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## GYNAECOLOGY

# Comparison of Effectiveness in Endometriosis Treatment and Patient Acceptability between Intramuscular Depot-Medroxyprogesterone Acetate and Oral Desogestrel

Pichavit Boonnum, M.D.*,
Worashorn Lattiwongsakorn, M.D.*,
Tawiwan Pantasri, M.D.*,
Opas Sreshthaputra, M.D.*

** Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*

## ABSTRACT

**Objectives:** To compare the effectiveness in the initial treatment of endometriosis and patient acceptability between intramuscular depot-medroxy progesterone acetate (DMPA) and oral desogestrel (DSG).

**Materials and Methods:** A comparative study based on patient preference was conducted on women aged 18-45 years who first presented with endometriosis-like symptoms, between July 2018 and February 2019 at Maharaj Nakorn Chiang Mai Hospital. The participants were assigned to either a DMPA or DSG group based on their preference, after being informed. The primary outcome was the effectiveness of treatment for 12 weeks, measuring by visual analog score (VAS) of dysmenorrhea, dyspareunia, and chronic pelvic pain. The secondary outcome was patient acceptability in terms of level of satisfaction with the medication, quality of life, side effects, and rate of continuation.

**Results:** Sixty-one patients, 39 in DMPA group and 22 in DSG group, were enrolled into the study. After treatment, the median VAS score for dysmenorrhea was significantly decreased in each group (DMPA: 7.61 to 2.92, $p < 0.001$; DSG: 7.81 to 2.86, $p < 0.001$) but the reduction score was not significantly different between the two groups. The quality of life (EuroQol group-5Dimensions-5Levels or EQ-5D-5L) also significantly improved in both groups. Breakthrough bleeding was the most common side effect and the highest level of concern. Satisfaction and rate of continuation were not significantly different between the two groups. The acceptability rate was not significantly different.

**Conclusion:** After 12 weeks of treatment, the effectiveness in treatment and patient acceptability in the DMPA and DSG group were comparable.

**Keywords:** desogestrel, depot medroxyprogesterone acetate, endometriosis, dysmenorrhea, quality of life.

***Correspondence to:*** *Worashorn Lattiwongsakorn , M.D., Department of Obstetrics and Gynaecology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. E-mail: worashorn.l@cmu.ac.th*

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# *การเปรียบเทียบประสิทธิภาพในการรักษาภาวะเยื่อบุโพรงมดลูกเจริญผิดที่และการยอมรับการรักษาของผู้ป่วย ระหว่างการฉีด Depot Medoxyprogesterone Acetate กับ Desogestrel แบบรับประทาน*

***พิชญ์วิทย์ บุญนำ, วรชร ลัทธิวงศกร, ทวิวัน พันธศรี, โอภาส เศรษฐบุตร***

***บทคัดย่อ***

***วัตถุประสงค์:*** *เปรียบเทียบประสิทธิภาพในการรักษาภาวะเยื่อบุโพรงมดลูกเจริญผิดที่และการยอมรับของผู้ป่วยที่เริ่มรักษาภาวะเยื่อบุโพรงมดลูกเจริญผิดที่ระหว่างการฉีด depot medroxy progesterone acetate (DMPA) กับ desogestrel (DSG) แบบรับประทาน*

***วัสดุและวิธีการ:*** *เป็นการศึกษาเปรียบเทียบตามความต้องการของผู้ป่วย ศึกษาในสตรีอายุ 18 ถึง 45 ปี ที่ได้รับวินิจฉัยภาวะเยื่อบุโพรงมดลูกเจริญผิดที่เป็นครั้งแรกระหว่าง กรกฎาคม 2561 ถึง กุมภาพันธ์ 2562 ที่ รพ.มหาราชนครเชียงใหม่ ผู้ป่วยจะเป็นคนเลือกยาที่ต้องการเองระหว่าง DMPA กับ DSG แบบรับประทานหลังจากได้รับข้อมูลยา ผลการศึกษาหลัก คือ ประสิทธิภาพการลดคะแนนปวด (visual analog scale) จากอาการปวดประจำเดือน, การปวดขณะมีเพศสัมพันธ์ และการปวดท้องน้อยเรื้อรัง หลังการรักษา 12 สัปดาห์ ผลการศึกษารอง คือ การยอมรับการรักษาของผู้ป่วยประเมินจากคะแนนความพึงพอใจ, คะแนนคุณภาพชีวิต, อาการข้างเคียง และ อัตราความต้องการรักษาด้วยยาเดิมต่อ*

