Original research article

Effects of an estrogen-free, desogestrel-containing oral contraceptive in women with migraine with aura: a prospective diary-based pilot study

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Abstract

Background: Migraine with aura (MA) is a contraindication to the use of combined oral contraceptives (COCs) because of the increased risk of ischemic stroke. Progestogen-only contraceptive pill (POP) is a safe alternative to COCs and it is preferable in women with cerebrovascular diseases or risk factors for stroke.

Study Design: Prospective diary-based pilot study. Thirty women with MA (n=15 who have never used COCs and n=15 who had previously used COCs were diagnosed according to the International Headache Society criteria. The observational period lasted 9 months during which women filled in a diary with the clinical characteristics of headache attacks. After a 3-month run-in period, each subject received an estrogen-free desogestrel (DSG) (75 mcg/day)-containing OC (Cerazette®; Schering-Plough, formerly NV Organon, Oss, The Netherlands). Follow-up evaluations were planned at the end of the third and sixth month of treatment.

Results: The number (mean±S.D.) of migraine attacks was significantly reduced both in previous COCs users (from 3.9±1.0 to 2.9±0.8; p<.001) and nonusers (from 3.2±0.9 to 2.6±1.3; p<.02) following 6 months of POP use in comparison with the run-in period. Duration of headache pain did not differ significantly in both groups throughout the study. Interestingly enough, a beneficial POP effect on the duration (mean±S.D.) of visual aura (from 16.3±9.5 to 11.4±5.6 min) and on the total duration (mean±S.D.) of neurological symptoms (from 33.6±23.3 to 18.6±18.0 min) was only significantly reported by previous COCs users (p<.001, for both) by the end of the study period. The POP was well tolerated by each woman and the bleeding pattern was variable with a tendency towards infrequent bleeding.

Conclusions: The present study supports the use of the POP containing desogestrel in a population of women with MA and underlines a positive effect on symptoms of aura, especially in MA sensitive to previous use of COCs.

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Keywords: Progestogen-only pill (POP); Migraine with aura; Desogestrel; Estrogen-free contraception; Headache diary

1. Introduction

The course of migraine with aura (MA) seems to be influenced by female reproductive life events and the role of high estrogenic states has been identified in the onset or exacerbation of MA in women [1,2]. The International Headache Society (IHS) criteria [3] describes MA as a “recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5–20 min and last for less than 60 min. Headache with the features of migraine without aura (MO) usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent.”

There is a general consensus that MA is a contraindication to the use of combined oral contraceptives (COCs) because...
of the increased risk of ischemic stroke [4]. The same is true when aura symptoms appear in COCs users with MO [5–7]. In addition, a clinic-based case-control study reported that the use of COCs worsened migraine in MA more frequently than in MO patients (MA 56.4%; MO 25.3%; OR 3.8; CI 1.6-9.3) [1]. Moreover, in a review of 36 women with MA and 86 women with MO using COCs, eight of the patients who reported a worsening in migraine patterns during the first cycle of COC use developed aura symptoms for the first time, associated with a worsening in pain intensity [8].

In spite of the considerable advances in terms of safety and tolerability of the new hormonal contraceptive formulations, exogenous estrogen use may be significantly associated with cerebrovascular diseases in migraine sufferers, especially under certain clinical conditions, including smoking, hypertension, diabetes, hyperlipidemia and thrombophilia and in women over age 35 years [9–11]. However, some women display great benefits from the prescription of hormonal contraception [12] and the challenge of MA deserves further research to guide daily clinical practice.

The progestogen-only contraception is a safe alternative to COCs and it is preferable in women with cerebrovascular diseases or risk factors for stroke [11,13]. Indeed, the avoidance of an estrogen component has many advantages not only for breastfeeding women but, in particular, for those with complaints associated with the use of COCs [14–16]. The progestogen-only pill (POP) containing desogestrel (DSG) at the daily dose of 75 mcg (Cerazette®; Schering-Plough, formerly NV Organon, Oss, The Netherlands) is available in Italy since 2001 and it has been shown to be a safe and reliable contraceptive method with an efficacy comparable with low-dose COCs [15]. The contraceptive mode of action of the POP containing DSG depends on the suppression of ovulation and the mid-cycle peaks of LH, as well as on effects on cervical mucus, Fallopian tube motility and endometrium [17]. However, irregular bleeding remains a major clinical problem [18] and satisfaction and long-term compliance of POP use seem to be strongly related to the presence of other potential clinical benefits. According to the most recent World Health Organization (WHO) guidelines for contraceptive use [11], there is no restriction on initiation and continuation of POPs for women with MA, but there are no published studies specifically assessing migraine associated with use of progestogen-only preparations.

