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Review Articles

Risk of Stroke Associated With Use of Estrogen Containing Contraceptives in Women With Migraine: A Systematic Review

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Objective.—Migraine with aura has been associated with increased risk of ischemic and hemorrhagic stroke. Prior studies have shown a further increase in risk in women using combined hormonal contraceptives (CHCs). This has led to guidelines recommending against use of CHCs in this population. We sought to assess whether the risk of stroke is associated with the dose of estrogen and whether there is evidence of synergism between migraine and CHCs. We also sought to assess whether an interaction effect exists between migraine and CHCs.

Methods.—We searched PubMed, the Cochrane Library, and EMBASE from inception through January 2016 for relevant English-language studies of adults, of any design. We included studies that examined exposure to CHCs and reported outcomes of ischemic or hemorrhagic stroke. Data extraction and assessment of study quality were conducted independently by reviewer pairs and quality was assessed with the GRADE and Newcastle Ottawa scales.

Results.—Of 2480 records, 15 studies met inclusion criteria and six provided odds ratios for the relevant population. The point estimates for the odds ratios for ischemic stroke in women with migraine who used CHCs with any dose of estrogen ranged from 2.08 to 16.9. Studies were generally small and confidence intervals were wide. No studies reported odds ratios for stroke risk as a function of estrogen dose in women with migraine, largely due to insufficient sample sizes. No interaction effect between migraine and CHCs was seen in the seven studies that assessed this. One study differentiated risk by presence or absence of migraine aura and found an increased risk in the migraine with aura population (OR 6.1; CI 3.1 to 12.1 in migraine with aura vs 1.8; CI 1.1 to 2.9 in the migraine without aura group). Studies generally had high Newcastle Ottawa scores and low GRADE levels of evidence. No studies met all three supplementary quality criteria (assessed migraine subtype, used International Classification of Headache Disorders criteria for diagnosis of migraine, and stratified risk by estrogen dose).

Conclusions.—This systematic review shows a lack of good quality studies assessing risk of stroke associated with low dose estrogen use in women with migraine. Further study in this area is needed. The available evidence is consistent with an additive increase in stroke risk with CHC use in women with migraine with aura. Since the absolute risk of stroke is low even in the presence of these risk factors, use of CHCs in women who have migraine with aura should be based on an individualized assessment of harms and benefits.

Key words: migraine, Combined oral contraceptive, COC, OCP, birth control, stroke

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INTRODUCTION

Migraine is a recurrent, frequently disabling neurologic condition affecting almost 36 million people in the United States.[1] Migraine affects women disproportionately, with a prevalence ratio of approximately 3:1.[2] The 1-year prevalence of migraine is highest

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between the ages of 25 and 55 and an estimated 22-37% of women will experience migraine during their reproductive years.[2,3] Stroke is also highly prevalent, with about 795,000 strokes a year in the United States. It is the third leading cause of death in the US and worldwide, as well as a leading cause of long-term disability.[4,5] Since both migraine and stroke are highly prevalent, any interaction between them may have significant public health implications.

A number of studies have shown that migraine is an independent risk factor for a variety of vascular disorders, including stroke. The risk of ischemic stroke in women with migraine is about two times higher than that of women without migraine, driven largely by increased risk in the subgroup of women who have migraine with aura.[6-10] An association between migraine and an approximately one and a half times increased risk of hemorrhagic stroke has also been shown.[11] The greatest increase in stroke risk is seen in women with migraine in their reproductive years, who are under the age of 45, and who otherwise have few stroke risk factors.[12] The elevation in risk of stroke is amplified by other risk factors, particularly smoking.[12,13] Two previous reviews concluded that an elevated risk of stroke is associated with the use of combined hormonal contraceptives (CHCs) and may be attributable to the estrogen component of these contraceptives.[14,15]

The estrogen content of commonly used CHCs has decreased over time. Most CHCs currently prescribed are considered low estrogen formulations, containing 20 to 25 micrograms of ethinyl estradiol (EE). The earliest formulations of CHCs, sometimes called first generation contraceptives, contained estrogen doses as high as 50 micrograms of EE and up to 100 micrograms of mestranol.[16] Only a few studies have attempted to evaluate stroke risk by estrogen dose in CHCs. It is therefore uncertain whether or how the generally lower doses of estrogen in currently prescribed CHCs affect the risk of stroke in women with migraine. Current World Health Organization (WHO) and American Congress of Obstetricians and Gynecologists (ACOG) guidelines regard migraine with aura as an absolute contraindication for the use of CHCs.[17,18] In contrast, an older statement from an International Headache Society task force recommends caution in the use of CHCs in women with migraine, especially those with aura, but nonetheless encouraged individualized assessment of benefits and harms when making decisions about the use of hormonal contraceptives in women with migraine.[19]

We hypothesized that currently used lower dose estrogen CHC formulations may be associated with a smaller or no increase in stroke risk in women with migraine, as compared with higher dose, older formulations. In this systematic review, we aimed to identify and assess the effect of CHC estrogen content on stroke risk in women with migraine, in an effort to update guidance on this matter for patients and doctors. When possible, we attempted to assess risk by migraine aura subtype.

