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ORIGINAL ARTICLE

Etiology of intracerebral hemorrhage during pregnancy or puerperium: A nationwide study

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Abstract

Background and purpose: Intracerebral hemorrhage during pregnancy or puerperium (pICH) is one of the leading causes of maternal death worldwide. However, limited epidemiological data exist on the etiology and outcomes of pICH, which are required to guide prevention and treatment.

Methods: A retrospective nationwide cohort study and a nested case–control study were performed in Finland for 1987–2016. We identified women with incident pICH by linking the Medical Birth Register (MBR) and the Hospital Discharge Register (HDR). The clinical details were collected from patient records. Three matched controls with a pregnancy without ICH were selected for each case from the MBR.

Results: In total, 49 pICH cases were identified. Half of these cases occurred during pregnancy, and the other half during peripartum and puerperium. Based on SMASH-U (structural vascular lesion, medication, amyloid angiopathy, systemic disease, hypertension, undetermined) classification, 35.4% of the patients had a systemic disease, most commonly preeclampsia, eclampsia, or HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome; 31.3% had a structural vascular lesion; 31.3% had undetermined etiology; and one patient (2.1%) had hypertension. The most important risk factor was hypertensive disorders of pregnancy (HDPs; odds ratio = 3.83, 95% confidence interval = 1.60–9.15), occurring in 31% of the cases. Maternal mortality was 12.5%, and 20.9% of the surviving women had significant disability (modified Rankin Scale = 3–5) 3 months after pICH. Women with systemic disease had the worst outcomes.

Conclusions: Even in a country with a comprehensive pregnancy surveillance system, the maternal mortality rate for pICH is high, and the sequelae are severe. Early recognition and treatment of the key risk factor, HDPs, are crucial to help prevent this serious pregnancy complication.

KEYWORDS
intracerebral hemorrhage, pregnancy, puerperium, risk factors, stroke

INTRODUCTION

Intracerebral hemorrhage during pregnancy or puerperium (pICH) is a rare event. Yet pICH is one of the leading causes of maternal deaths worldwide [1, 2]. Previous studies have reported that the incidence of ICH is 7.18 per 100,000 pregnancies [3]. In our prior nationwide study using register validation, this incidence was 2.8 (95% confidence interval [CI] = 2.1–3.7) per 100,000 and remained relatively stable during the study period of 1987–2016 [4].

The incidence of ICH has been shown to be higher among pregnant women than nonpregnant women of the same age and foremost during the third trimester, peripartum, and early puerperium [4, 5]. The underlying causes are thought to relate to the remarkable changes that occur in the cardiovascular and the coagulation systems during pregnancy [1, 6].

As the in-hospital mortality rate for pICH may be as high as 20.3% [7], it is important to recognize the causes of pICH to enable better guidance for prevention, diagnostic evaluation, and acute care. Previous studies have identified hypertension, preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, diabetes, smoking, advanced maternal age, nonwhite ethnicity, migraine, and coagulopathy as risk factors for pICH [3, 7]. However, only a few studies have examined the exact etiology of pICH [8–10] and related outcomes, and none of these is from a European country.

The aims of this study were to investigate the etiology, risk factors, and temporal connection to pregnancy as well as the outcomes of pICH using the etiological classification system called SMASH-U (structural vascular lesion, medication, amyloid angiopathy, systemic disease, hypertension, undetermined) [11].

METHODS

This article follows the STROBE [Strengthening the Reporting of Observational Studies in Epidemiology] reporting guidelines [12]. Detailed methods can be found in Data S1.

Study design

We have earlier implemented a retrospective nationwide cohort study and a nested case–control study in Finland (Stroke in Pregnancy and Puerperium in Finland [SIPP-FIN]) [4]. The cohort comprised all pregnant women who delivered during the period of 1987–2016. All women with stroke during pregnancy or puerperium and three matched controls with a pregnancy without stroke were included. A subcohort consisting of women with pICH and their controls with pregnancies without ICH were included in this analysis. The flowchart for the SIPP-FIN study, which also shows how the ICH subcohort was formed, is provided in Figure 1.

Use of formal registered data

The Hospital Discharge Register (HDR) and the Medical Birth Register (MBR) from 1987 to 2016 were utilized to identify women with an International Classification of Diseases (ICD)-9, ICD-10, or surgical procedure code implying a cerebrovascular event or its treatment in the HDR up to 270 days prior to or up to 90 days after the delivery date as noted in the MBR. The MBR data are collected by the nationwide system of public maternity clinics, and it registers all live births and stillbirths with gestational age of ≥22 weeks or with birth weight of ≥500 g. The details on diagnostic and procedural codes used for the register search and the content of the registers are offered in Data S1. To identify out-of-hospital deaths, the Register of Causes of Death (RCD) was searched using ICD codes 6740A and O99.4 from 1987 to 2016. All causes of deaths and death certificates for register-identified cases and controls to the end of 2016 were obtained from the RCD to determine the maternal mortality attributed to ICH.

pICH cohort and its outcomes

The patient records for the ICH cases were obtained from health care facilities where the ICD code for ICH or an ICH-related procedure code in the HDR was registered.

A stroke neurologist verified the diagnosis and temporal connection of ICH and pregnancy. Detailed clinical information on the symptoms, diagnostic investigations, treatment, procedures, and outcomes was collected. Complex cases were assessed by a panel of three neurologists, and disagreements were resolved by consensus. ICHs secondary to trauma, subarachnoid hemorrhage, or cerebral venous thrombosis were excluded from this current analysis.

