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CONDENSATION

Risk of stroke is increased among women with migraine with aura who use combined hormonal contraceptives.

SHORT VERSION OF TITLE

Migraine, hormonal contraceptives and stroke

ABSTRACT

Background: Migraine with aura and combined hormonal contraceptives are independently associated with an increased risk of ischemic stroke. However, little is known about whether there are any joint effects of migraine and hormonal contraceptives on risk of stroke.

Objective: To estimate the incidence of stroke in women of reproductive age and examine the association between combined hormonal contraceptive use, migraine type (with or without aura), and ischemic stroke.

Study Design: This study used a nationwide health care claims database and employed a nested case control study design. Women ages 15-49 years with first-ever stroke during 2006-2012 were identified using the International Classification of Diseases-9th Revision-Clinical Modifications inpatient services diagnosis codes. Four controls were matched to each case based on age. Migraine headache with and without aura was identified using inpatient or outpatient diagnosis codes. Current combined hormonal contraceptive use was identified using the National Drug Code from the pharmacy database. Conditional logistic regression was used to estimate adjusted odds ratios and 95% confidence intervals of ischemic stroke by migraine type and combined hormonal contraceptive use.

Results: Between 2006-2012, there were 25,887 ischemic strokes among women ages 15-49, for a cumulative incidence of 11 strokes per 100,000 women. Compared to women with neither migraine nor combined hormonal contraceptive use, the odds ratio of ischemic stroke was highest among women with migraine with aura using combined hormonal contraceptives (odds ratio 6.1, 95% confidence interval 3.1-12.1); odds ratios were also elevated for migraine with aura without combined hormonal contraceptive use (odds ratio 2.7, 95% confidence interval 1.9-3.7), migraine without aura and combined hormonal contraceptive use (odds ratio 1.8, 95% confidence interval 1.1-2.9), and migraine without aura without combined hormonal contraceptive use (odds ratio 2.2, 95% confidence interval 1.9-2.7).

Conclusion: The joint effect of combined hormonal contraceptives and migraine with aura was associated with a 6-fold increased risk of ischemic stroke compared with neither risk factor. Use of combined hormonal contraceptives did not substantially further increase risk of ischemic stroke among women with migraine without aura. Determining migraine type is critical in assessing safety of combined hormonal contraceptives among women with migraine.

KEY WORDS: aura, contraception, migraine, stroke

INTRODUCTION

Migraine headaches are common among women, with a lifetime incidence of 43%.[1] Approximately one-third of people with migraine have migraine with aura.[2] Aura represents a specific set of neurological symptoms that can include flashes of light, blind spots or lines, tingling pains and numbness, or temporary loss of speech, and generally occurs before the onset of the migraine.[3] Women of reproductive age who suffer from migraine, particularly those with aura, have an increased risk of ischemic stroke.[4-6] The association between migraine without aura and ischemic stroke among women of reproductive age is not as strong and results have been mixed.[4-6] The relationship between migraine with aura and stroke is multifactorial and may be related to vascular changes or other underlying mechanisms.[1,7] While few studies have reported national incidence rates, ischemic stroke is rare among women of reproductive age (4-9 cases/100,000 per woman-years).[8,9] However, stroke is a devastating event and a better understanding of risk factors among women of reproductive age is necessary to address whether there are any joint effects of migraine and hormonal contraceptives on risk of stroke.

Research has shown that women using combined hormonal contraceptives (CHCs), containing estrogen and progestin, have an increased risk of ischemic stroke.[10] CHCs include combined oral contraceptives (COCs), combined hormonal patch, and combined hormonal ring, and are used by approximately 29% of women currently using contraception in the United States.[11] The elevated risk of stroke is likely due to the hypercoagulable effects of estrogen.[12] The joint effects of migraine and CHCs on risk of stroke are not well understood. Several studies found that the risk of stroke among women with migraine was increased with use of COCs compared with non-use.[13-16] However, little is known about whether there is additional risk of stroke from COC use or CHC use overall for each migraine type (with or without aura).[17,18] Our study sought to estimate the incidence of stroke among women of reproductive age and to examine the joint effects of migraine (with or without aura) and CHCs on the risk of ischemic stroke.

