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Incidence and Time Trends of Pregnancy-Related Stroke Between 2010 and 2018

The Nationwide CONCEPTION Study

Alice Martin, BScPH, Grégory Lailler, MD, Yannick Béjot, MD, PhD, Amélie Gabet, PhD, Clémence Grave, MD, Nolwenn Regnault, PhD, Edouard Chatignoux, MS, Elodie Moutengou, MS, Catherine Deneux-Tharoux, MD, PhD, Sandrine Kretz, MD, Claire Mounier-Vehier, MD, PhD, Vassilis Tsatsaris, MD, PhD, Genevieve Plu-Bureau, MD, PhD, Jacques Blacher, MD, PhD, and Valérie Olié, PhD

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Correspondence

Dr. Olié
valerie.olie@
santepubliquefrance.fr

Abstract

Background and Objectives

Despite the potentially devastating effects of pregnancy-related stroke, few studies have examined its incidence by type of stroke. We aimed to study the nationwide incidence rates and recent temporal trends for all types of pregnancy-related stroke and to compare these incidences with stroke incidence in nonpregnant women.

Methods

We conducted a study of 6,297,698 women aged 15–49 years who gave birth in France between 2010 and 2018 with no history of stroke before pregnancy by collecting data from the French National Health Insurance Information System database. Poisson regression was used to estimate the incidence by types of strokes for the different pregnancy periods and the incidence rate ratio of stroke in pregnant vs nonpregnant French women.


Results

Among the 6,297,698 women, 1,261 (24.0 per 100,000 person-years) experienced a first ever stroke during, antepartum peripartum, or the first 6 weeks of postpartum. Of the pregnancy-related strokes, 42.9% were ischemic (IS), 41.9% were hemorrhagic (with similar proportion of intracerebral and subarachnoid hemorrhage), and 17.4% were cerebral venous thrombosis (CVT). Compared with nonpregnant women, incidence rates of stroke were similar during pregnancy for IS (adjusted incidence risk ratio [IRR] 0.9 [0.8–1.1]), slightly higher for all hemorrhagic strokes (IRR 1.4 [1.2–1.8]), and considerably increased for CVT (IRR 8.1 [6.5–10.1]). Pregnancy-related stroke incidence rose between 2010 and 2018 for IS and HS but was stable for CVT.

Discussion

The risk of pregnancy-related CVT was more than 8-fold higher than that observed in nonpregnant women. The incidence of pregnancy-related IS and HS is increasing over time, and efforts should be made for prevention considering treatable cardiovascular risk factors and hypertensive disorders in pregnant women.

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From the French Public Health Agency (A.M., G.L., A.G., C.G., N.R., E.C., E.M., V.O.), Saint-Maurice; Dijon Stroke Registry (Y.B.), University Hospital and Medical School of Dijon, University of Burgundy; Inserm U1153 (C.D.-T., G.P.-B.), Obstetrical, Perinatal and Pediatric Epidemiology Research Team (EPOPé), Research Center for Epidemiology and Biostatistics Sorbonne Paris Cité (CRESS); Paris-Descartes University (C.D.-T., V.T., G.P.-B., J.B.); Diagnosis and Therapeutic Center (S.K., J.B.), Hôtel Dieu, AP-HP, University Paris Descartes; Vascular Medicine and Hypertension Center (C.M.-V.), EA 2694, Santé Publique, University Lille; Department of Obstetrics and Gynecology (V.T.), APHP, Port-Royal Maternity, University Hospital Center Cochin Broca Hôtel Dieu, Groupe Hospitalier Universitaire Ouest; and Division of Gynaecology (G.P.-B.), APHP, Hôpital Cochin, Paris, France.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

BYM = Besag-York-Mollie; **CVD** = cardiovascular disease; **CVT** = cerebral venous thrombosis; **HDP** = hypertensive disorders of pregnancy; **HELLP** = hemolysis, elevated liver enzymes, low platelet count; **HS** = hemorrhagic stroke; **ICH** = intracerebral hemorrhage; **INSEE** = Institut national de la statistique et des études économiques; **IRR** = incidence risk ratio; **IS** = ischemic stroke; **OR** = odds ratio; **SAH** = subarachnoid hemorrhage; **SNDS** = Système National des Données de Santé; **VTE** = venous thromboembolism.

Cardiovascular diseases (CVDs) and strokes have become the primary cause of maternal death.¹ Although rare, stroke is a potentially devastating disease during pregnancy, which can lead to maternal death, fetal loss, and other severe outcomes and complications. In addition, stroke is also one of the most common causes of important long-term physical and cognitive disability after pregnancy.²

Several studies have shown an increasing temporal trend in the incidence of maternal stroke.²⁻⁶ A recent meta-analysis concluded that the incidence rate of pregnancy-related stroke was approximately 30 per 100,000 pregnancies,⁷ but a wide disparity in reported rates according to countries was shown, and little research has been conducted regarding the incidence of the different types of strokes (ischemic stroke [IS], hemorrhagic stroke [HS], or cerebral venous thrombosis [CVT]). Although a recent study showed a lower stroke incidence during pregnancy than in nonpregnant women of similar age, other reports revealed various vulnerabilities of women to stroke according to the peripartum and postpartum periods and stroke subtypes.^{2,3,5,7-17} For CVT, although the incidence in young and middle-aged women was higher than in men, data estimating the increase in incidence generated by different pregnancy periods are sparse.^{2,18}

Therefore, the aim of our study was to estimate nationwide incidence rates, their temporal trends, and associated characteristics of IS, HS (intracerebral hemorrhage [ICH] and subarachnoid hemorrhage [SAH]), and CVT during antepartum, peripartum, and postpartum in France between 2010 and 2018 and to compare the incidence of pregnancy-related stroke with stroke incidence in nonpregnant women.

