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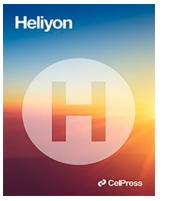

Research article

Pregnancy, delivery and neonatal outcomes in women with a cerebrovascular-accident history prior to delivery - Evaluation of a population database

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A B S T R A C T

Objective: Cerebrovascular accidents (CVA) in childbearing-age women are rare. We aimed to evaluate the association between CVA events prior to delivery and obstetrical and neonatal outcomes.

Methods: A retrospective cohort study was conducted using data from the Healthcare Cost and Utilization Project, Nationwide Inpatient Sample (HCUP–NIS) database. All pregnant women who delivered or had a maternal death in the US from 2004 to 2014 were included in the study. We performed a comparison between women with an ICD-9 diagnosis of CVA before the delivery admission and those without. Obstetrical and neonatal outcomes were compared between the two groups.

Results: In total, 9,096,788 women fulfilled the inclusion criteria. Among them, 695 women (7.6 per 100,000) were diagnosed with a CVA before delivery. Women with a history of CVA, compared to those without, were more likely to be Black, older than 35 years of age, and suffer from obesity, chronic hypertension, pregestational diabetes, and thyroid disease. Patients with a prior CVA, compared to those without, had higher rates of pregnancy-induced hypertension (aOR 6.41, 95% CI 5.03–8.39, $p < 0.001$), preeclampsia (aOR 7.65, 95% CI 6.03–9.71, $p < 0.001$), and eclampsia (aOR 171.56, 95% CI 124.63–236.15, $p < 0.001$). Additionally, they had higher rates of preterm delivery (aOR 1.72, 95% CI 1.33–2.22,$p = 0.003$), cesarean section (aOR 2.69, 95% CI 2.15–3.37, $p < 0.001$), and maternal complications such as a peripartum hysterectomy (aOR 11.62, 95% CI 5.77–23.41, $p < 0.001$), postpartum hemorrhage (aOR 3.39, 95 % CI 2.52–4.54, $p < 0.001$), disseminated intravascular coagulation (aOR 16.32, 95% CI 11.33–23.52, $p < 0.001$), venous thromboembolism (aOR 45.08, 95% CI 27.17–74.8, $p < 0.001$), and maternal death (aOR 486.11, 95% CI 307.26–769.07, $p < 0.001$). Regarding neonatal outcomes, patients with a prior CVA, compared to those without, had a higher rate of intrauterine fetal demise and congenital anomalies.

Conclusion: Women with a CVA event before delivery have a significantly higher incidence of maternal complications, including hypertensive disorders of pregnancy, and neonatal complications, such as intrauterine fetal demise and congenital anomalies. Rates of maternal death were dramatically increased, and this association requires further evaluation.

1. Introduction

A cerebrovascular accident (CVA) is defined as a sudden neurological deficit attributed to a focal injury of the central nervous system secondary to vascular damage [1]. It is considered a medical emergency with significant morbidity and mortality and is the second leading cause of death worldwide [2]. Although most strokes occur in the seventh decade of life onward [3], there is an

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increasing trend in stroke events in the younger population [4], and young women are more susceptible to stroke than young men [5]. A recent study showed that the incidence of CVA in women of childbearing age is 26 per 100,000 [3]. CVA in young adults tremendously affects one's life and causes a large economic impact by leaving victims disabled before their most productive years [6]. In the population of young women, besides facing lifelong consequences, it occurs in a period of life during which family planning begins.

While CVA events during pregnancy and the puerperium (pregnancy-associated stroke (PAS)) are well-described [7–9] and are known to have major maternal complications, including an increased risk for maternal death [7,8], CVA occurring specifically in the period before delivery has been much less studied. Whilst previous studies have found that only 5.5%–11 % of PAS [8,9] occur prior to delivery, they have reported the pregnancy outcomes of the entire study group, limiting the ability to draw conclusions regarding the outcomes in those cases where the CVA occurred prior to delivery. The only study that examined strokes occurring before delivery [10] comprised only 30 patients. Previous studies examining CVA prior to pregnancy also have several limitations, including small sample sizes (ranging between 15 and 68 pregnancies) [11–13], including only selected populations such as women with thrombophilia disorders [12], and examining only cerebral venous sinus thrombosis [14,15] or ischemic events [13].

Previous data regarding stroke before pregnancy has demonstrated conflicting conclusions. While some showed good prognoses in pregnancies in women with a history of a stroke [16,17], one of the largest studies (213 women), showed an increased risk for maternal complications, such as preeclampsia, gestational hypertension, and gestational diabetes mellitus (GDM) [18]. Previous studies have also only reported maternal outcomes [7,9] and not neonatal outcomes.

