Dienogest Versus Medroxyprogesterone Acetate for Control of Menstrual Pain in Chinese Women with Endometriosis

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Objective: This study aimed to compare dienogest with medroxyprogesterone acetate for management of endometriosis in terms of menstrual pain, quality of life, adverse effects, tolerability, and overall satisfaction.
Methods: This was a cross-sectional, observational study of 60 Chinese women with endometriosis aged 18 to 55 years who were receiving active treatment for ≥6 months with either medroxyprogesterone acetate (150 mg intramuscularly every 3 months) [n=30] or dienogest (2 mg oral daily) [n=30, since 2013]. A questionnaire together with a written consent was posted in July 2017 to patients for completion. The questionnaire comprised 11 questions about pain (n=4), quality of life (n=3), adverse effects and tolerability (n=3), and overall satisfaction with treatment (n=1). Pain symptoms included menstrual pain, chronic pelvic pain, dyspareunia, and dyschezia. Quality of life assessment was based on questions derived from the SF-36 questionnaire and included daily living, work life, and social life. An 11-point rating scale was used.
Results: 25 patients from the dienogest group and 26 patients from the medroxyprogesterone acetate groups returned the questionnaire, with an overall response rate of 83%. Before treatment, the two groups were comparable in terms of baseline characteristics, pain symptoms, and quality of life. After treatment, the mean score for menstrual pain in the dienogest and medroxyprogesterone acetate groups reduced from 5.5 and 4.88 to 1.8 and 3.65, respectively, with the dienogest group achieving a greater absolute reduction (6.6 vs. 4.69, p=0.044). Satisfaction score was higher with dienogest than medroxyprogesterone acetate (8.2 vs. 6.81, p=0.024).
Conclusion: Dienogest is more effective than medroxyprogesterone acetate in treating symptomatic endometriosis and control of menstrual pain, with higher tolerability and satisfaction rate.

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Keywords: Dienogest; Dysmenorrhea; Endometriosis; Medroxyprogesterone acetate

Introduction

Endometriosis is a common gynaecological condition that affects 5% to 10% of women of reproductive age[1]. Symptoms include menstrual pain and chronic pelvic pain. Medications for endometriosis include gonadotrophin-releasing hormone agonists, combined oral contraceptives, and progestins. Nonetheless, gonadotrophin-releasing hormone agonists are associated with symptoms of oestrogen deprivation so long-term use is not recommended[2]. Empirical use of combined oral contraceptives for treatment of menstrual pain may increase the risk of deep-infiltrating endometriosis[3].

Progestin such as medroxyprogesterone acetate is more effective than placebo in pain relief[4,5]. A levonogestrel-releasing intrauterine system is as effective as leuprolide in controlling endometriosis-induced pain[6]. Progestin inhibits the hypothalamic-pituitary-ovarian axis and leads to anovulation, reduced serum level of oestrogen, and atrophy of eutopic endometrium and endometriotic lesions. Progestin also decreases peritoneal inflammatory markers and modulates the immune response involved in the pathogenesis of endometriosis[7], with consequent improvement of symptoms and reduced recurrence. Progestin can be administered orally, subcutaneously, or intramuscularly. Medroxyprogesterone acetate is a type of progestin. It has been reported to completely eliminate pelvic pain and menstrual pain in 35 women with endometriosis[8], and over 80% of patients achieved improvement in pain symptoms, pelvic nodularity, and tenderness[9]. It is similarly effective to leuprolide acetate[10]. However, owing to its non-specific binding to androgen and glucocorticoid receptors, adverse effects of a negative lipid profile, excessive weight gain, and acne have been increasingly reported[4,11].

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Prolonged use remains controversial owing to its effect on carbohydrate metabolism[12]. Alternative medication should be considered in such patients.