Methods

Data Source

The CONCEPTION study, a prospective cohort including all French women who gave birth in France between January 1, 2010, and December 31, 2018, used data from the French National Health Insurance Information System database (Système National des Données de Santé, SNDS). This database contains data from the national hospital discharge database (PMSI) which records information about all public and private hospital stays diagnosis and data from the national health insurance database, containing information regarding reimbursements of health care expenditures, such as outpatient medical care.

Study Population

This analysis included all women of the CONCEPTION study aged between 15 and 49 years and who gave birth in a hospital after 22 weeks of amenorrhea between January 1, 2010, and December 31, 2018. Women with a history of stroke before pregnancy were excluded. The design of the CONCEPTION study is described elsewhere in detail.¹⁹

To compare with nonpregnant women, we also selected from the SNDS database all women from the French population aged between 15 and 49 years who had a stroke of any type and did not give birth during the study period.

Exposure Period

Pregnancy was defined in our study as lasting from the first day of pregnancy until the beginning of hospitalization for childbirth. Peripartum was defined as starting at the entry date of hospitalization for childbirth until the end of hospitalization for childbirth. Postpartum was defined as starting at the end of hospitalization for childbirth until 6 weeks after birth.

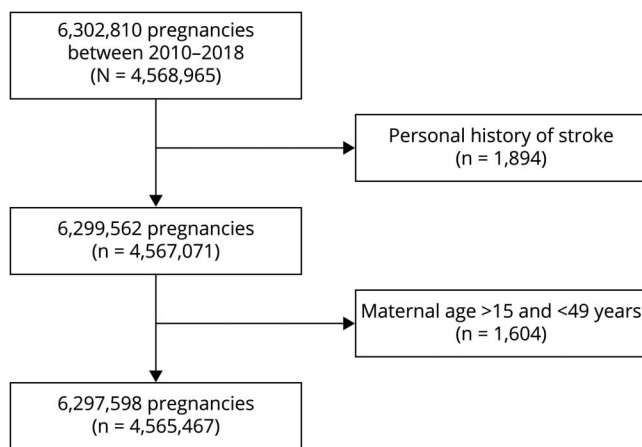
Outcome

Stroke was defined by the following *International Classification of Diseases-tenth revision* codes, which were registered as the main diagnosis of the entire hospital stay or one of the medical units where the patient stayed: HS, including ICH (I61), SAH (I60), and other nontraumatic intracranial hemorrhage (I62); IS (I63-I64; excluding I63.6); and CVT (I63.6, O22.5, and O87.3).

Women's Characteristics

Sociodemographic data; medical history; information related to antepartum, peripartum, and postpartum; and information regarding health care management of the women were recorded in the French National Health Insurance Information System. Women benefiting from Universal Medical Coverage, a social benefit in France available to those whose income is below a certain threshold, were defined as low socioeconomic status. Tobacco use was identified by specific coding at the hospital or by the reimbursement of nicotine replacement treatments before or during pregnancy. Obesity was identified in the hospital discharge summaries of the childbirth stay. Pre-existing diabetes was identified using an algorithm based on delivery of 3 antidiabetic drugs on 3 different dates in the year preceding pregnancy (or on 2 dates if at least 1 large package of antidiabetic drugs was dispensed). Gestational diabetes was identified using an algorithm combining delivery of insulin or glucose strips, or a diagnosis of

Figure 1 Flowchart of the Study Population



diabetes during pregnancy, and no pre-existing diabetes. Chronic hypertension was identified by at least 3 deliveries of antihypertensive drugs on different dates over a 12-month period or on 2 dates if at least 1 large pack (90 pills) of antihypertensive drugs was dispensed. Hypertensive disorders of pregnancy (HDP) were identified using an algorithm based on hospitalizations for pre-eclampsia (O14), hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome (O14.2), or eclampsia (O15). In women without pre-existing chronic hypertension, gestational hypertension was identified in our database by a hospitalization with a primary diagnosis of gestational hypertension during pregnancy (O13) or at least 1 delivery of antihypertensive medication between 20 weeks of gestation and 6 weeks of postpartum without differential diagnosis of preterm labor.¹⁹ Personal history of CVDs of each women, including acute coronary syndrome or heart failure, and personal history of venous thromboembolism (VTE), inflammatory disease, and cardiac malformation were all recorded using all hospital discharge summaries between 2006 and their pregnancy.

Statistical Analysis

We used Poisson regression to estimate the absolute rates of stroke per 100,000 person-years with 95% CIs for different pregnancy periods, different types of stroke and according to age, socioeconomic status, and region of residence. In non-pregnant women, stroke incidence was estimated by dividing the number of stroke in nonpregnant women by the mean annual estimations of the French population of women between 15 and 49 years as denominator. These data were obtained for the years between 2010 and 2018 from the National Institute of Statistic and Economic Studies (Institut national de la statistique et des études économiques [INSEE]).

Annual crude incidence rates for pregnancy-related stroke were calculated according to the stroke type. Age-standardized rates were estimated for each type using the

direct standardization method by applying the 5-year age-specific incidence rates to the age structure of the 2010 pregnant women of the cohort. Poisson regressions were used to study temporal trends of incidence between 2010 and 2018.

We described women's characteristics in the total population and according to a diagnosis of stroke during antepartum, peripartum, and postpartum, by displaying numbers and percentages for categorical variables, and mean and standard deviation for the only continuous variable, maternal age. Women's characteristics were described in the following subgroups: IS, HS (ICH and SAH and other intracranial hemorrhages), and CVT. Characteristics of pregnancy with and without stroke were compared using multivariate logistic regression analysis adjusted for maternal age, socioeconomic status, parity, multiple pregnancy, obesity, tobacco use, diabetes and gestational diabetes, chronic hypertension, and hypertensive disorders of pregnancy.

We performed age-adjusted Poisson models to estimate the incidence risk ratio (IRR) with 95% CI of stroke in pregnant vs nonpregnant women, with 95% CIs.

The data analysis was performed using SAS software (version 7.11; SAS Institute Inc., Cary, NC).