Here we aim to address this knowledge gap and provide data regarding pregnancy and perinatal outcomes, which we hope will contribute to improving the counseling for women who have experienced a CVA prior to pregnancy. Using a comprehensive contemporary nationwide database, we aimed to determine the incidence of CVA occurring prior to the delivery admission, as well as report the maternal and perinatal outcomes of pregnancies in women with a history of stroke.

2. Methods

2.1. Study design

This study was a retrospective population-based cohort study that utilized the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (HCUP–NIS) database during the years 2004–2014 [19]. The HCUP-NIS is the largest inpatient sample database in the USA and is comprised of hospital inpatient stays submitted by hospitals throughout the country. Each year, the database provides information relating to 7 million inpatient stays, including patient characteristics, diagnoses, and procedures. The data represent 20 % of admissions to US hospitals across 48 states and the District of Columbia.

The collected data encompassed demographic and obstetric parameters, details about the labor and delivery, as well short-term maternal and neonatal outcomes up until the time of discharge. Demographic parameters included maternal age, race, income, and insurance type. Medicare is federal health insurance for people 65 years of age or older, and some people under 65 with certain disabilities or conditions; whilst Medicaid is a joint federal and state program that helps cover medical costs for some people with limited income and resources. Maternal outcome data included: GDM; pregnancy-induced hypertension; eclampsia; preeclampsia; placenta previa; placental abruption; preterm delivery (<37 weeks); preterm premature rupture of membranes (PPROM); operative vaginal delivery; cesarean delivery (CD); postpartum hemorrhage (PPH); need for blood transfusion; disseminated intravascular coagulation (DIC); chorioamnionitis; wound complications; maternal infection; peripartum hysterectomy; maternal death; venous thromboembolism (VTE); deep vein thrombosis (DVT); and pulmonary embolism (PE). Neonatal outcomes examined included: congenital anomalies; small-for-gestational-age (SGA) neonates (defined as birthweight below the tenth percentile); and intra-uterine fetal death (IUFD).

2.2. Study participants

The pregnant subjects included in the study had to have either a maternal death or a delivery, ensuring that they were represented only once per pregnancy in the database. Our cohort included only a possibly viable pregnancy at 24 weeks or above and did not include earlier miscarriages.

The cohort was stratified into two groups based on the diagnosis of CVA – women diagnosed with a CVA before the delivery admission and women without a diagnosis of past CVA.

Patients' status was classified based on an ICD-9 diagnosis of CVA, encompassing any of the following codes: 430, 431, 432.x, 433.x, 434.x, 436, 437. Patients with a diagnosis of CVA during the delivery admission were excluded.

2.3. Statistical analysis

An initial analysis was conducted to determine the incidence of women diagnosed with a CVA prior to the delivery admission over the entire study duration. Following the establishment of this cohort, an evaluation of demographic characteristics revealed the presence of missing data, which were observed to be randomly distributed. Consequently, the Markov chain Monte Carlo (MCMC) method was applied for imputation. Thereafter, chi-square tests were utilized to compare the baseline characteristics between women with a CVA diagnosis and those without. Logistic regression analyses were subsequently conducted to evaluate both the unadjusted and adjusted effects of a CVA diagnosis prior to delivery on maternal and neonatal outcomes. This involved estimating odds ratio (OR)

and 95 % confidence intervals (CI). The regression models were adjusted to account for potential confounding effects, including maternal demographics, pre-existing clinical characteristics, and concurrently occurring conditions where p-values of <0.05 were identified in the chi-squared analysis.

In order to validate the results of the analysis of the entire cohort, we additionally performed an analysis matching women with a CVA diagnosis to women without a CVA diagnosis (controls), according to age, race, income, and health insurance type, in a ratio of 1:20. Pregnancy, delivery, and neonatal outcomes were compared between the two groups using multivariate logistic regression models to adjust for potential confounders.

All analyses were performed using SPSS 25.0 (IBM Corporation, Chicago, USA).This study solely utilized publicly accessible, anonymized data. As per articles 2.2 and 2.4 of the Tri-Council Policy Statement (2010) [20], institutional review board approval was deemed unnecessary.

3. Results

A total of 9,096,788 women fulfilled the criteria for inclusion. Of them, 695 (8/100,000) patients were diagnosed with a CVA prior to the delivery admission. Notably, the prevalence of pregnancies in women with a prior diagnosis of CVA increased significantly during the study period (2004–2014) ($p = 0.011$), Fig. 1.