That being so, in the present study we aimed at prospectively investigating the effect of the POP containing DSG on the course of MA in healthy women requesting hormonal contraception to prevent unwanted pregnancy or because of medical and/or gynecological conditions.

2. Materials and methods

This prospective, diary-based pilot study was carried out at the University Center for Adaptive Disorders and Headache, section of Pavia and at the Women’s Headache Center, Department of Obstetrics and Gynecology of the University of Turin, Italy. The study protocol was approved by the local university Ethical Committees.

Thirty women suffering from MA diagnosed according to the IHS criteria [3] entered the present study after they had signed informed consent. At the first visit, women underwent a general and neurological examination, laboratory testing, a gynecological general history and a structured interview for MA. The majority of women (60%) reported more than 1 MA attack per month during the last 3 months. In 93.3% of the study sample, visual symptoms were present, while sensory symptoms were present in 50% of cases and speech symptoms in 20%. Motor weakness was reported by 13.3% of the women.

The presence of other types of headaches was also recorded (namely, MO and tension-type headache (TTH)). The study sample included women (n=15) who have never used COCs and asked for the possibility to assume hormonal contraception to prevent unwanted pregnancy or because of medical and/or gynecological conditions and a comparable number of women (n=15) who were diagnosed with MA during COCs use and were willing to continue hormonal contraception for personal and/or clinical reasons. Women were using mainly nonsteroidal anti-inflammatory drugs to extinguish migraine attacks and were not using any migraine drug prophylaxis prior entering the study.

The observational period lasted 9 months during which women filled in a diary with the clinical characteristics of headache attacks. The following parameters were monitored: the number of MA attacks, the duration of aura and the duration of headache pain (expressed as min and h, respectively), the severity (expressed as number of hours/attack in which pain intensity was severe and prohibited daily activities; pain intensity was graded hourly on a three-point scale, where 1=mild, does not impair daily activities; 2=moderate, may inhibit, but does not prohibit daily activities; 3=severe, prohibits daily activities), the occurrence of reversible focal neurological symptoms (visual and/or sensory and/or speech symptoms and/or motor weakness expressed as number of episodes), the occurrence of associated phenomena (photophobia, phonophobia, nausea, vomiting, expressed as number of episodes) and analgesic use (number of analgesics/attack), as well as the number of days of spotting or bleeding. The course of other types of headaches was also recorded during the study period.

After a 3-month run-in period during which women were appropriately investigated, each subject received an estrogen-free DSG (75 mcg/day)-containing oral contraception (Cerazette®; Schering-Plough, formerly NV Organon, Oss, The Netherlands), the so-called POP. Follow-up evaluations were planned at the end of the third and sixth month of treatment.

2.1. Statistical analysis

The clinical characteristics of headache attacks were calculated from the diaries over 3 months (after run-in
period, third and sixth month). Details on bleeding profile were reported per month.

The data presented are expressed as mean±S.D. Within- and between-subjects analysis was performed by using Student’s t test or chi-square when appropriate.

3. Results

The main demographic and clinical characteristics of the study sample are reported in Table 1. The only significant difference at baseline between previous COCs users and nonusers was related, as expected, to the onset of MA which mostly occurred after COCs prescription. Indeed, in women who have never used COCs, MA onset occurred at the mean age of 17.6±SD 5.8 years, while in previous COCs users, it was significantly (p<.001) past the second decade of reproductive life (mean 30.9±SD 6.4 years). Onset of MA at menarche was identified only in six non-COCs users. Clinical characteristics of MA attacks collected by a structured interview according to IHS criteria were similar between previous COCs users in comparison to nonusers (data not shown).

3.1. Effect of POP in women with migraine with MA

Two women dropped out, stopping POP use after 4 months (1 previous COCs user because of prolonged bleeding and 1 non-COCs user because of a significant increase in the frequency and intensity of MO). Therefore, the effects of POP use on MA were calculated in 30 women after 3 months and in 28 after 6 months.