Spatial Poisson regression at a district level was used to study spatial disparities of pregnancy-related stroke incidence. In brief, the rate of stroke in a given district and combination of covariates was modeled as a linear combination of the covariates and an intercept random effect at the district level, which captures deviation in the districts not explained by the covariates. Using a random effect allows spatial smoothing in the estimates of specific district rates. These would have been difficult to estimate properly otherwise because districts with a low number of events have very imprecise incidence rates and are prone to present extremely spurious rates, appearing as either extremely high or extremely low incidence areas.²⁰

We applied a Bayesian spatial model using the Besag-York-Mollie (BYM) conditional autoregressive before the distribution for the random effects.²¹ This model was parametrized according to Riebler and implemented with Stan software.²² In BYM models, unexplained district deviations are estimated as the sum of a spatially structured component that accounts for spatial autocorrelation and an unstructured component. The resulting estimated deviation in a particular district is consequently a compromise between the mean effects of all neighboring districts (i.e., sharing a common border) and the effect of the district in question (observed rates map). Two parameters are provided by the model: an estimate of the geographical variability of the incidence rates across all France's districts and an estimate of the proportion of this variance that is explained by the spatial effect.

Because overseas districts have specific risk factors of stroke compared with mainland districts, a dummy variable

Table 1 Incidence per 100,000 Person-Years and Rate per 100,000 Pregnancies of Stroke Type During Antepartum, Peripartum and Postpartum, and Age-Adjusted IRR Between Incidence of Stroke in Pregnant Women and Incidence of Stroke in Nonpregnant Women in the French Population (2010–2018 Period)

	Pregnancy						Peripartum	Postpartum
	Total	First trimester	Second trimester	Third trimester	All trimesters			
All stroke types,^a N	1,261	171	156	127	454	287	520	
Rate of stroke (per 100,000 pregnancies)	20.0	2.7	2.5	2.0	7.2	4.6	8.3	
Incidence (95% CI) (per 100,000 person-years)	24.0 (22.6–25.4)	10.5 (9.0–12.4)	9.7 (8.2–11.5)	9.3 (7.7–11.2)	9.9 (9.0–10.9)	341.8 (302.2–386.5)	81.1 (74.0–88.8)	
Age-adjusted IRR (95% CI)^b	1.3 (1.1–1.4)	0.6 (0.4–0.7)	0.5 (0.4–0.7)	0.4 (0.3–0.6)	0.5 (0.4–0.6)	18.0 (14.3–22.7)	4.2 (3.5–5.0)	
Ischemic stroke, N	541	105	63	71	239	61	241	
Rate of stroke (per 100,000 pregnancies)	8.6	1.7	1.0	1.1	3.8	1.0	3.8	
Incidence (95% CI) (per 100,000 person-years)	10.3 (9.44–11.3)	6.5 (5.3–8.0)	3.6 (2.8–4.8)	5.1 (4.0–6.6)	5.1 (4.5–5.9)	74.0 (56.8–96.4)	38.4 (33.7–43.9)	
Age-adjusted IRR (95% CI)^b	0.9 (0.8–1.1)	0.6 (0.4–0.9)	0.4 (0.2–0.6)	0.4 (0.3–0.6)	0.5 (0.4–0.6)	6.6 (4.1–10.7)	3.3 (2.6–4.3)	
Cerebral venous thrombosis, N	219	22	19	36	77	58	84	
Rate of stroke (per 100,000 pregnancies)	3.5	0.3	0.3	0.6	1.2	0.9	1.3	
Incidence (95% CI) (per 100,000 person-years)	4.2 (3.6–4.8)	1.5 (1.0–2.3)	1.2 (0.8–1.9)	2.5 (1.8–3.6)	1.7 (1.3–2.2)	70.0 (53.3–91.8)	12.7 (10.1–16.0)	
Age-adjusted IRR (95% CI)^b	8.1 (6.5–10.1)	2.7 (1.7–4.3)	2.3 (1.3–4.2)	4.4 (3.0–6.6)	3.3 (2.5–4.4)	135.9 (96.9–190.5)	25.2 (16.8–37.6)	
Total hemorrhagic stroke, N	529	48	75	20	143	176	210	
Rate of stroke (per 100,000 pregnancies)	8.4	0.8	1.2	0.3	2.3	2.8	3.3	
Incidence (95% CI) (per 100,000 person-years)	10.1 (9.2–11.0)	2.7 (2.0–3.7)	4.9 (3.9–6.2)	1.6 (1.0–2.5)	3.2 (2.7–3.8)	208.6 (178.2–244.1)	32.5 (28.2–37.5)	
Age-adjusted IRR (95% CI)^b	1.4 (1.2–1.5)	0.4 (0.3–0.5)	0.6 (0.5–0.8)	0.2 (0.1–0.3)	0.4 (0.4–0.5)	28.1 (23.1–34.3)	4.3 (3.7–5.1)	
Intracerebral hemorrhage, N	288	25	48	10	83	101	104	
Rate of stroke (per 100,000 pregnancies)	4.6	0.4	0.8	0.2	1.3	1.6	1.7	
Incidence (95% CI) (per 100,000 person-years)	5.6 (5.0–6.3)	1.6 (1.0–2.4)	3.2 (2.4–4.3)	0.8 (0.4–1.5)	1.9 (1.5–2.4)	121.1 (98.5–148.9)	16.5 (13.5–20.2)	
Age-adjusted IRR (95% CI)^b	1.8 (1.6–2.1)	0.5 (0.4–0.8)	1.0 (0.8–1.3)	0.2 (0.1–0.4)	0.6 (0.5–0.8)	40.3 (32.0–50.9)	5.4 (4.5–6.5)	
Subarachnoid hemorrhage, N	259	25	35	9	69	81	109	
Rate of stroke (per 100,000 pregnancies)	4.1	0.4	0.6	0.1	1.1	1.3	1.7	
Incidence (95% CI) (per 100,000 person-years)	4.9 (4.3–5.6)	1.5 (1.0–2.3)	2.3 (1.6–3.2)	0.8 (0.4–1.5)	1.6 (1.2–2.0)	94.2 (74.5–119.1)	16.7 (13.7–20.4)	
Age-adjusted IRR (95% CI)^b	1.2 (1.0–1.4)	0.4 (0.2–0.6)	0.5 (0.3–0.8)	0.1 (0.1–0.3)	0.4 (0.3–0.5)	22.7 (16.4–31.4)	4.0 (3.1–5.0)	

Abbreviation: IRR = incidence rate ratio.

