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Safety of hormonal contraceptives among women with migraine: A systematic review☆

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Abstract

Background: Migraine is common among women of reproductive age and is associated with an increased risk of ischemic stroke. Combined oral contraceptives (COCs) are also associated with an increased risk of ischemic stroke. Use of hormonal contraception among women with migraine might further elevate the risk of stroke among women of reproductive age.

Objective: To identify evidence regarding the risk of arterial thromboembolism (stroke or myocardial infarction) among women with migraine who use hormonal contraceptives.

Methods: We searched the PubMed database for all articles published from database inception through January 2016. We included studies that examined women with migraine overall or separated by subtype (with or without aura). Hormonal contraceptives of interest included combined hormonal methods (COCs, patch and ring) and progestin-only methods (progestin-only pills, injectables, implants and progestin intrauterine devices).

Results: Seven articles met inclusion criteria. All were case–control studies of fair to poor quality reporting on use of COCs or oral contraceptives (OCs) not further described and all reported stroke outcomes. Four studies demonstrated that, among women with migraine (not separated by subtype), COC use was associated with approximately two to four times the risk of stroke compared with nonuse. The only study to examine specific migraine subtypes found an elevated risk of stroke among women with migraine with aura, and this risk was similar regardless of OC use, although these odds ratios were not reported. Two studies did not report risks among women with migraine and COC use combined, but both found increased risks of stroke with migraine and COC use independently. No evidence was found on other hormonal contraceptives or on risk of myocardial infarction.

Conclusion: Limited evidence suggests a two- to fourfold increased risk of stroke among women with migraine who use COCs compared with nonuse. Additional study is needed on the

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risks of hormonal contraceptives, including combined and progestin-only methods, among women with different migraine subtypes.

Keywords

Migraine; Combined oral contraceptives; Stroke; Systematic review

1. Introduction

Migraine is common among women, with a lifetime prevalence of 43% [1]. Migraine is divided into two major subtypes, those with or without aura [2]. Typical characteristics of migraine without aura include unilateral location, pulsating quality and moderate or severe intensity and may be associated with nausea, photophobia and phonophobia. Menstrual migraine is classified as migraine without aura [2]. Aura is a complex of neurological symptoms that occurs just before or at the onset of a migraine and includes symptoms such as visual changes, numbness or speech disturbance [2]. Migraine with aura occurs in about a third of people with migraine [3]. Although rare among women of reproductive age, stroke is a devastating event and is associated with migraine. Migraine with aura has been shown to be associated with an increased risk of stroke, particularly ischemic stroke [4]. Migraine without aura has not been consistently associated with an increased risk of stroke, although one study found an association [4].

The use of hormonal contraception, specifically use of combined oral contraceptives (COCs), has also been associated with an increased risk of stroke [5]. COCs are the most commonly used reversible method of contraception in the US and are even used as treatment of certain migraine subtypes responsive to hormonal manipulation, including menstrual migraine [6]. However, given the independent effects of migraine and COC use on stroke risk, there is theoretical concern that use of COCs among women with migraine headaches would further elevate the risk of stroke to an unacceptable level for contraceptive use. The US Centers for Disease Control and Prevention (CDC) publishes the US Medical Eligibility Criteria for Contraceptive Use (US MEC), which provides guidance for the safety of contraceptive methods among women with certain medical conditions including migraine [7]. This systematic review updates a previous review conducted for the World Health Organization (WHO) MEC, from which the US MEC is adapted [8]. The previous review concluded that among women with migraine, COC use was associated with a two- to fourfold higher risk of ischemic stroke compared with nonuse.

2. Materials and methods

We conducted this systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [9].

