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Review Article

Combined Hormonal Contraceptives: Is It Time to Reassess Their Role in Migraine?

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Objective.—This paper will review the extensive array of hormonal contraceptives. It will examine the benefits and risks associated with them – particularly with regard to stroke risk – and shed light on divergent findings in the literature.

Background.—Menstrual-related migraine is a particularly disabling presentation of migraine often deserving of specific prevention. There is accumulating evidence that hormonal preventives may offer such protection. Although a legacy of research shows an increased risk of stroke with high-dose oral contraceptives (OCs) (those containing 50-150 μg of estrogen), there is evidence to suggest that this does not apply to ultralow-dose OCs – those containing <25 μg ethinyl estradiol – when used in appropriate populations (ie, normotensive non-smokers). Migraine with aura (MwA) increases stroke risk, and that risk is directly correlated to the frequency of aura, a factor that can be modified – either upward or downward – by combined hormonal contraceptives (CHCs). The argument against using CHCs in MwA is based on the concerns that (1) OCs increase stroke risk, (2) MwA increases stroke risk, and (3) combining these risk factors might produce additive or synergistic risk. Evidence does not support concerns (1) and (3), and suggests otherwise.

Summary.—The risk/benefit analysis of CHCs is shifting. There is growing evidence for a potential role for CHCs in the prevention of menstrual-related migraine. At the same time, the risk of these products is declining, as newer and lower dose formulations replace their historical predecessors. And although migraine aura is a risk factor for stroke, there is not convincing evidence to suggest that the addition of a low-dose CHC alters that risk in non-smoking, normotensive users. Selected hormonal preventives could potentially decrease stroke risk in MwA via reduction in aura frequency achieved by reducing peak estrogen exposure. With this shift in risk/benefit analysis, it is time to reconsider the role of CHCs in migraine – both with and without aura.

Key words: oral contraceptive, migraine, stroke, menstrual migraine, estrogen, migraine with aura

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For many headache specialists, "oral contraceptives" (OCs) are fighting words. On one side are specialists whose position is that combined hormonal contraceptives (CHCs) worsen migraine and increase stroke risk. On the other side are headache specialists who routinely prescribe selected or modified CHCs to stabilize estrogen and prevent menstrual-related migraine (MRM). The goal of this paper is to explain and reconcile these 2 conflicting views of CHCs.

(Note: MRM will refer to migraine attacks that occur consequent to a decline in estrogen concentration, encompassing pure menstrual migraine, MRM and estrogen withdrawal migraines that accompany withdrawal bleeds on CHCs.[1])

Wherever generalizations are applied to widely diverse members, disagreement abounds. Such is the case with CHCs. This diverse category includes a spectrum of delivery systems from pills and patches

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through chewing gums and vaginal rings. Even recent reviews may be inadvertently misleading when they reference studies that reflect historical doses long since replaced with formulations a mere fraction of their potency.

HISTORY AND DIVERSITY OF CHCS

Though no CHCs contain progesterone, all have a synthetic *progestin* as the essential ingredient responsible for contraception via one or more of three progestin-dependent mechanisms.[2] Estrogen is not required for contraceptive efficacy and was originally included in CHCs to enhance cycle control, though it was later found to inhibit follicular development.[2]

The first CHC, Enovid-10®, received initial approval in the USA in 1957 – not as a contraceptive but as a treatment for menstrual disorders. Each active pill contained 9.85 mg of the progestin norethynodrel – equal in potency to more than an entire pack of today's OCs – and 150 μg of mestranol, a prodrug of ethinyl estradiol (EE), the dominant estrogen in today's pills. Over time, the estrogen dose has likewise dwindled to as low as 10 μg today.

At least 40 unique OC formulations are available worldwide. They differ pharmacologically, utilizing more than a dozen progestins, but more importantly for their impact on MRM, they differ *architecturally*, with monophasic, biphasic, triphasic, and even quadriphasic pills (Fig. 1). Among phasic options, pills can be estrogen phasic, progestin phasic, or both. Most are offered as conventional 28-day cycle formulations with 21-26 active pills and up to 7 placebos, with some adding estrogen during the final 5 days of a withdrawal bleed week. Additionally, extended-cycle formulations suppress bleeding for 3 months at a time (with or without supplemental estrogen in the 13th week), and continuous formulations suppress menses indefinitely. With such diverse offerings, it is evident why many consider it meaningless today to speak of the impact of "the pill" on migraine.