Dienogest is a fourth-generation progestin that has been used by our department since 2013. It binds to progesterone receptors more specifically, with a localised effect on endometriotic lesions by directly reducing proliferation and cytokine production in endometriotic stromal cells[13], while having little androgenic, oestrogenic, glucocorticoid, and mineralcorticoid activity. Thus, it exerts minimal impact on metabolic parameters[14]. In a study in Japan, dienogest resulted in ≥25% shrinkage of endometrioma in 77% and 85% of patients after 24 and 52 weeks of treatment, respectively[15]. It has also been shown to decrease the proportion of patients with severe endometriosis (stage III/IV) from 70% to 30%[16]. Treatment for 24 weeks markedly reduced endometriosis-related symptoms (dyspareunia, diffuse pelvic pain, menstrual pain, and premenstrual pain)[16]. Compared with placebo, dienogest significantly improved endometriosis-related pelvic pain while maintaining safety and tolerability[17]. Dienogest and a gonadotrophin-releasing hormone analogue showed a comparable efficacy and safety profile[18-20].

This study aimed to compare dienogest with medroxyprogesterone acetate for management of endometriosis in terms of menstrual pain, quality of life, adverse effects, tolerability, and overall satisfaction.

Methodology

This cross-sectional, observational study was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee of the Hospital Authority. The sample size was calculated with the primary consideration to reduce menstrual pain score. We hypothesised that dienogest was superior to medroxyprogesterone acetate in reducing endometriosis-associated menstrual pain. After 6 months of treatment, the mean reduction in pain score was 82% for dienogest[17] and 53% for medroxyprogesterone acetate[21]. A difference of 30% between the study cohorts was considered clinically significant. To have a 90% chance of detecting such a difference at an overall significance level of 0.05, 20 patients per cohort were required. We aimed to recruit 30 patients per cohort to allow for dropouts.

A questionnaire together with a written consent was posted in July 2017 to 60 Chinese women with endometriosis aged 18 to 55 years for completion. They were receiving active treatment for ≥6 months with either medroxyprogesterone acetate (150 mg intramuscularly every 3 months) [n=30] or dienogest (2 mg oral daily) [n=30, since 2013]. They had good compliance and were followed up in the general gynaecology outpatient clinic of Queen Elizabeth Hospital. The diagnosis of endometriosis was based on either pathology (after surgery) or ultrasonography (with evidence of endometrioma >3 cm, nodules of the rectovaginal septum and bladder, combined with clinical symptoms of menstrual pain or pelvic pain).

Clinical records of patients were reviewed to ensure that different hormone treatment options were offered unless contraindicated. The questionnaire was in two sections (before and after treatment) and comprised 11 questions about pain (n=4), quality of life (n=3), side-effects and tolerability (n=3), and overall satisfaction with treatment (n=1) [Table 1]. Pain symptoms included menstrual pain, chronic pelvic pain, dyspareunia, and dyschezia. The latter three symptoms were derived from the pain symptoms enquiry in the Biberoglu and Beham score[22,23]. Quality of life assessment was based on questions derived from the SF-36 questionnaire[24] and included daily living, work life, and social life. An 11-point rating scale was used, according to the recommendation of the Method, Measurements and Pain Assessment in Clinical Trials[22].

The primary outcome was the mean menstrual pain scores before and after treatment. Secondary outcomes were other pain symptoms (chronic pelvic pain, dyspareunia, and dyschezia), quality of life score, side-effect profile, overall satisfaction, and tolerability of the two groups. Statistical analysis was based on the intention to treat principle. Baseline characteristics of the two groups were compared using the unpaired Student's *t* test or Fisher's exact test, as appropriate. The Mann-Whitney *U* test was used to compare the two groups before and after hormonal treatment. Non-parametric tests were used to avoid distributional assumption. All tests were two-sided. A p value of <0.05 was considered statistically significant.

Results

25 patients from the dienogest group and 26 patients from the medroxyprogesterone acetate groups returned the questionnaire, giving an overall response rate of 83%. Before treatment, the two groups were comparable in terms of baseline characteristics, pain symptoms, and quality of life (Table 2). Endometriosis staging was not routinely documented, as some patients had undergone surgery in the private sector. Nonetheless, endometriosis staging has not been shown to be consistently related to pain symptoms in terms of the revised American Fertility Society score[25].