***ผลการศึกษา:*** *ผู้ป่วย 61 คน ในกลุ่ม DMPA มี 39 คน และในกลุ่ม DSG มี 22 คน ทั้งสองกลุ่มรับการรักษา 12 สัปดาห์ พบว่า ค่ามัธยฐานของ VAS score ของการปวดประจำเดือนลดลงอย่างมีนัยสำคัญทางสถิติในแต่ละกลุ่ม (DMPA จาก 7.61 เป็น 2.92, DSG จาก 7.81 เป็น 2.86) ($p<0.001$) แต่การลดลงไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ เมื่อนำทั้งสองกลุ่มมาเปรียบเทียบกัน ในส่วนของคุณภาพชีวิตนั้น [EQ-5D-5L] พบว่าดีขึ้นทั้งสองกลุ่ม อาการข้างเคียงที่พบบ่อยคือ เลือดออกผิดปกติจากโพรงมดลูกและเป็นสิ่งที่ผู้ใช้ยากังวลที่สุด หลังจากคำนวณทางสถิติ การยอมรับของผู้ป่วย, ความพึงพอใจ และอัตราความต้องการรักษาด้วยยาเดิมต่อ เมื่อเปรียบเทียบระหว่าง 2 กลุ่ม ไม่พบความแตกต่างกันทางสถิติ*

***สรุป:*** *DSG ให้ประสิทธิภาพการรักษาและความพึงพอใจเทียบเท่ากับ DMPA ในการเริ่มต้นรักษาภาวะเยื่อบุโพรงมดลูกเจริญผิดที่ในระยะเวลา 12 สัปดาห์*

***คำสำคัญ:*** *ยาคุมเดสโซเจสเทรล, ยาคุมกำเนิดแบบฉีด, เยื่อบุโพรงมดลูกเจริญผิดที่, ปวดประจำเดือน, คุณภาพชีวิต*

## Introduction

Endometriosis is an abnormal growth of endometrium outside the uterine cavity. This chronic disease can lead to progressive dysmenorrhea, pelvic pain, and infertility. The prevalence is 6-10% in general female population, but is up to 70% in the women experiencing chronic pelvic pain[1, 2].

Treatment of endometriosis consists of medical therapy and surgery. Medical treatment such as analgesics, combined oral contraceptives, progestins, and Gonadotropin-releasing hormone-agonist can be used for the initial treatment of pain in women suspected endometriosis[1, 3]. Progestin has long been known as an effective drug for treatment of endometriosis-associated pain. Currently, various forms of progestin are available, including injection, implant, and oral route. In treatment of endometriosis, the injectable form such as depot medroxyprogesterone acetate (DMPA) is widely used and proven to be very effective both as a contraceptive and also for the treatment of pelvic pain[4]. However, its side effects such as irregular bleeding, an increase in body fat mass and amenorrhea are the main reasons for discontinuation[2]. The third-generation progestin such as desogestrel, a highly selective progestin with low androgenic properties, has been introduced and expected to overcome the aforementioned side effects.