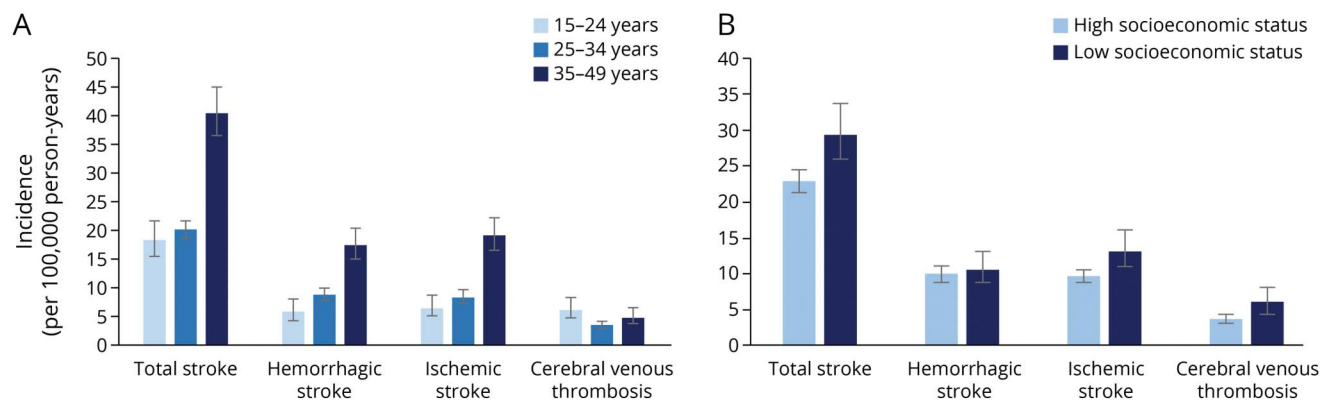
^a Some women had hemorrhage after ischemic strokes and were included in both stroke types.

^b Age-adjusted incidence rate ratio between incidence of stroke in pregnant women and incidence of stroke in nonpregnant women.

identifying oversea districts was included in the models. One should note that because those districts are islands, random effects could not benefit from neighboring.

Two spatial models were fitted to the data. The first one (null model) did not include any covariates (except oversea dummy), whereas the second one (full model) included

Figure 2 Incidence per 100,000 Person-Years of Pregnancy-Related Stroke by Age (A) and Socioeconomic Status (B)



stroke risk factor covariates age, low socioeconomic status, obesity, tobacco use, chronic hypertension, and hypertensive disorders of pregnancy. Comparing the estimated variances of the random effects between null and full models allowed for a quantification of the extent of spatial variability in incidence rates explained by the unequal spatial distribution of these risk factors.

For each risk factor and all risk factors combined, we drew maps of the relative risk of stroke caused by the unequal distribution of risk factors between districts. Predictions of the districts' random effects in the null and full models are also shown (eFigure 1, links.lww.com/WNL/C298).

Standard Protocol Approvals, Registrations, and Patient Consents

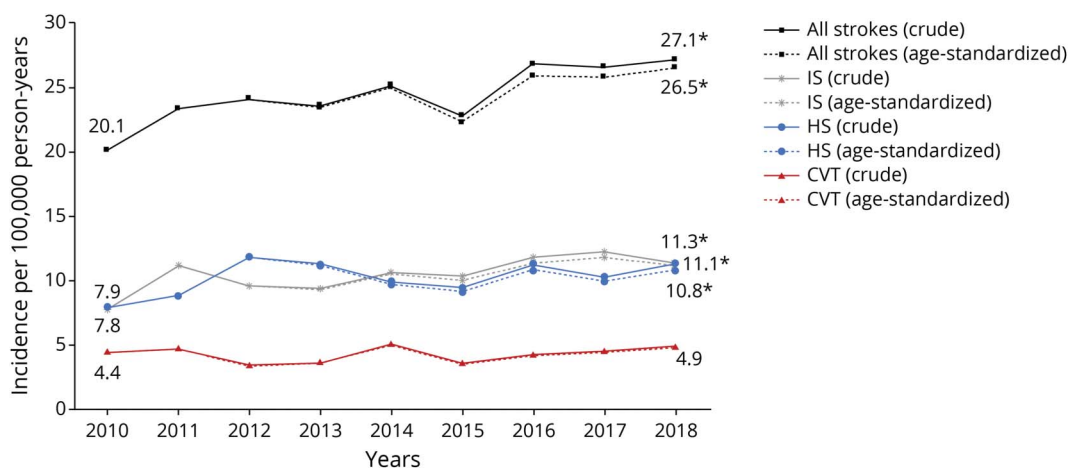
In line with French national regulations and ethics committee, participants' consent was not required for this study. To perform its public interest missions for health monitoring, the French Public Health Agency has been

granted by French law permanent access to the SNDS (code de la santé publique: articles L. 1413-1, L. 1461-3 I 2°, R. 1461-12, and following). The code de la santé publique (public health code) contains laws (articles beginning with L) and decrees (articles beginning with à D or R) taken by French authorities in the field of public health. The examination of the study protocol by the National Ethics Committee is not, in this case, required by French law. The French Public Health Agency is only required to keep an internal record of the studies it conducts on the basis of these data, as part of its public interest missions (article R 1461-17).