METHODS

We conducted this systematic review in accordance with the American Headache Society Headache Guidelines Development Protocol.[20] This review was initially developed as the basis for an anticipated update of guidelines for the use of CHCs in women with migraine. The review was not registered.

Search Strategy.—One investigator (HS) searched for relevant articles indexed in PubMed, the Cochrane Library, and EMBASE from inception through January 2016, with the help of a research librarian. The search was limited to articles in English. We checked references in identified articles as well as those in previously published meta-analyses and systematic reviews. We did not include conference presentations, unpublished studies, or other non peer-reviewed gray literature to ensure validity.

*Study Inclusion Criteria and Search Strategy.—*Studies were included if they met the following criteria: study design was a randomized controlled trial or observational study; the population studied was women over the age of 18, and outcomes included ischemic or hemorrhagic stroke. We included studies using monotherapy with CHCs or multidrug interventions involving estrogen-containing

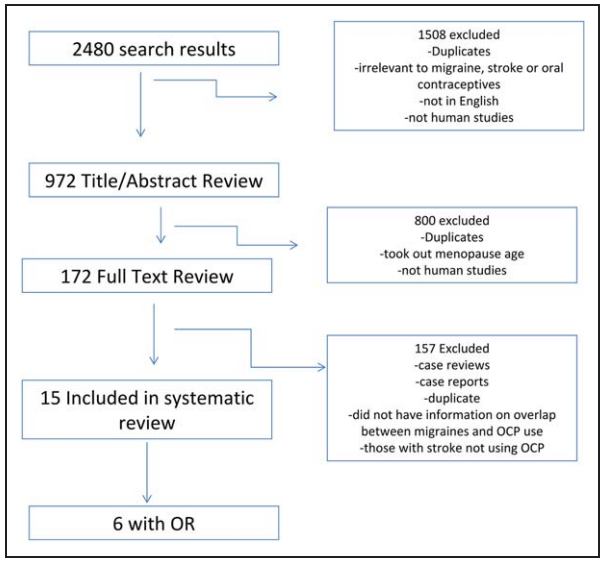

Fig. 1.—PRISMA study flow diagram. [Color figure can be viewed at wileyonlinelibrary.com]

contraception. The exact search terms are listed in Appendix A.

Data Abstraction.—One author (HS) independently reviewed titles and abstracts of references retrieved by the search and selected all potentially relevant studies. Full text articles were reviewed by two authors (HS and RB) and read in detail for evaluation of inclusion criteria. Disputes were resolved by a third author (JP) when necessary. Information was independently extracted by two authors (HS and RB) using a standardized form, included as Appendix B. Data extracted included the first author's last name, year of publication, country, study design, study population, how migraines were diagnosed, migraine subtype where available, type and dose of estrogen exposure, other risk factors such as smoking or hypertension, outcomes studied, and numerical results including effect estimates with 95% confidence intervals where available. If risk was not assessed specifically, we reported whether an interaction effect between migraine and CHC use was seen. Discrepancies were discussed and decided on by consensus.

Quality of evidence levels and study quality were assessed by two authors (HS and RB) using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group criteria and the Newcastle-Ottawa scale.[21,22] The Newcastle-Ottawa scale assesses three domains: selection of cases and controls, comparability of cases and controls, and ascertainment of exposure. A maximum score is 9 points and a higher score reflects better quality. We also assessed other important study characteristics, including whether structured International Classification of Headache Disorders diagnostic criteria were used, and the quality and rigor of stroke diagnosis, as well as whether the study assessed risk separately by migraine subtype (with or without aura).

RESULTS

Study Characteristics.—We identified 2480 studies in the initial search (Figure 1). Fifteen studies met the inclusion criteria, summarized in Tables 1 and 2. The majority, 11 were case-control studies.[23-32] Two used mixed methods with cohort analyses for incidence results and case control data for determination of risk.[33,34] One was a cohort study and another performed cross-sectional descriptive analyses.[35,36] Of the studies that reported a source for the control population, three used hospital controls,[24-26] six used neighbor controls[27,29,30,32-34] and four used both.[23,28,30,31]

Migraine was diagnosed with a structured interview using International Headache Society criteria in seven studies.[24-27,30,31,35] The other studies, where diagnostic methods were specified, asked patients if they were diagnosed with migraine or used looser criteria for migraine, with definitions provided. These included having "characteristic symptoms of migraine," or asking if a "doctor has ever diagnosed you with migraine."[23,31] Two studies used self-report of a physician diagnosis of migraine,[29,32] while one based diagnosis of migraine on receipt of a prescription for an anti-migraine medication[33] and another used ICD-9 discharge codes.[34] Four articles provided information about hemorrhagic stroke in addition to ischemic stroke.[23,26,31,36] Twelve studies specified that only subjects with a first diagnosis of stroke or TIA were included.[23-28,30-35] The majority of studies, 12, noted that they diagnosed stroke through independent data, including imaging or diagnosis by a neurologist.[23-31,33,35] Two relied mainly on discharge ICD codes,[32,34] while the last noted that they used