2.1. Literature search

We searched the PubMed database for all relevant articles published from database inception through January 2016 using the following search strategy:

((((((“*Migraine Disorders*”[*Mesh*]) *OR migrain**))) *AND* (((“*Contraceptives, Oral, Combined*”[*Mesh*] *OR* “*Contraceptives, Oral*”[*Mesh*] *OR* “*Contraceptives, Oral, hormonal*” [*Mesh*] *OR* “ *Contraceptives, Oral, Combined*” [*Pharmacological Action*]) *OR* (*contracept** *AND* (*oral OR pill OR tablet*)) *OR* ((*combined hormonal*) *OR* (*combined oral*) *AND contracept**) *OR* (*contracept** *AND* (*ring OR patch*)) *OR* “*ortho evra*” *OR NuvaRing*) *OR* (*progestin** *OR progestins* [*MeSH*] *OR Progesterone* [*MeSH*] *OR progesterone OR progestogen** *OR progestagen** *OR* “*Levonorgestrel*” [*Mesh*] *OR Levonorgestrel OR* “*Norgestrel*” [*Mesh*] *OR norgestrel OR etonogestrel AND contracept**) *OR dmpa OR* “*depo medroxyprogesterone*” *OR* “*depo provera*” *OR* “*net en*” *OR* “*norethisterone enanthate*” *OR* “*norethindrone enanthate*” *OR* (*contracept** *AND* (*inject** *OR implant*)) *OR* ((*levonorgestrel OR etonogestrel*) *AND implant*) *OR implanon OR nexplanon OR jadelle OR norplant OR uniplant OR sino-implant OR* (*levonorgestrel-releasing two-rod implant*) *OR* (“*Intrauterine Devices, Medicated*” [*Mesh*] *OR* ((*intrauterine OR intra-uterine*) *AND* (*device OR system OR contracept**)) *OR IUD OR IUCD OR IUS OR mirena OR Skyla*)))) *AND* ((“*cerebrovascular disorders*”[*MeSH Terms*] *OR* (“*cerebrovas-”[All Fields] AND “disorders”[All Fields]) OR “cerebrovascular disorders”[All Fields]) OR (“stroke”[MeSH Terms] OR “stroke”[All Fields]) OR ((((“brain”[MeSH Terms] OR “brain”[All Fields]) OR (“cerebrum”[MeSH Terms] OR “cerebrum”[All Fields] OR “cerebral”[All Fields] OR “brain”[MeSH Terms] OR “brain”[All Fields])) AND ((“infarction”[MeSH Terms] OR “infarction”[All Fields]) OR (“ischaemia”[All Fields] OR “ischemia”[MeSH Terms] OR “ischemia”[All Fields]) OR (“embolism”[MeSH Terms] OR “embolism”[All Fields]) OR (“thrombosis”[MeSH Terms] OR “thrombosis”[All Fields]))) OR (“myocardial infarction” [MeSH Terms] OR (“myocardial”[All Fields] AND “infarction”[All Fields]) OR “myocardial infarction”[All Fields] OR (“heart”[All Fields] AND “attack”[All Fields]) OR “heart attack”[All Fields]) OR (“myocardial infarction”[MeSH Terms] OR (“myocardial”[All Fields] AND “infarction”[All Fields]) OR “myocardial infarction”[All Fields])).

We searched for all primary research articles published in any language. We also searched reference lists of identified articles and relevant review articles for additional citations of interest. We did not consider unpublished studies, abstracts of conference presentations or dissertations.

2.2. Selection criteria

Articles were included in this review if they were primary research articles that examined arterial thromboembolism outcomes among women with migraine headaches using hormonal contraceptives. The population of interest was women with any subtype of migraine. The hormonal contraceptives of interest included combined hormonal contraceptives (COC, patch and ring) and progestin-only contraceptives (progestin-only pills (POPs), injectables, implants and levonorgestrel-releasing intrauterine device (LNG-IUDs)). The reference group of interest was use of nonhormonal contraceptives or no contraceptive method. The outcomes of interest were stroke (ischemic or hemorrhagic) or myocardial infarction. We included myocardial infarction as an outcome, given that some studies have found that migraine and COCs may be independently associated with myocardial infarction [1,10].

2.3. Study quality assessment and data synthesis

Two authors (NT and MW) summarized and systematically assessed the evidence. We assessed the quality of each individual piece of evidence using the system developed by the United States Preventive Services Task Force [11]. Summary measures were not calculated due to heterogeneity of studies.