Its active metabolite, 3-keto DSG or etonogestrel, can inhibit ovulation and inactivate proliferation of the endometrium[5, 6]. Due to its inhibitory ovulatory effects and low levels of endogenous estrogen, DSG is used in the treatment of endometriosis and might be effective for endometriosis-associated pain control as combined oral contraceptive pills[7]. DSG is effective and acceptable for postoperative therapy for patients with moderate-to-severe pain related to endometriosis[8]. Moreover, return of fertility after discontinuation of DSG is one year earlier than after discontinuation of DMPA[9, 10]. Nevertheless, to the best of our knowledge, no study comparing the effectiveness and patient acceptability between DMPA and DSG as an initial treatment of endometriosis has been reported. Accordingly, we conducted this study aimed to compare the effectiveness in pain control, quality of life, side effects, patient satisfaction, and continuation rate between the patients treated with DMPA and those with DSG as an initial treatment of endometriosis.

## Materials and Methods

From July 2018 to February 2019, the women with initial treatment for endometriosis were prospectively enrolled based on patient preference to compare the effectiveness and acceptability of DMPA and DSG. The study was conducted at Maharaj Nakorn Chiang Mai Hospital, with ethical approval by the Ethics Committee of the Faculty of Medicine, Chiang Mai University.

The patients who first presented with endometriosis-like symptoms were evaluated for the study criteria[11] and underwent ultrasound examination for diagnosis of endometriosis. The inclusion criteria were as follows: 1) a woman at age of 18-45 years, 2) presenting with one of followings; a) history of progressive dysmenorrhea, b) chronic pelvic pain defined as an intermittent or constant pain in the lower abdomen or pelvis for at least 6 months[12] in duration with suspicion of endometriosis after excluding a non-gynecologic cause, c) dyspareunia, d) nodules in the cul-de-sac, or pelvic tenderness on pelvic examination by a gynecologist or a third-year obstetricians and gynecologists resident, e) fixed ovary on pelvic examination with no other cause suspected for pelvic pain and f) ultrasound revealing an endometriotic cyst. The women meeting the inclusion criteria were invited to participate in the study. Exclusion criteria were 1) contraindications for progestins[13, 14]; e.g. known or suspected pregnancy, unexplained vaginal bleeding, breast cancer, liver disease[15], 2) taking medication such as anticonvulsants, rifampin, antiretroviral drugs, cyclosporine, theophylline, or other hormonal drug, 3) indicated for surgery 4) planning for

pregnancy in three months, 5) uterine anomalies, and 6) refusing to participate in the study.

After meeting the eligible criteria, the participants signed the informed consent document and received standard endometriosis treatment information on the methods available. In this trial, participants started with their preferred form of medication either DMPA or DSG for 12 weeks of treatment. The two groups were prescribed either: DMPA, a dose of 150 mg of DMPA intramuscular injection route every 4 weeks or DSG, a dose of 75µg of DSG progestin-only pill daily.

A validated symptom questionnaire for data collection was used enabling audit and comparison of the findings of the study. The symptoms of the women, such as pelvic pain, were assessed using a visual analog scale (VAS) score and level of acceptability by the women was assessed by quality of life questionnaires (EuroQol group- 5Dimensions-5Levels). Baseline data were assessed at the time of recruitment and then after 12 weeks of treatment. The patients completed the questionnaire again, with addressing bleeding, weight gain, the need for pain relief, and continuation rate after 12 weeks. The continuation rate was defined as a rate that the patient received same treatment for another 12 weeks. The need for pain relief was based on World Health Organization's analgesic ladder[16] which suggested initial treatment with non-opioid medication e.g. non-steroidal anti-inflammatory (NSAIDs), acetaminophen. It was explained to the patients that response to empiric therapy did not confirm a diagnosis of endometriosis and further treatment or follow- up depended on patient symptoms, recurrence rate and their level of satisfaction was evaluated by scale[1-10] where more points indicated greater satisfaction.