POP was well tolerated by each woman and the bleeding pattern was variable with a tendency towards infrequent bleeding. Indeed, the number of spotting days significantly increased (p<.001) during the study period (0.5±1.1 days at the run-in period vs. 5.9±2.1 days after 6 months of POP use), while amenorrhea (more than 3 months) was not achieved in any subject by the end of the study period. No significant relationship was evident between the days with erratic bleeding and the occurrence of MA attacks.

Fig. 1 shows significant effect of POP use on the number of MA attacks, but not on the duration of headache pain in our entire study sample (N=30 women). Indeed, by the end of the study period MA attack were significantly reduced (p<.001) in comparison with the run-in. Moreover, duration of the most reported neurological symptom (visual aura) and total duration of aura were significantly reduced (p<.03 and p<.02, respectively) following 6 months of POP use in comparison with the run-in period. However, Table 2 shows a different effect of POP administration on the course of MA according to the previous use of COCs. The mean number of migraine attacks was significantly reduced both in previous COCs users (p<.001) and nonusers (p<.02) at 6 months in comparison with the run-in period. Duration of headache pain did not differ significantly in both groups throughout the study. It was interesting to observe a different trend with a beneficial effect of POP use on visual and other neurological symptoms of aura only in those women in whom MA onset was related to previous COCs treatment. Indeed, the POP effect on the duration of visual aura and on the total duration of neurological symptoms was only significantly reported by previous COCs users (p<.001, for both) by the end of the study period.

Analgesic consumption was reduced by the end of the study period in both groups, without reaching statistical significance. In addition, we did not find any other significant difference in the clinical characteristics of headache attacks, as well as in the bleeding profile between previous COCs users and nonusers throughout the course of the study period. However, it is worth to mention that vomiting was reduced in more than half of the cases (from 22.5% to 10%), while nausea was only slightly affected by POP use (from 70% to 62.5%) by the end of the study. Finally, we observed a nonsignificant trend toward a reduction of episodes of MO (in two previous COCs users and in one nonuser) and an increase of TTH attacks (in one previous COCs user and in 1 nonuser).

Table 1

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics of the study sample</th>
<th>No previous COCs use (n=15)</th>
<th>Yes previous COCs use (n=15)</th>
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<tr>
<td>Age (years) (mean±S.D.)</td>
<td>30.6±5.4</td>
<td>31.5±6.5</td>
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<td>Married [n (%)]</td>
<td>8 (53.3)</td>
<td>8 (53.3)</td>
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<td>Education &gt;8 years [n (%)]</td>
<td>15 (100)</td>
<td>14 (93.3)</td>
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<tr>
<td>Migraine in relatives [n (%)]</td>
<td>10 (66.6)</td>
<td>11 (73.3)</td>
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<tr>
<td>Age of MA onset (years) [mean±S.D.]</td>
<td>17.6±5.8</td>
<td>30.9±6.4**</td>
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<tr>
<td>Onset of MA at menarche [n (%)]</td>
<td>6 (40.0)</td>
<td>0 (0.0)*</td>
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<td>Onset of MA with pregnancy [n (%)]</td>
<td>2 (13.3)</td>
<td>2 (13.3)</td>
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<td>Other types of headache [n (%)]</td>
<td>5 (33.3)</td>
<td>7 (46.6)</td>
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* p<.006.
** p<.001.

4. Discussion

The present prospective diary-based pilot study showed that 6 months of POP use significantly reduced the number of MA attacks and duration of visual and total aura in our entire study sample, being highly tolerated by women. Interestingly enough, the beneficial effect of POP use on visual and other neurological symptoms of aura was significantly present only in those women in whom MA onset was related to previous COCs treatment. Our results are the first to confirm the belief that POP containing 75 mcg/day DSG can be safely used, at least for a short period of time, in a clinical population of women with MA wishing to use hormonal contraception. Indeed, there is no
evidence that use of POPs is associated with an increased risk of ischemic stroke [19-23]. Long-term follow-up is, however, needed to further corroborate the safety profile of such a POP in MA, an established risk factor for cardiovascular diseases and ischemic lesions of the brain [24,25].

