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Effect of combined oral contraceptives on menstrual migraine frequency and severity: a narrative review

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Abstract

Migraine, a commonly occurring neurological disorder, disproportionately affects women during their reproductive years, and its symptoms are often intensified by hormonal fluctuations. This narrative review examines the impact of hormonal contraceptives, particularly combined oral contraceptives (COCs), on menstrual migraine (MM). This review assessed the impact of COCs on MM through a literature search in PubMed, Google Scholar, Web of Science, and Scopus using keywords like “menstrual migraine”, “hormone therapy”, and “COCs”. The selection criteria were peer-reviewed studies published between 2014 and 2024, written in English, and focused on MM treatment with COCs. Exclusion criteria were duplicates, editorials, irrelevant articles, and non-English studies. The literature reveals inconsistent results, with some studies reporting aggravation of migraine symptoms with COC use, whereas others indicate a decrease in the frequency and severity of attacks, especially with continuous use. Factors affecting these outcomes include patient age, menstrual cycle characteristics, and migraine type. It is crucial to choose contraceptives that suit individual patient profiles, considering the potential for increased migraine frequency or onset of migraine with aura in some women. Further studies are required to establish clear clinical guidelines. It is recommended to create personalized treatment plans that balance the effectiveness of migraine management with the overall health risks.

Keywords

Menstrual migraine, hormone therapy, combined oral contraceptives, migraine with aura

Introduction

Migraine is a prevalent chronic condition that commonly affects women of reproductive age, often starting during adolescence and menarche, when estrogen levels fluctuate [1]. Fluctuating sex hormone levels in the reproductive system, such as a 10–100-fold increase and decrease in estradiol levels during the menstrual cycle and a 1,000-fold increase in estradiol levels during pregnancy, followed by a decline, may contribute to the onset and severity of migraine [2, 3].

Menstrual migraine (MM) is triggered by natural estrogen reduction during the late luteal phase of the menstrual cycle, specifically within the perimenstrual window (two days before and three days after menstruation begins) [4]. Women with migraines may benefit from using systemic hormonal contraceptives, which maintain consistent, relatively low levels of circulating hormones, such as estradiol levels of approximately 25 pg/mL, to reduce the number of MMs, especially those with gynecological issues [5–7].

Combined oral contraceptives (COCs) have been associated with a reduction in MM frequency and severity, particularly when the hormone-free interval is shortened or removed [8, 9]. However, the relationship between COCs and migraines is complex. Some formulations, such as ethinylestradiol and drospirenone, have been shown to improve migraine symptoms [10]. Conversely, COCs can also trigger exogenous hormone-induced headaches and estrogen-withdrawal headaches, the latter typically occurring during hormone-free interval [11]. The type and dosage of hormones in COCs may impact headache incidence, with newer formulations being better tolerated by patients with migraine with aura (MwA) [11]. Progestogen-only pills are considered safe alternatives for women with MwA for whom COCs are contraindicated [12].

Thus, while COCs can benefit some women by managing MMs, they may worsen headaches in others. Selecting the appropriate COC formulation and regimen is crucial, considering individual patient characteristics and migraine patterns, and monitoring its effects on migraine symptoms is essential [8–12]. This review aimed to evaluate the impact of hormonal contraceptives, particularly COCs, on women with MM.

Effect of COCs on women with MM

COCs can have varying impacts on migraines, with 18–50% of women reporting worsened symptoms and 3–35% experiencing improvement [13]. Studies have shown that MwA worsens significantly in patients with COCs. A controlled trial found that only one-third of the patients experienced a headache or migraine risk in the second cycle and one-tenth in the third cycle [14]. Women with MwA are recommended to avoid COCs because of the increased risk of ischemic stroke associated with estrogen in this group [15, 16]. Headaches related to estrogen cessation may occur within 5 days of stopping estradiol intake for more than three weeks.

Hormonal contraceptives may decrease migraine frequency in women according to a German retrospective cohort study conducted at a clinic. Women who used COCs were younger and experienced more migraines related to menstruation, but there were no significant differences in other headache characteristics between the two groups [17].