The main outcome of this study was VAS score (score 0-10) changes in dysmenorrhea, pelvic pain, or dyspareunia. The secondary outcomes included quality of life, side effects, continuation, and satisfaction. Quality of life was assessed by EQ-5D-5L score, a simple, efficient method for evaluating quality of life in daily practice. The use with permission was granted by the owner of the tool (EuroQol Research Foundation)[17, 18]. The EQ-5D-5L contains five health dimensions (mobility, self-care, daily activity, pain or discomfort, and anxiety or depression) and a health score (score 0-100) based on VAS, when zero indicate the worst health status, and 100 indicate the best. In the five health dimensions, each question had five choices, ranging from no problems to extremely affected health. The side effects which were monitored were weight gain and abnormal vaginal bleeding.

Sample size calculation was based on the primary outcome of the endometriosis-associated pain score. A 1- cm difference in VAS between the two study groups was used as the smallest effect that could be of clinical significance. Referring to VAS standard deviations of 2.64 derived from our pilot study on the DSG group of 20 women, with the alpha value set at 0.05 and the power set at 75%. Considering the dropout rate, which we anticipated up to be 20%, we aimed to recruit 48 women. Statistical analysis was performed using Stata software version 11 (StataCorp LP). Comparison of continuous data (pain score / satisfaction outcome) of before and after treatment were analyzed using a Wilcoxon signed-rank test. The continuous data, such as VAS scores and quality of life were analyzed using a Mann-Whitney test to compare between the two groups. The categorical data were compared using Fisher's exact test. All statistical tests were compared two-sided and probability values of less than 0.05 were considered as significant.

## Results

During the study period, a total of 302 new cases of endometriosis were identified (Fig. 1). Of them, 61 patients met the inclusion criteria and were enrolled into the study, including 39 (63.9%) in the DMPA group and 22 (36.1%) in the DSG group. There was no patient lost to follow-up during the study. The demographic data and pretreatment VAS scores regarding dysmenorrhea, chronic pelvic pain, dyspareunia and quality of life of the two groups were not statistically different (Table 1).

