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Progestogen-only contraceptive pill compared with combined oral contraceptive in the treatment of pain symptoms caused by endometriosis in patients with migraine without aura

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ABSTRACT

Objective: Evaluate patient satisfaction at 6-month treatment in women with symptomatic rectovaginal endometriosis and migraine without aura with (progestogen-only contraceptive pill, POP versus sequential combined oral contraceptives, COC)
Study Design: A patient preference trial including 144 women (82 in the group COC and 62 in the group POP). Main outcome measure was the degree of patient satisfaction by using a Likert scale.
Secondary objectives were to evaluate differences in endometriosis-related pain and changes in migraine features during the treatment.
Results: In group POP, 38/62 women (61.2%) were satisfied or very satisfied after treatment, compared to 31/82 women (37.8%) in group COC ($p = 0.005$). The intensity of chronic pelvic pain and dyspareunia significantly decreased at 6-month treatment in both the groups. At 6-month treatment, the number of migraine attacks was lower than at baseline in group POP ($p = 0.002$), while it was not reduced in group COC ($p = 0.521$). The intensity of migraine attacks was significantly different between baseline and 6-month treatment in group POP ($p < 0.001$) but not in group COC ($p = 0.078$).
Conclusions: POP is better tolerated than COC and it seems to ameliorate migraine attacks compared to COC in symptomatic patients with rectovaginal endometriosis and migraine without aura. Both drugs efficaciously relieve endometriosis-related pain symptoms. This study supports the use of the POP in women with rectovaginal endometriosis and coexisting migraine without aura.

Introduction

Rectovaginal endometriosis usually causes pain symptoms including dysmenorrhea, chronic pelvic pain, dyschezia and deep dyspareunia. When pregnancy is not desired, hormonal therapies may be administered to symptomatic patients who decline surgery or to patients who previously underwent incomplete excision of deep endometriotic lesions and wish to avoid further surgery. Current medical therapies do not eradicate endometriotic lesions but they are efficacious and safe in relieving pain symptoms [1].

Several epidemiological studies showed that migraine is more frequent in women with endometriosis than in those without this disease; obviously, when endometriosis and migraine are co-morbidities, the well being of the patients is significantly impaired [2–7]. The clinical scenario of a patient with endometriosis-related pain symptoms and concomitant migraine is a challenge for the gynaecologist because the benefits of hormonal treatment on pain symptoms should be carefully balanced with the changes in the severity of migraine.

Contradictory results have been reported on the changes in headache severity during treatment with COCs; while some studies reported an exacerbation of headache in 25% of migraineurs women during treatment with COCs, other studies showed an improvement of migraine symptoms [8–11].

The progestin-only pill (POP) contraception is a safe and tolerable alternative to COCs and it is preferable in women with cerebrovascular diseases or risk factors for stroke [12]. Recent studies investigated the use of desogestrel (DSG, 75 μg/die) in women suffering from migraine with and without aura. The authors found that, during POP use, the frequency of migraine attacks was significantly reduced and the treatment improved health related quality of life in these patients (HRQoL) [13–15]

Given this background, this prospective, non-randomized, open label study compared the efficacy and tolerability of POP and COCs

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in treating pain symptoms caused by rectovaginal endometriosis in women suffering migraine without aura.

Materials and methods

Study population

This prospective, patient preference trial was performed in an academic centre for the diagnosis and treatment of endometriosis between January 2009 and October 2013.

Criteria for inclusion in the study were: diagnosis of rectovaginal endometriosis based on vaginal and rectal examinations and confirmed by rectal water contrast transvaginal ultrasonography [16–17]; endometriosis-related pain symptoms; desire to avoid surgery; diagnosis of migraine without aura according to the criteria of the International Headache Society [18]; age <35 years. Exclusion criteria for the study were: desire to conceive; therapies for endometriosis other than nonsteroidal anti-inflammatory drugs in the 3 months before inclusion in the study (6 months for GnRH analogues); undiagnosed vaginal bleeding; renal diseases and hypertension; premature ovarian failure; other type of headache that would confound the diagnosis of migraine without aura; chronic daily headache (≥15 headache days per month in the 6 months prior to inclusion in the study); use of other medications known to be effective in migraine prophylaxis (such as beta blockers, antidepressants, anticonvulsants); any focal neurologic sign and body mass index >30.0 kg/m^2.

Eligible patients were offered one of the following therapies for 6 months: oral desogestrel 150 μg and ethynilestradiol 20 μg (Mercilon®; Schering, formerly NV Organon, Oss, The Netherlands; group COC) or oral desogestrel (75 μ/day, Cerazette®; Schering-Plough, formerly NV Organon, Oss, The Netherlands; group POP).