Beyond pills, today's formulations also include a transdermal patch (OrthoEvra®) and a contraceptive vaginal ring (NuvaRing®). Combined hormonal injections – available in some developing countries – were withdrawn from the US market in 2003.

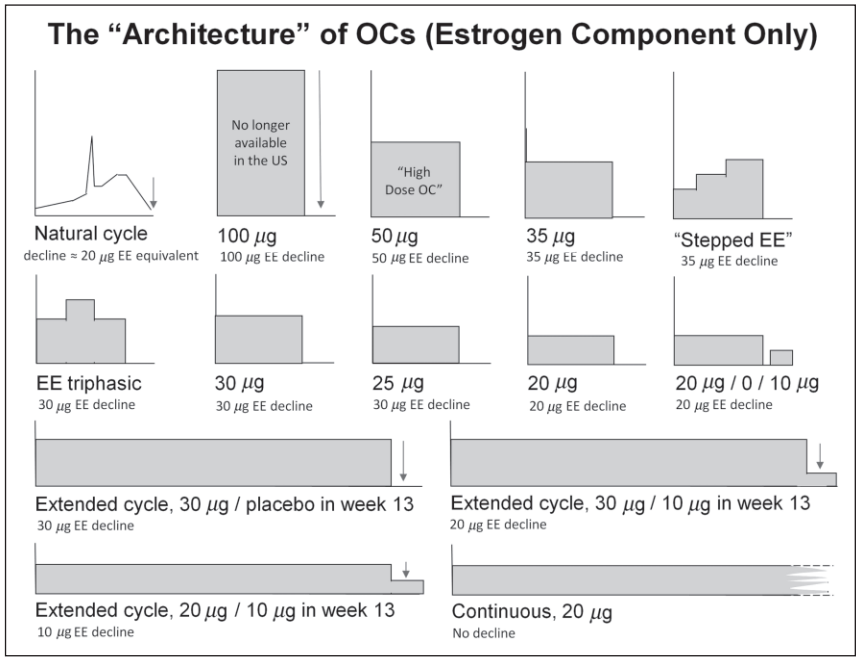

Fig 1.—Illustration of the structure and relative potency of the ethinyl estradiol (EE) content of various oral contraceptive formulations relative to estradiol concentrations in the native menstrual cycle. Declines in estrogen >10 μg EE may be adequate to precipitate MRM in susceptible individuals.

Table 1.—Contraceptive Choices Among US Women Who Practiced Contraception, 2006-2008

Method	# of Users (in Millions)	% of Users
Sterilization	14.2	38.0
Female	10.4	27.1
Male	3.8	9.9
Hormonal contraceptives	13.2	34.7
Oral	10.7	28.0
3-month injectable	1.2	3.2
Vaginal ring	0.9	2.4
Implant, 1-month injectable or patch	0.4	1.1
Condom	6.2	16.1
Intrauterine device	2.1	5.5
Withdrawal	2.0	5.2
Periodic abstinence	0.4	1.1
Other†	0.2	0.4

†Includes emergency contraception, female condom/vaginal pouch, foam, cervical cap, sponge, suppository or insert, jelly or cream, and other methods.
Diaphragm use figures did not meet standards of reliability or precision.

DEMOGRAPHICS OF CHC USE

Migraine disproportionately strikes reproductive-aged women who commonly practice contraception. In the USA, hormonal contraceptives are the most popular reversible method used by over one third of reproductive-aged women[3] (Table 1). This rate is even higher among younger women in whom sterilization – the second most common choice – is less appealing. Of the 2.9 million teenage women in the US practicing contraception, the majority – 54% – rely on the pill.[3] In this same culture, 43% of women will suffer from migraine headaches at some point in their lives.[4]

Furthermore, because migraine is comorbid with several gynecologic conditions that are customarily managed with CHCs, the likelihood of their use in this population is enhanced.

