Cumulative Recurrence Rates of Endometriosis-Associated Pain after Long-Term Intramuscular Depot Medroxyprogesterone Acetate Therapy

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Objective: *To determine the cumulative recurrence rates of endometriosis-associated pain after long-term intramuscular depot medroxyprogesterone acetate (DMPA) therapy.*

Material and Method: *Sixty-one patients with symptomatic endometriosis, who had been treated with DMPA for 15 months and were satisfied with the treatment, were included in the present study. Telephone questionnaires were used to collect information including pain recurrence. Medical records were reviewed to obtain more information. Estimates of cumulative recurrence rates of pain were calculated using the Kaplan-Meier technique and estimates of risk were computed using the Cox proportional hazards models.*

Results: *The cumulative recurrence rates of pain after DMPA treatment were 18%, 28%, 41%, 46%, and 50% at months 12, 24, 36, 48, and 60, respectively. Age >30 years (hazard ratio = 4.40 [95% CI, 1.45-13.37]; p = 0.009), moderate to severe stages of endometriosis (3.02 [1.30-7.03]; p = 0.010), and severe pain prior to treatment (7.80 [1.02-59.61]; p = 0.048) were found to be independent risk factors for the recurrence of pain.*

Conclusion: *Half of the patients had recurrent pain five years after DMPA treatment ended.*

Keywords: *Depot medroxyprogesterone acetate, Dysmenorrhea, Endometriosis, Pain, Recurrence*

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Endometriosis is one of the most common gynecologic disorders and its prevalence in women with chronic pelvic pain is very likely to be higher than 33%[1]. Endometriosis should be viewed as a chronic disease that requires a life-long plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures[2]. Because of the chronic nature of endometriosis, long-term or repeated courses of medical therapy are required to control pain symptoms[3]. Progestogens are generally well-tolerated, have a more limited metabolic impact than danazol or gonadotropin-releasing hormone (GnRH) agonists, are inexpensive and may be used on a long-term basis[4]. The efficacy and safety of intramuscular depot medroxyprogesterone acetate (DMPA)[5-9] and subcutaneous DMPA[10,11] have been studied and both regimens appear to be effective and safe in the treatment of endometriosis-associated pain. To the best of our knowledge, there have been no reports in the literature discussing long-term follow-ups of patients with symptomatic endometriosis treated with DMPA. Therefore, the aim of the present study was to determine the cumulative recurrence rates of endometriosis-associated pain after the termination of long-term treatment with intramuscular DMPA.

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Material and Method

The present study was approved by the institutional review board and conducted in a university hospital. The present study was the follow-up phase following the authors' previously reported clinical trial conducted between April 2003 and April 2008[8]. The protocol and inclusion criteria for the initial clinical investigation have been previously described in detail[8]. In that study, all of the enrolled patients were premenopausal women who had endometriosis-associated pain with no ovarian endometrioma and underwent a diagnostic laparoscopy. Endometriosis was staged using the revised American Fertility Society classification[12]. After giving written informed consent to the study, 112 patients were randomized to receive either intramuscular DMPA injections

every month for six months, then every three months until a total period of 15 months was reached or injections every three months for 15 months. Of these 112 patients, 65 patients completed the study, had pain relief, and were satisfied with the treatment. In November 2009 as well as in October 2012, telephone questionnaires were used to collect information concerning the recurrence of pain, pregnancy, treatment for infertility, hormonal drug use and surgery not related to endometriosis, and menopausal status. Outpatient and inpatient medical records were reviewed to obtain more information. Four patients were excluded from the present study because of unavailable information and the remaining 61 patients were included in the present study. The number of patients who were interviewed via telephone in November 2009 was 61 (100%) patients and the corresponding figure in October 2012 was 56 (91.8%) patients.

The recurrence of pain symptoms was defined as a return of pain of the same characteristics and severity experienced before medical treatment. The time between the start of the follow-up and pain recurrence was analyzed with the Kaplan-Meier technique. Cox proportional hazards models were used to estimate the effects of several covariates simultaneously. These covariates were the ages of the patients at the beginning of the follow-up, the stages of the disease before the treatment, and the severity of pain prior to medical therapy. The patients were divided into two age groups (≤30 years versus >30 years) and into two stage groups (minimal to mild versus moderate to severe stages). Severe endometriosis-associated pain prior to treatment was defined as severe dysmenorrhea and/or severe dyspareunia and/or severe non-menstrual pain. Severe pain was calculated as pain with a 10-cm visual analog scale (on which zero indicated absence of pain and 10 indicated unbearable pain) score of 7 to 10. Probability values <0.05 were considered statistically significant.