3. Results

The search identified 287 articles, of which 7 met inclusion criteria (Fig. 1 and Table 1) [12–18]. One article was newly published since the previous systematic review [15]. All included articles were case–control studies describing stroke risk among women with migraine using COCs or oral contraceptives (OCs) not further specified. No studies were identified that included other hormonal methods of contraception or reported on myocardial infarctions.

The one newly published study and only study to examine migraine type (with or without aura) was a case–control study conducted in the US [15]. This study examined 386 cases with ischemic stroke hospitalized at one of 59 hospitals participating in the Stroke Prevention in Young Women Study. Controls were 614 women identified by random-digit dialing and matched to cases on age and residence. Information on headaches and OC use was obtained by participant questionnaire. Stroke diagnoses were confirmed by review of medical records. The odds of ischemic stroke among women with migraine with aura were increased compared with no migraine [odds ratio (OR)=1.5, 95% confidence interval (CI)=1.1–2.0]. Increased odds were similar regardless of OC use, although the OR among OC users was not reported. The authors stated that OC use was not an independent effect modifier of the association between migraine with aura and stroke. Among women with migraine with aura, the combined effect of smoking and OC use elevated the risk of stroke (OR=7.0, 95% CI=1.4–22.8 compared to nonsmokers and non-OC users).

The remaining studies are discussed in order of publication date. One case–control study conducted in the US examined 140 cases of ischemic stroke and 196 cases of hemorrhagic stroke, compared with 429 hospital and 451 neighbor controls [12]. OC types were not specified, but study authors reported inclusion of women taking COCs with 50-mcg estradiol and 100-mcg mestranol. When using neighbor controls, the odds of ischemic stroke were increased among women with migraine currently using OCs (OR=5.9; 95% CI=2.9–12.2), women with migraine not using OCs (OR=2.0; 95% CI=1.2–3.3) and women without migraine currently using OCs (OR=4.9; 95% CI= 2.9–8.3), compared with nonusers without migraine. When using neighbor controls, the odds of hemorrhagic stroke were increased among women with migraine currently using OCs (OR=2.6; 95% CI=1.2–5.5), women with migraine not using OCs (OR=1.8; 95% CI=1.2–2.7) and women without migraine currently using OCs (OR=2.2; 95% CI=1.3–3.6), compared with nonusers without migraine. For both ischemic and hemorrhagic stroke, ORs were similar but lower when using hospital controls.

A case–control study conducted in France examined 72 cases with ischemic stroke and 173 hospital controls [18]. OC types were not specified. The odds of ischemic stroke were increased among women with migraine currently using OCs (OR=13.9; 95% CI=5.5–35.1), women with migraine not currently using OCs (OR=3.7; 95% CI=1.5–9.1) and women

without migraine currently using OCs (OR=3.5; 95% CI=1.5–8.3), compared with nonusers without migraine. The authors stated that there was no evidence of a statistical interaction between migraine and use of OCs.

A case–control study conducted in Denmark examined 497 cases with ischemic stroke and 1370 population-based controls [14]. COCs reportedly taken by participants contained 50-mcg estrogen and 30–40-mcg estrogen. Odds of stroke were elevated independently among women with migraine and among women using COCs. The authors stated that there was no interaction between migraine and COC use on the risk of stroke, although ORs for COC use combined with migraine status were not calculated due to small numbers.

A pooled analysis combined results from two case–control studies conducted in the United States [17]. The study examined 175 cases with ischemic stroke and 198 cases with hemorrhagic stroke, along with 1191 controls. All COCs taken by participants contained <50-mcg ethinyl estradiol (EE). Among women with migraine, the odds of ischemic stroke were elevated among current COC users compared with nonusers (OR=2.08; 95% CI=1.19–3.65). Among women with migraine, the odds of hemorrhagic stroke were also elevated among current COC users compared with nonusers, although the CI crossed 1 (OR= 2.15; 95% CI=0.85–5.45). Among women without a history of migraine, COC use was not associated with a significantly increased odds of ischemic or hemorrhagic stroke.