NON-CONTRACEPTIVE BENEFITS OF CHCs

A risk/benefit analysis of CHCs depends on who is looking. Neurologists may focus on their impact on migraine and stroke risk, whereas a gynecologist might be more concerned with effects on endometriosis and ovarian cancer risk. Yet, a patient's key concerns may be on contraceptive efficacy and acne.

Benefits of CHCs are evidence-based, established, and commonly applied in clinical practice. Compared with never users, CHC use for at least 5 years is associated with a 40% reduction in risk of ovarian cancer, a protective effect that increases to 80% risk reduction after 10 years of use.[5] Similarly, CHC use reduces the risk of endometrial cancer by 50% with 5 years of use and by 80% after 10 years of use. For both malignancies, the risk reduction persists for at least 20 years.[2]

Additionally, CHCs have been shown to decrease the risk of colorectal cancer and to improve endometriosis, menorrhagia, dysmenorrhea, premenstrual syndrome, anemia, hirsutism, pelvic inflammatory disease, and acne.[6,7] The rate ratio for overall mortality is significantly lower for CHC users than for never users at 0.87 (0.79-0.96).[8]

These are considerations commonly encountered in migraineurs. One study found that two thirds of subjects with MRM had one or more gynecologic comorbidities for which the preferred treatment was a CHC.[9]

Finally, there is the cornerstone issue of MRM, arguably the most common disabling condition encountered in women's health. These attacks have proven to be more painful, of longer duration, and more resistant to therapy than those occurring elsewhere in the cycle.[10,11] Amid reports of hormonal strategies that might potentially prevent these migraines, some headache specialists are revisiting the risk/benefit ratio of CHCs in migraineurs.[9,12,13]

CHCs AS POTENTIAL PREVENTIVES OF MRM: SIDE EFFECTS OF PLACEBO PILLS

It is a curious situation in pharmacology when adverse events associated with *stopping* an active medication are attributed to the drug, but such is the case with OCs. And considering the available information on the effects of estrogen in the central nervous system (CNS),[14-19] there is a relative paucity of data on the acute effects of estrogen *withdrawal* – such as occurs with menses or during the placebo week of OCs.

Sulak et al found that 70% of OC users experienced headache during the placebo week of their pill pack when estrogen is abruptly withdrawn. The peak incidence of these headaches occurred on the third day of the placebo week.[20] Elimination of placebo pills in an OC regimen was associated with improvement in mood scores, headache scores, and pelvic pain compared with the traditional 21/7 cycle, improvements which persisted throughout the year of follow-up on an extended regimen of active pills.[13]

But could some of the more serious side effects of OCs also be at least partially attributable to estrogen withdrawal – to taking placebos? Flow-mediated vasodilation parallels estradiol levels and is minimal just before menses and greatest in the follicular phase.[21] Reports of menstrual angina may be reflective of coronary vasospasm following declines in circulating estrogen concentration.[22,23] Myocardial ischemia is more easily induced when estrogen concentrations decline in the perimenstrual period.[24] This raises the intriguing question of whether the rare cardiovascular adverse events (as opposed to the more common nonischemic "triptan sensations") that have been attributed to triptans might cluster in the menstrual window.

CHCs AS POTENTIAL PREVENTIVES OF MRM: COMMON DENOMINATORS

The target of hormonal preventives is the premenstrual decline in estrogen that appears instrumental in precipitating MRM.[25,26] Successful strategies share a common factor: they eliminate or sufficiently minimize this decline.[27]

Strategies have included subcutaneous insertion of estradiol implants,[28] induction of medical menopause,[29] application of estradiol gels[30-32] or patches,[33] and various strategies employing hormonal contraceptives.[9,12,13,34]