Data Availability

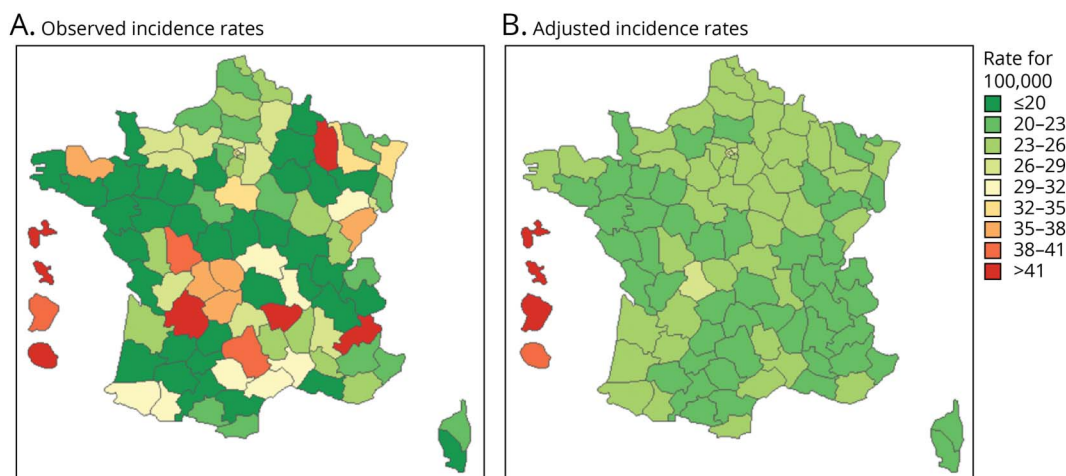
The data underlying this article cannot be shared publicly because of privacy reasons. Access to data is regulated by French legislation (request for access to data to the National Institute of Health Data [INDS] and authorization by the French Data Protection Authority [CNIL]). INSEE data are available at [insee.fr](https://www.insee.fr).

Figure 3 Temporal Trends of Stroke Incidence per 100,000 Person-Years by Stroke Type Between 2010 and 2018



CVT = cerebral venous thrombosis; HS = hemorrhagic stroke; IS = ischemic stroke. *p for trend <0.05.

Figure 4 District Incidence per 100,000 Person-Years of Pregnancy-Related Stroke



Observed (A) and adjusted (B) incidence rates.

Results

We identified 4,565,467 women who gave birth in France between 2010 and 2018 with no history of stroke before pregnancy (6,297,598 pregnancies) (Figure 1). Among these pregnancies, 1,261 (24.0 per 100,000 person-years) experienced a first ever stroke during antepartum, peripartum, or the first 6 weeks of postpartum (Table 1). Of the pregnancy-related strokes, 541 (42.9%) were IS, 529 (41.9%) were HS with a similar proportion of ICH and SAH, and 219 (17.4%) were CVT. The overall stroke incidence was quite similar for IS and HS (10.3 and 10.1 per 100,000 person-years, respectively) but was lower for CVT (4.2 per 100,000 person-years). The incidence of all types of strokes was 10.5 per 100,000 person-years during antepartum and was significantly greater during the peripartum (341.8) and postpartum periods (81.1). Among the nonpregnant population from the general French population, 31,883 cases of stroke occurred throughout the whole study period. Compared with nonpregnant women, incidence rates of stroke were lower during antepartum for IS (age-adjusted IRR 0.5 [95% CI 0.4–0.6]), ICH (IRR 0.6 [0.5–0.8]), and SAH (IRR 0.4 [0.3–0.5]) and higher for CVT (IRR 3.3 [2.5–4.4]) (Table 1). During peripartum and postpartum, the incidence of all stroke types was higher in pregnant women than in nonpregnant women, notably for CVT (IRR peripartum 135.9 [96.9–190.5] and IRR postpartum 25.2 [16.8–37.6]).

The incidence of total stroke increased with maternal age from 18.3 per 100,000 person-years for 15–24 years to 20.2 per 100,000 person-years for 25–34 years and 40.8 per 100,000 person-years for 35–49 years (Figure 2A, eTable 1, [links.lww.com/WNL/C299](https://www.lww.com/WNL/C299)). The same trend was observed for all types of strokes except for CVT, for which the incidence of first ever stroke due to CVT was greater in women aged between 15 to 24 years than in women aged between 35

to 49 years (6.3 per 100,000 person-years and 4.9 per 100,000 person-years, respectively). Stroke incidence was higher in pregnant, peripartum, and postpartum women with socioeconomic deprivation than in those without socioeconomic deprivation (29.6 per 100,000 person-years vs 22.8 per 100,000 person-years) (Figure 2B). This trend was observed in IS, SAH, and total HS, but not in CVT and ICH.

The overall incidence of stroke significantly increased throughout our study period, from 20.1 per 100,000 person-years in 2010 to 27.1 per 100,000 person-years in 2018 (Figure 3). Taking into account advancing maternal age during the study period did not modify the increase of incidence (20.1 in 2010 to 26.5 in 2018 for age-standardized incidence). The increase in stroke incidence was observed in antepartum, peripartum, and postpartum periods (data not shown). Regarding the type of stroke, comparable increasing trends were observed in IS and HS but not in CVT, for which a plateau was observed with incidence rates between 4.5 and 4.8 per 100,000 person-years in 2010 and 2018, respectively.

Characteristics of pregnancies included in our cohort are presented in Table 2. Compared with women without stroke, the mean maternal age was higher in pregnancies with IS (32.1 years) and HS (32.3 years) ($p < 0.001$), but similar in pregnancies experiencing CVT (29.4 years) ($p = 0.17$). HDP were one of the most frequent risk factors (24.7% of pregnancy-related stroke). This proportion rose up to 37.6% in HS. Traditional maternal cardiovascular risk factors (diabetes, obesity, chronic hypertension, and tobacco use), cardiac malformation, and personal history of CVD were observed more frequently in pregnancies with IS than in pregnancies with HS. Obesity, gestational diabetes, personal history of VTE, and low socioeconomic status were more frequently observed in pregnancies with CVT.