Dalton [18] found that current and past COCs users experienced more frequent and severe migraine attacks, with 34% and 60% improvement, respectively, upon discontinuation. During the first four days of menstruation, 35% of migraine episodes were recorded in current COCs users, while 32% were recorded in past users and 27% in non-users. COCs users experienced an increase in attacks in the middle of their cycle, specifically on days 13–14. Among 122 patients who had previously used COCs, 60% with a menstrual cycle duration of 27–30 days did not report worsening symptoms while taking COCs. In contrast, only 44% of

those who reported worsening of symptoms had similar cycle durations. Factors contributing to exacerbated migraines due to COCs use include age (particularly > 30 years), number of pregnancies, menstrual cycle duration, migraines during menstruation, improvement in late pregnancy, and onset during pregnancy [18].

A study by De Leo et al. [9] discovered that both 24 days of ethinyl estradiol 20 μg + drospirenone 3 mg and 21 days of ethinyl estradiol 20 μg + drospirenone 3 mg followed by 7 days of placebo reduced the severity and frequency of migraine attacks in 60 women with true MM without aura. However, the 24 active tablets/4 inert tablets per cycle regimen COCs therapy group showed greater improvement.

Nappi et al. [19] evaluated the effectiveness of 26 active tablets/2 inert tablets per cycle regimen of estradiol valerate and dienogest in 32 women with MM. The participants were divided into two groups based on their history of oral contraceptive use. Group 1 comprised women who had never used COCs, while group 2 included women who had discontinued COC use for at least three months before the study due to worsening migraines. By the third cycle, the average number of migraine days decreased from 2.7 to 2.2 ($p < 0.001$) and further reduced to 2.0 ($p < 0.001$) by the sixth cycle. The duration of headache and acute migraine pain also significantly decreased from 44.7 hours to 24.7 hours ($p < 0.001$) and 21.9 hours to 15.4 hours ($p < 0.001$), respectively, by the third cycle. Both groups experienced improvement, with a positive correlation between headache duration and dysmenorrhea days by the third and sixth cycles. Furthermore, the use of analgesics declined from 4.7 tablets to 3.3 tablets ($p < 0.001$) by the third cycle and further reduced to 2.9 tablets by the sixth cycle ($p < 0.001$) [19].

Calhoun [20] conducted a study to investigate the effects of ethinyl estradiol 20 mg and conjugated equine estrogen 0.9 mg on 11 women with either MMs or migraines resulting from discontinuing monthly COCs. During the hormone-free interval, participants experienced uterine bleeding. After one month of active treatment, there was a 50% reduction in headache days and a significant 77.9% decrease in headache severity [20].

A study by LaGuardia et al. [21] evaluated the effectiveness of the estradiol patch for 12 weeks in reducing the frequency and severity of MM. 12-week patch application, followed by a week-long break, and then three weeks of treatment. The outcomes demonstrated that both schedules led to an average of 0.63 migraine days per week during therapy compared to 1.19 days without treatment ($p < 0.001$). Headache frequency also significantly decreased ($p = 0.0002$) [21].

Effect of vaginal ring contraceptives on women with MM

A study by Calhoun et al. [22] used extended vaginal ring contraceptives significantly reduced the median frequency of MwA from 3.23 to 0.23 per month ($p < 0.0005$) over an average of 7.8 months, with no participants reporting increased aura frequency and 91.3% of evaluable subjects experiencing complete cessation of MwA.

Effect of hormonal drugs on women with MM

The use of hormone therapy for MM is increasing globally, particularly with the increase in COC use by women. Hormonal drugs can effectively reduce migraine attacks, leading to recommendations for their use in the treatment of MM [23]. A study by Coffee et al. [8] found that long-term COC use decreased headache severity in 32 women with MwA, as measured by the visual analog scale (1.29 ± 0.10 versus 1.10 ± 0.14, $p = 0.03$). Frovatriptan was more effective than placebo in reducing pain intensity during hormone-free intervals. However, when frovatriptan was withdrawn, there was an increase in pain intensity ($p > 0.01$) despite continued COC use [23].

Estradiol gel in reducing migraine attacks in women with MM

Estradiol gel, a topical form of hormone therapy, is applied to alleviate menopausal symptoms such as hot flushes by delivering estrogen, specifically estradiol, through the skin [24].

de Lignières et al. [25] conducted a randomized, double-blind, placebo-controlled trial on 20 women with MM, administering 1.5 mg estradiol gel transdermally for 7 days. Although the number of episodes decreased, there was no significant reduction in migraine severity. More patients experienced migraine during active therapy than in the placebo group. After discontinuing the gel, the patients experienced migraines for three days. In another trial by Dennerstein et al. [26], 22 women with monthly MMs received a 1.5 mg estradiol gel for 7 days. Although there was no reduction in migraine frequency, active therapy did show a significantly reduced attack severity and analgesics use. MacGregor et al. [27] found that a gel containing 1.5 mg estradiol was more effective than placebo in reducing the number and intensity of migraine attacks in women with MM. However, there was a temporary increase in migraine episodes within the first five days of estradiol administration, which may be due to insufficient dosage or exposure.

