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Research Submission

The Impact of Extended-Cycle Vaginal Ring Contraception on Migraine Aura: A Retrospective Case Series

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Objective.—To determine whether extended-cycle dosing of an ultralow dose vaginal ring contraceptive decreases frequency of migraine aura and prevents menstrual related migraine (MRM).

Background.—Many women are denied therapy with combined hormonal contraceptives due to published guidelines that recommend against their use in migraine with aura (MwA). The concern is that these products might further elevate the risk of ischemic stroke that accompanies aura. Stroke risk has been reported to vary directly with aura frequency, and aura frequency in turn has been shown to have a direct relationship to estrogen concentration. With the evolution of increasingly lower dosed combined hormonal contraceptives, we now have formulations that – provided that ovulation is inhibited – result in lower peak levels of estrogen than the concentrations attained during the native menstrual cycle. These formulations would thus be expected to result in a lower frequency of migraine aura. Furthermore, as extended-cycle therapy eliminates monthly estrogen withdrawals, this therapy would likewise be expected to prevent MRM.

Methods.—This pilot study is an institutional review board-approved retrospective database review. We queried our database of 830 women seen in a subspecialty menstrual migraine clinic to identify women who met all inclusion criteria: (1) current history of MwA; (2) confirmed diagnosis of MRM; and (3) treatment with extended-cycle dosing of a transvaginal ring contraceptive containing 0.120 mg etonogestrel/15 μg ethinyl estradiol. Standardized calendars that specifically document bleeding patterns, headache details, and occurrence of aura are required of all patients in this clinic.

Results.—Twenty-eight women met study criteria, none of whom were smokers. Of these, 5 discontinued use of etonogestrel/ethinyl estradiol within the first month, leaving 23 evaluable subjects. At baseline, subjects averaged 3.23 migraine auras/month (range: 0.1-12). With extended dosing of the vaginal ring contraceptive, median frequency was reduced to 0.23 auras per month following treatment after a mean observation of 7.8 months ($P < .0005$). No subject reported an increase in aura frequency. On this regimen, MRM was eliminated in 91.3% of the evaluable subjects.

Conclusion.—In this sample of women with both MwA and MRM, use of an extended-cycle vaginal ring contraceptive was associated with a reduced frequency of migraine aura and with resolution of MRM. This cannot be extrapolated to suggest that stroke risk in MwA will be similarly reduced. Studies to evaluate this relationship are warranted.

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

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OBJECTIVE

Migraine with aura (MwA) confers an increased risk of stroke,[1,2] and studies suggest that risk varies directly with the frequency of aura.[1,2] Frequency of migraine aura, in turn, appears to be directly related to estrogen concentration: high concentrations are

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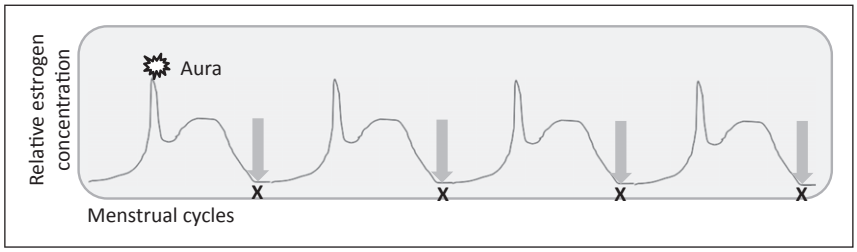

Fig 1.—Migraine aura is more common in high estrogen environments, accounting for its infrequent occurrence with menses. Menstrual related migraine, marked with "X," is associated with the late luteal phase decline in estrogen (arrows) in the 4 cycles depicted.

associated with an increase in aura frequency,[3] while low estrogen environments, such as with menses, are less likely to be accompanied by aura (Fig. 1). Traditionally, combined oral contraceptives (COCs) have been suspected of increasing frequency of aura and worsening menstrual related migraine (MRM). (Fig. 2) (Author's note: In this article, the term MRM will encompass MRM, true menstrual migraine, and estrogen withdrawal migraine that accompanies withdrawal bleeds on a hormonal contraceptive.)

