in systemic blood flow and hypercoagulation, which increases the risk of cerebral hemorrhage in pregnant women by 5.6 times compared to that in non-pregnant women[13] [14]. Moyamoya patients have very fragile cerebral vessels; thus, they are more sensitive to these physiological changes during pregnancy, and the risk of cerebrovascular disease is higher in pregnant women with Moyamoya than in those without [15]. Careful management through observation for cerebrovascular disease after delivery is required in women with Moyamoya even if the delivery occurred without any complications.

To date, although studies on the risk of cerebrovascular disease after delivery in pregnant women with Moyamoya have been conducted [14] [16], the number of study subjects has usually been very small due to the low prevalence of Moyamoya, and there is a need for large-scale studies. Therefore, we intend to elucidate the relationship of the risk of cerebrovascular disease after delivery in pregnant women with Moyamoya using national-wide cohort study.

Methods

Characteristics of the data

This study was conducted using the National Health Insurance (KNHI) claims database.

This study was conducted using the Korea National Health Insurance (KNHI) claims database. In South Korea, 97% of the population is eligible for enrollment into the Korea National Health Insurance (KNHI) excluding 3% of the population those who were under the Medical Aid Program. The KNHI Claims Database contains information on disease diagnosis and procedures for approximately 50 million Koreans. Therefore, almost all information about the prevalence of various diseases can be obtained from this central database.

Study population and outcome ascertainment

Using the KNHI claims database, we confirmed whether they had the diagnosis of Moyamoya disease (MMD) before pregnancy based on the International Classification of Diseases-10th Revision (ICD-10) codes in women who delivered from January 1, 2007 to December 31, 2014.

Women who were diagnosed primary or secondary with Stroke (ICD-10 code) and/or cerebral infarction and/or intracranial hemorrhage and/or subarachnoid hemorrhage were classified as Cerebrovascular disease (CVD) from childbirth to December 31, 2016 based on ICD-10 codes. It was confirmed that CVD was not diagnosed prior to pregnancy by using the KNHI claims.

We included the following as pregnancy outcomes: parity, cesarean delivery, preeclampsia, gestational diabetes, postpartum hemorrhage, placental abruption, placental previa, diabetes mellitus (DM) and hypertension (HTN) based on ICD-10 code, and evaluated using the NNHI Claims database.

Statistical analysis

Differences in continuous and categorical variables according to SSNHL were analyzed with the t-test and Chi-square test, respectively. Trying to determine the association between Moyamoya disease and CVD risk after delivery, we used Cox proportional hazard regression. A P value <0.05 was considered statistically significant. Statistical analyses were performed using SAS for Windows, version 9.4 (SAS Inc., Cary, NC, USA).

Results

Out of 3,611,216 Koreans who had delivered, 382 had Moyamoya. Table 1 shows basic characteristics relevant to Moyamoya. Compared to women without Moyamoya, those with Moyamoya had higher overt diabetes and overt hypertension. The cesarean section rate was higher in patients with Moyamoya, and gestational hypertension and gestational diabetes were also higher. Overt diabetes and essential hypertension were diagnosed from 1 year before delivery. There was no difference in the mean age between the two groups, and similar results were obtained when only subjects with an advanced maternal age of over 35 years were analyzed.

Table 1
Baseline characteristics of the study subjects.

Variables	Normal (n = 3610834)	Moyamoya (n = 382)	p-value
Age at delivery	30.74 ± 4.16	30.73 ± 4.41	0.9505
Advanced maternal age (> 35)	607681 (16.83)	69 (18.06)	0.5194
Primipara	1880566 (52.08)	210 (54.97)	0.2578
Cesarean section	1331262 (36.87)	293 (76.70)	< .0001
Gestational hypertension	136059 (3.77)	30 (7.85)	< .0001
Gestational diabetes	136289 (3.77)	23 (6.02)	0.0212
Postpartum hemorrhage	301718 (8.36)	29 (7.59)	0.5893
Placental abruption	12686 (0.35)	1 (0.26)	0.7674
Placenta previa	35204 (0.97)	5 (1.31)	0.5065
Overt DM*	78464 (2.17)	55 (14.40)	< .0001
Essential hypertension*	54536 (1.51)	96 (25.13)	< .0001
CVD diagnosis	47722 (1.32)	246 (64.40)	< .0001