The etiology was classified according to the SMASH-U classification [11]. In SMASH-U, hypertension was defined as (i) most recent pre-ICH blood pressure ≥160/100 mmHg, either on or off antihypertensive medication or, when pre-ICH blood pressure was not known, either (ii) mention of pre-ICH elevated blood pressure by patient, relative, or medical records together with left ventricular hypertrophy as a biomarker of hypertension, or (iii) any pre-ICH use of blood-pressure medication. According to this definition, the patients with hypertensive disorders of pregnancy (HDPs) could be classified into "hypertension" if they fulfill the criteria above, or "systemic" if they do not fulfill the criteria of hypertension but meet the criteria for preeclampsia (see below). Patients with gestational hypertension or chronic hypertension, that is, hypertension present before 20 weeks of gestation, were classified as "hypertension." Another feature of SMASH-U is hierarchical structure, whereby a patient can only be classified into one (the first or highest) etiology.

We used the CHARTS instrument [13] to classify the ICH cases according to anatomy if this classification was possible from a review of the radiological report. The degree of disability was estimated from the medical records using the modified Rankin Scale (mRS) [14]. Medical records from neurology, neurosurgery, and/or rehabilitation medicine containing details on residual symptoms and functioning were available for all cases with a minimum of 3 months of follow-up time.

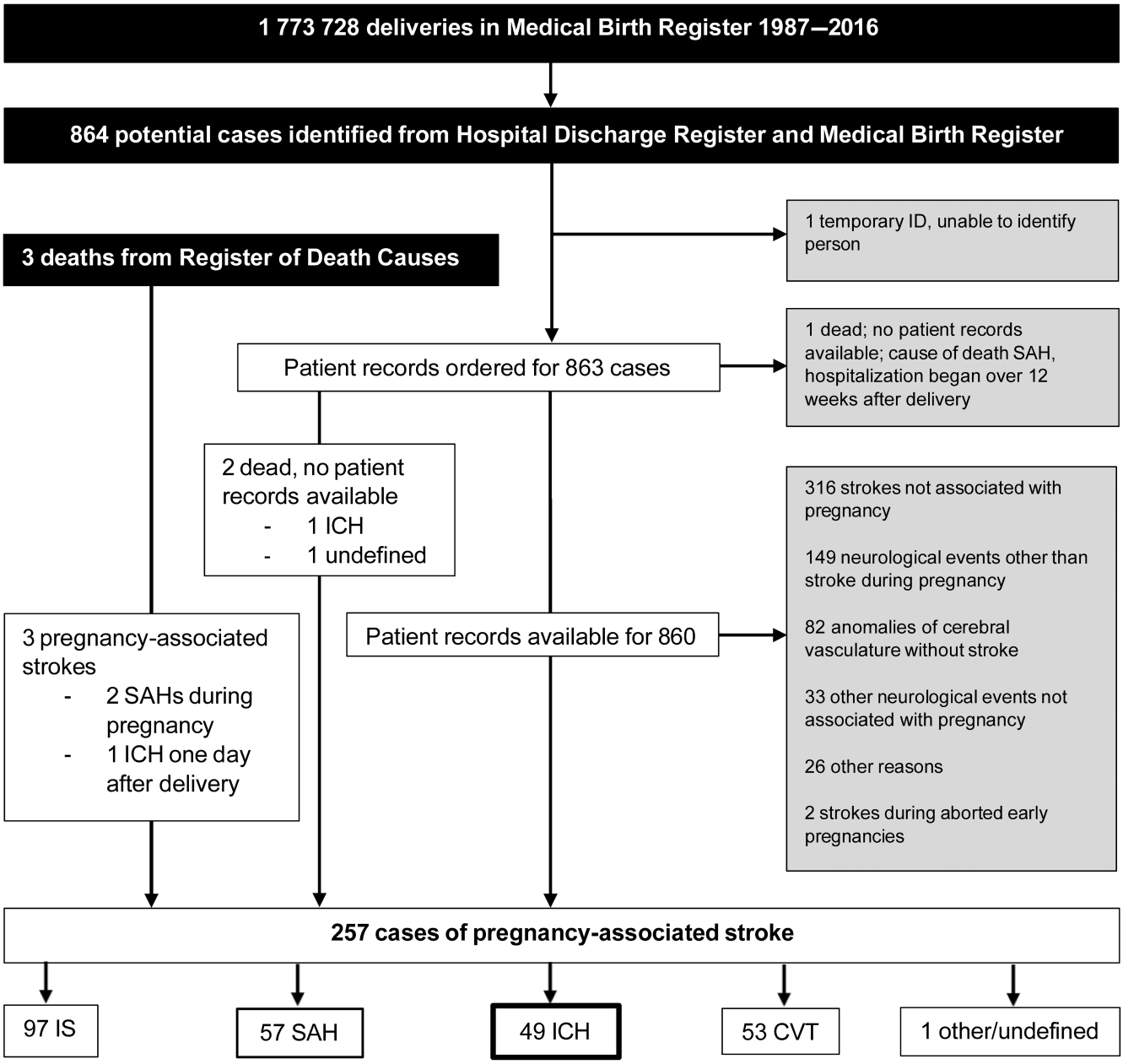

FIGURE 1 Flowchart of the SIPP-FIN (Stroke in Pregnancy and Puerperium in Finland) study. CVT, cerebral venous thrombosis; ICH, intracerebral hemorrhage; IS, ischemic stroke; SAH, subarachnoid hemorrhage.

The data on maternal deaths were acquired from the RCD, and perinatal mortality were gathered from the MBR from 22 weeks of gestation until the age of 1 week. All data from the registers were collected until 31 December 2016.

Case–control study and risk-factor analysis

For each case, three pregnant controls without stroke were identified from the MBR and matched according to delivery year, age, parity, and geographical area. Only two controls were available for one case because of advanced maternal age and a sparsely populated geographical area. Only register data were used for risk factor analyses, because medical records were not available from controls. Risk factors identified in the previous literature and available in the MBR and HDR were included in the analysis. In addition, pregnancy outcomes and maternal and perinatal mortality were compared.

