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REVIEW

Considerations for Contraceptive Use Among Patients with Migraines

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Abstract

Purpose of Review There is an overlap in the populations of patients who suffer from migraine headaches and patients who seek contraception. The purpose of this review is to present recent studies on contraception among patients with migraines and provide clinical recommendations.

Recent Findings Migraine with aura and combined hormonal contraceptive (CHC) use are associated with increased ischemic stroke risk. The use of CHCs in patients with migraine with aura produces a higher risk of ischemic stroke than either factor individually; therefore, CHC is contraindicated in this population by certain guidelines. However, recent studies suggest that oral contraceptive may reduce migraine days, pain scores, and migraine medication use.

Summary Certain guidelines recommend against use of CHCs in patients with migraine with aura. CHC use is acceptable among patient with migraines without aura. In patients with menstrual-related migraines, there may be benefit from continuous use of oral contraceptives. Further studies are needed on migraine and specific formulations of CHC, if the frequency of migraines with aura impacts ischemic stroke risk and the impact of oral and non-oral contraceptives on menstrual headaches.

Keywords Migraine · Contraception · Catamenial

Introduction

Migraine is a leading cause of disability-adjusted life years in women aged 15–49 [1], and there are biological sex disparities between those who experience migraines. The lifetime incidence of migraine for women is 43% compared to men which is 18%, and the 1-year prevalence is nearly 3 times higher in women than in men (17% vs. 6%) [2]. Of patients with migraines, approximately 15 to 33% will experience migraines with auras [3, 4].

As of 2019, 65.3% of female individuals aged 15–49 in the USA were actively using some form of contraception, with oral contraceptive pills (OCPs) making up 14% of those users [5]. There is an overlap in populations having migraines and using contraception, which raises the question of how clinicians can best counsel these patients.

A concern raised when discussing contraceptive use in patients with migraines, particularly in the case of migraines with aura, is increased risk of ischemic stroke affiliated with combined hormonal contraceptives (CHCs) [6••]. The American College of Obstetricians and Gynecologist (ACOG) and Centers Disease Control and Prevention (CDC) United States Medical Eligibility Criteria (USMEC) guidelines state that CHCs may be used in patients with migraines without aura who otherwise are at low risk for thrombosis, but cautions use of CHCs for women who have migraine with aura unless the benefits outweigh the risk (USMEC 3) [7, 8]. This guidance stems from the fact that both CHCs and migraines with aura are independently associated with an increased risk of ischemic stroke; however, the extent to which there is a synergistic effect when they are encountered together is based on limited studies [6••].

The literature exploring contraception and migraines is expanding and more nuanced questions are being investigated, including whether there should be further risk stratification based on frequency of aura and how to appropriately weigh the risks of unintended pregnancy. Contrastingly, there is a growing research studies exploring possible

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benefits that patients with migraines may experience from hormonal contraceptives. The purpose of this review is to present current research and to explore the risks versus benefits of contraceptive use among patients with migraines to help clinicians caring for these patients.

Migraines, CHCs, and Stroke Risk

Migraine Background and Physiology

Migraine is a complex, multifactorial disease characterized by a severe, pulsating, and often unilateral headache, lasting between 4 and 72 h, and the accompaniment of photophobia, phonophobia, and/or digestive symptoms [4]. Migraines are triggered by a stimulus, either internal or external, such as loss of sleep, weather changes, or stress. These triggers set off a cascade of cortical excitability, arterial dilation, and inflammation which trigger the pain impulses of the migraine [9]. Migraines may be present with or without aura, with diagnostic criteria displayed in Table 1 [3, 4, 10]. The most commonly supported hypothesis for the mechanism of aura is cortical spreading depression (CSD), though the origin of CSD is unclear [4].

Hormones may play a role in the pathogenesis of migraine, as evidenced by the relationship between migraine and the menstrual cycle. The luteal phase of the menstrual cycle is a common trigger for migraine [2, 11]. The characteristic steep estrogen drop in the luteal phase is thought to increase blood vessel permeability, leading to greater impact of pro-inflammatory mediators such as prostaglandins, which are elevated threefold during the same time period [11, 12]. Withdrawal from estrogen also contributes to migraine susceptibility by decreasing serotonergic tone and affecting central opioid tonus [11]. One study found that the rate of decline in estrogen levels following the luteal peak was significantly greater in patients with migraine compared to those without migraines [13]. By contrast, higher concentrations of estrogen have been associated with higher aura frequencies in patients who get migraines with aura [14]. Given the distinct interrelated nature of certain migraines with hormonal fluctuations, a subgroup of migraines are classified as menstrual migraines.

