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RESEARCH ARTICLE

Pregnancy-associated stroke and the recurrence of stroke and other complications in subsequent pregnancies: Population-based retrospective cohort study

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Abstract

Objective: To examine the outcomes of the subsequent pregnancies from women with a previous pregnancy-associated stroke (PAS) in comparison to matched controls.

Design: Population-based retrospective cohort study.

Setting and population: All women with a PAS in Finland 1987–2016 ($n = 235$) and controls ($n = 694$).

Methods: We identified all subsequent deliveries and induced and spontaneous abortions for women with a previous PAS and their matched controls from the Medical Birth Register and the Hospital Discharge Register until 2016. The number, course and outcomes of the subsequent pregnancies were compared. Patient records were studied for PAS recurrence.

Main outcome measures: PAS recurrence and pregnancy complications.

Results: Women with a previous PAS had fewer subsequent deliveries: 73 (31.1%) women had 122 deliveries in all, whereas 303 (47.3%) of the controls had 442 deliveries (age-adjusted odds ratio [OR] 0.54, 95% CI 0.38–0.76). Hypertensive disorders of pregnancy (HDP) (17.2% versus 5.7%, age-adjusted OR 4.0, 95% CI 1.7–9.3), especially chronic hypertension (age-adjusted OR 5.9, 95% CI 1.5–24.7), and any diabetes during pregnancy (24.6% versus 14.5%, age-adjusted OR 2.0, 95% CI 1.1–3.8) were more common in cases. Regarding HDP, the difference between groups was explained by underlying factors such as index pregnancy HDP (multivariable OR 2.4, 95% CI 0.8–6.7). PAS recurred in four cases (5.5%).

Conclusions: Subsequent pregnancies of women with a history of PAS are more often complicated with hypertensive disorders of pregnancy and any diabetes during pregnancy. PAS recurrence risk is considerable.

KEYWORDS
hypertensive disorders of pregnancy, maternal stroke, pregnancy, pregnancy-associated stroke, stroke

This article includes Author Insights, a video abstract available at: https://drive.google.com/file/d/15d6zt51HgcVftlTi8C1Y-ALzB8r57KYk/view?usp=sharing.

1 | INTRODUCTION

Pregnancy-associated stroke (PAS), usually defined as an acute cerebrovascular event during pregnancy or 6 weeks postpartum, is a rare pregnancy complication with an estimated incidence of 30 per 100 000 deliveries.[1] It is a life-threatening emergency for the mother and the child. The incidence is increasing in several countries,[2–5] possibly as the result of increasing maternal age and comorbidities.[2,3,6,7]

Pregnancy-associated stroke is a significant contributor to maternal mortality and morbidity,[8,9] but many women recover well enough to opt for further pregnancies.[10,11] Data on the course and risks associated with the subsequent pregnancies are needed for preconception counselling. There are no previous original studies solely focusing on the subsequent pregnancies of women with a previous PAS.[12] According to our earlier systematic review, which extracted data from a small number of studies on young stroke patients, around half of the women with a PAS history have subsequent pregnancies and their outcomes are generally comparable to those of the general population.[12] Based on a limited number of patients (26 women with 55 pregnancies) and one recurrent PAS, the recurrence rate was 2%.[12] Previous literature suggests that women with a PAS history may, regardless of the desire to have more children, decide against pregnancies because of residual disability or fear of a recurrent stroke.[13]

Our main objective was to investigate the stroke recurrence during pregnancy and puerperium and pregnancy outcomes in the subsequent pregnancies in women with a history of PAS in a population-based cohort with a nested case–control design. Additionally, we describe the secondary preventive medications used during the subsequent pregnancies and puerperal period using patient record data.

This article focuses on risks associated with subsequent pregnancies. General life-time stroke recurrence is not covered because of insufficient follow-up time for accurate reporting.