Definitions

Preeclampsia was defined as a systolic blood pressure of 140 mmHg or diastolic blood pressure of 90 mmHg emerging after the 20th week of pregnancy in a woman with normal blood pressure before pregnancy, accompanied by proteinuria [15]. In the absence of proteinuria,

the criteria for preeclampsia were met if the hypertension occurred together with thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or new onset headache unresponsive to medication [15]. Eclampsia was defined by new onset seizures without causative conditions, such as epilepsy [15]. HELLP syndrome is the clinical presentation of hemolysis, elevated liver enzymes, and low platelet count [15]. According to the international classifications, preeclampsia includes patients with severe features, namely, eclampsia or HELLP syndrome [15]. In the treatment of pregnancy-related hypertension and preeclampsia, Finnish health care professionals follow national guidelines based on international guidelines and recommendations [16]. During the period of 1987–2016 the guidelines were revised with minor updates in 2001, 2005, 2009, and 2014. Blood pressure management with medication, preferably labetalol or nifedipine, is recommended when the systolic blood pressure is ≥150 mmHg or the diastolic is ≥100 mmHg [16].

Statistical analysis

The incidence of pICH is reported here per the number of births. CIs for incidence rates were calculated using Poisson distribution. For analyzing incidence trends over the time periods and age groups, the Cochran–Armitage test for trends was used.

The data are presented as percentages for the dichotomous variables, mean and SD for continuous variables, and median and interquartile range (IQR) for categorical variables and continuous variables with nonnormal distribution. To test the differences between groups, χ^2 or Fisher exact test was used for dichotomous variables, a *t*-test or analysis of variance for continuous variables, and the Mann–Whitney *U*-test or the Kruskal–Wallis test for ordinal variables. A p-value < 0.05 was considered statistically significant. Unconditional logistic regression was used to calculate age-adjusted odds ratios (ORs). Statistical analyses were executed using IBM SPSS statistics, version 25.

Ethics statement

The study has been approved by the ethics committee of Helsinki University Central Hospital. The Finnish Institute for Health and Welfare and Statistics Finland gave permission to use their register data in this study. Finnish law allows researchers to view medical data without asking the patient directly for consent.

RESULTS

Clinical presentation, treatment, and outcome of ICH cases

In 1987–2016, there were 49 incident cases of pICH per 1,773,728 deliveries (Figure 1). Mean age was 30.5 years and ranged from 19 to 42 years. The incidence was highest among 35–39-year-old women at 4.4 (95% CI = 2.6–7.1) per 100,000 deliveries.

The clinical characteristics of the pICH cases are detailed in Table 1. Clinical details were not available from one patient who died at home, so 48 cases are included in this analysis. Half of the cases occurred during pregnancy, 22.9% during peripartum, and 27.1% during puerperium (Figure 2). Most hemorrhages (60.4%) had a lobar distribution, whereas approximately one third (29.2%) were deep or infratentorial. The location of the ICH was most frequently in the frontal lobe. Almost half of the patients had additional pathology; 25.0% patients had an intraventricular hemorrhage (IVH), 16.7% had posterior reversible encephalopathy syndrome (PRES) or reversible cerebral vasoconstriction syndrome (RCVS), 8.3% had a convexity subarachnoid hemorrhage (cSAH), 2.1% had a subdural hematoma, and 10.4% had multiple additional lesions in addition to the ICH.

Nearly half of the patients (39.6%) were treated with craniotomy, and 18.8% had other invasive treatments, such as ventriculostomy or embolization of a vascular anomaly. Approximately half of the patients were treated in the intensive care unit.

Six (12.5%) patients suffered an early death before hospital arrival or while in the hospital. As there were no further deaths, the mortality at 1 year was 12.5%. The median follow-up time of the surviving women was 7.85 years (IQR = 14.95 years, range = 0.27–32.75 years). The median mRS at discharge was 2 (IQR = 2) and 1 (IQR = 2) at 3 months, and 79.1% of the surviving patients had a good recovery (mRS = 0–2) at 3 months. At the end of the follow-up, the median mRS was 1 (IQR = 2) and 88.4% of the surviving women had a good recovery.

Diagnostic workup in the ICH cases

Details on diagnostic investigations can be found in Table S1. All but one ICH case had brain imaging during the hospital stay. This patient died at home, and diagnosis was done postmortem at autopsy. Brain computed tomography (CT) alone was performed for 50.0% of the cases, brain magnetic resonance imaging (MRI) alone for 18.8%, and both for 31.3% of the cases. Angiography was performed for 72.9% of the cases: conventional angiography (digital subtraction angiography [DSA]) for 41.7%, CT angiography (CTA) for 20.8%, and magnetic resonance angiography (MRA) for 29.2%. Additionally, 41.7% of ICH patients had a control imaging by MRI within 1–3 months.

Complete laboratory screening test for bleeding disorders (activated partial thromboplastin time, prothrombin time, thrombin time, fibrinogen, the clotting factors FII, FV, FVII, FVIII, FIX, FX, FXI, FXII, FXIII, and von Willebrand Factor antigen and activity) was completed for 39.6% of the patients.

Of the patients with undetermined etiology, 73.3% were examined with angiography, and the laboratory screening test for bleeding disorders was carried out for 40.0% of these patients.

TABLE 1 Clinical characteristics and outcomes of women with pICH per SMASH-U classification.