Table 1.—Case Control Studies

Author, Year, Setting	Cases, n	Stroke Free Controls, n	Age Range, y	Estrogen Exposure	Diagnostic Criteria for Stroke	Diagnostic Criteria for Migraine	Stroke Risk or Odds Ratio (95% Confidence Interval) for Stroke in Women with Migraine Using COCs
Collaborative Group, 1975, 12 cities in US	– 140 women with first diagnosis of ischemic stroke – 196 women with first diagnosis of hemorrhagic stroke	393 hospital controls matched for age, race, and geographic area, and 451 neighborhood controls matched for age and race	15-44	Either 100 μg mestranol or 50 μg of estradiol	Discharge diagnosis, verified by neurologist review of medical records	Self-reported description of headache during structured interview; 2 or more "characteristic symptoms of migraine" required	*Ischemic Stroke* Hospital control: 4.6 (2.2 to 9.6) Neighbor control 5.9 (2.9 to 12.2) *Hemorrhagic stroke* Hospital control 2.1 (1.0 to 4.6) Neighbor control 2.6 (1.2 to 5.5) Adjusted for age and race
Tzourio, 1993, Paris, 2 hospitals	75 women (and 137 men) with a hospital admission for ischemic stroke; prior history of stroke excluded	75 hospital controls with rheumatologic or minor surgical procedures, matched for age, sex, and history of HTN	18-80	Not specified Differentiated between past and current use of COC	Stroke defined clinically using WHO criteria and confirmed by imaging	Neurologist interview using IHS criteria Differentiated migraine with and without aura	Cases with migraine and under the age of 45 were more likely to be COC users than those without migraine, but the difference was not statistically significant (*P* value: .9)
Lidegaard, 1995, Denmark, national	497 women cerebral thromboembolic stroke	1370 population controls, matched for age	15-44	Four groups: – 30-40 μg estrogen – 50 μg estrogen – Progesterone only – Unknown type of COC	ICD codes in the National Patient Register, verified by patient and by imaging in 90% of cases	Self-reported migraine > once/month on questionnaire	All COC users with migraine: 2.8 (no CI given) Adjusted for HTN and DM Insufficient sample size to calculate risk by estrogen exposure Migraine and COC were independent factors
Tzourio, 1995, Three urban and 2 rural hospitals in France	72 women with hospital admission for first diagnosis of ischemic stroke	173 hospital controls with acute orthopedic or rheumatologic diagnoses	18-44	Four groups: – 20 μg estrogen – 30-40 μg estrogen – 50 μg estrogen – Progestin only Also assessed current vs former vs never use	ICD codes, confirmed by imaging	Neurologist interview using IHS criteria	In women with migraine using OCPs: 13.9 (5.5-35.1) compared to no migraine and no OCP use No statistical interaction between migraine and OCP use Stroke risk as a function of estrogen dose in women with migraine not reported

Table 1.—*Continued*

Author, Year, Setting	Cases, n	Stroke Free Controls, n	Age Range, y	Estrogen Exposure	Diagnostic Criteria for Stroke	Diagnostic Criteria for Migraine	Stroke Risk or Odds Ratio (95% Confidence Interval) for Stroke in Women with Migraine Using COCs
Carolei, 1996, Seven university hospitals in Italy	146 women (and 162 men) hospitalized with first diagnosis of stroke or TIA	One hospital control with illness other than stroke/TIA and one population control per case, matched on age, sex, and residence. Total 292 female controls	15-44	Not specified	Clinical diagnosis by a neurologist, brain imaging and follow-up for up to 5 years	Neurologist interview using a semistructured questionnaire Differentiated with and without aura	Insufficient sample size to calculate OR for interaction between migraine and OCP use
Schwartz, 1998, A health plan population and a 3-county population in the US	2 pooled studies – 175 with acute ischemic stroke – one of the studies looked at incident stroke – 198 with acute hemorrhagic stroke	1191 in total. One study matched 3 controls for age and facility of usual care. The other study used population controls stratified for age to mirror controls	18-44	Less than 50 μg within the last month of interview Compared current vs former OCP use	Discharge and health plan payment records, verified by neurologist review	Structured interviews: "has doctor said you have migraine" or "have you ever visited a doctor for migraine"	*Ischemic Stroke* Pooled OR 2.08 (1.19 to 3.65) *Hemorrhagic Stroke* Pooled OR 2.15 (0.85 to 5.45)
Chang, 1999, Eight cities in Europe	291 women with discharge diagnosis of first stroke including hemorrhagic stroke	Up to 3 controls from the same hospital as the case, matched for age and time of admission	20-44	Two groups: – Less than 50 μg of estrogen – More than 50 μg of estrogen	Clinical diagnosis confirmed with medical records review	Structured interview using IHS criteria Differentiated with and without aura	*Ischemic Stroke* Low dose: 6.59 (0.79 to 54.8) High dose: Could not be calculated All COC: 16.9 (2.72 to 106) *Hemorrhagic Stroke* Low dose: 0.52 (0.13 to 2.01) High dose: 2.66 (0.46 to 15.3) All COCs: 1.10 (0.4 to 2.97)
Lidegaard, 2002, Denmark, national	626 women with first diagnosis of thromboembolic stroke	4054 population controls, matched for age	15-44	Current OCP users grouped by dose-20, 30-40, 50, progestin type, duration of use, OCP generation. Former OCP use was another group	ICD codes in the National Patient Register, confirmed by hospital and by patient report	Self-reported migraine > once/month on questionnaire	No interaction or effect modification between migraine and OCP use