2 | METHODS

2.1 | Study setting and population

This is a retrospective nationwide population-based cohort study and nested case–control study in Finland (Stroke in Pregnancy and Puerperium in Finland, SiPP-FIN). The cohort includes all women with a pregnancy resulting in delivery during the period 1987–2016 (1 773 728 deliveries). From the cohort, all women with stroke during pregnancy or puerperium and three matched controls with no stroke during pregnancy or puerperium were included in the nested case–control study. The detailed study protocol for identification of women with PAS in Finland between 1987 and 2016 has been described previously.[5]

2.2 | Registers, chart validation and definitions

We consulted the Hospital Discharge Register (HDR) and Medical Birth Register (MBR) to identify women with PAS. The MBR includes all live births and stillbirths with gestational age of at least 22^{+0} weeks or with birthweight of 500 g or greater and the baseline characteristics of the mother, data on health care, interventions during pregnancy and delivery, and the outcome of the newborn.[14] The HDR has collected data of all inpatient hospitalisations since 1969 and outpatient visits in all public hospitals since 1998 in Finland.[15] The completeness and accuracy of both registers are rated from good to satisfactory and the coverage of the MBR is estimated to reach 100%.[16,17]

We obtained the patient records for all identified PAS cases and verified temporal connection of stroke and pregnancy (conception to 12 weeks postpartum) and the stroke type. Postpartum period extending over the usual 6 weeks was used because the risk of stroke seems to be elevated for beyond this period.[18,19] We included ischaemic stroke (IS), intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAH) and cerebral venous thrombosis (CVT) as stroke types. The American Heart Association/American Stroke Association consensus definitions were used for IS, ICH and SAH.[20] CVTs were included and coded as CVT regardless of whether the CVT had caused infarction, haemorrhage, or neither.

2.3 | Case–control study

Three controls for each PAS case were identified from the MBR and matched for delivery year (±2 years), mother's age (±1 year), parity (±0, where multiparas with four or more deliveries were grouped together), and geographical area (living within the same hospital district). No controls were available for two cases and only one control was available for one case because of extreme age and a sparsely inhabited geographic area.

2.4 | Outcomes

Our main outcomes of interest were PAS recurrence in women with a history of PAS and pregnancy complications, and neonatal outcomes in women with a PAS history and their controls.

We identified all subsequent deliveries of women with a PAS history and their controls until 2016 from the MBR. We excluded those who died within 1 year of the PAS and their controls from further analysis (Figure 1).

Recurrence of PAS was determined from the HDR and validated from the patient records. Patient records were obtained from the departments of obstetrics and gynaecology, neurology, neurosurgery and radiology covering the period of all subsequent pregnancies and 12 weeks postpartum. We