It has been difficult over the years to identify a unifying pathophysiological explanation linking MA to underlying hereditary or acquired cerebrovascular disorder. Genetic and epidemiological evidence suggest that changes in blood vessels, hypoperfusion disorders, and microembolization can cause neurovascular dysfunction and evoke cortical spreading depression, an event that is widely thought to underlie aura symptoms, which are transient and without enduring tissue damage [26]. Such electrophysiological phenomenon is modulated by estrogen which may affect neuronal excitability [27]. A continuum of vascular complications may be present in a subset of vulnerable patients carrying a higher risk of endothelial dysfunction and altered hemostasis, which can be amplified by the use of COCs [28]. Indeed, our results showing a significant older age of first onset in women with MA related to previous COCs treatment suggest that exogenous estrogen use may promote the clinical expression of aura in sensitive subjects due to genetic, vascular, and environmental risk factors.

Research suggests that aura may be more likely to affect women with underlying coagulation disorders [28]. Platelet activation and aggregation may explain the development of aura when starting COCs, as well as an impairment of the serotonergic system (5-HT), a crucial target of estrogens within the nervous system [29]. Indeed, platelets from patients with severe MA exhibited increased aggregation to 5-HT, and in women who developed MA following the use of COCs, increased platelet aggregation to 5-HT has been documented [30]. Moreover, in a case of a woman who developed typical MA associated with increased platelet

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<td>Previous use of COCs and POP effect on the course of MA</td>
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<td>MA attacks (n)</td>
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<td>Duration of MA attacks (h)</td>
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<td>Duration of visual aura (min)</td>
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<td>Analgesic use (n)</td>
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Mean values±S.D. of migraine parameters in the two groups of women treated with POP.
* p<.02.
** p<.001 vs. run-in period.

Fig. 1. Effect of POP use on the mean number of MA attacks, the duration of headache pain, the total duration of aura and the duration of the most reported neurological symptom (visual aura) in the study sample at 3 month intervals (N 30 women). Data are reported as mean±S.D. *p<.03; **p<.02; ***p<.001.
aggregability after starting COCs, the improvement was related to a gradual return to normal platelet activity after stopping COCs [31]. On the other hand, a vulnerable neuroendocrine homeostasis involving 5-HT system may favor the occurrence of MA, given the evidence that COCs are capable of stimulating the production of vasodilative markers, including 5-HT, an effect attributed most likely to the estrogenic component [32]. Our results showing a peculiar positive effect of POP use on duration of symptoms of aura in women with MA induced after starting COCs treatment further reinforce the idea that there are some women who display a specific sensitivity to exogenous estrogen use [3,7]. On the other hand, fluctuations in endogenous estrogen levels can still occur with most progestogen-only methods [33,34] and therefore hormonal triggers of migraine remains and may work in conjunction with other predisposing factors to cause the occurrence of head pain in the absence of exogenous estrogen.

A very recent interesting survey among primary care physician in Finland reported that 41% of the respondents did not recognize MA as a contraindication for prescribing COCs [35], suggesting gaps in knowledge in spite of the availability of WHO medical eligibility criteria for contraceptive use [11]. Since the 1-year prevalence rates for migraine in women are 11% for MO and 5% for MA, respectively [36], there is potentially a high number of women in whom estrogen-containing contraception may be contraindicated. In a large, cross-sectional, population-based study in Norway of 13944 women, a significant association between use of COCs and migraine (OR 1.4, 95% CI 1.2–1.8) was found [37]. The lack of a significant association between POPs and migraine (OR 1.3, 95% CI 0.9–1.8) reported in the same study [37] may be, however, due to the small number of POP users. There is a paucity of studies assessing headache in POP users and also data are scarce because diagnoses are often inaccurate and do not distinguish between the different forms of primary headaches. Comparative studies with progestogen-only preparations and placebo or COCs are not available in the literature.

Headache is a common complaint in contraceptive progestin implant users and may lead to discontinuation of the method [38]. Similarly, there is an increase in headache reported over time with both norethisterone enanthate and, especially with depot medroxyprogesterone acetate [39]. Anecdotally, migraine is more likely to improve in women who achieve amenorrhea [40], even though no significant relationship was evident between the days with erratic bleeding and the occurrence of MA in our study sample. However, it is critical to recognize that the present study was underpowered to detect differences in bleeding profiles and other outcomes related to clinical characteristics of the headaches.

In conclusion, the present diary-based pilot study supports the use of the POP containing DSG in a population of women with MA and underlines a positive effect on symptoms of aura, especially in MA sensitive to previous use of COCs.

Acknowledgments

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