One case–control study conducted in five European centers examined 86 cases of ischemic stroke and 187 cases of hemorrhagic stroke, along with 736 hospitalized controls [13]. COCs used contained ≥50-mcg or <50-mcg EE. The OR of ischemic stroke among OC users with migraine, compared to nonusers without migraine, was 16.9 (95% CI= 2.72–106). The odds were attenuated and no longer significant when examining those using low-dose (<50-mcg) OCs. Odds of ischemic stroke were elevated but not statistically significant for nonusers with migraine and users without migraine, compared with nonusers without migraine. Odds of hemorrhagic stroke were not statistically significantly elevated, regardless of OC use or migraine status.

One case–control study conducted in the United Kingdom examined 190 cases of ischemic stroke and 1129 controls [16]. COC types were not specified. Odds of ischemic stroke were statistically significantly elevated among women with a history of migraine (OR=2.33; 95% CI=1.04–5.21) and among women with current COC use (OR=2.30; 95% CI= 1.15–4.59). The authors stated that there were no significant interactions between variables, however OR for women with migraine stratified by COC use were not reported.

4. Discussion

This systematic review identified seven studies which reported associations between migraine headaches, OC use and ischemic or hemorrhagic stroke. Four studies demonstrated that the ORs for migraine and COC use were two to four times as high as ORs for migraine and no COC use [12,13,17,18]. However, CIs were wide, and direct comparisons with statistical testing were not performed, as both groups were compared to women without migraine not using COCs. Two of these studies specifically reported results among women

using COCs containing <50-mcg EE; one found a significant elevation in risk of ischemic stroke [17] and the other did not [13]. The only study to report specific migraine subtypes found an elevated risk of ischemic stroke among women with migraine with aura, and this risk was similar regardless of OC use, although these ORs were not reported [15]. Two studies did not report risks among women with migraine and COC use combined, but both found an increased risk of stroke with migraine and COC use independently [14,16].

A meta-analysis combined results from four studies [12,13,17] (one study not included in reference list of meta-analysis). This meta-analysis found that among OC users, the OR of stroke was 3.2 (95% CI=1.5–7.2) among women with migraine and 2.3 (95% CI=0.7–7.2) among women without migraine, both compared to nonusers without migraine [19]. Another meta-analysis (specific studies in this calculation not stated) reported that OC users with migraine had a relative risk (RR) of stroke of 8.7 (95% CI=5.1–15.1) compared with nonusers without migraine [20]. A third meta-analysis (specific studies in this calculation not stated) found that the OR for ischemic stroke among OC users with migraine was 6.3 (95% CI= 2.4–17.1) compared with nonusers without migraine [5]. However, none of the meta-analyses directly compared OC use to nonuse among women with migraine.

There are several limitations to this body of evidence, which was of poor to fair quality. Most studies did not distinguish between migraine subtypes [12,14,16–18]. Given the likely differential risk of stroke related to different migraine subtypes, it is possible that analyzing all migraine subtypes together would lead to bias of risk estimates. Definitions and ascertainment of migraine varied widely. One study defined migraine as whether a doctor ever said the woman had a migraine [17], one study defined migraine by prescription or diagnostic coding [16], and one study provided no details on how migraine was defined [14]. Only two studies attempted to distinguish migraine with and without aura [13,15], with only one study reporting results separately by subtype. However they deviated from International Headache Society (IHS) criteria by not including phonophobia, which may have led to underestimation of migraine [15]. Most of the studies did not report frequency of migraine [12,13,16–18] or timing of migraine relative to stroke [12–15,17,18], and therefore no conclusions can be drawn about the risk of stroke relative to the frequency and recency of migraine. Three studies did not differentiate OC type [12,15,18], and the oldest study included women taking COCs with higher doses and different estrogen formulations than found in modern COCs [12]. Most studies did not verify COC use beyond subject self-report [12–15,17,18], which may introduce recall bias. One study used only diagnosis codes to identify strokes, without additional verification [14]. Three studies did not calculate risk estimates for the combined effects of migraine and COCs [14–16]. Three studies did not adjust for important confounding factors such as hypertension and smoking [12,15,18]. Given that most of the studies did not distinguish between migraine with or without aura, this body of evidence provides little information on the relationship between migraine subtypes and hormonal contraceptives on risk of stroke. The one newly identified study was the first to present results separately by migraine subtype, and found that OC use did not further elevate the risk of stroke among women with migraine with aura, however these results should be interpreted with caution, given that migraine may have been underestimated and OC type may have included POPs [15].