Table 1.—*Continued*

Author, Year, Setting	Cases, n	Stroke Free Controls, n	Age Range, y	Estrogen Exposure	Diagnostic Criteria for Stroke	Diagnostic Criteria for Migraine	Stroke Risk or Odds Ratio (95% Confidence Interval) for Stroke in Women with Migraine Using COCs
Schwaag, 2003, Two university hospitals in Germany	75 women (and 85 men) with first diagnosis stroke or TIA	Mixed hospital and population controls: 1 age and sex matched control for each case, drawn from hospital staff, patients with peripheral trauma, and parents of pediatric patients	<46	Not specified	Clinical diagnosis of stroke or TIA, stroke confirmed by imaging	Structured interview using IHS criteria by 2 investigators Differentiated between migraine with and without aura	Logistic regression analysis: migraine and oral contraceptives were independent risk factors No difference in rates of oral contraception use in cases with and without migraine $P < .15$
MacClellan, 2007, 59 hospitals in Baltimore, US	386 women with first diagnosis of cerebral infarction	614 population controls matched for age, geographic area, and race	15-49	Current OCP use (defined as within the last month), dose not specified	Discharge diagnosis, confirmed by medical records review by a neurologist	Standardized questionnaire, using IHS criteria except phonophobia and headache duration Included only women with migraine with aura	Point estimates of OR for stroke in migraine with aura similar (numerical value not specified) between OCP users and non-users OC use was not an independent effect modifier
Abanoz et al, 2017,	120 women (and 82 men) with diagnosis of acute ischemic stroke	450 volunteer controls matched for age and gender	15-50	OCP use documented by medical records or patient report, dose not specified	Hospital diagnosis, confirmed by imaging	Structured interview using IHS/ICHD-3 criteria	Migraine and other risk factors were all independent
Nightingale and Farmer, 2004, General Practice Research Database in the UK Cohort for incidence, nested case control for risk factors	190 women with first diagnosis of stroke	Up to 6 controls per case from GPRD, matched for age and provider	15-49	Current COC use per database records, doses not specified	Diagnosis codes, confirmed by death from stroke, hospitalization for stroke, imaging or clinical sequelae	Prescription for a specific antimigraine therapy or diagnosis of migraine and a prescription for a potential antimigraine medication	No significant interaction between migraine and COC use

Table 1.—*Continued*

Author, Year, Setting	Cases, n	Stroke Free Controls, n	Age Range, y	Estrogen Exposure	Diagnostic Criteria for Stroke	Diagnostic Criteria for Migraine	Stroke Risk or Odds Ratio (95% Confidence Interval) for Stroke in Women with Migraine Using COCs
Champaloux et al, 2016, National Healthcare claims database, US Cohort for incidence, nested case control for risk factors	1884 women with first diagnosis of stroke	7536 controls matched on age, drawn from same database	15-49	Pharmaceutical claims database. Current COC, path or ring use (within 90 days of dx of stroke). Dose not specified	ICD-9 codes	ICD-9 codes, recorded prior to stroke	Migraine with aura: 6.1 (3.1-12.1) Migraine without aura: 1.8 (1.1-2.9)

Table 2.—Cohort and Cross-Sectional Studies

Author, Year, Setting	Study Design	Cases, n	Age Range, y	Estrogen Exposure	Diagnostic Criteria for Stroke	Diagnostic Criteria for Migraine	Results for Stroke in Women with Migraine Using COCs
Milhaud, 2001, Stroke registry in Switzerland	Prospective cohort	89 women (and 41 men) with diagnosis of first stroke and active migraine	16-91 years; study examined <45 years and ≥45 years as separate groups	Ascertainment method and dose not specified	Neurologist clinic diagnosis, confirmed by imaging	Neurologist interview using ICHD criteria	In women under 45, migraineurs were more likely to use OC than non-migraineurs Migraineurs in stroke group were more likely to use OCP but the difference was not statistically significant, $P = .056$
Farhoudi, 2012, Two university hospitals in Iran	Cross-sectional	178 women diagnosed with ischemic or hemorrhagic stroke	15-45	Low dose OCP usage only (defined as <50 μg ethinyl estradiol)	Hospitalization for stroke	Not specified	Migraine and simultaneous OCP consumption were significantly associated with the incidence of stroke ($P = .037$)

Abbreviations: OR = odds ratio; COC = combined oral contraceptives; HTN = hypertension; DM = diabetes mellitus; ICHD = International Classification of Headache Disorders.

patients who were "hospitalized for stroke."[36] Six studies reported odds ratios.[23,25,26,29,31,34]