Evidence suggests stable concentrations of estrogen – whether supraphysiological or physiological – have a beneficial impact on MRM.[28,29] A rising concentration, such as occurs in pregnancy, is similarly associated with improvement in migraine.[35] Despite ample reports of migraine accompanying the transition to placebo pills in OC packs, there is no evidence to suggest that the sudden rise in estrogen associated with resumption of active pills precipitates migraine. In fact, examination of the cyclic headache patterns of study subjects reveals a relative lack of headache intensity at this time.[13,20]

CHCs AS POTENTIAL PREVENTIVES OF MRM: TWO HYPOTHESES

These findings have prompted 2 different hypotheses. The "residual threshold" hypothesis argues that a minimum serum estradiol concentration (proposed to be 60-80 pg/mL) must remain after its premenstrual decline to prevent MRM.[15] An alternative explanation is the "magnitude of decline" hypothesis that there is a critical magnitude of decline in estrogen that can be tolerated without triggering an attack (proposed to approximate ≤10 μg EE).[36] This debate can be tested clinically with two commercially available products, Seasonique® and LoSeasonique®. If both products prevent MRM, the residual threshold hypothesis is supported because each has identical 10 μg EE pills in lieu of placebos in the withdrawal bleed week, pills that confer estradiol concentrations of at least 60-80 pg/mL. If, however, MRM persists on Seasonique® but not on LoSeasonique®, the magnitude of decline explanation holds because despite identical 10 μg EE pills in the withdrawal bleed week, Seasonique® produces a 20 μg decline with transition to those pills, whereas LoSeasonique® limits the decline to 10 μg.

No randomized clinical trials prove either theory, but a retrospective study lends support to the latter theory.[9] Hormonal strategies developed in accordance with the magnitude of decline hypothesis eliminated MRM in 77% of the intent to treat population and 81% of protocol adherers.[9]

Just as eliminating/minimizing the magnitude of the premenstrual estrogen decline would be expected to benefit MRM, increasing the magnitude of that decline should worsen it. This was demonstrated in an often-quoted yet frequently misinterpreted study that concluded that "low dose" OCs had a detrimental effect on migraine.[37] The pill used in that study contained 50 μg of EE. Although in 1977, this was considered low dose, it is today's definition of a high-dose pill. Compared with the natural menstrual cycle, this pill at least doubles the magnitude of the

premenstrual decline in estrogen (Fig. 1) and would thus be *expected* to worsen MRM as it did in 70% of subjects in that study. Similarly, most OC formulations available in the 1990s produced declines of at least 30 μg of EE with the transition to placebo pills, exceeding the magnitude of decline that triggers MRM in susceptible individuals. Because the timing of the attacks is not reported, it is possible that other factors may have contributed to the worsening of migraine with these high-dose pills.

To transform CHCs into MRM preventives, researchers have experimented with extended-cycle dosing of commercially available products[13] or have used supplemental estrogen in conjunction with CHCs to limit the decline in estrogen that accompanies withdrawal bleeds.[9,12,34] In a small, open-label study, women took an OC containing 20 μg EE for 21 days, followed by 0.9 mg of conjugated equine estrogens for 7 days (in lieu of the placebo pills). All patients reported a reduction in migraine frequency of at least 50%, with a mean reduction of 78%.[12]

Extended regimens that forego monthly withdrawal bleeds can afford migraineurs an indefinite reprieve from MRM. Options include Lybrel® or "extended dosing" of traditional monophasic products. Sulak et al showed that extended dosing of Yasmin®, an OC containing 30 μg EE and 3 mg of drospirenone, eliminated menstrual headaches in a cohort of 102 women treated continuously for 6 months.[13] If withdrawal bleeds are planned, supplemental estrogen can be added during that week to assure that the decline in EE does not exceed 10 μg.