MATERIALS AND METHODS

Data source

We identified women ages 15-49 during 2006-2012 included in the MarketScan Research Databases, Commercial Claims and Encounters.[19] These nationwide health care claims databases from Truven Health Analytics include individual-level health care claims information from employers, health plans, and hospitals. The databases provide information on both outpatient and inpatient health care services and linked information on filled outpatient prescription drug claims. Rigorous quality assessments, including validity and reliability checks, are conducted on these databases.[19] Because the data are de-identified, an institutional review board of the Centers for Disease Control and Prevention determined that this was not human subjects research.

Study cohort

We identified all initial cases of inpatient ischemic stroke during 2006-2012, using ICD-9-CM codes (433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01. 434.11, 434.91, 436.X) (Table 1 and Figure 1). We excluded women with inpatient or outpatient ischemic stroke codes during 2004-2005 to try to limit our analyses to first-ever strokes, as stroke history would likely impact CHC use. Among all women ages 15-49 during 2006-2012, we calculated the cumulative incidence of ischemic stroke per 100,000 women, by 5 year age bands. The cumulative incidence was calculated as the proportion of women with ischemic strokes over the total number of eligible women for a given year. We determined the average yearly cumulative incidence by dividing the overall incidence by seven, given that there were seven years of follow up (2006-2012). Due to the small number of stroke cases and to facilitate comparison between age groups, average yearly cumulative incidence was reported per 100,000 women.

Nested case-control analysis

For the nested case-control analysis, we restricted both cases and controls to women continuously enrolled in private insurance from January 1, 2004 to the index date. The date of the first stroke code was defined as the case index date. Controls were women without an inpatient ischemic stroke code from 2006-2012. Four controls were randomly assigned for each case and were matched by age in 2006. The index date of the controls was considered to be the same date as their matched case's index date. Two years of continuous enrollment prior to our study period was required to ensure adequate capture of migraine history and prior strokes. We excluded women with pregnancy codes within 6 weeks prior through the index date. We also excluded women with hysterectomy or sterilization from 2004 up until the index date (Table 1 and Figure 1).

Migraine headaches with and without aura were identified using inpatient or outpatient ICD-9-CM codes during 2004 until the index date (migraine with aura: 346.0, 346.3, 346.5, 346.6; migraine without aura: 346.1, 346.2, 346.4, 346.7, 346.8, 346.9) (Table 1). If a woman had codes for both migraine types (with and without aura), she was classified as having migraines with aura. To ensure that we captured migraine status before the stroke date, cases and controls were classified as having migraines only if the migraine codes occurred prior to the index date.

Current CHC use was identified using the National Drug Codes (NDC) from the MarketScan Pharmaceutical database. Current CHC use was defined as a filled prescription for COCs, patch or ring within 90 days prior to the index date. All CHCs were grouped together; analyses were additionally conducted including only COC use but numbers of women using the patch or ring were too small for separate analyses.

We examined other risk factors for ischemic stroke, including personal characteristics (age, obesity and smoking) and medical conditions (diabetes, hypertension, ischemic heart disease, and valvular heart disease) (Table 1). Smoking and obesity were identified by any outpatient or inpatient code before the index date. Smoking codes included a history of tobacco use, tobacco abuse, or smoking cessation counseling. Diabetes, hypertension, ischemic heart disease, and valvular heart disease were determined by either an inpatient or outpatient code before the index date. Women were defined as having these conditions if there was one inpatient code or two outpatient services codes at least 30 days apart. We considered inpatient diagnosis to be valid because these diagnosis codes are assigned at the time of hospital discharge and therefore likely to represent confirmed diagnoses. We required two outpatient codes at least 30 days apart to increase accuracy of outpatient diagnoses and exclude women who were tested but ultimately ruled out for the medical condition.

Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression to estimate the odds ratio of ischemic stroke associated with stroke risk factors of interest (migraines status and current CHC use), with age as a conditioning variable and adjusting for hypertension, diabetes, obesity, ischemic heart disease, and valvular heart disease. To determine joint effects of migraines and CHC use, we conducted conditional logistic regression to calculate adjusted OR (aOR) and 95% CI for odds ratio of stroke by migraine type and CHC use. SAS 9.3 (SAS Institute, Cary, NC) was used for all analysis.