Menstrual Migraine

Menstrual migraine, or catamenial migraine, is defined according to criteria set forth by the International Classification of Headache Disorders (ICHD). Pure menstrual migraine (PMM) is defined as a migraine which occurs only on days 1 ± 2 (i.e., days -2 to $+3$) of menstruation in at least 2 of 3 cycles and does not occur at any other point in the cycle [15•]. PMM may occur with either the presence or absence of aura. By contrast, menstrual-related migraine (MRM) is defined as migraine which occurs on days 1 ± 2 of menstruation in at least 2 of 3 cycles as well as at other points in the cycle. Similar to PMM, MRM may occur with or without aura, though both types of menstrual migraine occur almost exclusively without aura [2].

PMM is relatively uncommon, occurring in only 10–20% of people who menstruate [2]. However, migraine at this stage in the cycle is very common. When considering all phases of the menstrual cycle, migraine without aura occurs with the highest incidence during days -2 to $+3$ of menstruation. Further, menstrual migraines are of longer duration, higher severity and disability, higher risk of relapse, and less responsive to treatment than non-menstrual attacks [2].

Migraine and Stroke Risk

The risk of stroke with migraines is serious so that careful investigation of risk factors by clinicians is warranted [2, 11]. While there is extremely mixed data regarding patients with migraine without aura, there is a well-established

Table 1 Diagnostic criteria for migraine with aura

A) At least 2 lifetime attacks fulfilling criteria B and C
B) At least 1 of the following fully reversible aura symptoms:
• Visual, whether positive (i.e., flickering lights, spots) or negative (i.e., loss of vision)
• Sensory, whether positive (i.e., pins and needles) or negative (i.e., numbness)
• Speech and/or language disturbances (i.e., dysphasic speech)
C) At least 3 of the following characteristics:
• ≥ 1 aura symptom spreads gradually over ≥ 5 min
• ≥ 2 aura symptoms occur in succession
• Each individual aura symptom lasts 5–60 min
• ≥ 1 aura symptom is unilateral
• ≥ 1 aura symptom is positive
• Accompanying headache within 60 min
D) Symptoms cannot be attributed to another disorder

increased risk of ischemic stroke among patients with migraine with aura, although the cause is poorly understood [6••, 11]. Interestingly, aura frequency also directly impacts a patient's ischemic stroke risk. Compared to the individual without migraine headaches, the presence of < 1 migraine with aura per month increased ischemic stroke risk twofold, while > 1 migraine with aura per week conferred a fourfold increase in ischemic stroke risk [14].

One possibility is the migraine infarction, which is thought to be produced when the cortical spreading depression causing the aura produces such vasoconstriction that ischemia develops [16]. This can only be diagnosed if the symptoms of the stroke exactly mirror a patient's historical aura symptoms [11].

Migraine with aura is also associated with many other ischemic stroke risk factors. Patent foramen ovale is found in approximately twice as many patients with migraine with aura as in the general population, which can pose increased ischemic stroke risk [16]. Migraine with aura is also associated with vascular risk factors such as increased rates of systemic lupus erythematosus and antiphospholipid syndrome [6••, 11, 16].

CHC Use and Ischemic Stroke Risk

Estrogen-containing medications can increase risk of venous thromboembolic events, and the understanding of the mechanisms behind this phenomenon has advanced in recent years [17]. CHCs lead to an increase in various components of the procoagulant pathway, including fibrinogen, prothrombin, and factors VII, VIII, and X. Additionally, there is a decrease seen in hemostasis inhibitors antithrombin and tissue factor pathway inhibitor, which further increase coagulation risk [17]. These findings are seen regardless of route of administration, meaning CHCs in the form of oral contraceptives, contraceptive ring, and contraceptive patch confer the same risk [17].

The adverse effects of early CHCs became apparent shortly after the release of the first oral contraceptive. In response, prescribing guidelines were updated to advise against their use for patients with risk factors including histories of hypertension, stroke, deep vein thrombosis, and smoking [14]. A critical study published in 1975 demonstrated an increased stroke risk posed by COCs, with an incidence of stroke 4 to 5 times higher in users than nonusers. However, the study did not correlate the risk with the concentration of estrogen. Twenty-three of the 25 patients who suffered from a stroke while taking a mestranol-containing formulation were on a 100-µg dose, and all 20 of the 20 women who experienced a stroke on ethinyl estradiol were taking 50-µg pills. All formulations tested in the study were high doses compared to today's standard of ethinyl estradiol dosing between 10 and 35 µg [10].