We hypothesize that extended-cycle dosing of an ultralow dose parenteral contraceptive which inhibits ovulation would be associated with a decreased occurrence of migraine aura. This would be achieved via a net reduction in peak estrogen exposure on this contraceptive compared with the estrogen exposure in the native menstrual cycle (Fig. 3). We further hypothesize that eliminating the cyclic declines in estrogen would result in elimination of MRM.

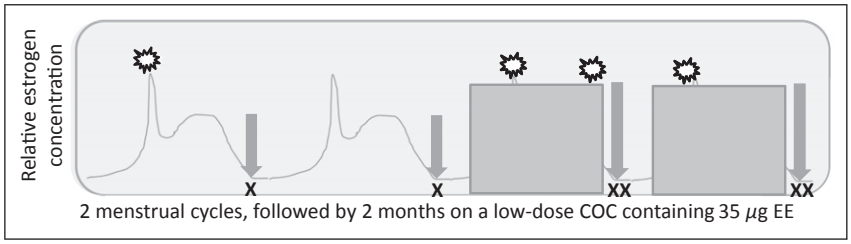

Fig 2.—Use of a typical "low dose" combined oral contraceptive (COC) containing 35 μg ethinyl estradiol (EE) (depicted in the last 2 cycles) increases the magnitude of estrogen withdrawal, which would be expected to worsen menstrual related migraine ("XX"). These COCs match or exceed the peak estrogen concentrations of the natural cycle and extend that higher concentration over 3 weeks. This would be expected to increase aura frequency (and potentially stroke risk).

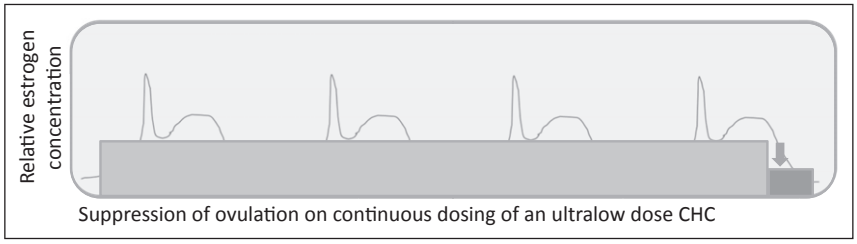

Fig 3.—Extended use of a 15 μg ethinyl estradiol ring contraceptive reduces peak exposure to estrogen by eliminating the natural ovulatory and luteal peaks, while replacing those levels with a continuous but lower concentration. This would be expected to decrease aura frequency. Addition of 0.075 mg of transdermal 17β estradiol in the withdrawal bleed week (far right) limits the magnitude of the decline in estrogen and may thus prevent menstrual related migraine. CHC = combined hormonal contraceptive.

BACKGROUND

There are diverse progestin-only contraceptive choices for women who have MwA, some of which may modestly reduce the overall frequency of migraine,[3] but none has demonstrated a beneficial effect on MRM. Furthermore, progestin-only products (POPs) have experienced historically low acceptance, in part due to higher pregnancy rates, acne, bloating, and considerable breakthrough bleeding.[4]

Today, reports of successful prevention of MRM with combined hormonal contraceptives (CHCs) are engendering renewed discussions of the role of these products in headache practices. Sulak et al[5] reported that extended-cycle dosing of a COC eliminated cyclic intensification of headaches in a cohort of 102 women treated continuously for 6 months. De Leo et al[6] compared the effect on MRM of 2 dosing regimens of the same COC formulation – one with 21 active days and 7 placebo pills, the other with 24 active days and 4 placebo pills. Compared with the first formulation, both duration and intensity of menstrual migraine (MM) was significantly reduced on the regimen with fewer placebo days. Calhoun and Ford[7] found that hormonal strategies were effective in eliminating MRM in 73% of the intent to treat population and in 81% of the per protocol regimen. One of the strategies used in that study was extended dosing of CHCs, in which the active product is continued beyond the traditional 28-day cycle, eliminating gaps in estrogen and withdrawal bleeds for 3 months or more at a time.