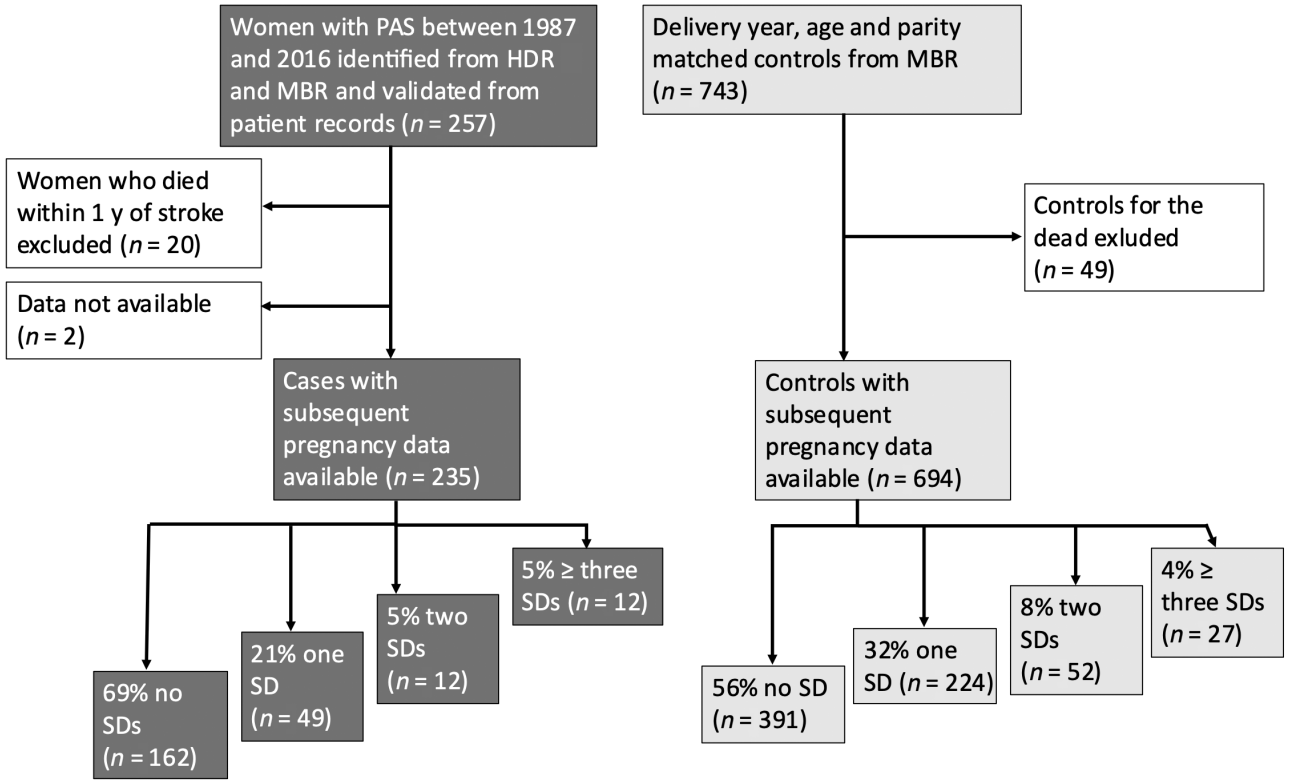

FIGURE 1 Flow chart of the study and the number of subsequent deliveries among women with a history of pregnancy-associated stroke and their controls. PAS, pregnancy-associated stroke; SD/SDs, subsequent delivery/deliveries.

used the same definitions for recurrent PAS as in the initial PAS identification. Patient records of women with a recurrent PAS were assessed by a stroke neurologist.

Pregnancy complications were defined as hypertensive disorders of pregnancy (HDP; including chronic hypertension, gestational hypertension, pre-eclampsia and eclampsia) and any diabetes during pregnancy (including diabetes diagnosed before pregnancy, gestational diabetes and undetermined diabetes during pregnancy). International Classification of Diseases (ICD) codes used for identification of pregnancy complications are presented in Table S1. Neonatal outcomes of interest were perinatal mortality, prematurity ($<37^{+0}$ weeks of gestation), low birthweight (<2500 g), Apgar score <7, child's hospitalisation at 7 days of age and the mode of delivery. Data on pregnancy complications and neonatal outcomes were collected from MBR and supplemented with corresponding ICD codes from the HDR from the time of the pregnancy (up to 9 months before or up to 3 months after the delivery date in the MBR) regarding pregnancy complications (Table S1).

As secondary outcomes of interest we collected data on induced abortions and miscarriages of women with a PAS history and the controls. Data after the index delivery until the end of 2016 were derived from the HDR using corresponding ICD codes (Table S1). If the interval between the ICD codes was over 42 days, the events were considered separate.[21]

To investigate possible causes for not having further deliveries, we compared women with a PAS history and subsequent deliveries with those without subsequent deliveries in terms of their recovery from the initial PAS, PAS subtype, age, parity and prevalence of stroke risk factors (HDP, any diabetes during pregnancy, smoking, migraine, body mass index, hypercholesterolaemia) during the pregnancy when the initial PAS occurred. Modified Ranking Scale (mRS) at 3 months was used in the assessment of recovery. It measures the degree of disability or dependence in the daily activities of people who have suffered a stroke. The mRS was estimated from the patient records by a neurologist. All controls were assumed to have mRS score zero (patient records were not available). Patient records were studied for the pregnancy follow-up and the secondary preventive medication used during the subsequent pregnancies.

2.5 | Statistical analysis

The chi-square or Fisher's exact test for categorical dichotomous variables was used to test for differences between stroke risk factors during the index pregnancy and numbers of pregnancies between the cases and the controls. Values of $p < 0.05$ were considered significant. Age-adjusted and multivariable odds ratios (ORs) and 95% CIs were calculated by binomial logistic regression using generalised linear models and generalised estimating equations due to correlations of repeated measures in case of several subsequent pregnancies per woman. Multivariable ORs were adjusted for age, smoking at the time of subsequent

pregnancy and HDP in the index pregnancy for pregnancy complications and neonatal outcomes. Additional analyses were performed including also perinatal problem in the index pregnancy (prematurity <37 weeks or birthweight <2500 g) in the model. Regarding delivery by caesarean section, also a history of caesarean section was entered into the model.

Among cases, differences between those with no subsequent deliveries and those with subsequent deliveries were tested with chi-square or Fisher's exact test for categorical variables, with independent samples *t* test for normally distributed continuous variables and with Mann–Whitney *U* test for ordinal variables not normally distributed.

Statistical analyses were performed using SPSS statistics version 25 (IBM, Armonk, NY, USA).