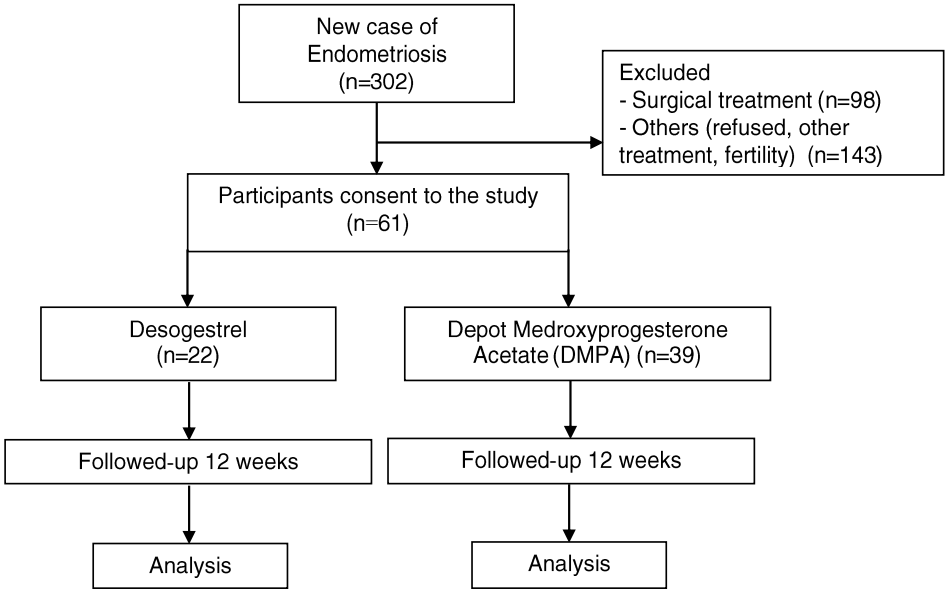


**Fig. 1.** Flow diagram of study.

**Table 1.** Baseline characteristics of patients with endometriosis in the study.

| | DMPA (n=39) | DSG (n=22) | p value |
|---|---|---|---|
| Age (years) [median (IQR)] | 35 (27-41) | 31 (25-36) | 0.20 |
| Nulliparous (n; %) | 19 (48.7) | 16 (72.7) | 0.07 |
| BW (kg) [median (IQR)] | 53 (47-59) | 54 (48-62) | 0.75 |
| BMI (kg/m$^2$) [median(IQR)] | 21.2 (18.8-24.7) | 22.3 (18.7-25.4) | 0.74 |
| Duration of symptoms (months) [median (IQR)] | 7 (5-12) | 10 (4-12) | 0.88 |
| Dysmenorrhea (VAS score) [median (IQR)] | 8 (7-9) | 8 (7-9) | 0.75 |
| Dyspareunia (VAS score) [median (IQR)] | 0 (0-5) | 0 (0-2) | 0.17 |
| Chronic pelvic pain (VAS score) [median (IQR)] | 4 (1-8) | 2 (0-6) | 0.63 |
| Quality of life [median (IQR)] | | | |
| - EQ -5D-5L | 9 (8-13) | 11 (7-15) | 0.25 |
| - Health Score | 65 (50-70) | 60 (50-62) | 0.17 |

DMPA: Depot Medroxyprogesterone Acetate, DSG: Desogestrel, BW: body weight, VAS: visual analog scale, BMI: Body mass index, IQR: interquartile range, EQ -5D-5L: EuroQol group-5Dimensions-5Levels.

**Effectiveness**

The improvement of dysmenorrhea, dyspareunia and chronic pelvic pain between the two groups at the first visit and at the end of 12 weeks of treatment, were not statistically different (Table 2). In comparison between before and after treatment in each group, VAS score of dysmenorrhea and chronic pelvic pain was significantly improved in both DMPA and DSG group (both $p < 0.001$). The percentage of the decrease in median VAS score of dysmenorrhea in the DMPA group (75%) and that in the DSG group (81%) was not statistically different.

**Table 2.** Comparison of the VAS pain score between first visit and end of treatment with DMPA and DSG.

| | First visit | 12 weeks | p value in group | p value between groups |
|---|---|---|---|---|
| Dysmenorrhea [median (IQR)] | | | | |
| - DMPA | 8 (7-9) | 2 (0-5) | < 0.001 | 0.915 |
| - DSG | 8 (7-9) | 1.5 (0-6) | < 0.001 | |
| Dyspareunia [median (IQR)] | | | | |
| - DMPA | 0 (0-5) | 0 (0-2) | 0.062 | 0.283 |
| - DSG | 0 (0-2) | 0 (0-1) | 0.561 | |
| Chronic pelvic pain [median (IQR)] | | | | |
| - DMPA | 4 (1-8) | 1 (0-3) | < 0.001 | 0.776 |
| - DSG | 2 (0-6) | 1 (0-2) | < 0.001 | |

VAS: Visual Analogue Scale, DMPA: Depot Medroxyprogesterone Acetate, DSG: Desogestrel, IQR: interquartile range

**Acceptability**

The acceptability in terms of the level of satisfaction with the medication via quality of life, side effect, satisfaction, and rate of continuation is presented in Table 3. Both groups had an improvement of EQ-5D-5L score; 9 (8-13) to 7 (5-8) in the DMPA group ($p < 0.001$) and 11 (7-15) to 7 (5-7) in the DSG group ($p < 0.001$). The health score was also significantly increased in both group; 65 (50-70) to 80 (70-80) ($p < 0.001$) in the DMPA group and 60 (50-62) to 80 (70-80) ($p < 0.001$) in the DSG group (Fig. 2). The percentage of weight gaining in DMPA (15.4%) was greater than that of DSG group (9.1%), but the difference was not statically significant ($p = 0.27$). Table 3 shows that both groups had high patient acceptability and DSG group tended to improve the quality of life and health score greater than DMPA.