STROKE RISK RELATED TO ESTROGEN: DOSE MATTERS

Shortly after their release, adverse events attributable to high-dose OCs began to surface, although serious events were relatively rare. In response, women with histories of deep venous thrombosis, myocardial infarction, stroke, or hypertension were no longer considered candidates, and the hormonal content of pills was reduced. With each reduction in estrogen, a measurable decrease was observed in venous thrombosis and pulmonary embolism.[38]

Stroke risk with OCs was highlighted in a landmark article in 1975. However, the authors were unable to correlate the risk with estrogen dose because 23 of the 25 women with thrombotic stroke on the mestranol-containing formulation took 100 μg pills, and all 20 taking the EE formulation took 50 μg pills.[39] Today's interpretation of this study is that *high dose* OCs confer a relative risk of 4.4 for ischemic stroke. The World Health Organization (WHO) study also reported an increased risk of stroke with high dose OCs but not with OCs containing less than 50 μg EE.[40]

Stratifying risk by estrogen content, a Danish 5-year case-control study looked at the risk of stroke in OCs[41] (Table 2). It found that risk varied directly with the estrogen content, from no increased risk with the lowest dose pills to an odds ratio of 4.7 with high-dose pills.

Although relatively recent international studies[40] continue to show a small but increased risk, it has been more than 3 decades since a US study has found an increased risk of stroke with OCs. A large US study[43] reviewing 3.6 million women-years of use found no increased risk (odds ratio [OR] = 0.96) with current low-dose OCs, nor did a pooled analysis of US studies.[44] The discrepancy between US and international studies is possibly explained by the strong relative contraindication in the USA to the use of OCs in smokers over the age of 35 and the more prevalent use of high-dose pills in international studies. High-dose pills accounted for the *majority* of stroke cases in the WHO study[40] but were used by only 0.8% of cases and controls in 2 pooled US studies.[44] Similarly, in those US studies, only 17% of cases and controls were smokers on OCs, whereas in the WHO study, 51% of cases and 38% of controls were smokers.

The Oxford-Family Planning Association study was a large prospective population study that monitored health outcomes of various contraceptive methods. A review published at its 30-year mark found that risk of myocardial infarction was not increased by OCs alone but required the co-occurring presence of heavy smoking. The adjusted relative risk of ischemic stroke was 2.9 (1.3-6.7), but the study's authors pointed out that this risk was heavily influenced by the fact that two thirds of the woman-years of exposure to OCs was to high-dose pills that, by the time of publication, had become relatively obsolete.[49]

Table 2.—Stroke Risk with Oral Contraceptives Varies with Estrogen Dose

Year	Author	Sample Size	Setting	µg EE	OC use [OR (95% CI)]
1975	Collaborative Group for the Study of Stroke in Young Women[39]	430 cases 151 controls	USA	≥50	4.9 (2.9-8.3)
1996	Carolei et al[42]	308 cases 591 controls	Italy	All doses	NS
1996	Petitti et al[43]	295 cases 774 controls	USA	<50	NS
1996	WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception[40]	697 cases 1962 controls	Europe	≥50	5.3 (2.6-11.0)
				<50	NS
1998	Schwartz et al[44]	175 cases 191 controls	USA	<50	NS
1999	Chang et al[45]	291 cases 736 controls	Europe	≥50	8.0 (1.9-32.6)
				<50	NS
2002	Kemmeren et al[46]	203 cases 925 controls	Netherlands	All doses	2.3 (1.6-3.3)
2002	Lidegaard and Kreiner[41]	626 cases 4054 controls	Denmark	50	4.5 (2.6-7.7)
				30-40	1.6 (1.3-2.0)
				20	NS
2003	Siritho et al[47]	234 cases 234 controls	Australia	All doses	NS
2004	Nightingale and Farmer[48]	190 cases 1129 controls	UK	<50	2.3 (1.2-4.6)

CI = confidence interval; EE = ethinyl estradiol; NS = not significant; OC = oral contraceptive; OR = odds ratio; WHO = World Health Organization.

Underlying this comparative safety of lower dose pills, data has shown that OCs containing 20 µg EE have little or no procoagulatory effect.[50] Slightly higher formulations with 30-35 µg EE do activate procoagulation parameters, but these effects – *in non-smokers* – are counterbalanced by anticoagulant activity from the fibrinolytic system, a compensation that does not occur in smokers.[50]

After reviewing 779 articles from 1970 to 2000, addressing the risk of stroke with OCs, Chan et al[51] concluded that "results cast doubt on a true association between low-dose OCs and stroke because of the low absolute magnitude of the ORs, the severe methodological limitations, and the ORs of less than 1.0 in the cohort studies. The association is tenuous at best and perhaps nonexistent."