Transdermal estradiol in the treatment of MMs

Transdermal estradiol involves administering estrogen via a patch or gel, allowing for direct absorption into the bloodstream and potential side effect reduction [28].

Almén-Christensson et al. [29] conducted a study on 38 women with MM. Women received estradiol patches at a dose of 100 mg/24 h for two weeks before the expected menstruation in three menstrual cycles. However, this treatment did not reduce the frequency or severity of migraine attacks. However, Smits et al. [30] found no significant changes in the frequency, duration, and intensity of migraine attacks following the use of a transdermal estradiol patch for six days during the perimenstrual period compared to a placebo.

Subcutaneous estrogen implants

Subcutaneous estrogen implants are a long-term hormone therapy option, where a small pellet is inserted under the skin to release estrogen steadily over time [6]. While primarily used for menopausal symptom management, these therapies' association with MM is a subject of clinical interest. MM is linked to the menstrual cycle and is often triggered by estrogen level drops.

Magos et al. [31] conducted a retrospective observational study on 24 women with MMs, administering an implant containing 100 mg of estradiol and 5 mg/day of norethisterone for 7 days to induce monthly bleeding. Therapy was administered for an average of 2.5 years. 46% of patients experienced complete regression of their headaches, 37.5% observed a significant decrease in attack frequency, and only one patient (4%) did not show improvement.

Combination with migraine drugs

Studies do not directly investigate the combination of estrogen therapies with migraine medications but provide insights into the role of estrogen in migraine management. Estradiol gel, transdermal estradiol, and subcutaneous estrogen implants offer different delivery methods, which may affect migraine management. Although direct interactions between these therapies and migraine medications remain unexplored, data on estrogen exposure and delivery methods enhance the understanding of hormone-related migraine treatments. Further research is needed to elucidate the effects of these therapies on migraine progression and their interactions with migraine medications [32–36].

Hormone therapy and cardiovascular risk in patients with MM

Studies have shown that patients with migraine are more likely to develop ischemic stroke than those without. Women with migraines using COCs have a significantly increased risk of ischemic stroke, especially MwA [37–45]. An American study conducted between 2006 and 2012 included 25,887 women aged 15–49 who had ischemic stroke. Women with MwA who used COCs had 1.8 times higher odds of ischemic stroke, with a 95% confidence interval (CI) of 1.1–2.9. The odds ratio for women with migraines without aura who did not use COCs was 2.2 (95% CI 1.9–2.7) when compared to women who did not have migraines and did not use COC. Among women with atrial fibrillation, the odds ratio for ischemic stroke was 2.7 (95% CI

1.9–3.7) when not using COCs compared to the reference data. When using COCs, the odds ratio for ischemic stroke was 6.1 (95% CI 3.1–12.1) compared to that in women without migraine who were taking COCs [40].

The use of ethinyl estradiol in COCs can increase the risk of developing venous thromboembolism owing to its ability to stimulate the production of coagulation factors. COCs containing > 50 μg of ethinyl estradiol can also increase the risk of thrombosis when combined with progestogens. Studies have indicated that even at a dose of 10 μg, ethinyl estradiol has a procoagulant effect [46]. A new COC introduced in 2009 contained estradiol valerate instead of ethinyl estradiol, believed to have a reduced procoagulant effect [47]. However, the use of COCs containing ethinyl estradiol and estrogen is not recommended for individuals with atrial fibrillation because of the higher risk of cardiovascular (CV) events [48]. Evaluating all previous migraine episodes and aura attacks is crucial when considering hormonal therapy with COCs for the management of menstrual-related migraines and associated gynecological conditions, particularly in individuals aged 35 years. Summary of the important studies on patients with MM was presented in Table 1.

Stroke risk and COCs

The link between COCs and stroke risk has been extensively investigated. Studies indicate that COC users face a higher risk of ischemic and hemorrhagic strokes than non-users. Andreeva et al. [49] examined how COCs might influence the hemostasis system, and genetic factors like antiphospholipid syndrome, thereby increasing stroke risk. Li et al. [50] reported a significantly higher relative risk of hemorrhagic stroke in Chinese women using low-dose COCs, a risk that persisted even after stopping COC use. Roach et al. [51] conducted a meta-analysis showing a 1.6-fold increase in the risk of myocardial infarction or ischemic stroke among COC users, linking higher estrogen doses to greater risk.