Although there is minimal direct evidence regarding the joint effects of migraine and hormonal contraceptives, there is theoretical concern about elevated risk because of the independent effects of migraine and estrogen use on stroke risk. Migraine with aura has been associated with an increased risk of ischemic stroke. Three meta-analyses have found a 2.3–2.5-fold increased risk of ischemic stroke among individuals with migraine with aura compared with no migraine [20–22]. None of the meta-analysis calculated risk estimates specifically for women of reproductive age with migraine with aura. However, studies have found an elevated risk of ischemic stroke among women of reproductive age with migraine with aura compared with no migraine [13,15,18]. Two of the meta-analyses reported an increased risk of ischemic stroke among women aged <45 years with migraine compared with no migraine (RRs=2.8 and 3.7); however, risks were not stratified by migraine subtype [20,21].

Several hypotheses support the relationship between migraine with aura and ischemic stroke. The migraine may lead directly to stroke due to cortical spreading depression related to the aura (migrainous infarction) [3]. Individuals with auras may have vascular risk factors, such as smoking and hypertension, which place them at higher risk of stroke [3]. Migraine with aura has also been found in high prevalence among individuals with certain vasculopathies or autoimmune diseases, such as antiphospholipid syndrome and systemic lupus erythematosus [23]. Migraine with aura has also been linked to patent foramen ovale, which can result in paradoxic microembolization [4].

Evidence on the relationship between migraine without aura and ischemic stroke is less consistent. One older meta-analysis found a 1.8-fold increased risk of ischemic stroke among individuals with migraine without aura compared with no migraine [20]. However, of the six studies included, only one found a statistically significant increased risk [18], and another found a borderline significant increased risk with wide CIs [24]. Two more recent meta-analyses which included additional studies and overall larger numbers of women did not find a statistically significant increased risk of ischemic stroke among individuals with migraine without aura compared with no migraine [21,22].

Evidence has demonstrated an increased risk of ischemic stroke among women who use COCs [5,10,19]. The risk is highest among women using high dose COCs (>50-mcg EE), however the risk may still be elevated among women using lower dose COCs [5,19]. One meta-analysis found that current use of COCs containing <50-mcg EE was associated with a 2.1-fold increased risk of ischemic stroke compared with nonuse [19]. However, several of the individual studies included in the meta-analysis did not find statistically significant increased risks associated with <50-mcg EE. The most recent meta-analysis found that the risk of ischemic stroke declined but remained significantly elevated with decreasing doses of EE; OR=3.28 (95% CI=2.49–4.32) for >50-mcg EE, OR=1.75 (9% CI=1.61–1.89) for 30–40-mcg EE, OR=1.56 (95% CI=1.36–1.79) for 20-mcg EE, all compared with nonuse [5]. Given that current COCs contain increasingly lower doses of EE, the risk of stroke associated with these COCs may be reduced further; however, there is little evidence specifically examining COCs with <20-mcg EE. One study found that the RR of stroke among users of the combined hormonal patch was 3.2 (95% CI=0.8–12.6) and among users of the combined vaginal ring was 2.5 (95% CI=1.4–4.4), compared to nonusers [25]. The

risk of stroke does not substantially differ when comparing COCs with different progestin types [26]. Studies have not found an increased risk of stroke among women using various progestin-only contraceptives, including POPs, injectables, implants and LNG-IUDs [25,27–31]. Therefore, the mechanism of ischemic stroke among COC users is likely attributable to the estrogen component and may be related to effects of estrogen on the coagulation system or blood pressure [32]. It is not clear, however, whether estrogen might interact with any of the mechanisms linking migraine with stroke. While some studies have demonstrated an increased risk of hemorrhagic stroke among women with migraine [33], COC use has generally not been associated with hemorrhagic stroke [10].