STROKE RISK RELATED TO PROGESTIN "GENERATION"

Debate continues over the relative safety of one "generation" of progestin over another, and compounding the confusion is the fact that these terms are inconsistently defined in the literature (Table 3).

First generation progestins are estranes, including norethynodrel, norethindrone, norethindrone acetate, ethynodiol diacetate, lynestrenol, norethisterone, and norethisterone acetate. Yet, in some references, the term "first generation" refers not to the progestin component but to a high-dose CHC. Caution is advised when interpreting studies that use this definition.

Table 3.—Inconsistent Definitions of Progestin "Generations" May Underlie Different Study Results

- In Kemmeren et al's[46] study, *all pills* contained 30 µg EE
- Generation definition:
  - First: Lynestrenol or norethindrone
  - Second: Norgestrel or levonorgestrel
  - Third: Desogestrel or gestodene
  - Other: Norgestimate or cyproterone acetate
- In Heinemann et al's[52] study, EE content of pills varied
- Generation definition:
  - First: High-dose pills (≥50 µg EE)
  - Second: Low-dose pills (≤50 µg EE) with progestins "other than third generation"
  - Third: Low-dose pills with either desogestrel or gestodene

EE = ethinyl estradiol.

Table 4.—Risk of Stroke by Progestin "Generation" of Oral Contraceptive

Study	Sample Size	Setting	COC Type	OR
WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception (1996)[40]	697 cases 1962 controls	21 centers in Africa, Asia, Europe & Latin America	First Second Third	6.0 (1.4-24.9) NS NS
Heinemann et al (1997)[52]	220 cases 775 controls	16 centers in Western Europe	First Second Third Third vs Second	4.4 (2.0-9.9) 3.4 (2.1-5.5) 3.9 (2.3-6.6) NS
Poulter et al (1999)[56]	122 cases 191 controls	21 centers in Africa, Asia, Europe & Latin America	Second Third	2.7 (1.8-4.1) NS
Kemmeren et al (2002)[46]	203 cases 925 controls	9 centers in the Netherlands	First Second Third Third vs Second	NS 2.4 (1.6-3.7) 2.0 (1.2-3.5) NS
Lidegaard and Kreiner (2002)[41]	626 cases 4054 controls	Denmark	First Second Third Third vs Second	4.5 (2.6-7.7) 2.2 (1.6-3.0) NS NS

COC = combined oral contraceptive; NS = not significant; OR = odds ratio.

Levonorgestrel, a more potent progestin, was developed about 1970. Along with its parent compound norgestrel, it is referred to as a "second generation" progestin.

Third-generation progestins, the gonanes, were developed in the 1990s to reduce the androgenic and metabolic side effects that plagued earlier agents. They include desogestrel, gestodene, and norgestimate. With minimal impact on blood glucose levels, plasma insulin concentrations, and lipid profile, third-generation pills are suitable for use in women with lipid disorders or diabetes. They also resolve or reduce acne and hirsutism, and do not adversely impact weight or blood pressure.[53]

Fourth-generation progestins include drospirenone, dienogest, nestorone, nomegestrol acetate, and trimegestone. Other progestins include chlormadinone acetate, cyproterone acetate, and tanaproget, a non-steroidal progestogen.

Reports have suggested an increased risk of venous thrombosis with third-generation OCs.[54] However, as studies emerge, prescribing habits are altered, which in turn influence results of subsequent studies. Additionally, because these pills have a beneficial effect on lipids, blood sugar, and weight, they may be offered to patients at greater risk of certain adverse events. Furthermore, these studies have been criticized for not adequately accounting for the effect of recent initiation of OCs; thrombotic risk is prominently influenced by inherited procoagulopathies, resulting in substantially higher risk in the first year of therapy.[55]

Best evidence continues to suggest that the increased risk of thrombosis in OC users is a class effect, dependent on the estrogen dose, and duration of use, and is independent of the progestin involved[46,55] (Table 4).