Contradictory findings suggest that the heightened risk of CV diseases, including stroke, may be confined to current COC users. Thorogood and Villard-Mackintosh [52] argued that only current COC users are at an increased risk of CV disease. Kamani et al. [53] noted that while COCs might elevate the risk of certain cancers, the overall cancer odds remain unchanged, and no consistent link has been found between COCs and breast cancer.

Combined use of migraine drugs and COCs

Evaluating the use of migraine medications with COCs requires careful consideration of the potential interactions and contraindications. Although COCs can both positively and negatively affect migraines, some studies have indicated symptom improvement with formulations containing ethinylestradiol and drospirenone [10]. However, COCs are contraindicated for MwA due to an increased risk of ischemic stroke, and caution is advised for migraine without aura, especially those with additional risk factors [11]. Although COCs may exacerbate migraines in some women, they can relieve symptoms in others. The prevalence of migraine among COC users is comparable to that of the general population, with some experiencing worsening symptoms and other improvements [10]. Migraine episodes frequently occur during the hormone-free intervals of COC use [10].

Non-hormonal or progestogen-only contraceptives

Non-hormonal contraceptives are recommended for migraine prevention, as they do not increase the risk of CV events. COCs should be avoided in women with MwA or other conditions. COCs are typically discouraged for women with MwA because estrogen increases the risk of ischemic stroke [15, 16]. Individualized doses and shortened hormone-free intervals can reduce the incidence of MM. A daily dose of 30–50 mcg of ethinyl estradiol can worsen MwA, but a dose of 20 mcg of ethinyl estradiol for 21 days, followed by 0.9 mcg of conjugated equine estrogen for seven days, may reduce the risk of MM by at least 50%. COCs can also reduce MM severity. The decrease in estradiol levels during the later part of the

Table 1. Summary of the studies in patients with MM

Number	Study and year	Participants	Intervention	Route of administration	Duration	Key findings
1.	Nappi et al., 2013 [19]	32 women	Contraceptive pill containing E2V/DNG	Oral	12–24 weeks	Migraine attacks, head pain duration, and severity significantly decreased in the third and sixth cycles of E2V/DNG use compared to baseline ($p < 0.001$ for all). Analgesic use also decreased significantly in the third cycle ($p < 0.001$) and further declined in the sixth cycle ($p < 0.001$). Among women with persistent dysmenorrhea, head pain duration and severity were significantly correlated with the number of dysmenorrhea days in both the third (r = 0.89, $p = 0.000$; r = 0.67, $p = 0.02$) and sixth (r = 0.76, $p = 0.000$; r = 0.62, $p = 0.04$) cycles.
2.	Calhoun 2004 [20]	11 women	Ethinyl estradiol (1–21 days) and conjugated equine estrogens supplementation (22–28 days)	Oral	4 weeks	All patients saw at least a 50% reduction in headache days per cycle, averaging a 77.9% decrease. Among the 11 women, 10 experienced at least a 50% reduction in weighted headache score, with an average decrease of 76.3%.
3.	LaGuardia et al., 2005 [21]	239 women	Norelgestromin/ethinyl estradiol transdermal system	Transdermal	4–12 weeks	Most women in the study experienced delayed menses and fewer mean headache days during the hormone-free interval with extended use of transdermal norelgestromin/ethinyl estradiol than with cyclic use.
4.	Calhoun et al., 2012 [22]	28 women	Etonogestrel/ethinyl estradiol	Transvaginal ring	4–70 weeks	The use of extended vaginal ring contraceptives significantly reduced the median frequency of MwA from 3.23 to 0.23 per month ($p < 0.0005$) over an average of 7.8 months, with no participants reporting increased aura frequency and 91.3% of evaluable subjects experiencing complete cessation of MwA.
5.	Coffee et al., 2014 [8]	32 women	Levonorgestrel and ethinyl estradiol	Oral	21/7 regimen and 168-day extended regimen	Daily headache scores significantly decreased ($p = 0.034$) from an average of 1.29 ± 0.10 in pre-study cycles, then further reduced to 1.10 to 0.14 with extended COCs. Frovatriptan prevented the increase in the headache score observed in the placebo group during hormone-free interval. However, after stopping frovatriptan, the headache scores increased ($p > 0.01$) despite resuming COCs.
6.	de Lignières et al., 2002 [25]	20 women	Estradiol gel	Transdermal	12 weeks	Transdermal estradiol gel significantly reduced the frequency and severity of MM.
7.	De Leo et al., 2011 [9]	60 women	COCs	Oral	12 weeks	COCs led to a reduction in the frequency, severity, and duration of MM.
8.	Almén-Christensson et al., 2011 [29]	38 women	Transdermal 17-β-estradiol vs. placebo	Transdermal	12 weeks	Perimenstrual transdermal 17-β-estradiol significantly reduced MM incidence compared to placebo.