Table 2 Characteristics of Pregnancies With and Without Stroke

	Pregnancies with ischemic stroke (N = 542)			Pregnancies with cerebral venous thrombosis (N = 219)			Pregnancies with hemorrhagic stroke (N = 529)			Total pregnancies with stroke (N = 1,262)			Total pregnancies without stroke (N = 6,298,205)	
	Mean	SD	p Value ^a	Mean	SD	p Value ^a	Mean	SD	p Value ^a	Mean	SD	p Value ^a	Mean	SD
Maternal age	32.1	5.6	<0.0001	29.4	6.1	0.17	32.3	5.6	<0.0001	31.7	5.8	<0.0001	29.9	5.3
	N	%	p Value	N	%	p Value	N	%	p Value	N	%	p Value	N	%
Socioeconomic status (CMUc)	119	22.0	0.01	54	24.7	0.01	99	18.7	0.46	268	21.3	0.001	1,102,245	17.5
Cesarean section	171	31.6	<0.0001	66	30.1	0.0004	269	50.9	<0.0001	495	39.3	<0.0001	1,264,123	20.1
Multiparity	330	61.0	0.01	128	58.5	0.34	274	51.8	0.14	716	56.8	0.22	3,466,424	55.1
Multiple pregnancy	7	1.3	0.62	5	2.3	0.43	21	4.0	0.001	33	2.6	0.02	108,341	1.7
Diabetes	8	1.5	0.01	3	1.4	0.13	3	0.6	0.75	13	1.0	0.01	31,077	0.5
Obesity	40	7.4	<0.0001	7	3.2	<0.0001	30	5.7	0.10	76	6.0	<0.0001	103,846	1.7
Chronic hypertension	50	9.2	<0.0001	29	13.2	0.11	33	6.2	<0.0001	111	8.8	<0.0001	296,473	4.7
Tobacco use	109	20.2	<0.0001	26	11.9	0.20	67	12.7	0.01	202	16.0	<0.0001	592,637	9.4
Gestational diabetes	62	11.5	0.14	29	13.2	0.07	54	10.2	0.60	142	11.3	0.04	602,151	9.6
Hypertensive disorders of pregnancy^b	92	17.0	<0.0001	27	12.3	<0.0001	199	37.6	<0.0001	311	24.7	<0.0001	374,413	6.0
Personal history of CVD^c	7	1.3	<0.0001	9	4.1	0.62	4	0.8	0.03	20	1.6	<0.0001	12,542	0.2
Personal history of VTE	8	1.5	0.0001	0	0.0	—	2	0.4	0.02	10	0.8	<0.0001	3,449	0.1
Infection during postpartum	44	8.1	0.01	19	8.7	0.03	91	17.2	<0.0001	150	11.9	<0.0001	334,266	5.3
Terminal kidney disease	2	0.4	0.048	1	0.5	0.13	3	0.6	0.01	6	0.5	0.0002	4,022	0.1
Inflammatory disease	6	1.1	0.49	3	1.4	0.45	4	0.8	0.74	13	1.0	0.55	55,924	0.9
Cardiac malformation	7	1.3	<0.0001	0	0.0	—	1	0.2	0.42	8	0.6	<0.0001	6,452	0.1

Abbreviations: CMUc = Universal Medical Coverage; CVD = cardiovascular disease; IHD = ischemic heart disease; VTE = venous thromboembolism.

^a p value for comparison with pregnancies without stroke.

^b Gestational hypertension or pre-eclampsia/eclampsia.

^c IHD, heart failure.

After adjustment for all confounding factors, characteristics associated with pregnancy-related stroke depended on stroke type except for HDP which were associated with all stroke type (Table 3). Age was associated with IS and HS risk (odds ratio [OR] 2.72 [95% CI 1.98–3.72] and OR 3.00 [2.16–4.17]), respectively, in women aged between 35 and 49 years as compared with women between 15 and 24 years, but not with CVT risk. Regarding other risk factors, low socioeconomic status, obesity, tobacco use, and chronic hypertension were significantly associated with IS. Tobacco use and chronic hypertension were associated with HS, whereas only obesity was associated with CVT.

The observed incidence rate of pregnancy-related stroke was significantly higher in Guadeloupe, Martinique, and Réunion (3 overseas districts) and in Dordogne, Haute-Loire, Hautes-Alpes, and Meuse (4 mainland districts). After taking into account the distribution of pregnancy-

related stroke risk factors and smoothing, all the overseas districts had a higher incidence of pregnancy-related stroke. The unexplained district variability of incidence rates was estimated at 0.10 and 0.09 on the log scale (which corresponds roughly to a ±20% variation in the rate scale) in null and full models, respectively, showing that the risk factors explained a modest part (20%) of the geographical variability of pregnancy-related stroke across the French territory (Figure 4 and eFigure 1, links.lww.com/WNL/C298).

Discussion

During the period comprising antepartum, peripartum, and 6 weeks postpartum, we observed a global incidence of all types of pregnancy-related stroke of 24 per 100,000 person-years with 42.9% of IS, 17.4% of CVT, and 41.9% of HS. The incidence of all strokes occurring during the peripartum was