Effect of Estrogen on Stroke Risk in Women With Migraine.—The point estimates for the odds ratio for ischemic stroke in women with migraine who used CHC with any dose of estrogen ranged from 2.08 to 16.9.[23,25,26,29,31,34] Many of these were small case control studies and confidence intervals were wide. Seven of the articles assessed for an interaction effect between migraine and oral contraceptive use. Four of them found that these were independent factors when determining the risk for ischemic stroke.[25,29,30] Carolei et al noted that they had an insufficient sample to calculate an OR.[28] The cross-sectional study by Farhoudi noted that migraine and simultaneous CHC consumption were significantly associated with incidence of stroke (*P* value .037).[36] MacClellan et al noted that hormonal contraceptive use was not an independent modifier for stroke risk.[27] Lidegaard and Kreiner noted that there was no effect modification between migraine and oral contraceptive use.[32]

Several studies that did not specifically calculate odds ratios for stroke in women with migraine who used CHCs did evaluate the likelihood of CHC use in cases compared to controls.[24,30,35] Two of these studies found that CHC use was more common in women with migraine who had a stroke, but these differences did not reach statistical significance.[24,35]

Dose of Estrogen.—Seven of the articles reported the type and dose of estrogen in the studied oral contraceptive.[23,25,26,29,31,32,36] The oldest of the included studies, from 1975, included women taking either 50 μg (not specified, but presumably ethinyl) estradiol or 100 μg mestranol.[23] Two studies indicated only that women were taking doses less than 50 μg EE.[31,36] Only one of these, Schwartz et al, reported an odds ratio for stroke in women with migraine using CHCs.[31] This was on the lower end of the range of ORs reported among studies in this review, 2.08. Tzourio (1995) evaluated four groups, progestin only vs 20 μg EE vs 30-40 μg EE, and 50 μg EE, but the risk of stroke as a function of estrogen exposure was not reported in this paper.[25] Chang compared two groups, less than and more than 50 μg of EE.[26] Lidegaard (1995) compared four groups as well, comparing 20 μg EE vs 30-40 μg EE, and 50 μg EE vs unknown type but was not sufficiently powered to assess risk by estrogen exposure. In the later study by Lidegaard and Kreiner, (2002) there were three groups, as an unknown dose group was not included.[29,32] This paper did not specifically assess how dose affected risk of stroke in those with migraine. Three studies did not list doses but noted only that the women were current users of oral contraceptives[24,27,31] and two compared current vs past use.[24,31]

Only one study reported risk of stroke in women with migraine as a function of EE dose. Chang et al compared women using hormonal contraceptives with an EE dose of either greater than or less than 50 μg.[26] They report that the likelihood of both ischemic and hemorrhagic stroke was higher in the high dose estrogen group regardless of migraine status, but they do not report the OR for the higher dose estrogen and migraine group in the paper. Three studies compared risk of stroke as a function of estrogen exposure independent of migraine status.[25,29,32] In these studies there appeared to be a dose dependent effect of estrogen on the risk of ischemic stroke, with higher stroke risk associated with a higher dose of estrogen. The adjusted OR for ischemic stroke in those using CHCs containing 50 μg EE ranged from 2.9 to 4.8, with 30-40 μg EE from 1.6 to 2.7, and with 20 μg was 1.7 in both studies that included this group. The adjusted OR in subjects using progestin only pills was 0.9 to 1 (reference for some studies). One additional study found that there was a higher risk of stroke with current but not past use of CHCs.[31]

Modification by Other Risk Factors.—Five of the articles evaluated the effect of smoking on stroke risk in women with migraine exposed to CHCs.[23-27] The Collaborative Group study did not assess risk specifically in women with migraine, but found ORs between 4.0 and 4.8 for various levels of smoking as compared to non smokers. Chang et al specifically evaluated risk of smoking and CHC use in women with migraine. They found that the combination of smoking with CHC use in women with migraine had a multiplicative effect, with an OR of

Table 3.—Study Quality: Newcastle Ottawa Scale

	Year	S1	S2	S3	S4	C1	C2	E1	E2	E3	Total
JAMA	1975	*	*	*	*	*		*	*		7
Tzourio	1993	*	*		*	*	*	*	*		7
Lidegaard	1995	*	*	*	*	*	*		*	*	8
Tzourio	1995	*	*		*	*		*	*	*	7
Carolei	1996	*	*	*	*	*			*		6
Schwartz	1998	*	*	*	*	*			*	*	7
Chang	1999	*	*		*	*	*	*	*		7
Milhaud	2001	*	*			*	*	*	*	*	7
Lidegaard	2002	*	*	*		*	*		*	*	7
Schwaag	2003	*	*	*	*	*		*	*		7
Nightingale	2004	*	*	*	*	*	*		*	*	8
MacClellan	2007	*	*	*	*	*		*	*		7
Champaloux	2016	*	*	*	*	*		*	*		7
Abanoz	2017	*	*	*	*	*	*		*		7

Selection: S1: Case definition, S2: Case representativeness, S3: Selection of controls, S4: Definition of controls.
Comparability: C1: Comparability of cases, C2: Study controls for essential elements.
Exposure: E1: Ascertainment of exposure, E2: Same method of ascertainment for cases and controls, E3: Similar non-response rate.