Table 1. Questions about pain, quality of life, adverse effects, and tolerability, and overall satisfaction with hormonal treatment for endometriosis

Question
Before treatment
How bad was the pain with your periods?
Did you ever experience these symptoms? If yes, how severe was it?
Chronic pelvic pain (pain that is not related with period)
Pain during sexual intercourse
Pain during bowel opening
Did dysmenorrhea or chronic pelvic pain affect your daily activity? If yes, how bad was the impact?
Daily activity
Working (leading to absence from work or sick leave)
Social activities
After treatment
How bad was the pain with your periods?
Did you ever experience these symptoms? If yes, how severe was it?
Chronic pelvic pain (pain that is not related with period)
Pain during sexual intercourse
Pain during bowel opening
Did dysmenorrhea or chronic pelvic pain affect your daily activity? If yes, how bad was the impact?
Daily activity
Working (leading to absence from work or sick leave)
Social activities
Did the hormonal treatment affect your period? (irregular period, absence of period, or no change)
Did the hormonal treatment affect the flow of your period? (heavy flow, decreased flow, or no change)
Was there any side-effect from the hormonal treatment? If yes, what was it?
Did the side-effect mentioned affect your daily activities?
Overall, do you satisfy with the hormonal treatment?
Would you continue current hormonal treatment? (yes or no)
What is the reason for not to continue the hormonal treatment? (side-effects, unable to relieve symptoms, or not convenience to use)

After treatment, the mean score for menstrual pain in the dienogest and medroxyprogesterone acetate groups reduced from 5.5 and 4.88 to 1.8 and 3.65, respectively, with the dienogest group achieving a greater absolute reduction (6.6 vs. 4.69, p=0.044, Table 2). Nonetheless, the two groups were comparable in terms of absolute reduction in score for chronic pelvic pain, dyspareunia, or dyschezia. Regarding quality of life for daily living, work life, and social life, both groups achieved a significant improvement and were comparable in terms of absolute reduction in scores (Table 2).

No major adverse effects were reported in either group; minor adverse effects were reported in 14 (56%) and 13 (50%) patients in the dienogest and medroxyprogesterone acetate group, respectively. The most common adverse effect reported was weight gain (n=9). The impact of adverse effects on quality of life score was similar in both groups. Persistent per vaginal spotting was reported in 10 (40%) and 15 (58%) patients, respectively; more patients (though not significantly) in the medroxyprogesterone acetate group had an irregular cycle (p=0.057).

Respectively, 22 (88%) and 23 (88%) patients in the dienogest and medroxyprogesterone acetate group opted to continue treatment. Satisfaction score was higher with dienogest than medroxyprogesterone acetate (8.2 vs. 6.81, p=0.024, Table 2).

Table 1. Comparison of the dienogest and medroxyprogesterone acetate groups in terms of baseline characteristics, pain symptoms, quality of life, satisfaction, and adverse effects before and after treatment