Baseline and demographic characteristics of women with and without a diagnosis of CVA prior to delivery are presented in Table 1. Women with a CVA diagnosis prior to delivery, compared to controls, were characterized by: a higher maternal age (22.6 % ≥ 35 years vs. 14.7 %, $p < 0.001$, respectively); were more likely to be of Black race (23.4 % vs. 13.7 %, $p < 0.001$, respectively); more likely to be in the lower income quartile (32.9 % vs. 27.3 %, $p = 0.041$, respectively); had a higher likelihood of having Medicare insurance (3.2 % vs. 0.6 %, $p < 0.001$, respectively); more likely to be obese (6.9 % body mass index≥30 vs. 3.6 %, $p < 0.001$, respectively); had a lower rate of previous CD (13.1 % vs. 16 %, $p = 0.039$, respectively); were more likely to suffer from chronic hypertension (12.7 % vs. 1.8 %, $p < 0.001$, respectively); were more likely to have pregestational diabetes mellitus (DM) (3.6 % vs. 1 %, $p < 0.001$, respectively); had a higher rate of illicit drug use (4.2 % vs. 1.4 %, $p < 0.001$, respectively); had a higher rate of thyroid disorders (4.7 % vs. 2.5 %, $p < 0.001$, respectively); and a higher rate of HIV infection (0.4 % vs. 0 %, $p < 0.001$, respectively). Other maternal characteristics, including cigarette smoking during pregnancy, in-vitro fertilization treatments to conceive the pregnancy, and multiple gestations, were comparable between the two groups.

Table 2 presents the association between a cerebrovascular accident (CVA) prior to delivery and pregnancy and delivery outcomes, after accounting for potential confounding factors. These factors include maternal age, race, insurance plan type, income quartiles, obesity, illicit drug use, thyroid disease, HIV infection, previous CD, chronic hypertension, and pregestational DM for pregnancy outcomes, with the addition of hypertensive disorders of pregnancy for the delivery and neonatal outcomes analysis.

Women who suffered from CVA prior to delivery, compared to those who did not, had a higher rate of pregnancy-induced hypertension (adjusted OR (aOR) 6.41, 95 % CI 5.03–8.39,$p < 0.001$); preeclampsia (aOR 7.65, 95 % CI 6.03–9.71, $p < 0.001$); eclampsia (aOR 171.56, 95 % CI 124.63–236.15, $p < 0.001$); and superimposed preeclampsia/eclampsia (aOR 2.6, 95 % CI 1.53–4.43, $p < 0.001$). Women with a CVA event prior to delivery also had a higher rate of preterm delivery (aOR 1.72, 95 % CI 1.33–2.22, $p < 0.001$); placental abruption (aOR 2.14, 95 % CI 1.3–3.51, $p = 0.003$); and CD (aOR 2.69, 95 % CI 2.15–3.37, $p < 0.001$); and a lower rate of spontaneous vaginal delivery (aOR 0.37, 95 % CI 0.3–0.47, $p < 0.001$). They also had a higher rate of peripartum hysterectomy (aOR 11.62, 95 % CI 5.77–23.41, $p < 0.001$); PPH (aOR 3.39, 95 % CI 2.52–4.54, $p < 0.001$); wound complications (aOR 5.04, 95 % CI 2.8–9.07, $p < 0.001$); maternal death (aOR 486.12, 95 % CI 307.26–769.07, $p < 0.001$); and blood transfusions (aOR 8.78, 95 % CI 6.69–11.52, $p < 0.001$); were more likely to suffer from maternal infection (aOR 2.42, 95 % CI 1.61–3.65, $p < 0.001$); had a higher rate of DVT (aOR 20.99, 95 % CI 9.01–48.88, $p < 0.001$); a higher rate of PE (aOR 81.13, 95 % CI 44.04–149.45, $p < 0.001$); a higher rate of VTE (aOR 45.08, 95 % CI 27.17–74.8, $p < 0.001$); and a higher rate of DIC (aOR 16.32, 95 % CI 11.33–23.52, $p < 0.001$). Other