2.6 | Ethical approval

The study was approved by the ethics committee of Helsinki University Hospital (HUH/2228/2016 13.12.2016). The Finnish Institute of Health and Welfare (THL/750/5.05.00/2017) and Statistics Finland (TK-53-783-17) granted permission to use confidential health data in this study. The European Union and Finnish data protection legislation allows the use of register data for appropriately approved research without a written patient consent.

3 | RESULTS

During the study period 1987–2016 there were 1 773 728 deliveries and 257 women suffered from PAS. After excluding the women who died within 1 year of PAS and their controls, data on the subsequent pregnancies were available for 235 women (Figure 1). In the index pregnancy, 90 (38.3%) of these women had IS, 43 (18.3%) had ICH, 50 (21.3%) had SAH and 51 (21.7%) had CVT as a PAS subtype. From these 235 women, 73 (31.1%) had a total of 122 deliveries (Figure 1, Table 1). The median follow-up time (from index delivery to the end of 2016) was 11.8 (interquartile range 16.2) years.

3.1 | PAS recurrence

Patient records were available for all but one woman with a previous PAS. There were four recurrent PAS cases: two IS, one CVT and one intraventricular non-aneurysmatic haemorrhage (Table 3). All recurrent PAS were the same type as the initial one. The IS manifested regardless of antithrombotic medication and the CVT occurred in early first trimester when anticoagulant medication had not yet been initiated. In addition to these recurrent PAS cases, one woman whose initial PAS was a second trimester IS, had a third-trimester transient ischaemic attack despite prophylactic anticoagulant medication.

3.2 | Pregnancy complications and neonatal outcomes

Data on pregnancy complications were available for all subsequent pregnancies in the MBR. HDP were more common in the post-PAS pregnancies, 17.2% compared with 5.7% among the controls (age-adjusted OR 4.0, 95% CI 1.7–9.3) (Table 2). This was mainly attributed to higher prevalence of chronic hypertension, 9.1% among the cases and 1.8% among the controls (age-adjusted OR 5.9, 95% CI 1.5–24.7). The difference in subsequent pregnancy HDP between cases and controls was attributed to underlying factors, mainly HDP in the index pregnancy (multivariable OR 2.4, 95% CI 0.8–6.7). The incidence of gestational hypertension (4.9% versus 2.7%; age-adjusted OR 2.0, 95% CI 0.5–5.5) and pre-eclampsia (3.3% versus 1.1%, age-adjusted OR 3.2, 95% CI 0.5–19.5) were similar. There were no cases of eclampsia in either group.

The prevalence of any diabetes during pregnancy was 24.6% in the post-PAS pregnancies and 14.5% in the controls (age-adjusted OR 2.0, 95% CI 1.1–3.8). Insulin treatment for any type of diabetes during pregnancy was more common (5.8%) in post-PAS pregnancies in comparison to control pregnancies (1.8%) (age-adjusted OR 3.5, 95% CI 1.2–10.5). There was no difference in the prevalence of gestational diabetes (ICD-10 code O24.4) (age-adjusted OR 1.3, 95% CI 0.6–2.7) (Table 2). No differences were observed in neonatal outcomes (Table 2).

Caesarean section was more common in the post-PAS pregnancies in comparison with the controls (32.5% versus 12.5%, age-adjusted OR 3.4, 95% CI 1.8–6.4) (Table 2). In the multivariable model including history of caesarean section, the difference between groups diminished regarding all caesarean sections (multivariable OR 1.9, 95% CI 0.9–3.9) and elective caesarean sections (multivariable OR 2.3, 95% CI 0.9–5.6). Based on patient record data, half of the elective caesareans of women with a PAS history were the result of maternal request or recommendation from the neurologist without an obstetric indication.

Additional multivariable analyses of pregnancy complications and neonatal outcomes including previous perinatal problem in the model did not change the results.

3.3 | Number of pregnancies

Seventy-three (31.1%) of the women with a previous PAS and 303 (47.3%) of the controls had at least one subsequent delivery (age-adjusted OR 0.54, 95% CI 0.38–0.76). The median interval between PAS and first subsequent delivery was 2.9 (interquartile range 0.7–5.1) years. Any type of pregnancy (including induced abortions and miscarriages) was found for 91 (38.7%) cases and 330 (45.3%) controls (age-adjusted OR 0.67, 95% CI 0.48–0.94).

Miscarriages were equally common between the groups, but induced abortions were more common among the women with a PAS history (age-adjusted OR 1.8, 95% CI 1.0–3.2) (Table 1).

TABLE 1 Demographics, PAS risk factors at the time of index pregnancy and the number of subsequent pregnancies for PAS cases and controls.