RESULTS

Stroke incidence

During 2006-2012, there were 25,887 ischemic strokes among 33,218,977 women ages 15-49 in the MarketScan Databases. The overall average yearly cumulative incidence of ischemic stroke was 11

strokes per 100,000 women. The average yearly cumulative incidence increased with increasing 5-year age band (1 per 100,000 women among ages 15-19 and 30 per 100,000 women among ages 45-49) (Figure 2).

Nested case-control study

Women with migraine with aura had an increased odds ratio of ischemic stroke compared with no migraines (aOR 2.9, 95% CI 2.2-3.9) (Table 2). Women with migraine without aura also had an increased odds ratio of ischemic stroke compared with no migraines, but of less magnitude that for migraine with aura (aOR 2.1, 95% CI 1.8-2.5). Women currently using CHCs had a slight but significantly increased odds ratio of ischemic stroke compared with never or former users (aOR 1.3, 95% CI 1.1-1.6). The odds ratios of ischemic stroke were also elevated among women with obesity, smoking, and medical conditions studied compared with women without the specific condition, with the highest odds ratio among women with ischemic heart disease (aOR 5.5, 95% CI 4.0-7.6).

When examining joint effects and including women with neither migraine nor CHC use as the referent group, we found that the odds ratio of ischemic stroke were highest among women with migraine with aura using CHCs (aOR 6.1, 95% CI 3.1-12.1) (Table 3). Odds ratios of ischemic stroke were also elevated among women with migraine with aura not using CHCs (aOR 2.7, 95% CI 1.9-3.7), women with migraine without aura using CHCs (aOR 1.8, 95% CI 1.1-2.9), and women with migraine without aura not using CHCs (aOR 2.2, 95% CI 1.9-2.7). Results were largely unchanged when examining only COC use (results not shown).

COMMENT

Our analysis found that the combined effect of migraine with aura and CHC use was associated with a 6-fold increased risk in ischemic stroke compared with women without either risk factor. The combined effect of migraine without aura and CHCs also elevated the risk of ischemic stroke, but to a lesser degree and similar to that among women with migraine without aura not using CHCs.

Similar to previous studies, we found that migraine with aura and use of CHCs were independently associated with increased risk of ischemic stroke.[6,10] There are several proposed mechanisms to explain the association between aura and stroke. The migraine may lead directly to stroke due to cortical spreading depression related to the aura ("migrainous infarction").[2] Individuals with auras may have vascular risk factors, such as seen in individuals who smoke or have hypertension, which place them at higher risk of stroke.[2] Migraines have also been found in high prevalence among individuals with certain vasculopathies or autoimmune diseases, such as antiphospholipid syndrome and systemic lupus erythematosus.[20] Estrogen has several biological effects including changes in coagulation factors, lipid levels and blood pressure, which may contribute to the increased risk of stroke.[12] It is therefore not surprising that our study found the highest odds ratio of ischemic stroke among women with migraine with aura currently using CHCs.

Although one other study also found a significant association between migraine without aura and ischemic stroke, most studies have not found such an association.[6] In our study, it is possible some women with migraine with aura may have been misclassified as migraine without aura if they had experienced aura in the past but not currently. In addition, our study identified only migraines which received medical attention and therefore likely represented more severe migraines. It is possible that these factors led us to overestimate the association between migraine without aura and stroke. The use of CHCs overall did not impact the relationship between migraine without aura and stroke. Our results

suggest the need for further study into the association between migraine without aura and stroke risk and potential interactions with CHC use.

The distinction of migraine type and identification of aura among women with migraine is key when considering contraceptive options. Efforts should be made by healthcare providers to define migraine type, using criteria to improve diagnosis of migraine types, which may allow for more accurate counseling about contraceptive methods. Our results suggest that CHCs should be avoided among women with migraine with aura. According to the US Medical Eligibility Criteria for Contraceptive Use, CHCs are a category 4 for women with migraine with aura and should not be used due to safety concerns.[21] However, most other contraceptive methods are safe for use among these women, including intrauterine devices and progestin-only methods, and women should be counseled about the range of options.