Table 3 ORs of Pregnancy-Related Stroke by Stroke Type

	Total stroke		Ischemic stroke		Cerebral venous thrombosis		Hemorrhagic stroke	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age 25–34 y (ref 15–24 y)	1.18	0.98–1.42	1.38	1.02–1.85	0.55	0.39–0.78	1.58	1.16–2.16
Age 35–49 y (ref 15–24 y)	2.15	1.77–2.62	2.72	1.98–3.72	0.70	0.46–1.06	3.00	2.16–4.17
Low socioeconomic status	1.25	1.08–1.43	1.29	1.04–1.59	1.23	0.89–1.70	1.18	0.94–1.48
Multiparity	1.00	0.89–1.13	1.11	0.92–1.32	1.23	0.92–1.63	0.85	0.71–1.01
Multiple pregnancy	1.11	0.79–1.57	0.59	0.28–1.24	1.24	0.51–3.01	1.44	0.93–2.24
Obesity	1.42	1.16–1.73	1.49	1.10–2.02	2.56	1.70–3.86	0.94	0.65–1.34
Tobacco use	1.81	1.56–2.11	2.39	1.93–2.95	1.16	0.77–1.75	1.43	1.11–1.85
Diabetes	1.06	0.61–1.85	1.49	0.73–3.04	1.94	0.61–6.20	0.55	0.18–1.74
Gestational diabetes	0.90	0.75–1.08	0.90	0.68–1.18	1.19	0.79–1.79	0.80	0.60–1.07
Chronic hypertension	2.48	1.95–3.15	3.18	2.28–4.44	1.45	0.67–3.13	2.18	1.50–3.18
Hypertensive disorders of pregnancy	4.70	4.12–5.35	2.90	2.31–3.64	2.01	1.34–3.03	8.76	7.32–10.49

Abbreviation: OR = odds ratio.

much more important than during other periods, especially in HS. The risk of CVT in pregnant women was more than 8-fold higher than that observed in nonpregnant women. We also noted a rise in the incidence of all types of strokes during pregnancy in our cohort from 2010 to 2018, and the temporal increase in the incidence of IS mainly accounted for this trend. More than 40% of pregnancies which experienced HS were reported as having hypertensive disorders of pregnancy. Regional disparities were observed, with high rates of stroke in the French overseas territories.

The incidence of all stroke observed in our study was similar with the one reported in a recent cohort study from the United Kingdom³ (24.7 per 100,000 person-years). Compared with 2017 meta-analysis⁷ which found a crude rate of pregnancy-related stroke of 30.0 per 100,000 pregnancies and a study from Finland⁵ in which the incidence was 25.2 per 100,000 deliveries, the incidence of stroke in our study was smaller, with 20.0 cases per 100,000 pregnancies (when reporting on a number of pregnancies rather than person-years). It has been shown that France typically has lower rates of cardiovascular events,²³ such as coronary event or myocardial infarction, compared with other countries.

Few studies reported the incidence per type of stroke. In Finland, the incidence of IS was 9.2 per 100,000 pregnancies, similar to our rate of 8.6 per 100,000 pregnancies.⁵ For SAH and ICH, incidence rates of similar magnitude were found, although slightly greater in our study. For CVT, however, whereas we found an incidence of 3.5 per 100,000 pregnancies, Karjalainen et al. reported a much larger incidence for CVT, at 8.5 per 100,000 pregnancies.

The most original result of our study was the comparison of stroke incidence by stroke type during all pregnancy periods with the age-controlled stroke incidence of nonpregnant women. We found that all 3 periods (antepartum, peripartum, and postpartum) significantly increased the incidence of CVT in women and especially peripartum and postpartum. Although pregnancy and postpartum are a well-described risk factor for common localization of VTE, data are lacking for cerebral localization. For now, the most powerful age-controlled study comparing the incidence of stroke during pregnancy with that of nonpregnant women failed to highlight a significant increase of incidence during antepartum but showed an increased incidence during the postpartum.¹⁸ This result contrasts with the 3-fold increase of incidence during pregnancy described in our study.

For IS and HS, the age-adjusted incidence of stroke during pregnancy was 2 times smaller than that observed in nonpregnant women. Multiple hypotheses could account for this finding. First, pregnant women are more likely to be in better health than women who are not pregnant (the Healthy Pregnancy Effect) because chronic diseases including CVDs could affect fertility and miscarriage.²⁴ Thus, pregnant women tend to present less cardiovascular risk factors, which can lead to a decrease in stroke incidence. In addition, at the beginning of the pregnancy, a high proportion of women decrease their tobacco and alcohol consumption, which in turn lowers their risk of stroke.²⁵ Another hypothesis is that a decrease in arterial pressure during the first trimester of pregnancy could act as a protective effect of pregnancy on the risk of stroke.²⁶ Furthermore, owing to the recruitment method of our study, which included only women who gave birth after 22 weeks of amenorrhea, we missed all potential strokes that occurred

before this period and that resulted in fetal loss or medical termination of pregnancy and strokes that resulted in maternal death. This fact could partly explain why the incidence during antepartum was lower than that in nonpregnant women.²⁷ However, given that previous studies³ reported a smaller incidence of stroke during antepartum and that the incidence of total strokes was not smaller during the first and second trimesters of pregnancy than that during the third trimester, this potential bias is unlikely to explain the smaller incidence of stroke observed during pregnancy.

The risk of stroke was particularly pronounced during peripartum and postpartum periods.^{2,3,5,7-17} To explain this result, it could be assumed that increased intracranial blood pressure provoked by Valsalva maneuver maternal during expulsive efforts of delivery could lead to a stroke, especially HS. In the Finnish study cited above, hypertensive disorders of pregnancy such as pre-eclampsia and HELLP syndrome⁵ were set forth to explain the elevated incidence of all types of strokes during peripartum. A previous study reported that the risk of thromboembolic events was estimated to be 15 to 35 times higher during the first week of postpartum than that in nonpregnant women.¹⁵ It was suggested that the high risk of stroke during postpartum could be due to a large decrease in blood volume or rapid changes in hormonal status after a birth, perhaps by means of hemodynamic, coagulative, or vessel wall change.¹⁷

An increase in the incidence of stroke over time was described in our study. This trend was still observed when taking into account the increasing age of women included in the cohort between 2010 and 2018. In an American study, the temporal increase was found to be 61.5% between 1995 and 2010–2011.⁴ As previously reported by Karjalainen et al.,⁵ the observed increase was mainly due to the increase in IS incidence. This temporal increase could be due to better diagnostic techniques, especially for IS, namely in the presence of mild symptoms, or because of an increase in the frequency of comorbid conditions in pregnant women, such as hypertensive disorders and heart disease.² A similar temporal trend was reported in the young general adult population in France, where an increase in IS incidence was also observed.²⁸