34.4 (CI 3.27 to 361).[26] This was based on only nine cases, however. MacClellan et al found that women with a history of migraine with aura who also used CHCs and smoked had a 7.0-fold higher odds of stroke (CI 1.4-73.7), compared to women who had migraine with aura but did not smoke or use CHCs.[27] The risk was 10-fold higher as compared to women with no migraine who did not smoke or use CHCs (95% CI, 1.4 to 73.7). Tzurio (1993) found that young women with stroke were more likely to have both migraine and smoking history than controls. Tzurio (1995) did not find an interaction effect between migraine and smoking. When mentioned, hypertension was found to be an independent risk factor in stroke, although some authors, for example, Tzourio (1993), noted that this was a more prominent risk factor in people aged greater than 35 or 45.[24,25]

Migraine Subtypes.—Six of the studies differentiated between migraine with or without aura.[25-28,30,34] However, only one study differentiated risk of stroke by subtype of migraine with aura or migraine without aura. Champaloux found that stroke risk was higher in those in the subcategory of migraine with aura.[34] MacClellan et al calculated stroke risk for only the subtype of migraine with aura.[27]

Hemorrhagic Stroke.—Four studies provided information about the effect of CHCs on hemorrhagic stroke risk.[23,26,31,36] Two of the studies showed an increased risk in women with migraines who used CHCs: OR 2.1 [1.0 to 4.6] and 2.15 [0.85 to 5.45].[23,31] Farhoudi et al found that the risk of stroke showed a statistically significant difference between cases and controls, although overall numbers were low.[36] The remaining study showed no statistically significant difference, OR 1.10 [0.4 to 2.97].[26]

Study Quality.—The majority, 12, of the studies received a Newcastle-Ottawa score of 7 or 8, indicating good study quality[23-27,29-35] (Table 3). All studies received a low level of evidence using the GRADE system, based on the observational nature of the studies (Table 4). No study met all three of our quality criteria: assessment of migraine subtype, diagnosis of migraine made using structured International Classification of Headache Disorders criteria, and stratified risk by estrogen dose.

DISCUSSION

This systematic review, which included 15 studies overall and six studies reporting odds ratios, attempted to determine if there was an increased risk of ischemic stroke in women with migraine

Table 4.—Other Assessments of Study Quality

	Year	GRADE Quality of Evidence	Assessed Migraine Aura Subtype	Migraine Diagnosis	Risk Stratified by Estrogen Dose
JAMA	1975	Low	No	Structured interview-loose criteria	
Tzourio	1993	Low	*	+	
Lidegaard	1995	Low	No	Self-report	*
Tzourio	1995	Low	No	+	*
Carolei	1996	Low	*	+	
Schwartz	1998	Low	No	+	
Chang	1999	Low	*	+	*
Milhaud	2001	Low	No	+	
Lidegaard	2002	Low	No	Self-report	*
Schwaag	2003	Low	*	+	
Nightingale	2004	Low	No	Prescription for anti-migraine	
MacClellan	2007	Low	Migraine with aura only	Interview with modified ICHD criteria	
Farhoudi	2012	Low	No	Not specified	
Champaloux	2016	Low	**	+	
Abanoz	2017	Low	No	+	

Abbreviations: GRADE = Grading of Recommendations Assessment, Development and Evaluation; ICHD = International Classification of Headache Disorders.
*Migraine aura subtype recorded, stroke risk not assessed as a function of subtype.
**Stroke risk assessed for migraine with vs without aura.
+Migraine diagnosed by structured or neurologist interview using IHS criteria or physician diagnosis.

who use estrogen containing contraceptives. The combined cohort/case control study done by Champaloux and colleagues was by far the largest, with 1884 cases. This study found an OR of 6.1 (3.1-12.1) for women with migraine with aura, and an OR of 1.77 (1.09-2.88) in women with migraine without aura, who used CHCs within 90 days prior to the first diagnosis of stroke. This was the only study to report the effect of stroke risk factors by migraine subtype (with/without aura).

Studies that evaluated the effect of CHC use on the risk of hemorrhagic stroke in women with migraine found conflicting results. Two of the studies showed an increased risk, with OR 2.1 and 2.15, while one did not and the other was inconclusive. Based on these results, it is unclear whether CHC use in women with migraine is a risk factor for hemorrhagic stroke.

The Effect of Estrogen Dose and Implications for Clinical Practice.—We found limited evidence regarding the effect of estrogen dosing on risk of stroke in women with migraine who use CHCs.

Newer studies were more likely to show no clear association between CHC use and stroke in women with migraine than older studies. This may reflect the decreasing doses of estrogen in CHCs over time. Many of the studies that evaluated estrogen dose response considered any exposure less than 50 μg EE to be low. The average dose of the estrogen component in modern contraceptives, however, is around 35 μg EE, and some contraceptives include estrogen dosing as low as 10 μg EE. None of the studies in our review reported odds ratios for a lower dose estrogen group in migraineurs. Information regarding the effect of estrogen dose on risk of stroke in women with migraine is therefore lacking and further studies are needed.