Some studies have found that ischemic stroke risk increases with increased migraine frequency, among women who have migraine with aura, and other studies demonstrated an increased risk of ischemic stroke if women had more than 12 attacks per year or at least 1 attack per week [15,34,35]. Certain women with migraine may experience reduction in migraine frequency when using combined hormonal contraceptives [6]. However, there is no evidence that treatment of migraine reduces risk of first stroke [36,37]. There is also little information on whether a remote history of migraine is associated with an increased risk of stroke, as certain studies which included women with a history of migraine did not specify timing relative to the stroke [13,17]. Therefore, it is not clear that stroke risk declines in women with reduced migraine frequency or remote history of migraine.

While the RR of stroke may be increased among women with migraine and who use COCs, the risk should be considered in the context of overall absolute risk among the population. The absolute risk of stroke among women of reproductive age is low, with an incidence of 4.3–8.9 per 100,000 per year [16]. This risk increases with increasing age, as well as presence of cardiovascular risk factors such as smoking, hypertension and diabetes [16]. However, the attributable risk of stroke at the population level related to risk factors of migraine headaches or COC use is likely to be low overall.

In conclusion, this systematic review identified limited fair to poor quality evidence on the risk of ischemic and hemorrhagic stroke among women with migraine headaches who use hormonal contraceptives. The evidence suggests a two- to fourfold increased risk of stroke among women with migraine who use COCs compared with nonuse. Additional evidence suggests that migraine and COCs are independently associated with increased risk of ischemic stroke. Evidence demonstrates an increased risk of ischemic stroke among women with migraine with aura and generally no significant risk between ischemic stroke and migraine without aura. Evidence also demonstrates an increased risk of stroke among women who use COCs at any dose, although studies are limited on the effect of ultra low-dose (<20-mcg EE) COCs and nonoral combined hormonal contraceptives. Additional study is needed on the risks of hormonal contraceptives, including combined and progestin-only methods, among women with different migraine subtypes. In addition, future studies should examine the relationship between migraine timing and remoteness relative to the risk of stroke. This review was conducted in preparation for a meeting convened by CDC in August 2015. The findings of this systematic review will be incorporated into the forthcoming updated US MEC.