Variable	Dienogest group (n=25)*	Medroxyprogesterone acetate group (n=26)*	p Value
Patient age, y	38±6.95	40±6.07	0.153
Previous delivery			
Primigravida	18 (72.0)	14 (53.8)	0.249
Multiparous	7 (28.0)	12 (46.1)	0.249
Treatment duration, m	25.16±13.2	41.26±43.8	0.085
Previous surgery for endometriosis	18 (72.0)	12 (46.1)	0.089
Endometriomas	21 (84.0)	15 (57.7)	0.064
Deep endometriosis	8 (32.0)	12 (46.2)	0.393
Previous use of other hormones	15 (60.0)	9 (34.6)	0.095
Pain symptom score			
Menstrual pain			
Before treatment	5.5 (4.03-7.01)	4.88 (3.47-6.3)	0.34
After treatment	1.8 (0.64-2.96)	3.65 (2.46-4.85)	0.008
Absolute reduction	6.6 (5.37-7.83)	4.69 (5.37-7.83)	0.044
Chronic pelvic pain			
Before treatment	5.04 (3.75-6.33)	5.00 (3.62-6.38)	0.970
After treatment	2.08 (0.9-3.26)	3.04 (1.85-4.22)	0.143
Absolute reduction	2.96 (1.5-4.42)	1.96 (0.41-3.52)	0.647
Dyspareunia			
Before treatment	2.72 (1.31-4.13)	2.5 (1.41-3.59)	0.833
After treatment	1.12 (0.19-2.05)	1.81 (0.91-2.71)	0.082
Absolute reduction	1.6 (0.35-2.85)	0.69 (-0.26-1.65)	0.828
Dyschezia			
Before treatment	2.64 (1.3-3.98)	2.85 (1.54-4.16)	0.829
After treatment	0.76 (0.02-1.5)	1.69 (0.7-2.69)	0.063
Absolute reduction	1.88 (0.66-3.1)	1.15 (0.43-1.87)	0.692
Quality of life score			
Impact on daily living			
Before treatment	7.32 (6.43-8.21)	7.23 (6.01-8.45)	0.600
After treatment	1.6 (0.52-2.68)	2.38 (1.28-3.49)	0.129
Absolute reduction	5.72 (4.5-6.93)	4.85 (3.31-6.38)	0.477
Impact on work			
Before treatment	7.2 (6.08-8.32)	7.19 (5.95-8.43)	0.803
After treatment	1.32 (0.35-2.29)	2.65 (1.47-3.84)	0.054
Absolute reduction	5.88 (4.65-7.1)	4.54 (2.87- 6.21)	0.324
Impact on social life			
Before treatment	6.6 (5.38-7.82)	7.42 (6.23-8.61)	0.211
After treatment	1.16 (0.18-2.14)	2.35 (1.24-3.45)	0.052
Absolute reduction	5.44 (4.26-6.61)	5.08 (3.42-6.72)	0.962
Adverse effects	14 (56)	13 (50)	0.668
Weight gain	4	5	
Headache	1	1	
Mood changes	4	1	
Insomnia	1	1	
Breast discomfort	1	0	
Tiredness	2	0	
Skin allergy	0	1	
Dizziness	0	2	
Non-specific	1	2	
Impact of adverse effects on quality of life score	2.16 (0.91-3.41)	2.58 (1.42-3.73)	0.33
Menstrual pain	5 (20)	6 (23)	0.79
Persistent per vaginal spotting	10 (40)	15(58)	0.21
Amenorrhoea	13 (52)	12 (46)	0.68
Irregular cycles	3 (12)	9 (35)	0.057
Overall satisfaction score	8.2 (7.43-8.97)	6.81 (5.83-7.78)	0.024

* Data are presented as mean ± standard deviation, No. or No. (%) of patents, or mean (range)

Discussion

Our study demonstrated that both dienogest and medroxyprogesterone acetate are an effective treatment for endometriosis-induced pain symptoms, with dienogest achieving a greater absolute reduction in menstrual pain than medroxyprogesterone acetate. This can be explained by dienogest's high specificity for the progesterone receptor and high oral availability. Dienogest has anti-androgenic activity but no mineralocorticoid or glucocorticoid activity. Dienogest creates a mild systemic hypoestrogenic and a potent local hyperprogestogenic environment that leads to atrophy of endometriotic lesions, in addition to a direct inhibitory effect on ovarian follicle development[15,16,26,27].

In our study, both dienogest and medroxyprogesterone acetate lessened the impact of endometriosis on daily living, social life, and work life. A study quantifying the impact of endometriosis symptoms on quality of life reported a mean of 13% loss in work time (absenteeism), 65% impairment in work (presenteeism), 64% loss in work productivity, and 60% impairment in daily activities[28].

In our study, both dienogest and medroxyprogesterone acetate were well tolerated with no severe adverse effects reported. Around half of the patients in each group experienced minor adverse effects such as weight gain, mood change, and headache. In a study that compared norethisterone with dienogest, 41% of patients with dienogest experienced an adverse effect after 6 months[29]. In another study, 86.9% of patients with subcutaneous medroxyprogesterone acetate experienced at least one side-effect during a treatment period of 6 months[30]. Dienogest is better tolerated than other progesterones, probably because dienogest conforms to the oestrogen threshold hypothesis that optimal endometriosis therapy enables suppression that is moderate enough to prevent hypoestrogenic adverse effects such as mood changes or bone mineral density loss[31]. It has been suggested that dienogest can be safely used for up to 5 years without adverse effects and can reduce the endometriosis recurrence rate to 4%, compared with 69% with placebo[32]. The VISADO study concluded that the efficacy of dienogest in relieving endometriosis-related symptoms in adolescents was comparable with that achieved in an adult population[33].