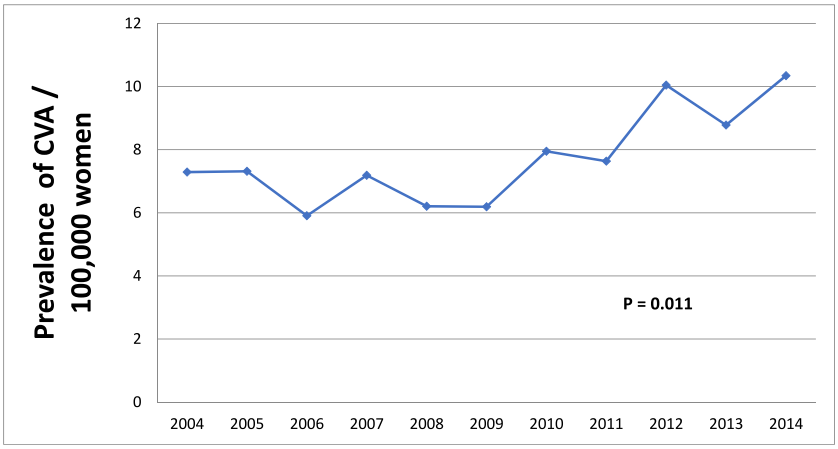

Fig. 1. Prevalence of CVA cases prior to delivery during the study period. Abbreviations: CVA – cerebrovascular accident.

Table 1
Maternal characteristics.

Characteristics	Acute CVA N = 695	No CVA N = 9,096,093	*P*-value
Age (years)			<0.001
<25	227 (32.7 %)	3,455,842 (38 %)	
25–34	311 (44.7 %)	4,298,679 (47.3 %)	
≥35	157 (22.6 %)	1,341,037 (14.7 %)	
Race			<0.001
White	246 (41.3 %)	3,958,065 (52.3 %)	
Black	139 (23.4 %)	1,035,266 (13.7 %)	
Hispanic	142 (23.9 %)	1,756,681 (23.2 %)	
Asian and Pacific	28 (4.7 %)	390,349 (5.2 %)	
Native American	<11	59,990 (0.8 %)	
Other	34 (5.7 %)	365,509 (4.8 %)	
Income quartiles			0.041
Less than 39,000	145 (32.9 %)	1,486,440 (27.3 %)	
$39,000–47,999	112 (25.4 %)	1,386,712 (25.5 %)	
$48,000–62,999	101 (22.9 %)	1,355,372 (24.9 %)	
$63,000 or more	83 (18.8 %)	1,218,862 (22.4 %)	
Plan type			<0.001
Medicare	22 (3.2 %)	56,566 (0.6 %)	
Medicaid	319 (46 %)	3,874,109 (42.7 %)	
Private including HMO	299 (43.1 %)	4,599,330 (50.7 %)	
self-pay	25 (3.6 %)	288,391 (3.2 %)	
No charge	<11	17,057 (2.7 %)	
Other	23 (3.3 %)	244,910 (2.7 %)	
Obesity (BMI≥30 kg/m^2)	48 (6.9 %)	324,128 (3.6 %)	<0.001
Previous CD	91 (13.1 %)	1,452,339 (16 %)	0.039
Smoking during pregnancy	37 (5.3 %)	443,553 (4.9 %)	0.584
Chronic hypertension	88 (12.7 %)	165,142 (1.8 %)	<0.001
Pregestational DM	25 (3.6 %)	86,590 (1 %)	<0.001
Illicit drug use	29 (4.2 %)	125,590 (1.4 %)	<0.001
Multiple gestation	11 (1.6 %)	137,292 (1.5 %)	0.874
Thyroid disease	33 (4.7 %)	223,245 (2.5 %)	<0.001
HIV	<11	2076 (0 %)	<0.001
IVF	0 (0 %)	10,532 (0.1 %)	0.668

Abbreviations and definitions: CVA – cerebrovascular accident; HMO – Health Maintenance Organization; BMI – Body Mass Index; CD – cesarean delivery; DM – diabetes mellitus; HIV – human immunodeficiency virus; IVF – in-vitro fertilization.
Per convention of the HCUP database, when N < 11, absolute cell number of subjects was not provided to protect patient anonymity (zero subjects could be reported because it would not affect anonymity).

pregnancy and delivery outcomes examined, such as GDM, placenta previa, operative vaginal delivery, PPROM, and chorioamnionitis were comparable between the groups.

Neonatal outcomes are presented in Table 3. Women with a diagnosis of CVA prior to delivery had a higher rate of IUFD (aOR 2.7, 95 % CI 1.33–5.48, p = 0.006) and a higher rate of neonates with congenital malformations (aOR 8.42, 95 % CI 5.39–13.15, p < 0.001). There was no difference in the rate of SGA between the two groups.