Results

The patients' mean (±SD) age was 34.4 (±7.0) years. Eighteen (29.5%) patients were ≤30-years-old and 43 (70.5%) were >30-years-old. Forty-eight (78.7%) patients had minimal to mild disease and 13 (21.3%) had moderate to severe disease. Fifty (82%) subjects experienced severe pain and 11 (18%) subjects had moderate pain prior to medical therapy. The mean (±SD) length of patient follow-up was 62.3 (±6.0) months. The overall crude recurrence rate of endometriosis-associated pain was 39% (n = 24). Fig. 1 shows the survival curve of pain-free patients. The numbers of patients who completed the evaluations at months 12, 24, 36, 48, and 60 were 43, 34, 24, 20, and 9 patients, respectively. Nine (14.8%), six (9.8%), three (4.9%), and five (8.2%) patients were censored because of pregnancy, hormonal drug use not related to endometriosis-associated pain, surgery for other indications, and menopausal status, respectively. The cumulative recurrence rates of endometriosis-associated pain after DMPA treatment were 18%, 28%, 41%, 46%, and 50% at months 12, 24, 36, 48, and 60, respectively (Fig. 1). Using Cox proportional hazards models, it was demonstrated that age >30 years (hazard ratio = 4.40 [95% CI, 1.45-13.37]; p = 0.009), moderate to severe stages of endometriosis (3.02 [1.30-7.03]; p = 0.010) and severe pain prior to treatment (7.80 [1.02-59.61]; p = 0.048) were independent risk factors for the recurrence of pain (Table 1).

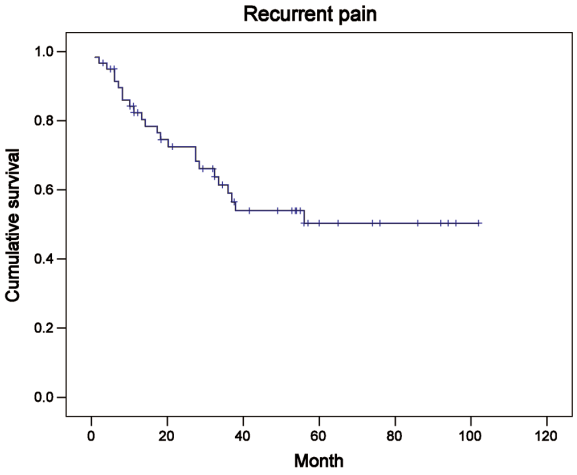

Fig. 1 Survival curve of pain-free patients.

Table 1. Factors associated with recurrent pain

Factor	Hazard ratio	95% confidence interval	p-value
Age >30 years	4.40	1.45-13.37	0.009
Moderate to severe endometriosis	3.02	1.30-7.03	0.010
Severe pain prior to treatment	7.80	1.02-59.61	0.048

Discussion

The findings in the present study demonstrated for the first time that half of the patients who received 15 months of DMPA therapy experienced recurrent pain at the end of the 5-year follow-up. A methodological drawback of the present study is that a comparative group was not included. Such a comparative group should be patients treated with GnRH agonists or other hormonal drugs.

In a prospective study, Barbieri et al[13] evaluated the efficacy of danazol in the treatment of endometriosis and demonstrated that, over a 5-year follow-up period, the overall crude recurrence rate of endometriosis was 33%. The crude recurrence rate of pain in the present study (39%) was in line with that in their study[13]. Waller and Shaw[14] determined the long-term recurrence rate of endometriosis after treatment with GnRH agonists. In their study, the cumulative recurrence rate for the fifth year after treatment ended was 53.4%[14]. Although DMPA caused prolonged anovulation after discontinuation[5] and the 15-month treatment phase in the authors' previous trial[8] was longer than the six months in their study[14], the cumulative recurrence rates of pain in the present study were similar to those in their study[14]. Hence, it seems to be that the recurrence rate of endometriosis-associated pain after DMPA treatment at the end of the 5-year follow-up was comparable to that after GnRH agonists as well as danazol therapy.

The results of the present study confirmed the findings of the other studies[13,14] in that advanced disease is a risk factor for the recurrence of pain. In a recent study[15], severity of chronic pelvic pain prior to surgery was demonstrated to be a significant factor in the prediction of recurrence of pain and endometriotic lesions. Similarly, the author found that severe pain prior to medical treatment was significantly associated with the recurrence of pain. Endometriotic lesions causing severe pain might represent an aggressive form of endometriosis[15], which manifests a rapid regrowth after medical therapy ended. Moreover, age >30 years is another risk factor identified in the present study, a finding not noted in earlier studies. The latter risk factor may perhaps be related to the discrepancy in derangement of immune system and/or the difference in genetic components of endometriosis between the two age groups.

In conclusion, half of the patients who received 15 months of DMPA therapy experienced recurrent pain at the end of the 5-year follow-up.

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Potential conflicts of interest

None.