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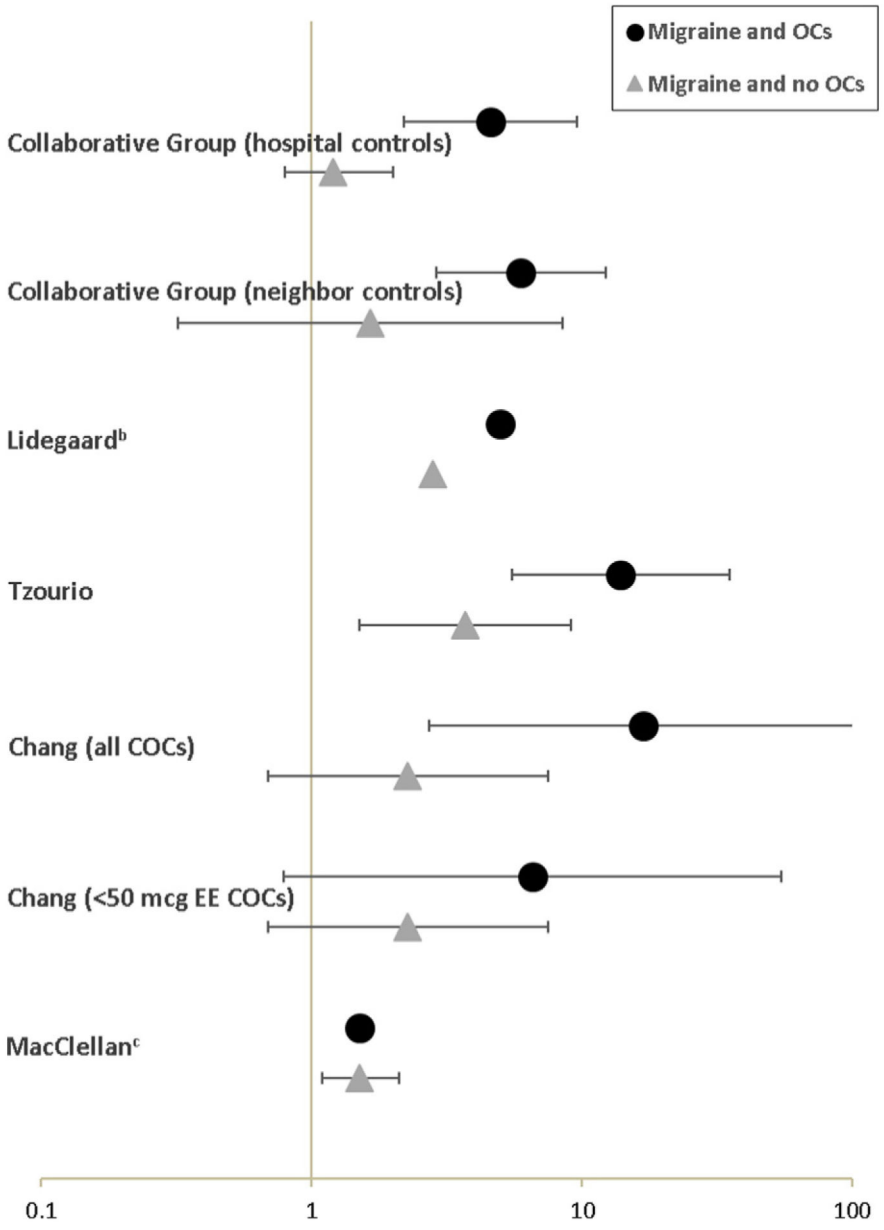

Fig. 1.

Stroke risk[a] among women with migraine using and not using OCs. [a] Reference group is nonusers without migraine. [b] ORs calculated for purpose of review [8]. [c] Exact estimates for COC users and migraine were not reported, but the risk estimate was similar to non-COC users.

Table 1

Evidence for risk of stroke in users of combined hormonal contraceptives who have migraine headaches