STROKE RISK RELATED TO MIGRAINE AURA: FREQUENCY MATTERS

Use of OCs in women whose migraines are accompanied by aura remains controversial based on good evidence that aura increases stroke risk[57] and good evidence that high-dose OCs increase stroke risk.[39]

A cohort study encompassing over 470,000 person-years with a median follow-up of 26 years found that while migraine without aura (MwoA) conferred no increased all-cause mortality risk, migraine with aura (MwA) did.[58]

The longitudinal Women's Health Study analyzed data from 27,798 women over the age of 45 and found that MwA conferred an increased risk of cardiovascular disease that varied directly with aura frequency.[59] Women whose aura frequency was less than once a month had a 2-fold increased risk of major cardiovascular disease compared with women without migraine. This risk rose to more than 4-fold when aura frequency exceeded once a week. Similarly, an analysis of the WHO study of stroke in young women found that the adjusted risk of ischemic stroke was significantly and directly associated with aura frequency.[57]

The pathophysiology of this increased stroke risk related to migraine aura is unknown and is likely complex, but potential explanations include a causal relationship via changes induced during spreading cortical depression, shared genetic predispositions, or common underlying comorbidities such as patent foramen ovale[60-63]

SHOULD CHCs BE CONTRAINDICATED IN MWA?

Higher concentrations of estrogen are associated with increased aura frequency; conversely, low estrogen concentrations, such as the environment of menses, are less likely to be associated with aura.[64] Today, however, some CHCs inhibit ovulation with mid-physiological doses of estrogen, resulting in *lower* peak concentrations than those produced in the natural menstrual cycle.

A recent pilot study[34] provided a preliminary look at the effect of one of these products on migraine aura. A retrospective database review of 830 women seeking treatment at a headache specialty clinic identified 28 women with MwA, as well as intractable MRM, who had been prescribed therapy with extended-cycle dosing of NuvaRing®. This ultra-low-dose parenteral CHC releases only 15 μg EE/24 hours. Therapy was associated with a reduction in aura frequency from 3.5 auras per month at baseline to 0.6 auras per month after a mean follow-up of 8 months. No subject experienced an increase in aura frequency, and MRM was eliminated in 91.3% of women.[34]

EXPLORING AMERICAN COLLEGE OF OBSTETRICS AND GYNECOLOGY'S CONCERNS

In 2006, a consensus statement of the American College of Obstetrics and Gynecology (ACOG) recommended against use of combined OCs in women with migraine and focal neurologic deficits. They cited three reasons:[65]

1. Concerns remain that *all* women with migraines are at increased risk of stroke if they take OCs.
2. A pooled analysis of two large US population-based case-control studies identified a statistically significant 2-fold increased risk of ischemic stroke among current users of OCs who reported migraine compared with women with migraines who did not use OCs.
3. A large Danish population-based case-control study found that among women with a history of migraine, the risk of stroke was elevated approximately 3-fold.

Some of the concerns raised were:

1. Are all women with migraine at increased risk of stroke with OCs?

   There has been a concern for decades that if the stroke risk of OCs was combined with the stroke risk of migraine, the resultant hazards ratio would be unacceptably high. Evidence for this remains elusive. In the 1975 article that reported a relative risk of 4.4 with high-dose OCs, the risk in *migraineurs* taking those pills was not significantly different at 4.6.[39] More recently, a population-based case-control study compared 386 reproductive-aged women who had suffered a first ischemic stroke with 614 controls. Subjects were classified as having no migraine, probable migraine without visual aura, or probable migraine with visual aura (PMVA). Although PMVA, *in combination with smoking*, was a significant risk factor for stroke (and that risk was synergistically increased by the addition of OC use), there was no increased risk for women with PMVA who used OCs but did not smoke.[66]