Regardless of any potential enthusiasm for using CHCs to prevent MRM, their role in MwA has remained highly controversial. This is based on good evidence from a 1975 study that high-dose COCs – those that contained 50 μg or more of ethinyl estradiol (EE) – increased stroke risk[2] (CHCs containing more than 50 μg EE are no longer available in the US). The concern is that combining this risk with the risk from MwA might prove even more hazardous.

There can be little doubt that MwA increases stroke risk. In the international, hospital-based, case–control World Health Organization study, the adjusted risk of ischemic stroke in young women (20-44) was significantly associated with 3 factors: (1) migraine of more than 12 years' duration odds ratio (OR) 4.61 (1.27-16.8); (2) MwA, OR 8.37 (2.33-30.1); and (3) frequency of MwA attacks greater than 12 times per year, OR 10.4 (2.18-49.4). Overall, the risk of ischemic stroke was directly correlated with increased frequency of migraine aura (trend $P \leq .03$). However, when the authors adjusted for contraceptive use, they found that "*in no case did correction for OC usage significantly alter these odds ratios*."[1]

Similarly, in the longitudinal Women's Health Study, analysis of data from 27,798 women over the age of 45 found that MwA conferred an increased risk of cardiovascular disease that varied directly with aura frequency.[8] Women whose baseline frequency of aura was less than once a month had a 2-fold risk of major cardiovascular disease compared with women without migraine. This risk rose to more than 4-fold when migraine aura occurred at a frequency greater than once a week. These results, while significant, reflect *relative risk*. Absolute risk remains low. In women with MwA, compared with women without headache, the excess absolute 10-year risk of cardiovascular disease mortality (including both heart disease and stroke) at age 50 has been calculated at 0.1%.[9]

Although the evidence against aura is compelling, the case against CHCs may prove less solid, and recently, there has been a call for reconsideration of their role in migraine.[10]

An ultralow dose vaginal ring contraceptive (etonogestrel [E]/EE) releases only 0.120 mg E and 15 μg EE over 24 hours. A randomized pharmacokinetic study compared this ring with a COC containing 30 μg EE. Maximum levels of EE were only 30 percent of those seen with the COC, yet systemic progestogen exposures were comparable with the 2 contraceptives.[11] This product has been found to completely and effectively prevent ovulation, thereby preventing the attendant ovulatory spike in estradiol that represents the highest natural estrogen exposure encountered in healthy nonpregnant women.[11] It also prevents the subsequent sustained estrogen surge of the luteal phase, whose abrupt decline precipitates MRM. Instead, these 2 peaks are replaced with the lower and sustained 15 μg EE concentration that is

continuously released from the E/EE ring. The net effect is that the ring produces a lower peak exposure to estrogen while simultaneously lessening the premenstrual decline that precipitates MRM.

Nevertheless, when used in the traditional regimen whereby the ring is inserted for 3 weeks then removed for one week to allow for a withdrawal bleed, there is an attendant 15-μg decline in EE that accompanies the bleed. Anecdotally, this decline appears to be sufficient to precipitate an estrogen withdrawal migraine in women who experience MRM with their native cycles. In this study, we are examining the effects of extended-cycle dosing of E/EE, in which the intention is to inhibit ovulation, stop withdrawal bleeds, and replace the (higher) native levels of cyclic estrogen with the continuous but lower concentration of estrogen that this particular contraceptive affords. As some studies have suggested that MRM can be prevented by limiting the premenstrual decline of estrogen to the equivalent of 10 μg EE or less, estrogen was added back during any scheduled withdrawal bleeds[7,12] (Fig. 3).