Demographics, risk factors during index pregnancy and data on subsequent pregnancies	All	Cases	Controls	*p* value	Age-adjusted OR (95% CI)
Number of women	929	235	694		
Age (years, mean ± SD)	31.3 ± 5.6	31.3 ± 5.6	31.2 ± 5.7	0.776	
Obesity (body mass index >30 kg/m^2)[a]	63 (13.3%)	20 (17.1%)	43 (12.0%)	0.208	1.5 (0.9–2.7)
Smoking[b]					
Nonsmoking	716 (83.4%)	582 (85.2%)	179 (77.8%)	0.011	0.6 (0.4–0.9)
Cessation by 12 weeks	39 (4.3%)	11 (4.8%)	28 (4.1%)	0.706	1.2 (0.6–2.4)
Continued smoking after 12 weeks	113 (12.4%)	40 (17.4%)	73 (10.7%)	0.008	1.8 (1.2–2.7)
Chronic hypertension[c]	10 (1.1%)	8 (3.4%)	2 (0.3%)	<0.0001	12.2 (2.6–57.8)
Pre-gestational diabetes[d]	5 (0.5%)	3 (1.3%)	2 (0.3%)	0.106	4.5 (0.7–27.0)
Hypercholesterolaemia	20 (2.2%)	11 (4.7%)	9 (1.3%)	0.004	3.7 (1.5–9.1)
Migraine	23 (2.5%)	19 (8.1%)	4 (0.6%)	<0.0001	15.3 (5.2–45.7)
Pre-eclampsia or eclampsia	46 (5.0%)	28 (11.9%)	18 (2.6%)	<0.0001	5.1 (2.8–9.4)
Hypertensive disorders of pregnancy	104 (11.2%)	58 (24.7%)	46 (6.6%)	<0.0001	4.7 (3.1–7.3)
Any diabetes during pregnancy	108 (11.6%)	34 (14.5%)	74 (10.7%)	0.126	1.4 (0.9–2.2)
Number of women with subsequent deliveries	376 (40.5%)	73 (31.1%)	303 (47.3%)	0.001	0.54 (0.38–0.76)
Number of subsequent deliveries (median ± IQR)[e]	563 (1 ± 10)	122 (1 ± 6)	442 (1 ± 10)	0.164	
Number of children born	578	123	455		
Number of women with at least one spontaneous abortion	80 (8.6%)	20 (8.5%	60 (8.6%)	1.000	0.99 (0.58–1.79)
Number of spontaneous abortions	103	24	79		
Number of women with at least one induced abortion	55 (5.9%)	20 (8.5%)	35 (5.0%)	0.056	1.8 (1.0–3.2)
Number of induced abortions	76	25	51		
Number of ectopic pregnancies	8 (0.9%)	1 (0.4%)	7 (1.0%)	0.476	0.42 (0.052–3.5)
Number of women with any type of subsequent pregnancy	421 (45.3%)	91 (38.7%)	330 (45.3%)	0.023	0.67 (0.48–0.94)

Note: Demographics and stroke risk factors recorded at the time of pregnancy during which initial PAS occurred/during the 'matched' pregnancy for controls (=index pregnancy). Number of children born exceeds the number of deliveries due to multiple gestations. Spontaneous abortion includes hydatidiform mole and other abnormal outcomes of conception.

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio; PAS, pregnancy-associated stroke; SD, standard deviation.

[a]Available for 475 women (117 cases and 358 controls).

[b]Available for 913 women (230 cases and 683 controls).

[c]Including ICD codes I10–I13 only.

[d]Including ICD codes e10–e15 only.

[e]Median and range calculated for only women with subsequent deliveries in each group and *p* value for this non-normally distributed variable with Mann–Whitney *U* test.

Estimated mRS scores at 3 months after the initial PAS were available for 234 women. Of the women with a PAS history and mRS score two or lower (i.e. women who need no help in the activities of daily living), 34.0% had at least one subsequent delivery compared with 43.8% of the controls (age-adjusted OR 0.12, 95% CI 0.03–0.47). Only one woman with estimated mRS of four or more had a subsequent delivery.

When comparing women with a PAS history and no subsequent deliveries ($n = 162$) to those with subsequent delivery ($n = 73$), the former group was older (mean age 32.8 versus 28.1 years, $p < 0.0001$) and had higher parity at the time of the initial stroke ($p < 0.0001$). Their estimated mRS scores at 3 months were also higher ($p = 0.013$). There were no differences in the stroke risk factor frequencies at the time of PAS between the groups. The distribution of different stroke subtypes was similar in both groups ($p = 0.163$).