* Diagnosis at 1 year before from delivery

Values are presented as Mean±SD or N(%)

CVD Cerebrovascular disease / MMD Moyamoya disease

The overall incidence of CVD in patients with Moyamoya is shown in Fig. 1. Among women with Moyamoya, 64.4% developed CVD after delivery, and the majority of them (87.3%) developed the CVD within 2 years after delivery. Although the incidence rate was lower than that of patients with Moyamoya, CVD occurred after delivery even in subjects without Moyamoya (1.32%), with stroke having the highest incidence rate (19.11%), followed by intracranial hemorrhage (10.47%), cerebral infarction (7.59%), and subarachnoid hemorrhage (2.36%).

Table 2 shows the adjusted hazard ratios (HRs) of CVD in women with Moyamoya according to Cox proportional hazard regression analysis. In women with Moyamoya, the risk of CVD after delivery was increased (adjusted HR 108.24; 95% confidence interval (CI) 95.37–122.86), even when adjusted for the maternal age, primiparity, gestational hypertension, gestational diabetes, overt diabetes, and overt hypertension. Subgroup-analysis performed for each intracerebral hemorrhage, cerebral stroke, cerebral infarction, and subarachnoid hemorrhage also demonstrated similar associations. Intracerebral hemorrhage (adjusted HR 146.39; 95% confidence interval (CI) 105.51–203.10) was found to have the highest increased risk of occurrence across all subgroups of cerebrovascular diseases, followed by stroke (adjusted HR 49.46 95% CI 39.14–62.49), subarachnoid hemorrhage (adjusted HR 31.73; 95% CI 16.35–61.57), and cerebral infarction (adjusted HR 27.76; 95% CI 19.20–40.13) in Table 3.

Table 2
Hazard ratios for cerebrovascular disease according to Moyamoya disease

	Unadjusted HR (CI)	Adjusted HR (CI)
Moyamoya disease	140.66 (124.08,159.45)	108.24 (95.37,122.86)
* Adjusting for maternal age, parity, pregnancy induced hypertension, gestational diabetes mellitus, overt diabetes, chronic hypertension		

Table 3
Hazard ratios for each for each intracerebral hemorrhage, cerebral stroke, cerebral infarction, and subarachnoid hemorrhage according to Moyamoya disease

	Unadjusted HR (CI)	Adjusted HR (CI)
<i>Intracranial hemorrhage</i>	230.507 (168.611, 315.126)	146.395 (105.519, 203.104)
<i>Cerebral stroke</i>	83.977 (66.712, 105.711)	49.464 (39.148, 62.498)
<i>Cerebral infarction</i>	50.249 (34.904, 72.340)	27.760 (19.202, 40.131)
<i>Subarachnoid hemorrhage</i>	56.016 (29.118, 107.762)	31.732 (16.353, 61.575)
* Adjusting for maternal age, parity, pregnancy induced hypertension, gestational diabetes mellitus, overt diabetes, chronic hypertension		

Discussion

On this national-wide study, we can confirm that the risk of CVD increases after delivery in women with Moyamoya. There have been several studies on cerebrovascular diseases during pregnancy and after childbirth in pregnant women with Moyamoya, but no large-scale studies have been conducted due to the low prevalence of the disease itself. [14] [16] [17]

The diagnosis of Moyamoya is showing an increasing trend in recent years, which can be presumed to be due to an increase in accessibility to imaging diagnosis. According to previous studies, cerebral hemorrhage in pregnant women with Moyamoya occurs mainly in the second trimester of pregnancy, and cerebral ischemia occurs mainly after delivery. [9] The cause of CVD after delivery in women with Moyamoya is not known yet, but increased cardiac output is maintained 24–48 hours after delivery and only returns to normal within 10 days of delivery. It is hypothesized that the increase coagulability and the decrease in cerebral blood flow following the lower cardiac output cause ischemic cerebral disease after delivery in Moyamoya. [2, 12] [13] Moreover, blood flow, which rapidly increases until the second trimester of pregnancy, slows down when pregnancy reaches 24–26 weeks before increasing again; this is predicted to be the cause of the increase in cerebral hemorrhage