In the matched analysis we performed (Tables 1–3, Supplementary material), there were 12 patients less included in the study group, compared to the initial analysis (683 women versus 695 with a CVA, respectively), since they could not be matched. Regarding maternal characteristics, there were no differences in the rates of obesity and thyroid disorders, as opposed to what we found in the initial analysis (Table 1, Supplementary material). Regarding pregnancy and delivery outcomes, the two analyses showed similar results (Table 2, Supplementary material). The only differences were that GDM and operative vaginal deliveries were shown to be significantly higher in the study group as compared to the control group in the matched analysis, whereas the rates of these complications were comparable in the initial analysis. Neonatal outcomes were similar to the results of the initial analysis (Table 3, Supplementary material).

4. Discussion

We compared pregnancy, delivery, and neonatal outcomes between women with a history of a CVA that preceded their delivery admission and those without. Our principal observations were the following: 1) There was an increased incidence in the number of pregnancies in women with a history of stroke across the study period; 2) Pregnant women with a history of stroke prior to delivery were characterized by increasing maternal age, Black race, lower income quartile, drug abuse, obesity, chronic hypertension, pregestational DM, thyroid disease, and HIV infection; 3) Women with a CVA before delivery had an increased risk of hypertensive disorders of pregnancy (HDP), preterm delivery, placental abruption, CD, peripartum hysterectomy, PPH, wound complications, blood transfusion, maternal infection, DIC, thromboembolic events, and maternal death. 4) They also had increased rates of IUFD and congenital anomalies compared to women without a history of CVA.

Table 2
Pregnancy and delivery outcomes.

Outcomes	Acute CVA (%)	No CVA (%)	Crude OR (95 % CI)	Adjusted OR (95 % CI)	Adjusted p-value
Pregnancy outcomes[a]					
Pregnancy-induced hypertension	367 (52.8 %)	974,989 (10.7 %)	9.32 (8.03–10.82)	6.41 (5.03–8.39)	<0.001
Preeclampsia	180 (25.9 %)	327,210 (3.6 %)	9.37 (7.9–11.1)	7.65 (6.03–9.71)	<0.001
Eclampsia	101 (14.5 %)	6843 (0.1 %)	225.85 (182.65–279.26)	171.56 (124.63–236.15)	<0.001
Preeclampsia and Eclampsia superimposed	43 (6.2 %)	47,322 (0.5 %)	12.61 (9.26–17.17)	2.6 (1.53–4.43)	<0.001
GDM	34 (4.9 %)	523,158 (5.8 %)	0.84 (0.6–1.19)	0.76 (0.5–1.16)	0.198
Placenta previa	<11	49,973 (0.5 %)	2.38 (1.23–4.58)	2.04 (0.84–4.94)	0.114
Delivery outcomes[b]					
PPROM	<11	103,614 (1.1 %)	0.5 (0.19–1.34)	0.42 (0.1–1.67)	0.216
Preterm delivery	150 (21.6 %)	653,745 (7.2 %)	3.55 (2.97–4.26)	1.72 (1.33–2.22)	<0.001
Abruptio placenta	29 (4.2 %)	97,450 (1.1 %)	4.02 (2.77–5.83)	2.14 (1.3–3.51)	0.003
Chorioamnionitis	<11	165,321 (1.8 %)	0.71 (0.37–1.37)	0.86 (0.41–1.82)	0.694
Operative vaginal delivery	47 (6.8 %)	489,354 (5.4 %)	1.28 (0.95–1.72)	1.15 (0.73–1.81)	0.549
CD	443 (63.7 %)	2,939,475 (32.3 %)	3.68 (3.15–4.3)	2.69 (2.15–3.37)	<0.001
SVD	205 (29.5 %)	5,667,264 (62.3 %)	0.25 (0.22–0.3)	0.37 (0.3–0.47)	<0.001
Peripartum hysterectomy	<11	7089 (0.1 %)	19.01 (10.18–35.51)	11.62 (5.77–23.41)	<0.001
PPH	89 (12.8 %)	263,876 (2.9 %)	4.92 (3.94–6.14)	3.39 (2.52–4.54)	<0.001
Wound complications	22 (3.2 %)	32,711 (0.4 %)	9.06 (5.92–13.85)	5.04 (2.8–9.07)	<0.001
Maternal Death	54 (7.8 %)	584 (0 %)	1312.05 (982.42–1752.28)	486.12 (307.26–769.07)	<0.001
Transfusion	139 (20.4 %)	90,228 (1 %)	25.47 (21.14–30.69)	8.78 (6.69–11.52)	<0.001
Others					
Maternal infection	37 (5.3 %)	199,231 (2.2 %)	2.51 (1.8–3.5)	2.42 (1.61–3.65)	<0.001
DVT	<11	3823 (0 %)	31.2 (16.15–60.27)	20.99 (9.01–48.88)	<0.001
Pulmonary embolism	16 (2.3 %)	1643 (0 %)	130.43 (79.26–214.64)	81.13 (44.04–149.45)	<0.001
VTE	24 (3.5 %)	5286 (0.1 %)	61.51 (40.9–92.51)	45.08 (27.17–74.8)	<0.001
DIC	70 (10.1 %)	18,174 (0.2 %)	55.94 (43.68–71.65)	16.32 (11.33–23.52)	<0.001