Variable	All patients, $N=48$	Structural vascular lesion, $n=15$	Systemic disease, $n=17$	Hypertension, $n=1$	Undetermined, $n=15$	p[a]
Age, mean (SD)	30.5 (6.0)	29.0 (5.0)	31.1 (5.8)	36.1	31.2 (7.3)	0.575
Parity, median (IQR)	0 (2)	0 (1)	0 (2)	0	0 (2)	0.417
Risk factors, *n* (%)						
Smoking, current or past	10 (20.8%)	4 (26.7%)	1 (5.9%)	0	5 (33.3%)	0.115
Substance abuse	1 (2.1%)	0	0	0	1 (6.7%)	0.636
Anemia	2 (4.2%)	0	1 (5.9%)	0	1 (6.7%)	1.000
Migraine	4 (8.3%)	1 (6.7%)	0	0	3 (20.0%)	0.065
Hypertension prior pregnancy	2 (4.2%)	0	0	1 (100.0%)	1 (6.7%)	0.638
Diabetes mellitus, type I or II	1 (2.1%)	0	1 (5.9%)	0	0	1.000
Prior antiplatelets	2 (4.2%)	0	1 (5.9%)	0	1 (6.7%)	1.000
Prior antihypertensives	1 (2.1%)	0	1 (5.9%)	0	0	1.000
Clinical presentation						
GCS at admission, median (IQR)	15.0 (4)	14.5 (2)	15.0 (8)	15.0	15.0 (2)	0.181
SBP at admission, mean (SD)	138.8 (31.7)	119.7 (14.4)	165.8 (30.3)	–	122.8 (19.8)	<0.05
Diagnostics, *n* (%)						
Angiography	35 (72.9%)	13 (86.7%)	11 (64.7%)	0	11 (73.3%)	0.413
Conventional angiography	20 (41.7%)	9 (60.0%)	5 (29.4%)	0	6 (40.0%)	0.207
CTA	10 (20.8%)	3 (20.0%)	6 (35.3%)	0	1 (6.7%)	0.176
MRA	14 (29.2%)	3 (20.0%)	3 (17.6%)	0	8 (53.3%)	0.079
Complete screening for bleeding disorders	19 (39.6%)	4 (26.7%)	9 (52.9%)	0	6 (40.0%)	0.287
Anatomic location of ICH, *n* (%)						
Lesion side[b]						
Right	23 (48.9%)	10 (66.7%)	9 (52.9%)	0	4 (26.7%)	0.086
Left	18 (38.2%)	4 (26.7%)	4 (23.5%)	1 (100.0%)	9 (60.0%)	
Midline	2 (4.3%)	0	1 (5.9%)	0	1 (6.7%)	
Multiple	4 (8.5%)	1 (6.7%)	3 (17.6%)	0	0	
Location[b]						<0.05
Deep and infratentorial	14 (29.2%)	3 (20.0%)	4 (23.5%)	1 (100.0%)	6 (40.0%)	0.506
Basal ganglia	8 (16.7%)	0	4 (23.5%)	1 (100.0%)	3 (20.0%)	
Thalamic	1 (2.1%)	0	0	0	1 (6.7%)	
Brainstem	2 (4.2%)	2 (13.3%)	0	0	0	
Cerebellar	3 (6.3%)	1 (6.7%)	0	0	2 (13.3%)	
Lobar	29 (60.4%)	11 (73.3%)	10 (59.9%)	0	8 (53.3%)	0.564
Frontal	10 (20.8%)	7 (46.7%)	3 (17.6%)	0	0	
Parietal	8 (16.7%)	2 (13.3%)	3 (17.6%)	0	3 (20.0%)	
Temporal	7 (14.6%)	2 (13.3%)	2 (11.8%)	0	3 (20.0%)	
Occipital	3 (6.3%)	0	1 (5.9%)	0	2 (13.3%)	
Multiple	5 (10.4%)	0	4 (23.5%)	0	1 (6.7%)	
Uncertain	2 (4.2%)	0	1 (5.9%)	0	1 (6.7%)	NA
Additional pathology, *n* (%)						
IVH	12 (25.0%)	2 (13.3%)	6 (35.3%)	0	4 (26.7%)	0.401
cSAH	4 (8.3%)	1 (6.7%)	3 (17.6%)	0	0	0.363
Subdural hematoma	1 (2.1%)	0	0	0	1 (6.7%)	NA
PRES/RCVS	8 (16.7%)	0	8 (47.1%)	0	0	<0.05
Multiple	5 (10.4%)	0	5 (29.4%)	0	0	<0.05
Any additional pathology	20 (41.7%)	3 (20.0%)	12 (70.6%)	0	5 (33.3%)	<0.05

(Continues)

TABLE 1 (Continued)

Variable	All patients, $N=48$	Structural vascular lesion, $n=15$	Systemic disease, $n=17$	Hypertension, $n=1$	Undetermined, $n=15$	p[a]
Pregnancy-associated factors						
Timing of ICH						
During pregnancy, *n* (%)	24 (50.0%)	9 (60.0%)	5 (29.4%)	0	10 (66.7%)	0.085
Pregnancy week of ICH, median (IQR)	28 (16)	20 (17)	35 (9)	0	27 (20)	0.075
Peripartum, *n* (%)[c]	11 (22.9%)	0	8 (47.1%)	1 (100.0%)	2 (13.3%)	<0.05
Puerperium, *n* (%)	13 (27.1%)	6 (40.0%)	4 (23.5%)	0	3 (20.0%)	0.506
Hypertensive disorders of pregnancy, *n* (%)						
Gestational hypertension	1 (2.1%)	0	1 (5.9%)		0	NA
Preeclampsia[d]	13 (27.1%)	0	13 (76.5%)	0	0	<0.05
All HDPs[e]	15 (31.3%)	0	13 (76.5%)	1 (100.0%)	1 (6.7%)	<0.05
Gestational diabetes	4 (8.3%)	1 (6.7%)	0	0	3 (20.0%)	0.147
Delivery method, *n* (%)						
Spontaneous vaginal/ breech birth/vacuum extraction/forceps delivery	23 (47.9%)	8 (53.3%)	9 (52.9%)	1 (100.0%)	5 (33.3%)	0.479
Elective cesarean	10 (20.8%)	4 (26.7%)	1 (5.9%)	0	5 (33.3%)	0.115
Emergency cesarean	15 (31.3%)	3 (20.0%)	7 (41.2%)	0	5 (33.3%)	0.460
Prognosis[f]						
Follow-up time, median, years (IQR)	4.0 (14)	3.0 (16)	4.0 (14)	22.0	3.0 (16)	
Early death (death in hospital or at home), *n* (%)	6 (12.5%)	1 (6.7%)	3 (17.6%)	0	2 (13.3%)	0.348
One-year mortality, *n* (%)	6 (12.5%)	1 (6.7%)	3 (17.6%)	0	2 (13.3%)	0.348
mRS at discharge, median (IQR)	2.0 (3)	2.0 (2)	3.0 (4)	4.0	2.0 (3)	0.462
mRS at 3 months, median (IQR)	2.0 (3)	2.0 (1)	2.0 (4)	2.0	1.0 (3)	0.643
Good recovery [mRS = 0–2] at 3 months, *n* (%)	34 (70.8%)	12 (80.0%)	10 (68.8%)	1 (100%)	11 (73.3%)	0.445
mRS at the end of the follow-up, median (IQR)	1.0 (2)	1.0 (2)	1.0 (3)	0.0	1.0 (3)	0.577
Good recovery [mRS = 0–2] at the end of the follow-up, *n* (%)	38 (79.2%)	13 (86.7%)	13 (76.5%)	1 (100.0%)	11 (73.3%)	0.742