3.4 | Surveillance and secondary prevention during the subsequent pregnancy

Of the 73 women with a subsequent delivery after PAS, 90.4% had their pregnancies monitored in the specialised antenatal care unit at least once. Antihypertensive medication was used by 9.7% during the subsequent pregnancy. There were 33 women with a history of an ischemic PAS. Of these women, 87.9% used medications for secondary stroke prevention: acetylsalicylic acid (ASA) was used by 44.8%, low-molecular-weight heparin (LMWH) by 27.6%, 17.2% used both, and 10.3% used first ASA and changed to LMWH at 36 weeks or after delivery. Of these women, 65.5% continued either or both antithrombotic or anticoagulant medication for at least 6 weeks postpartum. There were 13 women with a previous CVT during pregnancy or puerperium. Of them, 12 (92.3%) used prophylactic LMWH during the subsequent pregnancy. The one recurrent CVT happened to a woman

TABLE 2 Pregnancy complications and neonatal outcomes in subsequent pregnancies of PAS cases and controls.

Pregnancy complications and neonatal outcomes	All pregnancies	Pregnancies of women with a PAS history	Pregnancies of controls	*p* value (age-adj)	Age-adj OR (95% CI)	Multivariable OR (95% CI)[a]
Number of pregnancies resulting in delivery	564	122	442			
Number of children born	578	123	455			
Hypertensive disorder of pregnancy	46 (8.2%)	21 (17.2%)	25 (5.7%)	0.001	4.0 (1.7–9.3)	2.4 (0.8–6.7)
Chronic hypertension	19 (3.1%)	11 (9.1%)	8 (1.8%)	0.012	5.9 (1.5–24.7)	4.4 (0.8–24.8)
Gestational hypertension	18 (3.2%)	6 (4.9%)	12 (2.7%)	0.157	2.0 (0.7–5.5)	1.3 (0.5–3.7)
Pre-eclampsia	9 (1.6%)	4 (3.3%)	5 (1.1%)	0.214	3.2 (0.5–19.5)	1.4 (0.3–7.3)
Any diabetes during pregnancy	94 (16.7%)	30 (24.6%)	64 (14.5%)	0.019	2.0 (1.1–3.8)	1.9 (1.0–3.5)
Gestational diabetes (O24.4)	64 (11.3%)	16 (13.1%)	48 (10.9%)	0.488	1.3 (0.6–2.7)	1.2 (0.5–2.6)
Diabetes, insulin treatment	15 (2.7%)	7 (5.8%)	8 (1.8%)	0.024	3.5 (1.2–10.5)	3.6 (1.2–10.8)
Perinatal mortality	5 (0.9%)	3 (2.5%)	2 (0.4%)	0.087	5.4 (0.8–37.6)	4.1 (0.4–41.4)
1 minute Apgar score <7[b]	26 (4.5%)	9 (7.4%)	17 (3.7%)	0.085	2.1 (0.9–4.9)	2.1 (0.9–4.9)
Birthweight <2500 g[c]	29 (5.0%)	11 (9.0%)	18 (4.0%)	0.097	2.4 (0.9–6.5)	2.4 (0.9–6.3)
Gestational age <37 weeks[d]	41 (7.1%)	11 (9.0%)	30 (6.6%)	0.512	1.4 (0.5–3.5)	1.1 (0.4–3.1)
Child hospitalised at 7 days of age[e]	51 (8.9%)	13 (10.8%)	38 (8.4%)	0.527	1.3 (0.6–3.0)	1.1 (0.5–2.5)

Abbreviations: CI, confidence interval; HDP, hypertensive disorder of pregnancy; OR, odds ratio; PAS, pregnancy-associated stroke.

[a]Multivariable OR adjusted for age, smoking at the time of subsequent pregnancy and HDP in index pregnancy and additionally for a previous caesarean section regarding caesarean section and elective caesarean.

[b]Data available for 575.

[c]Data available for 275.

[d]Data available for 575.

[e]Data available for 574.

whose anticoagulant medication was not yet initiated. One used both LMWH and ASA and one used ASA but changed to LMWH postpartum. All these women continued preventive medication for at least 1 month postpartum, 12 out of 13 until 6 weeks postpartum. Preventive medications of women with a recurrent PAS are described in Table 3.