Allocation to treatment

Treatment allocation was decided on the basis of the preference of the patients, in particular, their desire or not to achieve amenorrhea. Patients invited to participate into the study were informed that medical treatments are effective in relieving pain symptoms caused by endometriosis but they are not curative, and that pain symptoms often recur to a degree similar to baseline when the treatments are discontinued [19]. Patients were also informed that both treatments have previously been shown to significantly decrease the intensity of pain symptoms caused by endometriosis [20–21]. Patients were counselled that oral desogestrel might cause irregular uterine bleeding more frequently than COC [22]. The local Institutional Review Board approved the study protocol. Patients enrolled in the study signed a written informed consent.

Assessment of symptoms during follow-up

The intensity of pain symptoms was evaluated before starting the therapy, after 3 and 6 months of treatment using a 10 cm visual analogue scale (VAS) given to the patients before the visit in the clinic. The left extreme of the scale indicated the absence of pain and the right indicated the worst pain possible.

During the study period, patients filled in a diary with the clinical characteristics of headache attacks. The following characteristics of migraine were recorded: number of attacks; duration of headache (minutes); intensity of pain (graded on a four point scale, where 0 = no pain; 1 = mild, does not impair daily activities; 2 = moderate, may inhibit, but does not prohibit daily activities; 3 = severe, prohibits daily activities); occurrence of associated phenomena (photophobia, phonophobia, nausea and vomiting) [23].

Rescue medications were allowed and recorded throughout the study. They consisted in a non-steroidal anti-inflammatory drugs when needed to treat endometriosis-related pain symptoms (naproxen sodium, 550 mg tablet, synflex forte 550, Recordati Industria Chimica e Farmaceutica, Milan, Italy); paracetamol (tachipirina 1000 mg tablet, Aziende Chimiche Riunite Angelini Francesco, Rome, Italy) and sumatriptam (Imigram 500–100 mg tablet, GlaxoSmithKline Verona, Italy).

Health related quality of life

Validated language versions of the Short Form-36 version 2 (SF36v2) questionnaire were used to measure HRQoL [24]. The SF-36v2 is a valid, self-administered questionnaire measuring 8 domains of health, divided as summaries in physical and mental scores. The summaries and 8 domain scales are adjusted with scores ranging from 0 to 100 (maximum), with higher scores indicating higher levels of functioning or well-being. After the completion of treatment, the women rated the overall degree of satisfaction with their treatment by answering the following question: 'Taking into consideration the variations in pain symptoms, in overall well-being and quality of life, as well as the adverse effects experienced, if any, how would you define the level of satisfaction with your treatment?' as previously described [25]. Answers were based on a 5-point Likert scale (very satisfied, satisfied, uncertain, dissatisfied, very dissatisfied).

Sample size calculation

In calculating the sample size required, the primary consideration was the rate of satisfied patients (very satisfied plus satisfied) after 6 months of therapy [21]. No previous study investigated the efficacy of oral progestins and COC in treating symptoms caused by rectovaginal endometriosis and concomitant migraine. COC are usually well tolerated in patients with rectovaginal endometriosis with 67% of patients' satisfaction after 12 month follow-up [21]. Both COC and DSG-only pill are effective and safe, without statistical difference, in the treatment of endometriosis [20]. Patients' satisfaction with COC in women with concomitant migraine showed contrasting results, with 25% of the patients experiencing worse headache symptoms during COC treatment [18]. When we set up the study there were only few studies investigating the use of progestins in patients with migraine but they did not evaluate patients' satisfaction [26–29]. Based on this background, we hypothesized that hormonal therapies would be successful in relieving pain in about 60% of the patients studied (POP group). We considered clinically relevant a difference of 25% in the satisfaction rate (satisfied and highly satisfied) between the study groups (35% in the COC group versus 60% in the POP group). To have an 80% chance of detecting such a difference at an overall statistical significance level of 5%, 62 patients per group were required (two sided test). The secondary objectives of the study were to evaluate the changes in endometriosis-related pain symptoms after 6-month treatment with the two study protocols and to compare the course of migraine during the treatment.

Statistical analysis

The comparison of pain intensity between the two study groups was performed by using the Student's *t*-test and the Mann–Whitney *U*-test according to the data distribution and one-way ANOVA with Dunnett's multiple comparisons test according to data distribution when comparing three or more categories. Categorical variables were compared by using the chi-square test. $p < 0.05$ was considered statistically significant. Data were analyzed using the PRISM software version 6 (GraphPad Software, La