METHODS

The university's institutional review board approved this retrospective database review. We queried our comprehensive electronic database of 830 women who had attended a subspecialty clinic devoted expressly to hormonal issues in women's headaches. The abbreviated version of this outcomes database contains 72 fields. Study personnel first queried it for MwA, next for MRM, and finally for hormonal preventive therapy with E/EE dosed in extended cycle. A headache specialist conferred the diagnoses of MwA and MRM in accordance with International Classification of Headache Disorders, 2nd edition (ICHD-2) criteria.[13]

The diagnosis of MwA for purposes of this study followed strict criteria. Specifically, auras that were atypical in duration (lasting less than 5 minutes or longer than 1 hour) or character (such as visual blurring) were excluded. MRM was defined as outlined in the appendix criteria of ICHD-2, requiring that the migraine predictably occurred within a 5-day window spanning 2 days before the onset of bleeding through the third day of flow. The only deviation from these appendageal criteria related to the stipulation that MRM necessarily exclude attacks accompanied by aura; when subjects reported a consistent history of MRM – confirmed by calendars – and a clear history of true migraine aura, they were deemed to have met inclusion criteria.

All therapy was initiated between March of 2004 and October 2010. Standardized calendars which document menstrual bleeding, headache intensity, and aura are required of all patients in this clinic and are routinely reviewed not only for completion but for internal consistency. We reviewed archived calendars that were available for all subjects. On these calendars, headache intensity was registered on a 4-point scale: 0 = no pain, 1 = mild, 2 = moderate, and 3 = severe. A headache index was calculated by summing the pain intensity for a 28-day period. Bleeding is marked with 1 to 3 red "O" marks indicating spotting, normal flow, or excessively heavy bleeding; and aura is marked with a blue "A" mark.

A menstrual week headache index was calculated by totaling the headache intensity for the menstrual week, which was defined as 7 consecutive days, beginning 2 days before the onset of bleeding. Successful elimination of MRM was determined by meeting the requirement that the menstrual week headache index was no greater than the headache index of the nonmenstrual weeks.

Statistical Analyses.—Analysis was conducted using Statistical Package for the Social Sciences (SPSS version 17.0, SPSS, Inc, Chicago, IL, USA). Wilcoxon signed rank test was conducted to determine whether extended-cycle dosing of an ultralow dose vaginal ring contraceptive decreases frequency of migraine aura. The accepted level of statistical significance was $P < .05$ (2-tailed).

RESULTS

Of the 830 women in the database, 28 met study criteria. When subjects returned for evaluation 6 weeks after initiation of treatment with extended-cycle E/EE, 5 were no longer using the prescribed product. All 5 had discontinued use within the first month (range: 2 days to 4 weeks) – 2 for nausea, 2 for ring expulsion, and one for facial swelling and abdominal pain – leaving 23 evaluable subjects.

All 23 evaluable subjects used extended dosing of E/EE – 8 using it continuously without interruption. The remaining 15 used the ring for 12 consecutive weeks, followed by 1 week of 0.075 mg transdermal 17β estradiol patches to prevent estrogen withdrawal migraine during the scheduled withdrawal bleed. (Interruption of the contraceptive's progestin component results in a withdrawal bleed, regardless of whether estrogen is continued during that week.)

Demographic characteristics of subjects and those who discontinued treatment are in the Table. Subjects had a mean Hit-6[14] score of 63.5 (population norm for episodic migraine = 50; standard deviation = 10. On this standardized, validated inventory, a score above 60 implies a very significant impact of headache on the subject's life.)[14] None of the subjects were smokers. Ten women (43.5 percent) were using hormonal products when seen for their initial consultation at the headache clinic. These products varied in composition:

- 1 COC contained 35 μg EE
- 3 COCs contained 30 μg EE
- 1 COC contained 25 μg EE
- 1 COC contained 20 μg EE
- 1 E/EE transvaginal ring, used with conventional dosing (inserted for 3 weeks/removed for 1 week)
- 1 targeted estrogen therapy (patches used 2 weeks a month: 1 week for attempted prevention of MRM and 1 week for attempted prevention of postovulatory migraine)
- 2 POPs

Discontinuers had a mean Hit-6 score of 61.5. Unlike those who continued on the ring, none of the discontinuers were using hormonal products at baseline. Review of discontinuers' calendars showed no aura occurrence during the brief interval (range: 4 days to 3 weeks) that they were using E/EE.