A recent meta-analysis[67] reviewed 14 studies to determine the relationship between migraine and risk of ischemic stroke. They reported significant relative risks of 2.27 for women with MwA and 1.83 for those with MwoA, while migraineurs who took OCs had a relative risk of 8.72. A more critical look, however, reveals that only 3 of those 14 studies were conducted in this century, indicating that results reflect older OC formulations. Of the 3 recent studies, one showed no risk associated with OC use in migraineurs,[68] while the other two[48,57] showed more modest risk ratios (1.6 and 2.3, respectively). Furthermore, one of these 2 studies[57] clarified that among stroke cases, the *majority used high-dose pills*. The study's authors concluded that MwA and high frequency of aura were major risk factors for ischemic stroke but "in no case did correction for OC usage significantly alter these odds ratios."[57]

2. A look at the 2-fold increased risk of ischemic stroke in the pooled analysis of 2 large US studies

A pooled analysis of 2 large US population-based case-control studies showed no increased risk of stroke with OC use.[44] Reflecting today's lower doses and current prescribing habits in the US, fewer than 1% of cases and controls used high-dose OCs, and only 17% of OC users were smokers.

In that study, the reported "2-fold increased risk of ischemic stroke" among migraineurs using low-dose OCs was based on only *4 cases*.[44] Raw prevalence of migraine was actually identical in cases and controls – 7.8% vs 7.7%, respectively (4/51 cases and 14/182 controls). Thus, the relative risk of 2.08 was attained only after adjustment for other factors in *4 cases*.

The study's authors urged caution in interpreting these data as "imprecise methods," which differed between the 2 study sites, were used to assign migraine diagnosis. Given the overlapping confidence intervals and the results of formal tests of heterogeneity, the authors' final statement was, "Taken together, no firm conclusions can be drawn. . . ."

3. A look at the 3-fold increased stroke risk in the Danish case-control study

A large Danish population-based case-control study[41] also found no increased risk of stroke with low-dose OCs. Progestin-only pills were used by 0.6% of stroke cases and 0.7% of controls (NS); CHCs containing 20 μg EE were used by 2.9% of cases and 4.0% of controls (NS); 30-40 μg EE pills were used by 24.0% of cases and 23.7% of controls (a difference which was found to be significant only after adjustment for other factors; odds ratio 1.7); but high dose 50 μg EE pills were used by 4.2% of cases and only 1.1% of controls, giving an adjusted odds ratio of 4.7 – similar to the risk associated with high-dose pills since 1975.

The 3-fold increased risk in *migraineurs* using OCs is suspect, however, as only 6% of *controls* were identified as migraineurs in a population where 19% of women are reported to have migraine[69] (17% of cases were identified as migraineurs). Although it is possible that migraineurs in Denmark were selectively excluded from receiving OCs, a similar study in France[70] found an equal distribution of migraine diagnosis between stroke cases and controls – with both groups actually exceeding the published prevalence of migraine in French women.

INDIVIDUALIZING THERAPY

ACOG further recommended against the use of CHCs in migraineurs – with or without aura – over the age of 35.[65] For comparison, in the same position paper, ACOG only recommended "individualizing" that decision in women with hypertension, a condition that increases stroke risk to a similar or greater degree as migraine while highlighting the need to consider noncontraceptive benefits of CHCs in the deliberation.

Familial thrombophilic syndromes confer an increased risk of venous thromboembolism with CHC use.[71] Approximately 5% of CHC candidates in the USA have factor V Leiden mutation, yet most will never experience venous thromboembolism even with CHC use. Screening more than one million women for this mutation would prevent, at most, 2 CHC-associated deaths.[72]

CONCLUSION

In summary, as CHCs evolve, their risk/benefit analysis continuously shifts. Accumulating evidence supports a role for CHCs in the prevention of MRM, while their risk declines as novel formulations replace historical predecessors. Migraine is a risk factor for stroke, but there is no evidence to suggest that the addition of low-dose CHCs alters that risk in non-smoking, normotensive users. The bulk of migraine's increased stroke risk is attributable to MwA, and that risk is directly proportional to aura frequency. A selected few CHCs now provide lower peak estrogen environments than the native menstrual cycle, and preliminary evidence suggests that aura frequency may decrease with their use. Whether a reduction in aura frequency will confer a reduction in stroke risk remains to be seen. With this shift in risk/benefit analysis, it is time to reconsider the role of CHCs in migraine.

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