Other studies that showed the increased risk of stroke in CHC users rarely stratified risk by hormone dosing, and as the hormone levels in CHCs were reduced with new formulations over the years, decreases in adverse events have been consistently observed across numerous studies [13]. One pooled US study reviewed 3.6 million woman-years and found no increased stroke risk in users of low-dose COCs. While some European studies have continued to find a minimal increase in risk, this difference may be explained by an increased incidence of smoking and higher doses of estrogen used in those studies [14].

CHC Use in Migraine Patients

In a 2017 national-scale case–control study, Champaloux et al. identified first-ever strokes among women aged 15–49 between 2006 and 2012 based on healthcare claims data of a private insurance, ultimately reporting 25,887 ischemic strokes among 33,218,977 females. They sought to investigate the individual and combined associations between migraines, with and without aura, and contraceptive use, with ischemic stroke [6••]. In their study, migraine with aura had an increased OR of ischemic stroke of 2.9 (95% CI, 2.2–3.9). Migraine without aura had a smaller increased OR of ischemic stroke of 2.1 (95% CI, 1.8–2.5). Compared to never- or former-users of CHCs, current CHC-users had an increased OR of 1.3 (95% CI, 1.1–1.6). This data supports previous studies which have shown that migraines and CHC use are independently associated with increased ischemic stroke risk.

They also examined combined effects, creating a reference group who had no diagnosis of migraine and were not using CHCs. The highest increased risk of ischemic stroke was found as a six-fold increased risk in patients with migraine with aura using CHCs (OR 6.1, 95% CI, 3.1–12.1), followed by patients with migraine with aura not using CHCs (OR 2.7, 95% CI, 1.9–3.7). Migraine with and without aura was found to elevate risk when used with CHCs; however, the risk was not significantly different than that found in patients with migraine without aura not using CHCs. This study was notable for its large sample size and statistically significant findings which align well with many prior studies in their identification of the additive effects of migraine with aura and CHCs on ischemic stroke risk [14, 18]. However, their finding of increased risk associated with migraine without aura is less consistently reported and therefore needs further research.

Although studies of this magnitude are helpful in gaining confidence in clinical recommendations, there are still many limitations. Given the timeline of this study, the study population using CHCs were exposed to modern dosing of estrogens, though in previous studies and older reviews, the same assumption cannot be made as easily [10, 13, 14].

Even among lower dosed prescriptions, there are many different formulations of CHCs with a range of estrogen levels and different types of progestin which were not individually compared. Additionally, a limitation of this study and others like it is that in basing data points off diagnostic billing codes, patients are reduced to a binary of having or not having a condition, which does not represent the spectrum of a disease experience. For instance, given the evidence that aura frequency significantly impacts the magnitude of individual ischemic stroke risk, it would be beneficial to understand the frequency of migraines among the individuals who experienced a stroke in the study.

Another limitation is that migraine, both with and without aura, is a highly prevalent disease and is underdiagnosed [19]. This suggests that individuals may be excluded or incorrectly assigned as patients without migraines if they have not sought or have not had access to medical care for a formal migraine diagnosis. Also, patients coded as having migraines may also represent a more severe end of the migraine disease spectrum [6••]. Another consideration is that a prescription for a CHC noted in a patient chart does not equate to consistent use of that CHC. Finally, many studies are not able to control for other risk factors for stroke, such as smoking and hypertension.

Birth Control as Migraine Management

Progestin-Only Methods as Treatment

Some forms of birth control may improve the symptoms of migraine. Progestin-only hormonal contraceptives are safe in patients with migraines [15•]. Since progestin-only pills (POPs) work by suppressing ovulation via inhibiting the production of luteinizing hormone, POPs also decrease fluctuations in estrogen levels and prevent an estrogen peak [10, 12]. The estrogen withdrawal in the menstrual cycle may function as a trigger for migraine.

Previous studies support that POPs may reduce migraine frequency and intensity. In a retrospective, observational study, Merki-Feld et al. found that treatment with POPs was associated with a significant reduction in migraine days, frequency, pain, and use of triptans in women with migraine with and without aura [20]. Fifty-five percent of participants experienced a 25% post-treatment reduction in migraine days, and 60% of participants experienced a 30% post-treatment reduction in pain [21••]. These findings are supported by many observational studies [15•]. However, these studies have been limited by retrospective study designs, lack of control groups, and small sample sizes [12]. In addition, these studies used desogestrel 75 µg that is not availability in the USA.