Wilcoxon signed rank test showed a statistically significant reduction in MwA following hormonal therapy ($Z = -4.58$, $P < .0005$). Median aura frequency was reduced from 3.23 to 0.23 following treatment after a mean observation of 7.8 months (range: 2 to 30 months) (Fig. 4). No subject reported an increase in aura frequency.

Although most subjects did not report a baseline history of aura accompanying their menstrual attacks, 3 of the 28 women (10.7%) did. One experienced scotoma, one had both visual aura and unilateral cheiro-oral numbness (which she reported was less intense with menstrual attacks), and one described fortification spectra.

With this regimen, MRM was eliminated in 91.3% of the evaluable subjects.

DISCUSSION

These results confirm our hypothesis that providing prolonged stabilization of estrogen at a reduced concentration below those of the endogenous peaks of the native menstrual cycle would decrease the frequency of MwA while eliminating MRM.

One POP was found by Nappi et al[15] to offer a much more modest reduction in the frequency of MwA. The authors of that study acknowledged that fluctuations in endogenous estrogen concentrations are known to persist with most POPs due to the lack of inhibition of ovulation that frequently occurs with these methods. The authors further noted that women who attained amenorrhea fared better. This would be expected because failure to inhibit ovulation allows the hormonal precipitants of menstrual migraine to persist unchecked, an explanation that echoes Somerville's observation[16] when he studied continuous progesterone for prevention of menstrual migraine: success was more likely to be attained when amenorrhea was achieved.

The authors urge caution with the interpretation of these results. As reported earlier, Donaghy et al[1] found that the adjusted risk of ischemic stroke in reproductive aged women was highest in those with frequent MwA, defined as an aura frequency of >12 times year (OR = 10.4). Although it might seem logical that a reduction in aura frequency would, in turn, diminish this risk, any such beneficial impact on stroke risk is conjectural and remains to be tested.

Published guidelines – written shortly after E/EE was introduced – still advise against the use of CHCs in MwA due to concern over ischemic stroke. Of note, the guideline authors specifically addressed E/EE in their opening comments, acknowledging that the new product rendered significantly lower estrogen

Table.—Demographics and Aura Characteristics in Subjects Who Continued or Discontinued Therapy