This analysis has several strengths. The use of a nationwide database comprising millions of individuals allowed for examination of the rare outcome of ischemic stroke. The large sample size allowed us to examine all types of CHCs (COCs, patch or ring). We were also able to separately examine migraine type. By linking inpatient, outpatient, and pharmacy databases over several years, we were able to ensure more complete capture of medical conditions and contraceptive use. This analysis also has several limitations that should be considered. The use of diagnosis codes may be subject to some degree of misclassification and we were unable to validate diagnoses with medical records. However we attempted to minimize misclassification by requiring two outpatient codes, which can avoid overdiagnosis of individuals who were evaluated for the condition but ruled out. We were only able to capture migraine headaches that received medical attention. Most individuals with ischemic stroke in the United States likely receive inpatient medical care, however it is possible that we missed first-ever

cases of ischemic stroke managed in outpatient or other settings. Use of prescription information to classify contraceptive use may overestimate actual use. Residual confounding may exist for characteristics such as smoking and obesity which may not be fully captured in a claims database. We were unable to examine certain other potential confounding factors, such as race and ethnicity, because these were not available in the database. We did not examine use of anticoagulant medication because information about over-the-counter medications (i.e. aspirin) was not available in the database and prescription anticoagulation (i.e. warfarin) may be highly correlated with valvular heart disease, therefore leading to collinearity in the models. We excluded prior strokes during 2004-2005, however it is possible that we included women who had experienced a stroke before the time frame of our study. This may have impacted our results if women with a history of stroke are less likely to be prescribed CHCs, however there would likely be a small effect due to the low incidence in this population. Finally, we only examined women with private commercial insurance and therefore our results are not nationally representative and may not be generalizable to individuals with other or no insurance.

The findings of this study confirm the elevated relative risk of ischemic stroke for women with migraine with aura who also use CHCs: a 6-fold increase over women with neither risk factor in this study population. Women with migraine but without accompanying aura also had an elevated relative risk of ischemic stroke, but odds ratios were similar for CHC users and non-users, suggesting that CHC use may not be associated with further risk among this population. While overall incidence of stroke among women of reproductive age is low, stroke can be a devastating event and further study is needed to better understand and prevent modifiable risk factors. Accurately distinguishing migraine type and presence or absence of aura is critical for both future investigations and clinical decision-making.

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296 Table 1. Diagnosis and procedure codes

297

Condition	**Timing**	**ICD-9-CM**	**CPT**	**HCPCS**
Migraine	During 2004-2012; before index date (date of stroke for cases or same date for controls)			
Migraine without aura		346.1, 346.2, 346.4, 346.7, 346.8, 346.9		
Migraine with aura		346.0, 346.3, 346.5, 346.6		
Ischemic stroke	First ever incidence during 2006-2012; excluded women with previous stroke between 2004-2006	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01. 434.11, 434.91, 436.X		
Pregnancy	Up to 6 weeks before and through index date	V27, V91, 63X.X, 64X.X, 65X.X, 66X.X, 67X.X, 69.X, 72.X, 73.22, 73.59, 73.6, 69.X, 74.X, 75.X DRG 2006 or before 2006: 370 - 375, 378, 380, 381	59409, 59612, 59514, 59620, 59840, 59841, 59850, 59851, 59852, 59855, 59856, 59857	

		DRG after 2006: 765 – 768, 770, 774, 775, 777, 779		
Hysterectomy	Before index date	68.3 – 68.9	45126, 58956, 58210, 51597, 58954, 58200, 59525, 58953, 58180, 59135, 58951, 58152, 59100, 58573, 58150, 58572, 58571, 51925, 58570, 58554, 58548, 58543, 58542, 58541, 58294, 58293, 58292, 58291, 58290, 58285, 58280, 58275, 58270, 58267, 58263, 58262, 58553, 58552, 58550, 58260, 58240, 58544	
Sterilization	Before index date	V25.2, 66.2- 66.3	58600, 58605, 58565, 58611, 58615, 58670, 58671, 58579	A4264
Medical conditions	During 2004-2012; 2 outpatient codes or 1 inpatient code before index date			
Hypertension		401.X-405.X		
Diabetes		250.X		
Obesity		278.0X		
Smoking		V15.82, 305.1, 649.0	99406, 99407	
Ischemic heart disease		410.X-414.X		

Valvular heart disease		394.X, 395.X, 396.X		

Abbreviations: ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; CPT, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; DRG, diagnosis-related group.