Abbreviations and definitions: CVA – cerebrovascular accident; GDM – gestational diabetes mellitus; PPROM – preterm premature rupture of membranes; CD – cesarean delivery; SVD – spontaneous vaginal delivery; PPH – post-partum hemorrhage; DVT – deep vein thrombosis; PE – pulmonary embolism; VTE – venous thromboembolism; DIC – disseminated intravascular coagulation.
Per convention of the HCUP database when N < 11, absolute cell number of subjects was not provided to protect patient anonymity.
[a] Pregnancy Outcomes: Adjusted for Age, Race, Plan type, Income quartiles, Obesity, Illicit drug use, Chronic hypertension, Thyroid Disease, HIV, Pregestational DM, and previous CD.
[b] Delivery Outcomes: Adjusted for Age, Race, Plan type, Income quartiles, Obesity, Illicit drug use, Chronic hypertension, Thyroid Disease, HIV, Pregestational DM, previous CD, Pregnancy-induced hypertension, Preeclampsia, Eclampsia Preeclampsia superimposed, and Eclampsia.

Table 3
Neonatal outcomes[a].

Outcomes	Acute CVA (%)	No CVA (%)	Crude OR (95 % CI)	Adjusted OR (95 % CI)	Adjusted p-value
SGA	23 (3.3 %)	198,047 (2.2 %)	1.54 (1.02–2.33)	0.88 (0.53–1.45)	0.605
IUFD	13 (1.9 %)	38,246 (0.4 %)	4.51 (2.61–7.82)	2.7 (1.33–5.48)	0.006
Congenital Anomalies	33 (4.7 %)	38,211 (0.4 %)	11.82 (8.33–16.76)	8.42 (5.39–13.15)	<0.001

Abbreviations and definitions: CVA – cerebrovascular accident; SGA – small for gestational age; IUFD – intrauterine fetal death.
[a] Neonatal Outcomes: Adjusted for Age, Race, Plan type, Income quartiles, Obesity, Illicit Drug use, Chronic hypertension, Thyroid Disease, HIV, Pregestational DM, previous CD, Pregnancy-induced hypertension, Preeclampsia, Eclampsia Preeclampsia superimposed, and Eclampsia.

The prevalence of pregnant women with a pre-delivery diagnosis of CVA was 8/100,000. While the prevalence of PAS has been well-studied [7,8], with a cited incidence of 30/100,000 [21], the prevalence of pregnancies with a CVA diagnosis prior to delivery is much less well described. A previous Australian study [16] found the prevalence of pregnancies with a history of stroke occurring prior to pregnancy to be 25/100,000, higher than we have identified. This discrepancy could be explained by the fact that they limited their study to primiparous women, whilst we did not. It is more reasonable that a woman without children will seek pregnancy than a woman who already has children and has suffered from a stroke. It is also possible that the rate of previous stroke was under-represented in our study population.

During the 10-year study period, there was an increase in the prevalence of a prior CVA diagnosis in patients admitted to delivery ($p = 0.011$). This corresponds to the rising incidence of CVA events in young adults [4] but may also reflect an increasing willingness of women who have experienced a stroke to consider conceiving. This increased incidence of strokes is likely due to the increasing prevalence of vascular risk factors, such as obesity, hypertension, dyslipidemia, and diabetes [22]. This hypothesis correlates with the

higher rates of traditional cardiovascular risk factors in the CVA group, such as obesity, chronic hypertension, and pregestational DM.

We found that women with a pre-delivery CVA diagnosis were more likely to be of Black race, above the age of 35, with low income, and Medicare insurance. Similarly, a large prospective study [23] examining racial variation in stroke risk among women found a higher risk in the general Black women population and those with a low household income. Additionally, a study examining stroke in young women found that women aged 35–49 had an incidence of stroke that was three times higher compared to those aged 25–34 [24].