Author, publication, location, support	Study design, years	Population	Migraine definition and ascertainment	Contraceptive	Outcome	Results	Strengths	Weaknesses	Quality grading
Collaborative Group for the Study of Stroke in Young Women [12], 1975, United States, Funded by NIH	Case–Control 1969–1971 [38]	Ages 15–44 Cases (*N*=430; 140 ischemic, 196 hemorrhagic): admitted with first stroke, 91 hospitals in 12 cities Controls (*N*=429 hospital, 451 neighbor): admitted to same hospital or residing in same neighborhood, matched on age and race Exclusions: pregnancy within 30 days, history stroke (for cases) [38]	Migraine: defined as two or more symptoms (unilateral headache, throbbing, prodromal visual scintillation, vomiting and other symptoms) Participant questionnaire	OC (not further specified; included some taking 50-mcg estradiol COCs and 100-mcg mestranol COCs) Current use (at reference date) [38] Participant questionnaire	Stroke (ischemic and hemorrhagic) Identified by neurologists or review of discharge rosters, confirmed by medical records [38]	Ischemic stroke: Migraine / OC use / Stroke RR* (95% CI) vs hospital controls / Stroke RR* (95% CI) vs neighbour controls No / No / Ref / Ref No / Yes / 4.4 (2.5-7.8) / 4.9 (2.9-8.3) Yes / No / 1.2 (0.8-2.0) / 2.0 (1.2-3.3) Yes / Yes / 4.6 (2.2-9.6) / 5.9 (2.9-12.2) Hemorrhagic stroke: Migraine / OC use / Stroke RR* (95% CI) vs hospital controls / Stroke RR* (95% CI) vs neighbour controls No / No / Ref / Ref No / Yes / 1.9 (1.1-3.4) / 2.2 (1.3-3.6) Yes / No / 1.2 (0.8-1.8) / 1.8 (1.2-2.7) Yes / Yes / 2.1 (1.0-4.6) / 2.6 (1.2-5.5) *Adjusted for age and race	Multiple sites Stroke diagnosis confirmed by medical record review	Did not exclude history of stroke among controls No information on migraine subtype No information on timing of migraine relative to stroke No information on OC type OC use not verified Included TIA Included only surviving cases Did not adjust for other confounders	II-2, poor
Tzourio [18], 1995, France, Funded by GLAXO France	Case–Control 1990–1993	Ages 18–44 Cases (*N*=72): first stroke from hospital diagnosis codes Controls (*N*=173): hospitalized during same period for acute orthopedic or benign rheumatologic illnesses Exclusions: history stroke	Migraine: asked 23 headache questions and defined as migraine based on IHS criteria Participant questionnaire	OCs (type not specified) Current use (within 1 month) Participant questionnaire	Ischemic stroke Diagnosis codes, confirmed with imaging studies	Migraine / OC use / Ischemic stroke OR (95% CI) No / No / Ref No / Yes / 3.5 (1.5-8.3) Yes / No / 3.7 (1.5-9.1) Yes / Yes / 13.9 (5.5-35.1) No evidence of statistical interaction between migraine and OC use	High interobserver agreement of migraine diagnosis in subset interviewed by second neurologist Stroke diagnosis confirmed by radiologic imaging	23% nonresponse rate among controls No information on migraine subtype No information on timing of migraine relative to stroke No information on OC type OC use not verified ORs not adjusted for potential confounders	II-2, poor
Lidegaard [14], 1995, Denmark, Funded by Helse Foundation, Danish Heart Foundation, National Health Research Council	Case–Control 1985–1989	Ages 15–44 Cases (*N*=497): first stroke from hospital discharge diagnoses Controls (*N*=1370): National Personal Register, matched on age Exclusions: history stroke	Migraine (not further defined) More than once per month Participant questionnaire	COCs (50-mcg estrogen and 30–40-mcg estrogen) Participant questionnaire	Ischemic stroke Diagnosis codes, confirmed by participants	Exposure / Ischemic stroke OR Migraine (>1/month) / 2.8 COC (50 mcg estrogen) / 2.9 COC (30-40 mcg estrogen) / 1.8 Migraine and COC use were "independent exposures" and there was "no tendency to synergism", but specific ORs not reported due to small numbers	National data	No information on migraine subtype or migraine definition No information on timing of migraine relative to stroke COC use not verified Stroke diagnosis not confirmed by medical records Included TIA ORs not reported for migraine and COC use combined	II-2, poor
Schwartz [17], 1998, United States, Funded by NIH	Case–Control pooled from studies conducted by Kaiser Permanente (1991–1994) and University of Washington (1991–1995)	Ages 18–44 Cases (*N*=175 ischemic stroke, 198 hemorrhagic stroke): first stroke from hospital records Controls (*N*=1191) Kaiser: same insurance, matched on age and facility of	Migraine: defined by whether doctor ever said she had migraine (Kaiser) or whether she had ever visited doctor for migraine (University of Washington)	COCs (<50-mcg EE) Current use (within 1 month) Participant questionnaire	Stroke (ischemic and hemorrhagic) Identified from hospital records, death records and letters to physicians; confirmed with medical record review	Ischemic stroke: Migraine / COC use / Stroke OR* (95% CI) No / No / Ref No / Yes / 0.88 (0.44-1.76) Yes / No / Ref Yes / Yes / 2.08 (1.19-3.65) Hemorrhagic stroke: Migraine / COC use / Stroke OR* (95% CI) No / No / Ref No / Yes / 1.00 (0.46-2.19) Yes / No / Ref Yes / Yes / 2.15 (0.85-5.45)	Stroke diagnosis confirmed by medical records Adjusted for important confounders	No information on migraine subtype Migraine history assessed differently at different sites No information on timing of migraine relative to stroke COC use not verified	II-2, fair

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index; GPRD, General Practice Research Database; NIH, National Institutes of Health; TIA, transient ischemic attack; VTE, venous thromboembolism.