4 | DISCUSSION

In this population-based cohort study we observed that PAS recurred in 5.5% of cases, despite the use of anticoagulant or antithrombotic medication in 90% of the cases. This was more than double the previous estimate.[12] Also, HDP and any diabetes during pregnancy, including any diabetes with insulin treatment, were more common among those with a PAS history. After adjusting for the risk factors of pregnancy complications these differences became nonsignificant, demonstrating that PAS itself is not an independent risk factor for these complications but most likely there are shared risk factors. The neonatal outcomes were similar between post-PAS pregnancies and the controls.

The strengths of our study include a nationwide population-based cohort, well-established matching criteria for the controls, and supplementing the MBR data with HDR data for the pregnancy complications. Extensive patient record review was essential for unbiased reporting of the PAS recurrence rate[5] and enabled reporting of secondary preventive medication use. However, regardless of the nationwide population-based study design, the size of our cohort is relatively limited because of the small population in Finland. In addition, 7.7% of women had the index delivery between 2015 and 2016 leaving insufficient follow-up time for the subsequent pregnancies. These factors limit the number of subsequent deliveries, which may mask differences between the groups when rare pregnancy complications are studied. The statistical power of our results might also be limited by the small cohort. This should be noted when interpreting the results. The maternity care system in Finland is free of charge for all, and the population is homogeneous, mainly white Caucasian. The results may therefore represent the 'lower end' of risk associated with subsequent pregnancies of women with a previous PAS. The global generalisability of our results may be limited by these population characteristics and the high-quality equal healthcare system.

To our knowledge, this is the first comprehensive nationwide study of the subsequent pregnancies of women with a PAS history. In previous cohort studies, usually including a few PAS patients among other young non-pregnancy-associated stroke patients, the results on the course of the subsequent pregnancies have varied. A study on young IS and transient ischaemic attack patients reported more miscarriages, fetal deaths, HDP and preterm deliveries before 32 weeks of gestation among women with a stroke history when compared with the national perinatal registry data.[22] Another study including post-IS pregnancies and using matched controls found no differences in the incidence of gestational diabetes, birthweight less than 2500 g, preterm deliveries before 37 weeks of gestation, Apgar score 6 or less, child hospitalised at 1 week of age or perinatal mortality.[23] There are several studies[13,24–26] on young stroke patients including some women with a PAS history reporting post-stroke pregnancy outcomes as the number of term deliveries,

TABLE 3 Recurrent PAS cases.

Recurrent PAS cases	Details on initial PAS and corresponding pregnancy	Secondary preventive medication used during subsequent pregnancy	Details on recurrent PAS and corresponding pregnancy	Aetiology of recurrent PAS	Recovery from recurrent PAS	Other subsequent pregnancies
Case 1	Age 25–30 years, 2nd trimester IS, term vaginal delivery	ASA 100 mg and enoxaparin 40 mg × 1 (due to DVT in family)	Age 25–30 years, 0–3 weeks postpartum IS, term vaginal delivery	Unknown (cervical and intracranial MRA, TEE, no genetic or acquired thrombophilia, repeated after pregnancy), hypercholesterolaemia, hypertension diagnosed after second IS	Residual symptoms from the recurrent stroke	Between the stroke pregnancies one uncomplicated pregnancy and delivery, ASA 100 mg and enoxaparin 40 mg × 1 used 6 weeks postpartum
Case 2	Age 25–30 years, 0–3 weeks postpartum IS, term caesarean delivery	ASA 100 mg, which was discontinued 1 week before planned caesarean.	Age 25–30 years, 0–3 weeks postpartum IS, term caesarean delivery	Moyamoya syndrome	Fully recovered, no symptoms	One pregnancy at age 30–35 years, ASA 100 mg until 1 day before elective caesarean, additionally enoxaparin started 1 week before caesarean and continued along with ASA 100 mg 1 week postpartum, term caesarean delivery
Case 3	Age <20 years, 2nd trimester IVH, term caesarean delivery	None	Age 20–25 years, 2nd trimester IVH, term caesarean delivery	Unknown	Fully recovered, no symptoms	Two pregnancies, both term caesarean deliveries
Case 4	Age 25–30 years, 1st trimester CVT, term caesarean delivery	None but there was a plan to start	Age 30–35 years, 1st trimester CVT, term caesarean delivery	No prothrombotic state detected, controlled thrombophilia testing normal 3 months after delivery	Fully recovered, no symptoms	No other pregnancies

Abbreviations: ASA, acetosalicylic acid; CVT, cerebral venous thrombosis; DVT, deep vein thrombosis; IS, ischemic stroke; IVH, intraventricular haemorrhage; MRA, magnetic resonance angiography; PAS, pregnancy-associated stroke; TEE, trans-oesophageal ultrasound.

preterm deliveries, miscarriages and induced abortions. None of these studies compared these rates to those of healthy controls. To our knowledge there are no studies on the complications of subsequent pregnancies or the outcomes of women with previous ICH or SAH.