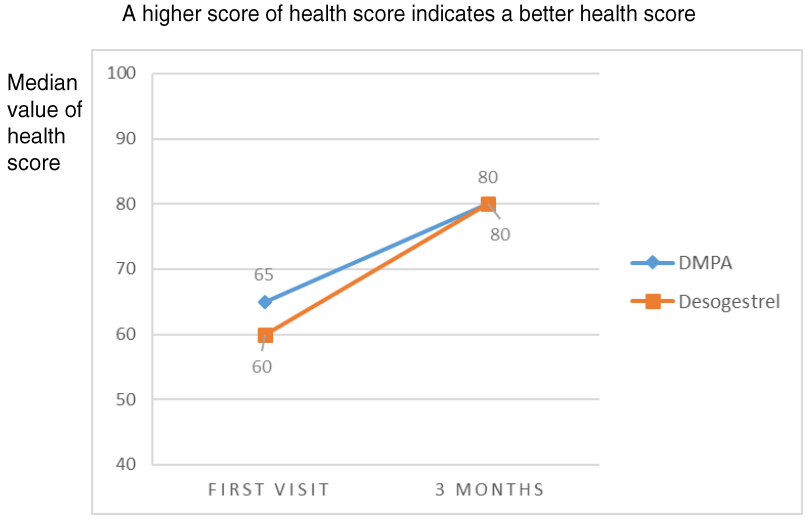


**Fig. 2.** Graph of change in the median value of health score at first visit and end of treatment between depot medroxyprogesterone acetate (DMPA) and desogrestrel (DSG).

**Table 3.** Comparison between the difference (Δ) in quality of life at the first visit and after 12 weeks of treatment between DMPA and DSG and comparison of the side effects, level of satisfaction and continuation rate after 12 weeks of treatment.

| Variable | DMPA (n=39) | DSG (n=22) | p value |
|---|---|---|---|
| Quality of life [median (IQR)] | | | |
| - (Δ) EQ-5D-5L | 3 (0-5) | 4 (2-8) | 0.76 |
| - (Δ) Health score | 10 (0-30) | 20 (10-31) | 0.80 |
| Side effects (n; %) | | | |
| - None | 5 (12.8) | 8 (36.4) | 0.11 |
| - Bleeding | 28 (71.8) | 12 (54.5) | |
| - Weight gain | 6 (15.4) | 2 (9.1) | |
| Satisfaction (0-10) [median (IQR)] | 8 (7-9) | 8 (7-8) | 0.41 |
| Continuation (n; %) | 30 (76.9) | 17 (77.3) | 0.98 |
| Change of BW (kg) [median (IQR)] | 0.7 (0-1.3) | 0 (0-1) | 0.27 |
| Analgesic used (n; %) | 15 (38.5) | 6 (27.3) | 0.38 |

DMPA: Depot Medroxyprogesterone Acetate, DSG: Desogestrel, BW: body weight, IQR: interquartile range, EQ -5D-5L: EuroQol group-5Dimensions-5Levels.
* An EQ-5D-5L lower score indicates a better quality of life.

There was no statistically significant difference in the change of body weight of patients between the two groups (DMPA 0.7 (0-1.3), DSG 0 (0-1), p = 0.27). The most common side effect in both groups was bleeding (DMPA 71.8%, DSG 54.5%). The most common bleeding pattern was spot bleeding in the first two months. There were no serious side effects found in any group during the study and no significant differences in the continuation rate and satisfaction between both groups.