Subject	Age	BMI	Baseline HA Index	F/U HA Index	Resolution of MRM	Gynecologic Comorbidities	Aura	Baseline Auras/Mon	Follow-Up Auras/Mon
Continuers									
1	33	23.3	17	18	Yes	None	Tunnel vision, scotoma ×20-30 minutes	0.4	0.4
2	25	20.7	48	16	Yes	Dysmenorrhea	Cheiro-oral numbness, scotoma	0.4	0.0
3	42	23.0	58	41	Yes	None	L cheiro-oral numbness ×60 minutes before RSL migraine	4.0	0.0
4	38	19.8	28	19	Yes	Dysmenorrhea	Fortification spectra, scotoma	0.1	0.0
5	24	32.0	52	26	Yes	Dysmenorrhea, menometrorrhagia	Wavy lines up to 20 minutes duration	1.0	0.0
6	22	22.5	61	9	Yes	Menorrhagia	Fortification spectra ×30 minutes	12.0	0.1
7	39	24.2	84	63	Yes	Dysmenorrhea	Photopsia ×15 minutes	0.3	0.0
8	21	19.3	43	49	Yes	Dysmenorrhea	Fortification spectra and groups of bull's eyes	11.0	5.5
9	39	23.6	53	26	No	Dysmenorrhea	Tunnel vision ×20 minutes, followed by HA	6.0	0.0
10	27	19.3	21	5	Yes	None	Photopsia 30 minutes before HA	3.0	0.1
11	38	26.7	39	14	Yes	Menorrhagia	Scotoma, cheiro-oral numbness, motor weakness	3.0	1.0
12	55	19.9	54	44	Yes	Perimenopausal symptoms	Scotoma ×30 minutes	0.3	0.0
13	28	28.5	29	20	Yes	Dysmenorrhea	Photopsia before migraine	4.0	0.3
14	42	31.4	51	38	No	Dysmenorrhea	Wavy lines for 30 minutes before HA	1.0	0.5
15	46	25.0	28	31	Yes	None	Fortification spectra	0.1	0.0
16	43	26.5	21	9	Yes	Menorrhagia, dysmenorrhea	Wavy lines ×10 minutes before HA	6.0	0.0
17	22	22.6	27	6	Yes	None	Photopsia ×15-30 minutes	0.5	0.3
18	23	23.1	59	43	Yes	Dysmenorrhea	Wavy lines ×30 minutes, precedes HA	10.0	3.0
19	25	22.6	24	14	Yes	Menorrhagia, dysmenorrhea	Fortification spectra ×10-15 minutes	0.3	0.0
20	26	33.8	58	10	Yes	Dysmenorrhea, PCOD	Unilateral cheiro-oral numbness before HA	4.0	2.0
21	44	37.6	66	67	Yes	None	Dark spots/scotoma for 20 minutes before HA	4.0	0.0
22	19	20.1	47	24	Yes	Dysmenorrhea	Cheiro-oral numbness, scotoma	0.1	0.1
23	25	26.1	37	30	Yes	None	Scotoma ×5-10 minutes before HA	8.0	0.3
	32.4	24.9	43.7	27.0	91.3%		Median aura frequency:	3.2	0.2*
Discontinuers									
24	51	23.3	32.0	34.0	No	Perimenopausal symptoms	Scotoma and fortification spectra	2.3	2.0
25	48	20.7	34.0	53.0	No	None	Tunnel vision, fortification spectra, and strobing	0.4	0.5
26	34	23.0	56.0	58.0	No	Menometrorrhagia, dysmenorrhea	Cheiro-oral numbness	3.5	3.3
27	39	19.8	63.0	28.0	No	Dysmenorrhea	Photopsia × several minutes	0.2	0.2
28	33	32.0	18.0	12.0	No	Ovarian cysts, pelvic pain	C-shaped white light for 20 minutes	1.5	1.5
	41.0	23.8	40.6	37.0	0%		Median aura frequency:	1.5	1.5

Wilcoxon signed rank test ($Z = -4.58$, $P < .0005$) *$P < .0005$.

BMI = body mass index; F/U = follow-up; HA = headache; Mon = month; MRM = menstrual related migraine; PCOD = polycystic ovarian disease; RSL = restless leg syndrome.