We also found a higher frequency of thyroid disorders and illicit drug use in the CVA group. This accords with the known demonstrated association between drug use and an increased risk of CVA in young adults [25,26]. Hyperthyroidism can provoke atrial fibrillation and thereby cause cardioembolic stroke, while hypothyroidism is also associated with an increase in dyslipidemia and atherosclerotic vascular disease [27].

Within our cohort, there was a significantly increased rate of HDP in the CVA group, with eclampsia being the most pronounced. Although previous studies on PAS have found a similar association between HDP and stroke [9,28], the data regarding CVA occurring prior to pregnancy and its association with HDP has been conflicting, with one previous study [18] also demonstrating this association, while others did not [13,16]. This discrepancy could be explained by the relatively small number of cases in the studies that did not find any association, ranging between 68 and 124 pregnancies. HDP is well-described as a risk factor for future cardiovascular events with a two-fold higher risk compared to normotensive pregnancies [29,30], but, to date, only a few studies demonstrated the opposite causation [15,18]. Several possible hypotheses exist for the increased incidence of HDP in our cohort. First, CVA and HDP may share common risk factors. Although we adjusted for maternal risk factors such as obesity, pregestational DM, and chronic hypertension, there are other factors we did not adjust for, such as hyperlipidemia and thrombophilia. Another possible explanation is endothelial dysfunction, postulated to be one of the causative factors in preeclampsia [31], which also plays a role in the pathogenesis of CVA [32]. Lastly, the high rate of eclampsia in our cohort (14.5 %) may partially be explained by a misdiagnosis of a repeat stroke, with the peripartum and postpartum periods incurring the highest risk for stroke in pregnancy [33].

Concerning the mode of delivery, there was a significantly higher rate of CD in the group of women with a prior CVA, consistent with findings in a previous study examining CVA before pregnancy, which found an OR for pre-labor CD of 2.83 [16]. One may postulate that CD may be a consequence of pregnancies complicated by HDP, for which the risk of CD is higher [34]. However, even after adjusting for HDP, this association still existed. It is possible that CD is being performed more often in this population to mitigate risks related to the Valsalva maneuver and maternal hemodynamic changes during the second stage of labor [16].

We found that women with a prior CVA had an increased risk for preterm delivery, with a rate of 21.6 %. Previous studies have shown conflicting results, with some not finding any correlation between CVA and preterm delivery [8,13,16,35]; whilst a prospective Dutch study [18] found a two-fold higher incidence of preterm delivery amongst patients with a pre-pregnancy CVA. These discrepancies may be explained by the relatively small number of patients in the studies which did not find an association [13,16]. Another explanation is that in the study that included patients with PAS, almost half of the events occurred in the postpartum period [8], hence diluting any association between antepartum stroke and subsequent preterm delivery. Notably, a limitation of our study is the lack of data regarding the nature of preterm deliveries (iatrogenic versus spontaneous), while in the Dutch study [18], 55.2 % of the preterm deliveries were iatrogenic.

In our study, after adjusting for confounders, we found that patients with a CVA prior to delivery had significantly higher risks for a myriad of adverse events. While several maternal complications such as PPH, blood transfusion, VTE, and maternal infection have been described as risk factors for PAS [8,36,37], they have not previously been described as outcomes in patients who have experienced a stroke prior to the intrapartum period. Most previous studies on patients with a CVA prior to pregnancy did not examine these complications [16–18], and those that did included only 45 patients and 68 pregnancies [13], limiting the impact of any conclusions drawn.

There are a few plausible explanations for the increased rate of PPH, blood transfusion, and DIC in the CVA group, including the increased CD and preterm delivery rates, which are both known risk factors for PPH [38,39]. Furthermore, women with a history of ischemic stroke will likely be receiving anticoagulant treatment during pregnancy as a secondary prevention measure [33], potentially exposing them to a higher risk of PPH [38]. The higher incidence of VTE in the CVA group could be explained by the increased CD rate and by increased maternal complications during delivery, including PPH and blood transfusion, which are risk factors for VTE [40]. Additionally, there may have been a higher prevalence of women with acquired and inherited thrombophilia in the CVA group. A study that examined the prevalence of thrombophilia in young adults with ischemic stroke found that the thrombophilia positivity rate was 20 % [41]. Data on the association between thrombophilia and stroke is mainly from studies on PAS which found an OR of between 4.2 and 16 for PAS in the presence of thrombophilia [8,9], while there is a paucity of data regarding this association in the pre-pregnancy stroke population [12,18]. Notably, a limitation of our study is that we lacked knowledge regarding patients' thrombophilia status.