E2V/DNG: estradiol valerate and dienogest; MwA: migraine with aura; COCs: combined oral contraceptives; MM: menstrual migraine

menstrual cycle, similar to stopping the intake of 20 mcg ethinyl estradiol in COCs, may initiate MM. A decrease in estradiol levels, comparable to the discontinuation of 10 mg ethinyl estradiol, can positively affect MM. The volume and speed of the decrease in estrogen levels play a crucial role in triggering an assault during the perimenstrual window.

Ketogenic diet and women with MM

A ketogenic diet may be a helpful preventive therapy for migraines as it can help reduce weight and fat mass [54]. It has also been found to be useful in managing various health conditions such as high cholesterol, epilepsy, CV disease, and type 2 diabetes [55, 56]. The most effective migraine treatment primarily targets the cortical region and may involve the gut microbiota, similar to the ketogenic diet [57]. This diet, which is influenced by factors such as ketone bodies, other dietary components, and reduced simple carbohydrates, has shown promising results in the treatment of migraine [58]. Studies have found that both ketogenic diet and low glycemic index treatments may be effective in preventing migraine and that the addition of medium-chain triglycerides has similar effects to those of a ketogenic diet [23, 59, 60].

Previous studies have examined the prevalence, pathophysiology, and treatment of MM, emphasizing hormonal fluctuations, particularly estrogen withdrawal, as key factors [61, 62]. They also highlighted the impact of a multidisciplinary approach on the quality of life [63, 64]. However, none have addressed ketogenic diet as a treatment option for MMs, rendering a summary of its effects or efficacy impossible. Collectively, these studies underscore the complexity of MMs and the need for further research including dietary interventions [61–66]. Although the ketogenic diet is of interest for neurological disorders, current research does not address its use in MM, necessitating future exploration in this area.

Conclusions

Hormone therapy can benefit patients with MM by lowering estrogen levels and potentially reducing the frequency of migraine. COCs, a hormonal medication type, may decrease migraine frequency but are not suitable for all women. Women with a history of CV disease, smoking, high blood pressure, obesity, diabetes, dyslipidemia, thrombophilia, or genetic predisposition should use progestogen-only contraceptives. Women with MwA, hypertension, a history of thromboembolism, or smoking should avoid COCs because of the increased risk of ischemic stroke and other CV complications. Although external hormonal therapies might address other health concerns, their impact on migraine progression is limited. Personalized treatment plans should be tailored to each patient's specific needs and health status.

Subcutaneous estrogen implants are more effective than other methods for treating MM, suggesting that it should be a primary treatment option. Further research and clinical trials are recommended to validate these findings and understand the mechanisms underlying the increased efficacy.

In summary, although COCs are widely used, their application in women with migraines, particularly those with MwA, requires careful consideration and personalization. The benefits of COCs in managing MM must be weighed against their increased risk of cerebrovascular events. Ongoing research and updated clinical guidelines are essential to optimize contraceptive choices and ensure the safety of women with MM.

The association between COCs and migraines is intricate and varies by individual. Healthcare providers need to weigh the risks and benefits of COC use in women with migraine, considering MwA and other personal risk factors. Although the ketogenic diet has been discussed for various neurological disorders, its relevance in MM remains unexplored. Future studies should investigate this topic and determine the efficacy of a ketogenic diet for treating MMs in women.

Abbreviations

CI: confidence interval

COCs: combined oral contraceptives

CV: cardiovascular

MM: menstrual migraine

MwA: migraine with aura

Declarations

Author contributions

YV, MS, and PJ: Writing—original draft, Writing—review & editing, Conceptualization, Supervision. RG, SA, ST, LHBR, YJ, SPD, and KCM: Conceptualization, Supervision. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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