Prior research suggests that the increased risk of stroke in women with migraine is driven by the migraine aura subtype, and may in fact be confined

to this subtype.[37] There is also some evidence that frequency of migraine aura may modify stroke risk, with higher risk of stroke associated with attacks more than 12 times a year, with an OR of 10.4 [2.18 to 49.4].[38] Our review identified only one study that evaluated risk in women with migraine with aura specifically and this study did not stratify by estrogen dose or assess migraine aura frequency. This is therefore another area that would benefit from further study. Interestingly, a small study showed that use of the vaginal ring contraceptive decreased aura frequency in women with migraine with aura. It remains unclear whether decreased aura frequency results in a decreased risk of stroke.[39]

No interaction effect between migraine and CHCs was seen on the outcome of ischemic stroke in studies that assessed this question. This may mean that the risk of stroke in women with migraine who use CHCs can be estimated by adding the additional risk of stroke associated with migraine to that found in CHC users without migraine.

Prior meta-analyses have looked at the effect of CHC use on the risk of ischemic stroke. Gillum et al published a meta-analysis including 16 articles that found a three times higher overall risk of ischemic stroke with current use of oral contraceptives, (RR 2.75, CI 2.24-3.38).[40] They distinguished between estrogen exposure greater than or less than 50 μg EE and found an elevated risk for low-estrogen contraceptives as well as those with higher doses, which was apparent even after controlling for smoking and hypertension (RR, 1.93; 95% CI, 1.35-2.74).[37] A report of risk with modern, low estrogen doses was not given, possibly because the studies in this review tended to be older.

A more recent Cochrane review looked at 24 studies evaluating the effect of oral contraceptives on risk of myocardial infarction and ischemic stroke.[41] They also concluded that there is a risk of ischemic stroke with use of oral contraceptives, but a dose response was seen. The OR for risk of ischemic stroke or MI with 20 μg EE was 1.6 (95% CI 1.4-1.8), for 30-49 μg EE 2.0 (1.4, 3.0), and for >49 μg 2.4 (1.8, 3.3).[41] Although there is good evidence that high doses of estrogen can increase the risk of arterial stroke, an increase in stroke risk is not clear at the lower (20-35 μg EE) estrogen doses used in modern contraceptives. One question is whether risk might vary by country, due to differences in CHC prescribing guidelines. For example, some authors have suggested that looser restrictions on CHC use in smokers might account for higher stroke risk in European countries compared the US. A pooled analysis of two US case-control studies found that use of contraceptives containing less than 50 μg of EE was not associated with increased risk of stroke.[42] A large cohort study in Denmark found that stroke risk with 20 μg EE ranged from 0.88 (0.22-3.53) to 1.53 (1.26-1.87) depending on the progestin component of the CHC. The authors of the recent Cochrane review suggested that pills containing 30 μg of EE or less are the safest form of hormonal contraception, and available evidence suggests that 20 μg EE CHCs confer even lower risk.[41]

Although all of the studies in this review found an increased risk of stroke in women with migraine who used CHCs, it should be noted that the absolute risk of stroke in reproductive-aged women is low. The crude, unadjusted incidence of stroke was 3.56 per 100,000 women of reproductive age per year in the UK population-based study by Nightingale and Farmer, and this is consistent with other studies specifically evaluating incidence in premenopausal women.[33] In our review, the best quality evidence regarding risk in women with migraine with aura who use CHCs comes from the Champaloux study. Based on these OR from that study, 6.1 (95% CI 3.1-12.1), annual stroke incidence in women with migraine with aura who use CHCs would be expected to increase to 21.7 per 100,000 women per year (CI 11.03-43.1). The corresponding excess risk from the combination of migraine aura and CHC use is about 18 per 100,000 women per year.[14] The risk of stroke associated with pregnancy is also increased in women with migraine, with ORs ranging from 7.9 to 30.7 per a recent systematic review.[43] Pregnancy is also associated with other health risks other than stroke, such as venous thromboembolism. Combined oral contraceptives

are a convenient and reliable form of contraception for many women. This competing risk of pregnancy and associated comorbidities with prohibition of CHCs should therefore also be considered. There are also other medical reasons that women may benefit from CHC use, such as treatment of endometriosis, menstrual cramps, dysmenorrhea, menorrhagia and associated anemia, acne, and hirsutism. There is also evidence that CHC use reduces the risk of endometrial and ovarian cancer. There is evidence to suggest that CHCs can effectively treat menstrual migraine as well.[44,45] Given all of these factors, it may be reasonable to base the decision regarding use of CHCs in women with migraine with aura on an individualized assessment of risks and benefits rather than continuing a strict prohibition on use. Other risk factors for stroke, such as age over 35, family history, and obesity, should be taken into account.