The maternal mortality rate in the CVA group in our cohort was 7.8 % (54 cases). Data in the literature is limited mainly to the PAS population, which cited a similar maternal mortality rate of 4.1%–14.7 % [8,35,42,43]. This high incidence could potentially be explained by the higher incidence of HDP in the CVA group, but even after adjustment for HDP, this risk remained significantly higher. The higher rate of PPH and VTE may also have contributed to the high mortality rate in the CVA group, given that these are respectively the third and fourth most frequent causes of maternal mortality in the developed world [44].

IUFD and congenital anomalies increased in prevalence in the CVA group, while the SGA rate was comparable between the two groups. Previous studies on PAS have focused on maternal outcomes [7,8,37,45], and only a few have described neonatal outcomes, with these being limited to a small number of cases, ranging between 16 and 30 pregnancies [10,46]. Previous studies examining stroke prior to pregnancy showed similar results regarding comparable SGA rates [16] and the increased rate of IUFD [18], while congenital anomalies were not reported. The increase in the IUFD rate in the CVA group could be explained by the higher maternal

mortality rate, with 54 cases of maternal death and 13 cases of IUFD. Additionally, it could be explained by the increased rate of placental abruption in the CVA group, a known risk factor for IUFD [47]. Furthermore, Antiphospholipid Antibody Syndrome is a well-described risk factor for ischemic stroke in young adults [48], as well as a risk factor for IUFD [49]. However, we did not have data regarding acquired thrombophilia, and this possible association will have to be elucidated in future studies.

Notably, the increased rate of congenital anomalies in the CVA group remains an enigma since we adjusted neonatal outcomes for possible confounders that may be associated with congenital anomalies, such as age, pregestational diabetes, and illicit drug use [50, 51]. A potential explanation for this finding is maternal medications taken in the first trimester. Depending on the stroke etiology and the time interval from the event, some patients may be taking oral anticoagulants with a teratogenic effect, such as Warfarin [52]. Also, it is possible that patients with a prior CVA were taking antihypertensive medications as a secondary prevention measure [33], with some having a known teratogenic effect in the first trimester, such as angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers [53].

Our study is not without limitations. First, our group of CVA patients included different categories of strokes (ischemic and hemorrhagic), which may exhibit different risk factor profiles that differentially influence perinatal outcomes. Second, owing to its retrospective nature, we could not determine the timing of the diagnosis; if the event occurred before or during pregnancy, and what time interval had elapsed between the diagnosis of the CVA and delivery. Third, due to the anonymized nature of the study, we were unable to detect if a patient had more than one delivery during the study period. Furthermore, some maternal characteristics were missing, such as autoimmune disease, congenital heart disease, thrombophilia, and medications before and during pregnancy, which could affect obstetrical outcomes. Additionally, possible treatments for patients with a past CVA and medications to prevent pre-eclampsia (such as low-dose aspirin) were not documented in our cohort. Notably, our cohort was limited to the period before 2015 due to differential coding in later data within HCUP, rendering it incomparable.

Nevertheless, our study has numerous strengths. Our cohort was composed of a large sample size over a period of 11 years, enabling sufficient power to ascertain differences between the study groups. We also examined various obstetrical and delivery complications, some of which have not been previously studied, thus supplying physicians with more comprehensive data with which to counsel and treat their patients. To the best of our knowledge, our study is the largest to date that has examined maternal and neonatal outcomes in women with a CVA occurring before delivery. Finally, as our data was derived from a population-based cohort, the results have the potential for generalizability to the entire North American population.

In conclusion, CVA prior to delivery has numerous associated maternal and neonatal complications, necessitating management by a multidisciplinary team specializing in all aspects of neurological, obstetrical, and neonatal care. Due to the inherent increased pregnancy complications in these women, pre-conception counseling should be provided to all those in whom CVA predates pregnancy, addressing co-morbidities and medical treatments, combined with diligent follow-up and prompt treatment once complications arise in pregnancy. Further prospective studies are needed to better delineate maternal and neonatal risks and appropriate management strategies in this patient population.

Ethics approval

This study used anonymized data that is publicly available, and hence it was exempted from institutional review board approval according to articles 2.2 and 2.4 of the Tri-Council Policy Statement (2018) [20].

Data availability statement

Data will be made available upon request.

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CRediT authorship contribution statement

Uri Amikam: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Ahmad Badeghiesh:** Methodology, Formal analysis, Data curation, Conceptualization. **Haitham Baghlaf:** Methodology, Formal analysis, Data curation, Conceptualization. **Richard Brown:** Writing – original draft, Supervision, Methodology, Conceptualization. **Michael H. Dahan:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25631.

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