This study included only women who were diagnosed with Moyamoya before pregnancy. The diagnosis of Moyamoya is usually made before pregnancy, and women diagnosed during pregnancy have a poorer prognosis than those diagnosed before pregnancy.[10] [18] [19] This is thought to be due to stricter blood pressure control and the administration of appropriate treatment for women diagnosed with Moyamoya before pregnancy. [10] On the other hand, the diagnosis of Moyamoya during pregnancy or after delivery is often due to the occurrence of a cerebrovascular event, which would lead to a worse prognosis. In a nationwide survey conducted in Japan, among 64 pregnant women with Moyamoya, 5 were newly diagnosed during pregnancy due to cerebral events. [10]

In this study, pregnant women with Moyamoya showed significantly higher rates of cesarean section than normal people during delivery, because the cesarean section is preferred as a delivery method for women with Moyamoya. [9] [10] Hemodynamic changes that can occur during labor include an increase in the blood pressure due to performing the Valsalva maneuver and a decrease in cerebrovascular blood flow due to hypercapnia caused by hyperventilation.[2, 9] These are likely to cause problems in people with Moyamoya, who have weaker blood vessels. Besides, it is thought that the significantly higher rate of associated diseases such as pregnancy-induced hypertension and gestational diabetes mellitus in people with Moyamoya is a cause for the high cesarean section rate. However, a recent study on vaginal delivery without complications in pregnant women with Moyamoya reported that maintaining more stable vital signs was more relevant to the prognosis of pregnant women with Moyamoya than the delivery method. [5, 20] [19] However, studies comparing the results of cesarean section and vaginal delivery have not been conducted yet. Several recent studies have investigated whether the stroke risk varies with the delivery method. ³[10, 21] A recent study concluded that there were no complications with vaginal delivery in pregnant women with Moyamoya under epidural anesthesia. [21] [22] [23] Studies have shown that if single-photon emission computed tomography showed normal cerebral circulation one year before pregnancy, it is worth trying vaginal delivery under epidural anesthesia. The common

conclusion across all these studies is that vaginal delivery attempts are possible only when the cerebral blood flow is stable. [3, 21]

Several limitations should be considered when interpreting the present findings. First, this study was based on insurance claim data in the KNHI Claims Database, which was designed for cost claim issues, not research. Thus, the exact cause of CVD was not available. Second, due to the nature of retrospective observation studies, in the case of CVD in pregnant women without Moyamoya, there was no review of whether or not Moyamoya was present but undiagnosed. Last, in cases where CVD occurred in the acute phase after delivery, this study did not take note of whether the woman with Moyamoya received appropriate treatment at the time of delivery. Despite these limitations, this study is significant in that it is the large-scale study on CVD in pregnant women with Moyamoya, and the results of this study were consistent with those of previous studies, confirming their conclusions. Although it is well known that patients with Moyamoya have a higher risk of developing CVD than people without Moyamoya, research has not been conducted on how long the follow-up should be after delivery.

Conclusion

In this study, most of the CVD occurred within 2 years of delivery, but even if a pregnant woman with Moyamoya delivered normally, CVD may only occur after a fairly long time, suggesting that long-term management is necessary.

Abbreviations

CVD: Cerebrovascular disease; MMD: Moyamoya disease; HR: Hazards ratio; ICD-10; International Classification of Diseases-10th Revision; DM: diabetes mellitus; HTN: hypertension; CI: confidence interval

Declarations

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Authors' contributions

YHK was responsible for the conception of the study. YJJ, YHK and GJC advised on the design. GJC, MJO and EN were responsible for data analysis and interpretation of findings. EN analyzed the data and interpreted the findings. YSJ drafted and revised the manuscript. All authors approved the final draft.

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Availability of data and materials

The datasets used in the present study are available from the corresponding author (yhkim522@yuhs.ac) on reasonable request only.