Abbreviations: cSAH, convexity subarachnoid hemorrhage; CTA, computed tomographic angiography; GCS, Glasgow Coma Scale; HDP, hypertensive disorder of pregnancy; HELLP, hemolysis, elevated liver enzymes, and low platelets; ICH, intracerebral hemorrhage; IQR, interquartile range; IVH, intraventricular hemorrhage; MRA, magnetic angiography; mRS, modified Rankin Scale; NA, not applicable; pICH, ICH during pregnancy or puerperium; PRES, posterior reversible encephalopathy syndrome; RCVS, reversible cerebral vasoconstriction syndrome; SBP, systolic blood pressure; SMASH-U, structural vascular lesion, medication, amyloid angiopathy, systemic disease, hypertension, undetermined.

[a]*p*: One patient with hypertension was excluded from the analysis.

[b]Only 47 patients were included in this analysis.

[c]Defined as 2 days before to 1 day after delivery.

[d]Of these, 6 (12.5%) patients also had eclampsia and 6 (12.5%) HELLP syndrome.

[e]Includes chronic hypertension, gestational hypertension, preeclampsia, eclampsia, and HELLP.

[f]All women included.

Etiology, clinical characteristics, and outcomes of ICH by SMASH-U classification

The etiological categories by SMASH-U are illustrated in Figure 3, and the clinical data are detailed in Tables 1 and S1. The etiology of ICH was a systemic disease for 17 patients (35.4%), of whom 13 (27.1%) had preeclampsia, six (12.5%) had eclampsia, six (12.5%) had HELLP syndrome, and eight (16.7%) had RVCS or PRES. One patient (2.1%) fulfilled the criteria for "hypertension." There were 15 (31.3%) patients with a structural vascular lesion, of whom six

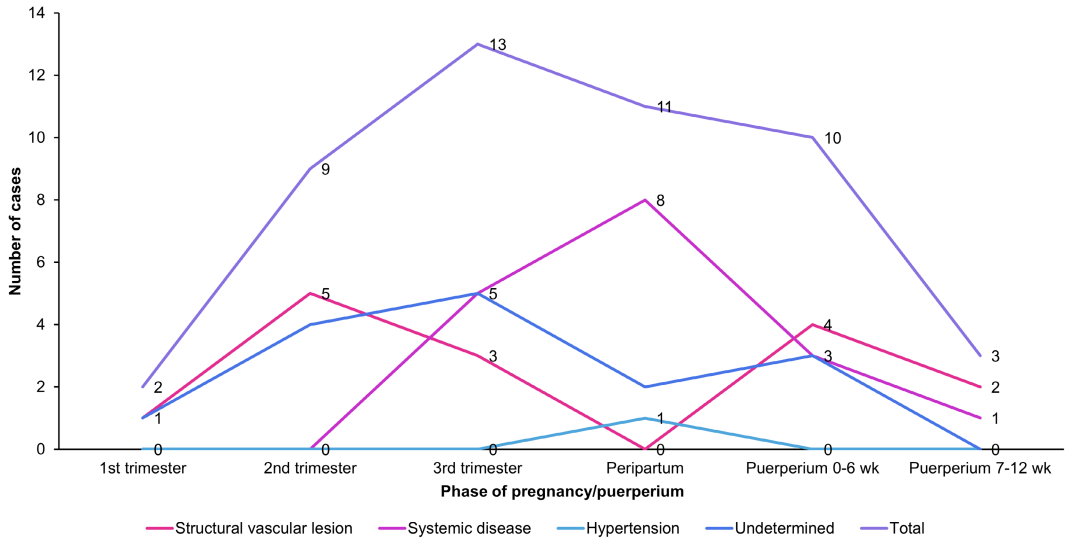

FIGURE 2 Intracerebral hemorrhage cases per pregnancy/puerperium period according to the SMASH-U (structural vascular lesion, medication, amyloid angiopathy, systemic disease, hypertension, undetermined) classification.