Study Limitations.—Most of the studies in our analysis were considered good quality per the Newcastle Ottawa score, reflecting good study design and reporting. Based on the observational design of the included studies, however, they all received low GRADE levels of evidence. The included studies have many limitations, several of which are described in detail in a recent article by Calhoun.[46] Odds ratios in some studies are based on a small number of cases, as low as 4 in one study.[31] Many of the articles do not give the doses of the hormonal contraceptives that are being used.[46]

One major limitation of the studies in this review was how the diagnosis of migraine was made. In some cases it was self-reported and thus subject to recall bias or limitations of recall, although later studies did use ICHD criteria to assign diagnoses. With regard to the focus of this review, however, the most significant limitation is the poor reporting of estrogen type and dosing. Many studies did not provide any information about the estrogen exposure. Several studies reported estrogen dosing as being over or under 50 μg EE, but the current clinical relevance of this cutoff point is limited. No current CHCs contain EE doses of over 50 μg, and most current CHCs contain 20-35 μg EE. CHCs with EE doses as low as 10 μg are now available, and no available studies include relevant information about modern low dose CHCs. Only two studies attempted to examine groups with lower estrogen exposure, and neither of these reported sufficient data for meaningful statistical calculations. In addition, studies did not report risk of stroke in migraine as a function of progestin type. CHC generation/progestin type has been shown to affect stroke risk in prior studies where migraine status was not assessed.[47]

The majority of studies either did not evaluate migraine with vs without aura or did not report subgroup analyses using this information. Since the increased risk of stroke is most pronounced in the migraine with aura subtype, the reported OR for the combined migraine group may overestimate the risk of those with migraine without aura and underestimate the risk for those with migraine with aura. Many of the studies were small and therefore may have had sample sizes too small to show a true effect, or to allow potentially informative subgroup analyses.

Comparison to Other Studies.—Etminan et al published a systematic review assessing the risk of ischemic stroke in people with migraine.[9] They included a total of 14 studies, and found that migraine with aura was a risk factor for stroke in patients with migraine. They also concluded that this risk is further increased in women who were using oral contraceptives, based on data from three studies. Two previous systematic reviews evaluating the risk of stroke in women with migraine who use CHCs have been published, in 2006 and 2016, respectively.[48,49] Both of these prior reviews included similar articles. Although the summary finding was that women who have migraine and used oral contraceptives did have an increased risk of ischemic stroke, there was significant heterogeneity with regard to ascertainment of exposure and outcome, as well as doses of estrogen. The most recent systematic review, by Tepper et al found four studies that there was limited evidence, but it did suggest a two- to fourfold increased risk of stroke among women with migraine who use CHCs compared with nonuse.[49] Our systematic review includes the previous articles as well as two additional studies published within the last year.[30,34] We further collected information about the

presence or absence of an interaction effect for CHCs on stroke for women with migraine. We have also assessed the quality of the included studies in more depth.

Suggestions for Further Research.—This systematic review indicates that further studies assessing the risk of stroke in women with migraine with aura who use low dose contraceptives are needed. Current preparations of CHCs contain 20 μg in low dose formations and range from 30 to 40 μg for regular dose formulations. We therefore recommend that future studies stratify CHC use into groups of 20 μg, 30-40 μg, and 50 μg, and that these groups are compared to progestin only users. There should also be an effort to compare the different formulations of contraceptives, including patches or implants. Future studies should also make efforts to assess risk in women with migraine aura vs without aura.

CONCLUSION

This review of the current literature confirms an increase in risk of stroke among women with migraine who use estrogen containing contraceptives. The association was clear for women using high estrogen dose (50 μg EE or greater) CHCs. There is insufficient evidence to determine whether stroke risk is also increased with the use of low estrogen dose (35 μg EE or lower) CHCs in this population. Studies of stroke risk in women with migraine with aura who use low dose CHCs are needed. Our review confirmed previous findings that concurrent use of CHCs and smoking had a multiplicative increase in risk in women with migraine. The ACOG considers smoking a contraindication for the use of CHCs.

None of the studies that looked for an interaction effect found such an effect, suggesting that the risk of stroke in a woman with migraine who uses CHCs may be the addition of the increased stroke risk associated with migraine and the risk associated with CHC use. Studies of stroke risk in women without migraine with use of low estrogen dose CHCs have been largely reassuring. It seems reasonable to recommend that the lowest possible dose of estrogen be used if a CHC is prescribed to a woman with migraine. There may be limitations to this approach, however. Women who use CHCs for other medical conditions may require higher doses, for example. Progestin-only contraceptive methods are effective and reliable for many women, and CHCs should only be used after careful consideration in women with migraine with aura. An individualized assessment of risks and benefits of CHC use in women with migraine with aura remains appropriate.

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SEARCH STRATEGY-APPENDIX

Performed 08/2015

The following databases were searched: MEDLINE, Cochrane Library and EMBASE

All possible keyterms:

1. Exp migraine, aura, chronic headache, exp headache disorders, chronic migraine
2. Exp contraceptives, exp contraception, exp estrogen, estradiol, progesterone, oral contraceptives, exogenous, birth control, hormonal, hormones, combined oral contraceptives, progestin

Search Strategy:

1. Exp migraine
2. Exp aura
3. Exp chronic headache
4. Exp headache disorders
5. Chronic migraine
6. 1 or 2 or 3 or 4 or 5 or 6
7. Observational trial
8. Case-control
9. Cohort
10. Randomized control trials
11. 6 or 7 or 8 or 9 or 10
12. Exp contraceptives
13. Exp contraception
14. Exp estrogen
15. Estradiol
16. Progesterone
17. Oral contraceptives
18. Exogenous
19. Birth control
20. Hormonal
21. Hormones
22. Combined oral contraceptives
23. Progestin
24. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
25. 23 and 10

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