302 Table 2: Characteristics of cases and controls and odds ratios of ischemic stroke among women ages 15-
303 49, MarketScan databases, 2006 – 2012

304

Characteristic	**Cases N (%)**	**Controls N (%)**	**Ischemic stroke Adjusted OR* (95% CI)**
Total	1,884	7,536	
Personal characteristics			
Age†, mean (SD)	42.0 (7.7)	42.0 (7.7)	-
<35	251 (13.3)	1,004 (13.3)	-
≥35	1,633 (86.7)	6,532 (86.7)	-
Obesity	231 (12.3)	505 (6.7)	1.30 (1.08 – 1.58)
Smoking	167 (8.9)	257 (3.4)	2.59 (2.05 - 3.25)
History of migraines‡			
Migraine with aura	93 (4.9)	146 (1.9)	2.89 (2.16 – 3.88)
Migraine without aura	279 (14.8)	543 (7.2)	2.08 (1.75 – 2.48)
No migraine	1,512 (80.3)	6,847 (90.9)	1.0 (ref)
CHC use			
Current use§	235 (12.5)	871 (11.6)	1.34 (1.13 – 1.59)
Former/never use	1,649 (87.5)	6,665 (88.4)	1.0 (ref)
Medical conditions‖			
Hypertension	707 (37.5)	1,110 (14.7)	2.63 (2.31 – 3.01)
Diabetes	320 (17.0)	340 (4.5)	2.78 (2.30 – 3.35)
Ischemic heart disease	164 (8.7)	69 (0.9)	5.49 (3.97 – 7.59)
Valvular heart disease	NR¶	NR¶	4.99 (1.90-13.12)

305 Abbreviations: OR, odds ratio; CI, confidence interval; SD, standard deviation; CHC, combined
306 hormonal contraception.

307

* Odds ratios were derived by conditional logistic regression with age as conditioning variable and were adjusted for migraines, current CHC use, hypertension, diabetes, obesity, smoking, ischemic heart disease, and valvular heart disease.

† Age at index date.

‡ Migraine diagnosis during 2004-2012, prior to stroke or index date: History of Migraines is presented as 2 categorical variables, 1) Any migraine vs No Migraine and 2) Migraine with aura, Migraine without aura and No migraine.

§ Combined oral contraceptives, patch or ring use within 90 days prior to index date.

|| Compared to those without the medical condition.

¶ Not reported because of small numbers (< 30), as per Truven Health Analytics reporting standards. Estimates may be unstable.

Table 3: Odds ratios of ischemic stroke among women ages 15-49 by history of migraine subtype and combined hormonal contraceptive use

History of migraines N=9,420	**Current CHC use***	**Cases (N)**	**Controls (N)**	**Ischemic stroke Adjusted OR† (95% CI)**
Migraine with aura‡	Yes	NR§	NR§	6.08 (3.07 – 12.05)
	No	74	126	2.65 (1.91 – 3.67)
Migraine without aura‡	Yes	NR§	77	1.77 (1.09 – 2.88)
	No	255	466	2.24 (1.86 – 2.69)
No migraine	Yes	192	774	1.39 (1.16 – 1.67)
	No	1,320	6,073	Ref

Abbreviations: CHC, combined hormonal contraceptive; COC, combined oral contraceptive; OR, odds ratio; CI, confidence interval.

* COC, patch or ring use within 90 days before stroke or index date.

† Adjusted for hypertension, diabetes, obesity, smoking, ischemic heart disease, and valvular heart disease.

‡ Migraine diagnosis during 2004-2012, prior to stroke or index date.

§ Not reported because of small numbers (< 30), as per Truven Health Analytics reporting standards. Estimates may be unstable.

331 Figure 1: Inclusion of cases and controls, 2006-2012.

332 Flow chart of selection of cases and controls.

333

334 Figure 2: Average yearly cumulative incidence of ischemic stroke among women ages 15-49, 2006-

335 2012.

336 Graph of ischemic stroke incidence among women of reproductive age by 5-year age group.