Irregular bleeding is a characteristic of progestin use[34]. In our study, both dienogest and medroxyprogesterone acetate groups reported comparable rates of persistent per vaginal spotting and irregular menstrual cycles. Nonetheless, longer-term treatment with dienogest has been reported to reduce bleeding intensity and frequency[35]. Although bleeding irregularities associated with progestin may adversely affect quality of life, the overall continuation rate was high in both groups, with the dienogest group reporting a significantly higher satisfaction score. Adequate counselling about the likely course of altered bleeding patterns is vital to promote treatment adherence and satisfaction.

Weight gain is a common adverse effect of progestin and often leads to discontinuation of treatment, particularly in young patients[36]. Dienogest has been reported to result in weight gain so small that it does not substantially differ to placebo[37].

In our study, 28% of patients in the dienogest group and only 7.7% of patients in the medroxyprogesterone group complained of mood changes. However, two studies that compared dienogest with norethisterone or gonadotrophin-releasing hormone analogue reported less mood changes or depression with dienogest[18,28]. One case report mentioned the use of dienogest to treat premenstrual mood changes in a patient with schizophrenia who was refractive to other hormonal treatment[38]. Whether dienogest is associated with more mood changes remains controversial. Further study is needed to confirm this suggestion, and the Hospital Anxiety and Depression Scale should be used to determine any clinically significant difference[39].

The resumption of ovulation is delayed following discontinuation of medroxyprogesterone acetate, potentially affecting pregnancy planning[40]. There is no such report for dienogest and hence it may be a more desirable choice. In our study, although 12% of patients in each group opted for discontinuation (mostly because of adverse effects and failure to respond to treatment), patients were more satisfied with dienogest than medroxyprogesterone acetate. Dienogest achieved significantly greater improvement in endometriosis-related menstrual pain. It achieved better control of other pain symptoms, improvement in quality of life, and adverse effect profile than medroxyprogesterone acetate, although not significantly. Dienogest has demonstrated its effectiveness in treating endometriosis in Chinese women[41]. Nonetheless, medroxyprogesterone acetate is a licensed contraceptive that can be delivered orally, subcutaneously, or intramuscularly to manage endometriosis[42]. These benefits may be useful for patients with poor compliance.

There are several limitations in our study. The sample size was small. Dienogest was only introduced in 2013 and was not widely used initially. The pre- and post-test design

is commonly used to compare different medications[43], and has been used to compare dienogest with norethisterone[28]. Nonetheless, the design lacks randomisation and thus any association observed may be due to confounding factors rather than hormonal treatment. In addition, there may have been recall error, as patients were asked to complete both before and after treatment questionnaires at the same time. Objective measurement was lacking. Change in haemoglobin or endometrioma size was not measured, nor was the effect of treatment on bone mass density or lipid level. Medroxyprogesterone acetate is associated with a negative impact on lipid metabolism[44], but no such impact has been reported for dienogest[45,46]. Medroxyprogesterone acetate is associated with a small loss of bone mass density that can be recovered after discontinuation of treatment[47]. Dienogest is associated with minimal change in bone turnover markers and lumbar spine bone mass density after 24 weeks of use[36]. Larger-scale randomised controlled studies are warranted.

Conclusion

Dienogest is potentially more effective than medroxyprogesterone acetate in treating symptomatic endometriosis, especially in control of menstrual pain, with higher tolerability and satisfaction rate.

Declaration

The authors have no conflict of interests to declare.