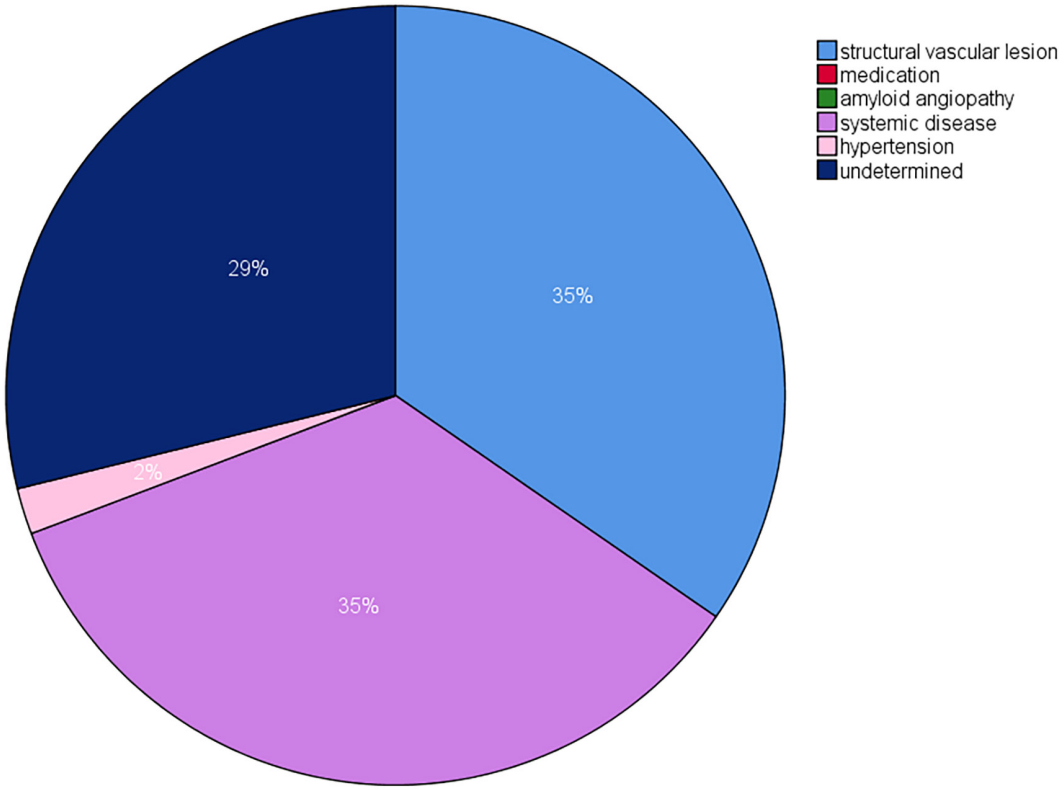

FIGURE 3 Pie chart for SMASH-U (structural vascular lesion, medication, amyloid angiopathy, systemic disease, hypertension, undetermined) subtypes.

(12.2%) had a cavernoma and nine (18.4%) had an arteriovenous malformation (AVM). There was no overlap between the three SMASH-U categories "vascular lesion," "systemic disease," and "hypertension." Particularly, none of the patients with systemic disease fulfilled the SMASH-U criteria for "hypertension" (detailed in Methods). For 15 (31.3%) patients, the etiology remained undetermined. No medication- or amyloid angiopathy-related ICHs were identified.

ICH occurred most often during peripartum when the etiology was a systemic disease (47.1%, $p < 0.05$), whereas ICHs caused by structural vascular lesions (60.0%) or undetermined cause (66.7%) occurred during pregnancy (Figure 2). The systolic blood pressure at admission varied significantly between the groups and was highest in patients with systemic etiology ($p < 0.05$). Hypertension prior to pregnancy was rare, present in only two patients. Extension of ICH to other locations such as IVH or cSAH, and PRES or RCVS,

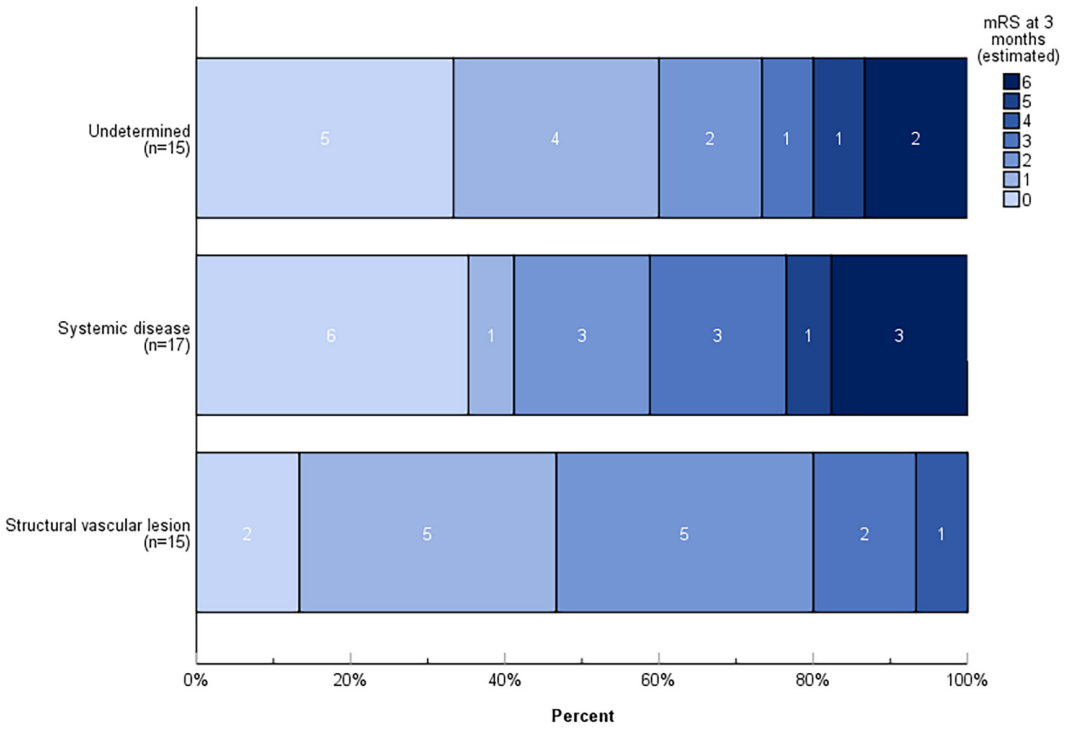

FIGURE 4 Modified Rankin Scale (mRS) at 3 months according to SMASH-U (structural vascular lesion, medication, amyloid angiopathy, systemic disease, hypertension, undetermined) classification.

were more common (70.6%) in patients with systemic etiology than in other etiologies ($p < 0.05$). No other significant differences were noted between etiologic groups.