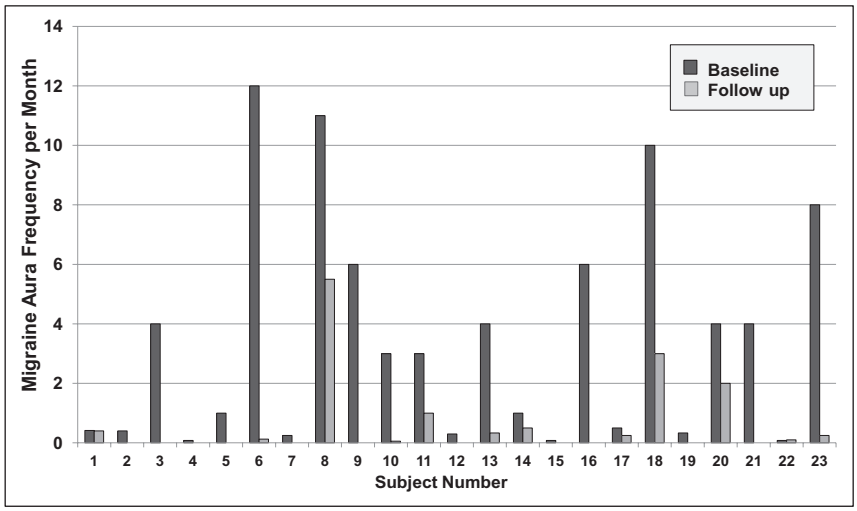

Fig 4.—Extended-cycle dosing of a ring contraceptive containing 15 μg ethinyl estradiol was associated with a reduction in aura frequency. Median aura frequency was reduced post-treatment compared with baseline. Wilcoxon signed rank test (Z = –4.58, *P* < .0005).

concentrations than traditional COCs, yet there were little if any data at that time to guide its use in women with underlying medical conditions such as MwA.[17]

The observation that a few of the subjects experienced aura with menstrual attacks is not in keeping with the ICHD-2 appendageal criteria that cite menstrual attacks of migraine to be migraine without aura. One possible explanation is that although high estrogen environments enhance the likelihood of aura generation, low estrogen environments – such as those associated with menses – are not fully protective. Regardless of the mediating effect of estrogen, other factors appear to be central to the initiation of migraine aura.

Strengths of this study include (1) expert diagnosis according to accepted diagnostic criteria; (2) quantitative, prospective information about both aura and headache frequency and intensity; and (3) utilization of a standardized treatment regimen. Obvious limitations in this pilot study include its small size and its open-label and retrospective design. The study population consisted of women attending a specialty headache clinic who experienced higher than average headache burdens; results may not be generalizable to the larger population of women who experience both MwA and MRM. Clearly, larger prospective studies are warranted.

For proper interpretation of these results, it is important to stress 3 points:

1. Many so-called "low dose" CHCs contain concentrations of estrogen that would be expected to increase aura frequency. Low dose refers to any CHC containing less than 50 μg EE, allowing for a substantial range in estrogen concentrations from supraphysiologic to low physiologic levels. The higher spectrum of these formulations – certainly those containing ≥30 μg EE – not only replicate or exceed the high concentrations of estrogen found in the natural menstrual cycle, but extend those levels for a greater duration (see illustration of this concept in Fig. 2). Results from the E/EE ring study should not be generalized to other CHCs.
2. It is of critical importance for the reduction in aura that the CHC *reliably inhibits ovulation*, and does so while adding back a lower concentration of estrogen than ovulation would have stimulated. Even today's lowest dose CHCs can result in a net *increased* concentration of estrogen if they fail to inhibit ovulation. In these instances, the estrogen of the CHC is added to the estrogen of the native menstrual cycle. Contraceptives do not depend on inhibition of ovulation for contraceptive efficacy; it is merely one of 3 progestin-dependent mecha-

nisms that can achieve that end. Continuous – or extended cycle – estrogen-containing regimens more reliably prevent dominant follicle development and breakthrough ovulation.[18,19] Birtch et al compared 36 healthy young women taking either conventionally dosed or continuous CHCs. A dominant follicle developed in 8 of the women taking conventional CHCs; in a quarter of them, the follicle ovulated. In contrast, dominant follicles developed in none of the women on continuous regimens.

3. Migraineurs treated with this approach should be monitored to assure that their frequency of aura does not increase.

CONCLUSION

In this sample of 23 women with MwA and MRM, extended use of an E/EE vaginal ring contraceptive was associated with a reduced frequency of migraine aura and with resolution of MRM. This cannot be extrapolated to suggest that stroke risk in MwA is similarly reduced. This study is too small and of too short duration to provide definitive answers. But clearly, larger studies to evaluate this relationship are warranted.

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