References

1. Bazot M, Lafont C, Rouzier R, Roseau G, Thomassin-Naggara I, Darai E. Diagnostic accuracy of physical examination, transvaginal sonography, rectal endoscopic sonography, and magnetic resonance imaging to diagnose deep infiltrating endometriosis. *Fertil Steril* 2009; 92:1825-33.
2. Moghissi KS, Schlaff WD, Olive DL, Skinner MA, Yin H. Goserelin acetate (Zoladex) with or without hormone replacement therapy for the treatment of endometriosis. *Fertil Steril* 1998; 69:1056-62.
3. Chapron C, Souza C, Borghese B, et al. Oral contraceptives and endometriosis: the past use of oral contraceptives for treating severe primary dysmenorrhea is associated with endometriosis, especially deep infiltrating endometriosis. *Hum Reprod* 2011; 26:2028-35.
4. Selak V, Farquhar C, Prentice A, Singla A. Danazol for pelvic pain associated with endometriosis. *Cochrane Database Syst Rev* 2007; 4:CD000068.
5. Brown J, Farquhar C. Endometriosis: an overview of Cochrane Reviews. *Cochrane Database Syst Rev* 2014; 3:CD009590.
6. Petta CA, Ferriani RA, Abrao MS, et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. *Hum Reprod* 2005; 20:1993-8.
7. Crosignani P, Olive D, Bergqvist A, Luciano A. Advances in the management of endometriosis: an update for clinicians. *Hum Reprod* Update 2006; 12:179-89.
8. Moghissi KS, Boyce CR. Management of endometriosis with oral medroxyprogesterone acetate. *Obstet Gynecol* 1976; 47:265-7.
9. Luciano AA, Turksoy RN, Carleo J. Evaluation of oral medroxyprogesterone acetate in the treatment of endometriosis. *Obstet Gynecol* 1988; 72:323-7.
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. Sonmezer M, Atabekoglu C, Cengiz B, Dokmeci F, Cengiz SD. Depot-medroxyprogesterone acetate in anticoagulated patients with previous hemorrhagic corpus luteum. *Eur J Contracept Reprod Health Care* 2005; 10:9-14.
12. Lopez LM, Grimes DA, Schulz KF. Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes mellitus. C*ochrane Database Syst Rev* 2014; 4:CD006133.
13. Yamanaka K, Xu B, Suganuma I, et al. Dienogest inhibits aromatase and cyclooxygenase-2 expression and prostaglandin E2 production in human endometriotic stromal cells in spheroid culture. *Fertil Steril* 2012; 97:477-82.
14. Sasagawa S, Shimizu Y, Kami H, et al. Dienogest is a selective progesterone receptor agonist in transactivation analysis with potent oral endometrial activity due to its efficient pharmacokinetic profile. *Steroids* 2008; 73:222-31.
15. Harada T, Momoeda M, Taketani Y, et al. Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis: a randomized, double-blind, multicenter, controlled trail. *Fertil Steril* 2009; 91:675-81.
16. Köhler G, Faustmann TA, Gerlinger C, Seitz C, Mueck AO. A dose-range study to determine the efficacy and safety of 1, 2, and 4mg of dienogest daily for endometriosis. *Int J Gynaecol Obstet* 2010; 108:21-5.
17. Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study. *Eur J Obstet Gynecol Reprod Biol* 2010; 151:193-8.
18. Strowitzki T, Marr J, Gerlinger C, Faustmann T, Seitz C. Detailed analysis of a randomized, multicenter, comparative trial of dienogest versus leuprolide acetate in endometriosis. *Int J Gynaecol Obstet* 2012; 117:228-33.
19. Strowitzki T, Marr J, Gerlinger C, Faustmann T, Seitz C. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24-week, randomized,