Traditional cardiovascular risk factors (diabetes, obesity, chronic hypertension, and tobacco use) were frequently observed in IS compared with other strokes, whereas hypertensive disorders of pregnancy was often observed in HS, as found in other studies.^{5,8,10} The high proportion of hypertensive disorders of pregnancy in pregnancy-related strokes calls for monitoring and early detection of hypertensive disorders of pregnancy to reduce the risk of cardiovascular complication.⁴ For women suffering from CVT, low socioeconomic status, obesity, gestational diabetes, and personal history of VTE were prominent characteristics. Similar to our results, Karjalainen et al.⁵ found that both obesity and gestational diabetes were frequently observed characteristics in the women suffering from CVT, but unlike us, they also identified diabetes as a prominent characteristic.

Finally, the regional disparities we observed were probably mainly because of the disparities of risk factors, especially tobacco use, hypertension, and hypertensive disorders of pregnancy and diabetes.²⁶

The main strengths of our study include its exhaustiveness, the nationwide setting, and a large study period of 9 years from 2010 to 2018, thus making it possible to collect a large number of cases to study incidence rates by stroke subtypes during various periods of pregnancy. Furthermore, to the best of our knowledge, this is the first French study that reports the incidence of stroke in pregnant women in a recent period. The French Hospitalization Discharge codes used to identify stroke in our database have been validated as having a strong positive predictive value (up to 92% for all stroke type and up to 96% for IS), thus being a good tool to measure the burden of stroke in France.²⁹ Finally, more than 91% of strokes included in our study had a cerebral imaging (MRI or CT) reported in the discharge summary, although imaging is not exhaustively reported in hospital discharges.

Our study also has limitations. Owing to the recruitment method of our study which included only women who gave birth after 22 weeks of amenorrhea, we missed all potential strokes that occurred before this period and that resulted in fetal loss or medical termination of pregnancy and strokes that resulted in maternal death. As stated above, it is unlikely that this bias is quantitatively important. We may have underestimated the prevalence of obesity because the condition was identified through hospital records for hospitalization for childbirth, leading to a probable nondifferential bias between women with or without stroke. Similarly, we probably underestimated tobacco use because it was only assessed by hospital records and the delivery of nicotine replacement therapy before or during pregnancy. Although it has been shown that SDNS diagnosis of stroke was highly reliable, the underlying cause of stroke cannot be clearly identified based on our data source. This is a gap that has remained in most studies except when close medical record review has been performed. There is still a need for prospective registries to better understand the clinical characteristics of pregnancy and pregnancy-unrelated strokes in young women.

A major drawback of the spatial methodology we applied here is that it relates the low number of cases at the district level. Indeed, low numbers induce high variability, so smoothing was very pronounced in the prediction of random effects. As a result, the consistent part of unexplained geographical disparities estimated by the models is only loosely apparent in the maps. District predictions of random effects are the best possible predictions of total error, but they fail to precisely describe the exact distribution of incidence rates over the districts. Another consequence of the low number of cases is the large uncertainties surrounding the estimation of some parameters. Finally, the low number of cases did not allow the study of the stability of the spatial distribution of pregnancy-related strokes over time with spatio-temporal regression.

Stroke affected pregnant women with an incidence of 24.0 per 100,000 person-years. The risk of CVT in pregnant women was more than 8-fold higher than that observed in non-pregnant women. Regarding the increased incidence of pregnancy-related IS and HS over time, more efforts should be made for prevention, considering the frequency of treatable cardiovascular risk factors and hypertensive disorders in pregnant women.

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Appendix Authors

Name	Location	Contribution
Alice Martin, BScPH	French Public Health Agency, Saint-Maurice, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Grégory Lailler, MD	French Public Health Agency, Saint-Maurice, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

Appendix (continued)

Name	Location	Contribution
Yannick Béjot, MD, PhD	Dijon Stroke Registry, University Hospital and Medical School of Dijon, University of Burgundy, France	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Amélie Gabet, PhD	French Public Health Agency, Saint-Maurice, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Clémence Grave, MD	French Public Health Agency, Saint-Maurice, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Nolwenn Regnault, PhD	French Public Health Agency, Saint-Maurice, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Edouard Chatignoux, MS	French Public Health Agency, Saint-Maurice, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Elodie Moutengou, MS	French Public Health Agency, Saint-Maurice, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Catherine Deneux-Tharaux, MD, PhD	Inserm U1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (EPOPé), Research Center for Epidemiology and Biostatistics Sorbonne Paris Cité (CRESS); Paris-Descartes University, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Sandrine Kretz, MD	Diagnosis and Therapeutic Center, Hotel Dieu, AP-HP, University Paris Descartes, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Claire Mounier-Vehier, MD, PhD	Vascular Medicine and Hypertension Center, EA 2694, Santé Publique, University Lille, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Vassilis Tsatsaris, MD, PhD	Paris-Descartes University; Department of Obstetrics and Gynecology, APHP, Port-Royal Maternity, University Hospital Center Cochin Broca Hôtel Dieu, Groupe Hospitalier Universitaire Ouest, Paris, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data

Continued

Appendix (continued)

Name	Location	Contribution
Genevieve Plu-Bureau, MD, PhD	Inserm U1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (EPOPE), Research Center for Epidemiology and Biostatistics Sorbonne Paris Cité (CRESS); Paris-Descartes University; Division of Gynaecology, APHP, Hôpital Cochin, Paris, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Jacques Blacher, MD, PhD	Paris-Descartes University; Diagnosis and Therapeutic Center, Hotel Dieu, AP-HP, University Paris Descartes, France	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Valérie Olié, PhD	French Public Health Agency, Saint-Maurice, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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