References

1. Guo SW, Wang Y. The prevalence of endometriosis in women with chronic pelvic pain. Gynecol Obstet Invest 2006; 62: 121-30.
2. Practice Committee of American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis. Fertil Steril 2008; 90 (5 Suppl): S260-9.
3. Schweppe KW. Current place of progestins in the treatment of endometriosis-related complaints. Gynecol Endocrinol 2001; 15 (Suppl 6): 22-8.
4. Vercellini P, Fedele L, Pietropaolo G, Frontino G, Somigliana E, Crosignani PG. Progestogens for endometriosis: forward to the past. Hum Reprod Update 2003; 9: 387-96.
5. Vercellini P, De Giorgi O, Oldani S, Cortesi I, Panazza S, Crosignani PG. Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis. Am J Obstet Gynecol 1996; 175: 396-401.
6. Arowojolu AO. Treatment of endometriosis with depot medroxyprogesterone acetate: a preliminary experience. Afr J Med Med Sci 2000; 29: 55-8.
7. Walch K, Unfried G, Huber J, Kurz C, van Trotsenburg M, Pernicka E, et al. Implanon versus medroxyprogesterone acetate: effects on pain scores in patients with symptomatic endometriosis —a pilot study. Contraception 2009; 79: 29-34.
8. Cheewadhanaraks S, Peeyananjarassri K, Choksuchat C, Dhanaworavibul K, Choobun T, Bunyapipat S. Interval of injections of intramuscular depot medroxyprogesterone acetate in the long-term treatment of endometriosis-associated pain: a randomized comparative trial. Gynecol Obstet Invest 2009; 68: 116-21.
9. Wong AY, Tang LC, Chin RK. Levonorgestrel-releasing intrauterine system (Mirena) and Depot medroxyprogesterone acetate (Depoprovera) as long-term maintenance therapy for patients with moderate and severe endometriosis: a randomised controlled trial. Aust N Z J Obstet Gynaecol 2010;

50: 273-9.
10. Crosignani PG, Luciano A, Ray A, Bergqvist A. Subcutaneous depot medroxyprogesterone acetate versus leuprolide acetate in the treatment of endometriosis-associated pain. Hum Reprod 2006; 21: 248-56.
11. Schlaff WD, Carson SA, Luciano A, Ross D, Bergqvist A. Subcutaneous injection of depot medroxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis-associated pain. Fertil Steril 2006; 85: 314-25.
12. American Fertility Society. Revised American Fertility Society classification of endometriosis: 1985. Fertil Steril 1985; 43: 351-2.
13. Barbieri RL, Evans S, Kistner RW. Danazol in the treatment of endometriosis: analysis of 100 cases with a 4-year follow-up. Fertil Steril 1982; 37: 737-46.
14. Waller KG, Shaw RW. Gonadotropin-releasing hormone analogues for the treatment of endometriosis: long-term follow-up. Fertil Steril 1993; 59: 511-5.
15. Coccia ME, Rizzello F, Palagiano A, Scarselli G. Long-term follow-up after laparoscopic treatment for endometriosis: multivariate analysis of predictive factors for recurrence of endometriotic lesions and pain. Eur J Obstet Gynecol Reprod Biol 2011; 157: 78-83.

อัตราอาการปวดซ้ำสะสมในผู้ป่วยเยื่อบุมดลูกต่างที่ หลังการรักษาระยะยาวด้วยการฉีดยาคุมกำเนิดเข้ากล้าม

โสภณ ชีวะธนรักษ์

วัตถุประสงค์: *เพื่อประเมินอัตราอาการปวดซ้ำสะสมในผู้ป่วยเยื่อบุมดลูกต่างที่ หลังการรักษาระยะยาวด้วยการฉีด depot medroxyprogesterone acetate (DMPA) เข้ากล้าม*

วัสดุและวิธีการ: *การศึกษานี้มีผู้ป่วยเยื่อบุมดลูกต่างที่จำนวน 61 ราย ผู้ป่วยเคยได้รับการรักษาอาการปวดด้วยการฉีด DMPA นาน 15 เดือน และทุกรายมีความพึงพอใจต่อการรักษา ผู้นิพนธ์สัมภาษณ์ผู้ป่วยทางโทรศัพท์โดยใช้แบบสอบถามเพื่อเก็บข้อมูลอาการปวดซ้ำ และศึกษาเวชระเบียนเพื่อค้นหาข้อมูลเพิ่มเติม การประเมินอัตราอาการปวดซ้ำสะสมใช้วิธี Kaplan-Meier และการระบุปัจจัยเสี่ยงใช้ Cox proportional hazards models*

ผลการศึกษา: *อัตราอาการปวดซ้ำสะสมหลังการรักษาด้วย DMPA คิดเป็นร้อยละ 18, 28, 41, 46 และ 50 เมื่อติดตามผู้ป่วยนาน 12, 24, 36, 48 และ 60 เดือนตามลำดับ ปัจจัยเสี่ยงอิสระต่อการเกิดอาการปวดซ้ำ ได้แก่ อายุมากกว่า 30 ปี (hazard ratio = 4.40 [95% CI, 1.45-13.37]; p = 0.009) พยาธิสภาพขั้นปานกลางถึงรุนแรง (3.02 [1.30-7.03]; p = 0.010) และอาการปวดรุนแรงก่อนการรักษา (7.80 [1.02-59.61]; p = 0.048)*

สรุป: *เมื่อติดตามผู้ป่วยนาน 5 ปี หลังการรักษาด้วย DMPA พบว่าผู้ป่วยกึ่งหนึ่งมีอาการปวดซ้ำ*