Patients with structural vascular lesions had the best prognosis, as 80.0% had a good recovery (mRS = 0–2) at 3 months (Figure 4). Only 68.8% of the patients with a systemic disease and 73.3% of the patients with an undetermined etiology had a good recovery. Of the six patients who died from ICH, one had a structural vascular lesion, three had a systemic disease, and two had an undetermined etiology.

Risk factors and pregnancy outcomes in ICH patients and controls

The risk factors and pregnancy outcomes for ICH cases and controls are summarized in Table 2. The only significant risk factor was HDPs (including chronic hypertension, gestational hypertension, preeclampsia, eclampsia, and HELLP syndrome); 27.1% of the ICH patients had any HDP, compared to 9.1% of controls ($p < 0.002$, OR = 3.8, 95% CI = 1.6–9.2). Preeclampsia was registered in 18.8% of ICH patients and for only 2.8% of controls ($p < 0.0002$, OR = 8.1, 95% CI = 2.4–27.6). These numbers vary from the cohort study (Table 1), because the case–control study is based on the register data from the MBR and HDR, whereas the information for the cohort study was collected from actual patient records.

Elective and emergency caesarean sections were more common in ICH patients. There were no differences in perinatal mortality between the ICH cases and controls.

DISCUSSION

In this nationwide cohort study, one third of pICH cases were caused by systemic disease attributable mainly to different manifestations of preeclampsia and another third were caused by vascular structural lesions that comprised AVMs and cavernomas. The etiology for one third of the patients remained undetermined. One-year mortality was 12.5%, and one fifth of the surviving women had significant disability 3 months after the pICH. The poorest prognosis was seen among patients with a systemic disease, whereas patients with structural vascular lesions had the best prognosis. HDPs were the only significant risk factor for pICH in our study. To our knowledge, this is the first nationwide study on the etiology of pICH in Europe and the first nationwide study on pICH where the data have been chart-validated.

Previous studies have reported that preeclampsia, eclampsia, and HELLP syndrome are considerable risk factors for pICH [7, 8, 17–19]. In our study, 27.1% of the patients had preeclampsia, and 31.3% of patients had any HDP. In many of these patients, the symptoms of systemic disease developed abruptly during peripartum, leaving little time to start treatment before ICH occurred. Most of these ICHs had a lobar distribution, and patients had additional complicating pathology such as IVH, cSAH or RCVS or PRES. Not surprisingly, these patients had the worst prognosis, emphasizing the importance of this entity. Other studies from the United States, Canada, and France have reported that 14%–50% of patients with pICH have preeclampsia or eclampsia [3, 7, 20]. Preeclampsia and HELLP syndrome have been associated with a poor outcome after ICH in previous studies from China [8] and Japan [19, 21].

TABLE 2 Demographics, risk factors, and outcomes of ICH cases and controls.

Variables	All	ICH cases	Controls	*p*	Age-adjusted OR (95% CI)
Cases, *n*	191	48 (49 days)	143		
Age, years (SD)	30.5 (5.9)	30.6 (6.0)	30.5 (5.9)	1.000	
Multiparity, yes	35 (18.3)	9 (18.8)	26 (18.2)	1.000	
Risk factors					
Smoking, *n*[a]	188	48	140		
Nonsmoker	147 (78.2)	34 (70.8)	113 (80.7)	0.161	0.579 (0.273–1.227)
Continued smoking after 12 weeks	29 (15.4)	9 (18.8)	20 (14.3)	0.490	
BMI *n*[a]	93	22	71		
BMI, kg/m^2 (SD)	24.4 (5.6)	23.4 (5.5)	24.7 (5.7)	0.343	
Obesity [BMI > 30]	12 (12.9)	3 (13.6)	9 (12.7)	1.000	
Migraine	6 (3.1)	3 (6.3)	3 (2.1)	1.000	
Chronic hypertension	2 (1.0)	1 (2.1)	1 (0.7)	0.440	
Hypercholesterolemia	4 (2.1)	0	4 (2.8)	0.574	
Hypertensive disorders of pregnancy	26 (13.6)	13 (27.1)	13 (9.1)	0.003	3.83 (1.60–9.15)
Gestational hypertension	17 (8.9)	7 (14.6)	10 (7.0)	0.141	2.31 (0.81–6.59)
Preeclampsia	13 (6.8)	9 (18.8)	4 (2.8)	<0.001	8.06 (2.35–27.64)
Any diabetes	25 (13.1)	6 (12.5)	19 (13.3)	1.000	
Anemia during pregnancy	7 (3.7)	2 (4.2)	5 (3.5)	1.000	
Pregnancy outcomes					
Gestational age, full weeks, mean (SD)	39.0 (2.4)	37.7 (3.6)	39.4 (1.7)	0.006	
Mode of delivery	191	48	143		
Spontaneous vaginal/breech birth/ vacuum extraction/forceps delivery	144 (75.4)	24 (50.0)	120 (83.9)	<0.00001	0.21 (0.09–0.49)
Elective caesarean	16 (8.4)	9 (18.8)	7 (4.9)	0.005	4.48 (1.57–12.81)
Emergency caesarean	31 (16.2)	15 (31.3)	16 (11.2)	0.003	3.62 (1.62–8.09)
Perinatal mortality[b]	2 (1.0)	1 (2.1)	1 (0.7)	0.440	
Maternal death[c]	192	49	143		
Within 42 days	5 (2.6)	5 (10.2)	0 (0.0)	<0.001	ND
Within 1 year	6 (3.1)	6 (12.2)	0 (0.0)	<0.001	ND

Note: The results vary from Table 1 because the case–control study is based on the Medical Birth Register and Hospital Discharge Register, whereas the information for the cohort study was collected from patient records. Data are given as number (percentage) if not otherwise indicated.Abbreviations: BMI, body mass index; CI, confidence interval; ICH, intracerebral hemorrhage; ND, not determined; OR, odds ratio.