Merki-Feld et al. also conducted a prospective, nonrandomized controlled study to assess the effect of POPs on migraine frequency, intensity, and use of triptans among patients with migraine who presented for contraceptive counseling [12]. Over the course of the 180-day intervention period, patients using POPs experienced a reduction in migraine frequency, intensity, pain, and use of triptans and other pain medications compared to the control group. This trend was observed in patients with migraine with and without aura. The intervention group additionally experienced an improvement in quality of life, including time spent in leisure activities and fewer missed workdays. The improvement in both menstrual and non-menstrual migraine suggests that POPs may also function through non-hormonal migraine triggers.

POP use is less common due to side effects including unscheduled bleeding [15•, 22]. Further, POPs have shorter half-lives than CHCs and must be taken the same time every day to minimize side effects and to provide moderately effective contraception [10]. Although issues of adherence may be mitigated with the use of long-acting progestin-only birth control, such as Depo-Provera or contraceptive implant, available data surrounding progestin-only methods and migraine only involve oral progestin contraceptive. Information is not currently available regarding the impact of the new POPS containing drospirenone. In addition, there is a dearth of information on non-oral progestin-only contraceptive methods and migraines. Theoretically, the LNG-IUDs may not improve menstrual migraines since these IUDs only minimally inhibit ovulation therefore is not our treatment of choice for patients with menstrual migraines [21••].

Continuous CHC as Treatment in Migraine Without Aura

While contraceptives containing estrogen are contraindicated in patients with migraine with aura, estrogens are considered safe for use in patients with migraine without aura. A prospective study by Merki-Feld et al. found that the highest attack frequency for CHC-users with menstrual migraine occurs between days 3 and 6 of the hormone-free interval (HFI) of the menstrual cycle [23]. The risk of migraine during the HFI was found to be 4 times higher than during the days of CHC (ethinyl estradiol) use. Pain scores and number of migraine days were also significantly higher during the HFI.

The association between the HFI and migraine frequency suggests that departure from the typical 21/7 regimen of CHCs, or continuous strategies, may improve symptoms and decrease the frequency of migraine. Continuous strategies include extended CHC regimens in which the HFI, or placebo week, is eliminated for extended periods, continuous vaginal ring contraceptives, or an estradiol patch [22]. These

methods aim to eliminate or decrease estrogen withdrawal. However, while these strategies might improve MRM, this benefit may only be felt during days of the eliminated placebo periods and have no effect on non-MRM [23].

Morotti et al. conducted a retrospective pilot study analyzing headache charts of female patients with migraines without aura to evaluate the effects of a POP compared to a continuous COC regimen on migraine patterns [22]. Consistent with the findings of other studies, 6 months of POP use led to a significant reduction in migraine days, headache days, pain intensity, and days with pain medication. While a reduction in these measures was also observed in the continuous COC group, the change was only significant for the number of headache days and days with pain medication. The only significant difference in these measures when comparing the 2 groups was in the number of days with pain medication, which was lower in the POP group [22]. Differences were also noted when comparing quality of life, measured using a physical component score (PCS) and a mental health component score (MCS). Both groups had similar qualities of life at baseline. After 6 months, the POP group experienced a significant improvement in both MCS and PCS. This trend was also noted in the continuous COC group, though the improvement was not statistically significant [22].

The findings of the study by Morotti et al. suggest that both progestin-only and continuous COC therapies are effective at improving migraine patterns and quality of life after 6 months of treatment in patients with migraine without aura, though treatment with POP leads to slightly better outcomes [22]. In contrast to CHCs, POPs do not increase vascular risk. Considering the increased vascular risk that migraine alone carries, POPs may offer a safer and more efficacious form of contraception and treatment for female patients with migraines.

Discussion

The use of CHCs in patients with migraine with aura carries a potential increased risk of adverse effects, particularly ischemic stroke. However, there are several considerations that must be discussed to contribute to shared decision-making between clinicians and patients when discussing contraceptive options.