Pregnancy complications of the index pregnancy (i.e. the pregnancy with which the initial PAS was associated) also impact the prognosis of the subsequent pregnancies. HDP complicated 24.7% and pre-eclampsia complicated 11.9% of the index pregnancies of the women with PAS in our cohort (Table 1). In comparison, the incidence rate of HDP was 17.2% and that of pre-eclampsia was 3.3% in their subsequent pregnancies (Table 2, Figure S1). Hence HDP, especially pre-eclampsia, was less common in the subsequent pregnancy in comparison to the index pregnancy. This is logical considering the greater risk of pre-eclampsia associated with nulliparity.[27] As shown by the multivariable analysis, the HDP of the index pregnancy largely explains the excess incidence of HDP in the subsequent pregnancies of the cases. Any diabetes during pregnancy was more common in the subsequent pregnancies in comparison to the index pregnancy (24.6% versus 14.5%; Tables 1 and 2, Figure S1), probably resulting from the advancing maternal age by advancing parity.[28] Moreover, the relationships between the risk factors for stroke and pregnancy complications are complex and multidirectional. HDP and any diabetes during pregnancy being more common in subsequent pregnancies of cases does not imply them being consequences of stroke but rather reflects the disease burden of the women with a PAS history.

In this study, PAS recurred in 5.5% of cases, corresponding to over 180-fold incidence in comparison with women without previous PAS (incidence 30 per 100 000 deliveries[1]). According to our earlier systematic review, which is the sole existing study including only post-PAS pregnancies, the recurrence rate was 2% ($n = 1$).[12] The systematic review was, however, limited by the small number of women with PAS history (26 women with 55 pregnancies) found in the studies reporting pregnancies of young female stroke patients. In our current study, we found the recurrence to be more common, although most patients of our cohort were under surveillance during pregnancy and used secondary prevention. Our results demonstrate that PAS is not a random event but the women with previous PAS are high-risk patients regarding recurrent PAS and other pregnancy complications. This excess risk may be attributed to accumulated cardiovascular risk factors or as yet unidentified genetic risk factors; the risk also depends on the use of secondary prevention. Whether they have higher cardiovascular risk later in life is not known but could be hypothesised.

We found women with PAS history to have fewer subsequent deliveries in comparison to controls. Also, induced abortions were more frequent among women with a previous PAS. The difference may partly be explained by residual disability; although the difference persisted among women who recovered well (mRS ≤ 2). We hypothesise that the fear of a recurrent PAS or other pregnancy complications or counselling against subsequent pregnancy may contribute to the difference and may also explain the higher frequency of induced abortions.

Caesarean delivery rate was around three times higher in the post-PAS pregnancies, partly due to previous caesarean delivery being more common in this group. Half of the elective caesareans of cases were the result of maternal request or recommendation from the neurologist without an obstetric indication based on the patient records. Current guidelines are consensus rather than evidence based and recommend individualised consideration of the delivery mode for women with a PAS history, and in the majority it can be chosen according to obstetric indications.[29] Avoiding unnecessary caesarean sections in this patient group is important acknowledging the increased stroke and thrombosis risk associated with caesarean section (OR 1.3–3.3).[30,31]

5 | CONCLUSION

Women with a PAS history constitute a high-risk group in their subsequent pregnancies and require thorough monitoring in specialised antenatal care units. The results of our study can be used in counselling women with a PAS history when they consider a subsequent pregnancy.

AUTHOR CONTRIBUTIONS

LV, PI, MT, OÄ, KA, KR, HL and MG had a major role in study conception and planning. LV, PI, KA, KR, AK and AR participated in data acquisition and patient record review. LV, PI and MG conducted the data analysis. All authors contributed to writing and editing of the work.

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CONFLICT OF INTEREST STATEMENT

None declared. Completed disclosure of interests form available to view online as supporting information.

DATA AVAILABILITY STATEMENT

Because the data collected for this study contain potentially identifying and sensitive patient information, the data cannot be shared in open data depositories. De-identified aggregated data that support the findings of this study can be made available to qualified investigators on reasonable request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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