[a]Data not available for all 191 women.

[b]Stillbirth or death by 7 days after birth.

[c]Data for one woman who died at home is only included in the mortality data.

Almost one third of the pICH patients had a structural vascular lesion. This finding is in line with a previous study from Taiwan [9], which reported that 26% of pICHs were caused by cerebrovascular malformations. However, in a single-center study from Canada [10], AVM was the etiology for four of the six ICH cases. In our study, 18.4% of ICH patients had an AVM and 12.2% had a cavernoma. In comparison, these percentages were 41.0% for AVMs and 5.1% for cavernomas in a Chinese study [8]. Whether these discrepancies reflect methodological factors or true differences in the risk factors or ethnicities will require further studies.

The etiology remained undetermined in one third of the cases. Among these patients, the ICH occurred more often in the second and third trimester than in the other etiologies and over half were lobar. Preeclampsia was suspected based on clinical symptoms and imaging in one third of the patients, but the diagnostic criteria, usually the blood pressure values, were not met. The mean systolic blood pressure at admission was lower among these patients compared to the patients with a systemic disease as etiology (122.8 vs. 165.8 mmHg), supporting the idea that preeclampsia may in some instances develop at lower blood pressure values that stated by the current diagnostic criteria. Furthermore, half of undetermined cases were registered before the year 2000, possibly associating with more incomplete investigations and chart recording. DSA was performed for only 40.0% of patients, which may arise from clinicians' hesitation to use DSA in pregnant women, as DSA is associated with a higher risk of complications [22]. This may have left small AVMs undiagnosed, because DSA is more accurate than MRA and CTA in detecting them [23]. As a conclusion, we hypothesize that the undetermined group is heterogenous

and comprises small undetectable vascular malformations and pre-eclampsia left undiagnosed or manifesting at a lower blood pressure.

At the time of this study, there were only two algorithms for classifying ICH causes, SMASH-U [11] and H-ATOMIC [12]. These classifications bear many similarities, eight categories are almost concordant, and both report high interrater reliabilities [24]. We evaluated possible discrepancies between the classifications, but all our patients would have been classified concordantly into structural vascular lesion ("arterio-venous malformation and cavernoma" in H-ATOMIC), systemic ("infrequent causes of ICH" in H-ATOMIC), hypertension (same in both classifications), or undetermined ("cryptogenic" in H-ATOMIC). One potential source for discrepancies arises from different definitions of hypertension, but in our cohort, none of the patients with preeclampsia met the SMASH-U criteria of hypertension and none of the patients with undetermined etiology fulfilled the more permissive H-ATOMIC criteria of hypertension. Thus, both classifications grouped the same patients with preeclampsia into the systemic/infrequent causes of ICH group and another group of patients into the undetermined/cryptogenic group.

Our study has some limitations. Although the sampling time was 30 years, the pICH cohort was small due to the small size of the Finnish population. In some cases, especially at the beginning of the study period, the medical records were limited regarding both history and risk factors. We estimated clinical grading scales from patient records, which may have led to more favorable estimates, and thus these findings must be interpreted with caution. Furthermore, pregnancies that resulted in spontaneous or induced abortion before 22 weeks of gestation were not included, and thus, some women with an early ICH might have been missed. According to data from the Register of Induced Abortions, four pregnant women had an induced abortion on grounds of ICH during 1983–2016. According to Finnish law, induced abortion is legal if the continuation of the pregnancy would threaten the life or the health of the woman. Therefore, we can speculate that these women had either severe ICH or a severe underlying condition. However, we do not have their medical records and thus cannot report whether these women had a current pregnancy-associated ICH or a history of earlier ICH that led to the decision of the induced abortion. The information in Tables 1 and 2 varies in some instances, as the case–control study is based on the MBR and HDR and the cohort study is based on patient records. Additionally, as >90% of the Finnish population is of Finnish origin, its ethnic composition is very homogenous. Health care in Finland is available for all, which is believed to minimize the inequalities due to socioeconomic factors. For these reasons, our results might not be generalizable globally.

CONCLUSIONS

In this retrospective, nationwide cohort study, systemic diseases were the most common etiology for pICH, and these patients had the poorest outcome. Structural vascular lesions were also common, but prior non-European studies have reported a larger percentage of vascular malformations than our study. The etiology remained undetermined in one third of these cases. The most significant risk factor was HDPs, which were present in one third of the women. Early recognition and treatment of this increasingly frequent risk factor is crucial for the prevention of this serious pregnancy complication.

AUTHOR CONTRIBUTIONS

Teresa Vest: Conceptualization; investigation; writing–original draft; methodology; visualization; writing–review & editing; formal analysis; software; validation; data curation. **Kirsi Rantanen**: Writing–review & editing; investigation; data curation. **Liisa Verho**: Investigation; writing–review & editing; data curation; visualization; project administration; software. **Karoliina Aarnio**: Investigation; writing–review & editing; data curation. **Aino Korhonen**: Investigation; writing–review & editing; data curation. **Anna Richardt**: Investigation; writing–review & editing; data curation. **Daniel Strbian**: Investigation; writing–review & editing; data curation. **Mika Gissler**: Investigation; writing–review & editing; methodology; software; resources; data curation. **Hannele Laivuori**: Investigation; writing–review & editing; data curation. **Minna Tikkanen**: Investigation; writing–review & editing; data curation. **Petra Iljäs**: Supervision; resources; funding acquisition; conceptualization; visualization; methodology; writing–review & editing; investigation; validation; project administration; formal analysis; data curation; software.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Because the data collected for this study contains potentially identifying and sensitive patient information, the data cannot be shared in open data repositories. 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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