While we focused on migraines and CHCs as risk factors for ischemic stroke thus far, it is important to consider the inherent risks associated with pregnancy. Strokes in pregnancy are responsible for over 12% of maternal deaths, and the risk of stroke associated with pregnancy is 16-fold higher than the risk of stroke associated with CHC use [10, 17]. The risk of ischemic stroke in pregnancy is even higher among patients with migraines [24]. CHCs remain a leading form of preventing unwanted pregnancy and if CHC is discontinued or contraindicated, it is crucial to work with the patient to identify a suitable alternate for their own lifestyle [5]. One estimate suggested that if all OCP users were to switch to male condoms, another widely used but less effective method, there would be approximately 687,000 more unintended pregnancies each year, with an associated 26 additional maternal strokes and 33 maternal deaths [18].

In patients with migraines seeking contraception, it is also notable that the hormonal triggers of migraines are often exacerbated in times of hormonal fluctuation, such as puberty and perimenopause, which are two periods of the reproductive lifespan correlated with unintended pregnancies [14].

Lastly, it is important to actively help patients identify a plan to prevent pregnancy when they present with a history of migraines, as the risk of ischemic stroke affiliated with a CHC needs to weigh against the risk of an unplanned pregnancy. Also, if a patient with migraines with aura is counseled not use CHCs, it is important to spend time reviewing non-hormonal or progestin-only methods.

Additionally, a health equity consideration when approaching counseling in a patient with migraines is the population being served. Migraines are most prevalent in those who are unemployed at 16.6%. In addition, people living below the poverty line have the highest prevalence of migraine at 21.7%. These trends highlight both the vulnerability of the affected population and the disability that migraine causes, hindering patients with migraines' ability to work, which decreases access to treatment and healthcare resources [1]. These statistics also represent a population that is often missed in studies of medical risk, as they are less likely to have received consistent medical care, less likely to have their conditions diagnosed and treated by clinicians, and thus less likely to have diagnoses that are captured in reviews of billing codes.

Another potential gap in care for these patients is clinician comfort diagnosing migraines with aura which may lead to delays in prescribing CHC. A recent study by Verhaak et al. explored the comfort of OB/GYN clinicians diagnosing, managing, and treating patients with migraines [19]. They found that while 20–40% of patients consider their OB/GYN to be their primary care clinician, only 37% of the OB/GYNs surveyed reported having headache or migraine education, yet nearly two-thirds had made the diagnosis of migraine and just over half of them reported regularly asking about headaches on the yearly exam. This data shows that there is a gap in the screening of patients who might seek CHCs or other hormonal contraception for migraines, made more concerning in patients with less frequent access to healthcare appointments. This data also highlights the importance of OB/GYNs becoming comfortable both screening for migraine headaches and delineating between migraines with

and without auras. Further studies are needed on neurologist comfort providing contraception counseling.

Lastly, it is important to acknowledge that differences exist between guidelines used by neurologists and gynecologists, with the former generally taking a more liberal approach [13]. In 2000, a Task Force by the International Headache Society (IHS) provided official recommendations regarding the use of COCs and hormone replacement therapy in patients with migraines. These guidelines indicate no contraindication to use of oral contraceptive in patients with migraine without aura, given they lack other stroke risk factors [25]. For patients with migraine with aura, the guidelines have no specific guidelines against the use of CHC. Rather, they warned of a potential increase in stroke risk but recommended an individualized risk assessment, leaving open the possibility of CHC use. This IHS guidance has not be updated since the 2000, though in our clinical experience, the approach of an individualized risk assessment is reflected in the practices of some neurologists [10, 14, 26].

The OB/GYN community recommends a more cautious approach. Official guidelines by the ACOG, updated in 2016, recommend a similar approach for women with migraine without aura, finding no contraindication to use of CHCs in women with migraine without aura [27]. However, they rate the risk for women with migraine with aura as "unacceptable," recommending complete avoidance of CHCs in this population. In our practice, we tell patients about the difference in the guidance from the OB/GYN and neurology organizations. We assess other risk factors for the ischemic stroke in addition to exploring alternatives of CHCs. We then make a shared contraceptive method decision.

Conclusion

Migraines and contraception counseling is nuanced based on individualized risk. Several of the existing studies used the higher amount of estrogen and did not include migraine frequency. There is a role for continuous contraception use for management of menstrual migraines, but more rigorous research is needed especially for non-oral contraceptive methods. It is important to acknowledge that there is different guidance regarding CHC safety for patients with migraines with aura from the OB/GYN and neurology organizations [8, 25].

Data Availability The data that support the findings of this study are available upon reasonable request.

Compliance with Ethical Standards

Conflict of Interest Dr. Mody is a consultant for Bayer, Cadence Health Inc, is a Organon Nexplanon trainer, has received grant funding from Organon, and is an UpToDate author.

The other authors have no conflict of interest to report.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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