## Discussion

Endometriosis is a common gynecologic problem with the gold standard of diagnosis based on surgical findings and pathological reports. However, the non-invasive tests such as history taking, pelvic examination, pelvic ultrasound, and serum cancer antigen 125 (CA 125) are also acceptable for early diagnosis and to avoid invasive tests especially for young women. The combination of vaginal examination and transvaginal ultrasound (TVUS) for rectal endometriosis has a high sensitivity of 0.96 (95% confidence interval (CI) 0.86 to 0.99), and specificity of 0.98 (95% CI 0.94 to 1.00)[11]. Endometriosis has been known as estrogen-driven disease and the main aim of the medical treatment is to lower estrogen levels. DSG is prescribed for contraceptive used as it inhibits ovulation in 97% of the cycle, which leads to decrease in the estrogen level, with low androgenic properties[5, 19, 20]. Compared to a previous study[21], the DMPA group decreased 53% of VAS score dysmenorrhea after the first six months. A systematic review examined the evidence for efficacy of the use of hormonal contraception to improve disease-related pain and decrease postoperative risk of disease recurrence. Combined hormonal contraceptives and progestin-only contraceptives were found to be effective for the relief of endometriosis-related dysmenorrhea, pelvic pain and dyspareunia, and improvement of quality of life[22]. These findings were consistent with our study.

Our study showed that DSG was as effective as DMPA in the role of initial treatment of endometriosis with high patient acceptability. It may provide another choice of endometriosis treatment for patients with

contraindications for the use of estrogen and also in women who wished to avoid drug injections[23].

While the effectiveness is comparable, DSG has more theoretical advantage in terms of fertility return after discontinuation. Compared to DMPA, DSG has earlier return of fertility after discontinuation. DMPA, a progestogen derivative with moderate androgenic activity, has slow return of fertility after discontinuation[14], with a mean time for returning of 260 days[2], whereas DSG returned to ovulation as early as seven days, with an average of 17.2 days[24]. Additionally, DSG might have advantage of less bone loss than DMPA. Previous studies showed that DMPA could help improve endometriosis pain as a GnRH agonist[7, 12, 13] but the DMPA users might have lower bone mineral density (BMD) after two years of use (a decrease in BMD of hip and spine of 7.7% and 6.4% in 2 years, respectively) [25], whereas DSG might have less effect on BMD (a decrease in BMD of vertebra of 2.6% in 2 years)[26].

The main side effect of both groups was breakthrough bleeding which was similar to what was found in the previous studies and other progestogen treatments[27, 28]. Nevertheless, based on previous studies, DSG seems to have less effect. For an example, Vercellini 1996[28] reported that 65% of DMPA patients had spotting bleeding and 53% of patients had weight gain at the 1-year assessment while Razzi 2007[7] reported a 20% breakthrough bleeding in DSG users. Likewise, during of 12 weeks of our study, the rates of abnormal bleeding tended to be more frequent in DMPA users (71% vs 54%). Similarly, weight gain is probably more problematic in DMPA users. Our study found that percentage of participants who had weight gain in DMPA users (15%) was greater than that in DSG users (9.1%).Cochrane review 2016[29] also found that mean weight gain after use of DSG at 6 or 12 months was less than 2 kg.

The results of our study showed both DMPA and DSG were effective for pain control; decreased dysmenorrhea, dyspareunia and chronic pelvic pain, improved quality of life with comparable side effects, high patient satisfaction in endometriosis treatment, which were consistent with the findings in previous studies[22]. After patients completed 12 weeks of this study, 76.9% of the DMPA group and 77.3% of the DSG still preferred continuous treatment. From the literature reviews, there was no study in comparing effectiveness between DMPA and DSG in endometriosis treatment. So, this was our strength and our study was not only study in the effectiveness, but also included patient's acceptability. This study had two main limitations including: 1) non-randomization in which known and unknown confounding factors could not be perfectly controlled; and 2) relatively small sample size which had too low power to compare several secondary outcomes such as rates of weight gain, BMD or return to fertility. However, based on previous studies[2, 9-10, 24-26], DSG resulted in a more rapid return to fertility with lesser effects on BMD than DMPA. Nevertheless, with our data, DSG can be used as effectively as DMPA for endometriosis treatment, and both are safe for women who have contraindications for estrogen.

## Conclusion

Progestin, either DSG or DMPA, as an initial treatment for endometriosis could significantly reduce pain and improve the quality of life.

## Potential conflicts of interest

The authors declare no conflicts of interest.

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