Declarations

Ethics approval and consent to participate

No informed consent was obtained from the patients because the study was retrospective. Administrative permissions for the data were acquired by the authors for research purposes.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

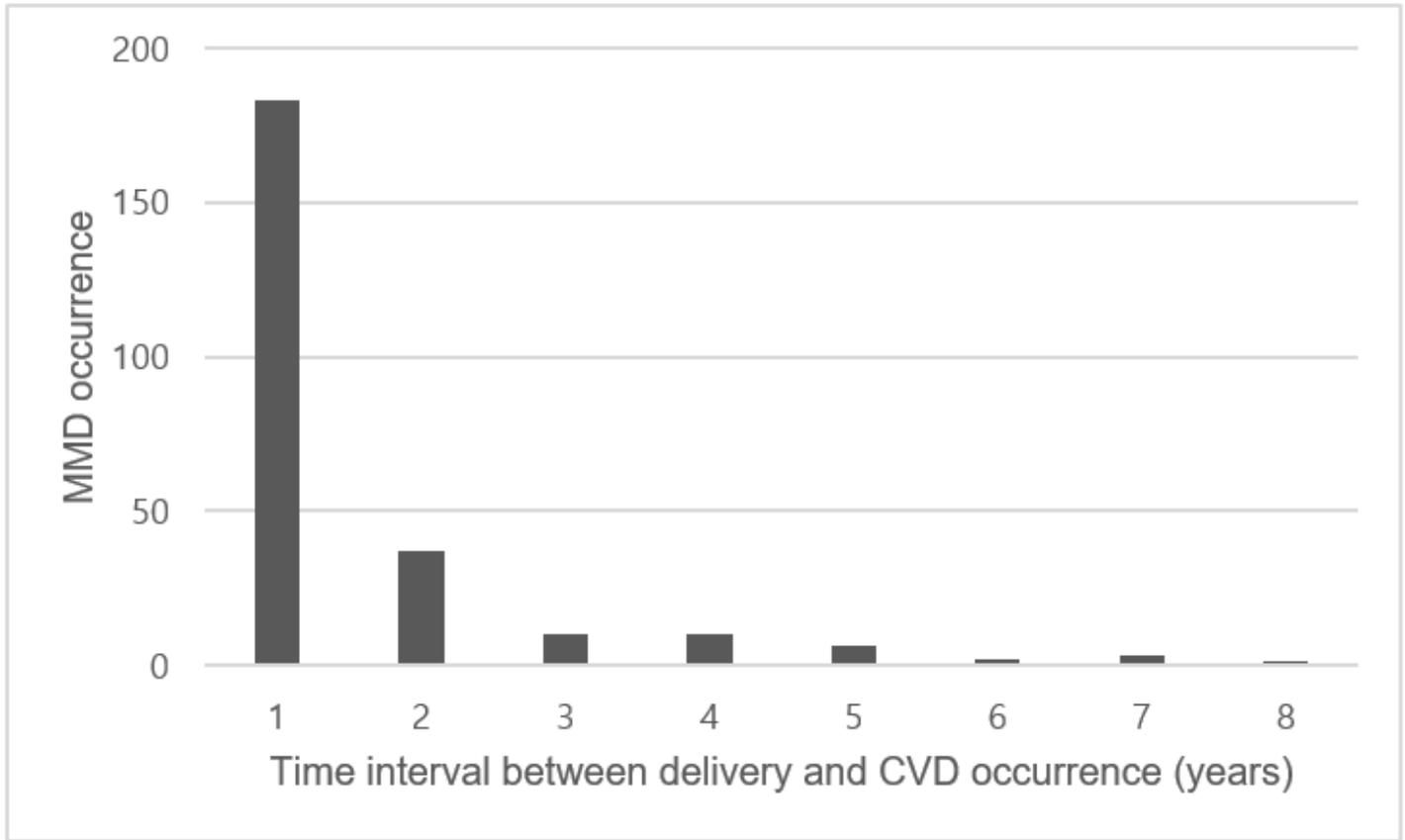


Figure 1

The occurrence CVD in women with MMD