multicentre, open-label trial. *Hum Reprod* 2010; 25:633-41.
20. Andres Mde P, Lopes LA, Baracat EC, Podgaec S. Dienogest in the treatment of endometriosis: systematic review. *Arch Gynecol Obstet* 2015; 292:523-9.
21. Walch K, Unfried G, Huber J, et al. Implanon versus medroxyprogesterone acetate: effects on pain scores in patients with symptomatic endometriosis: a pilot study. *Contraception* 2009; 79:29-34.
22. Vincent K, Kennedy S, Stratton P. Pain scoring in endometriosis: entry criteria and outcome measures for clinical trials. Reports from the Art and Science of Endometriosis meeting. *Fertil Steril* 2010; 93:62-7.
23. Bourdel N, Alves J, Pickering G, Ramilo I, Roman H, Canis M. Systematic review of endometriosis pain assessment: how to choose a scale? *Hum Reprod Update* 2015; 21:136-52.
24. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-item Short-Form Health Survey (SF-36): II. Psychometric and clinical test of validity in measuring physical and mental health constructs. *Med Care* 1993; 31:247-63.
25. Vercellini P, Trespidi L, De Giorgi O, Cortesi I, Parazzini F, Crosignani PG. Endometriosis and pelvic pain: relation to disease stage and localization. *Fertil Steril* 1996; 65:299-304.
26. Cosson M, Querleu D, Donnez J, et al. Dienogest is as effective as triptorelin in the treatment of endometriosis after laparoscopic surgery: results of a prospective, multicenter, randomized study. *Fertil Steril* 2002; 77:684-92.
27. Momoeda M, Taketani T. Randomized double-blind, multicentre, parallel-group dose-response study of dienogest in patients with endometriosis [in Japanese]. *Jpn Pharmacol Ther* 2007; 35:769-83.
28. Fourquet J, Báez L, Figueroa M, Iriarte RI, Flores I. Quantification of the impact of endometriosis symptoms on health-related quality of life and work productivity. *Fertil Steril* 2011; 96:107-12.
29. Vercellini P, Bracco B, Mosconi P, et al. Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. *Fertil Steril* 2016; 105:734-43.e3.
30. 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.
31. Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. *Am J Obstet Gynecol* 1992; 166:740-5.
32. Ota Y, Andou M, Yanai S, et al. Long-term administration of dienogest reduces recurrence after excision of endometrioma. *J Endometr Pelvic Pain Discord* 2015; 7:63-7.
33. Ebert AD, Dong L, Merz M, et al. Dienogest 2 mg daily in the treatment of adolescents with clinically suspected endometriosis: The VISanne Study to *Assess Safety in ADOlescents*. J Pediatr Adolesc Gynecol 2017; 30:560-7.
34. 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.
35. Momoeda M, Harada T, Terakawa N, et al. Long-term use of dienogest for the treatment of endometriosis. *J Obstet Gynaecol* Res 2009; 35:1069-76.
36. Paul C, Skegg DC, William S. Depot medroxyprogesterone acetate. Patterns of use and reasons for discontinuation. *Contraception* 1997; 56:209-14.
37. Strowitzki T, Faustmann T, Gerlinger C, Schumacher U, Ahlers C, Seitz C. Safety and tolerability of dienogest in endometriosis: pooled analysis from the European clinical study program. *Int J Womens Health* 2015; 7:393-401.
38. Kamada Y, Sakamoto A, Kotani S, Masuyama H. Treatment of premenstrual mood changes in a patient with schizophrenia using dienogest: a case report. *J Obstet Gynaecol Res* 2018; 44:797-800.
39. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67:361-70.
40. 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.
41. Lang J, Yu Q, Zhang S, et al. Dienogest for treatment of endometriosis in Chinese women: a placebo-controlled, randomized, double-blind phase 3 study. *J Womens Health (Larchmt)* 2018; 27:148-55.
42. Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod* 2014; 29:400-12.
43. Sedgwick P. Before and after study designs. *BMJ* 2014; 349:g5074.
44. Berenson AB, Rahman M, Wilkinson G. Effect of injectable and oral contraceptives on serum lipids. *Obstet Gynecol* 2009; 114:786-94.
45. Nikschick S, Kohler G, Mannchen E. Carbohydrate metabolism during treatment of endometriosis with the progestin dienogest. *Exp Clin Endocrinol* 1989; 94:211-4.
46. Köhler G, Lembke S, Brachmann K, Foth D, Happke S. Behavior of parameters of liver metabolism in intermediate-term use of the gestagen dienogest in the treatment of endometriosis [in German]. *Zentralbl Gynakol* 1989; 111:807-10.
47. Lopez LM, Chen M, Mullins S, Curtis KM, Helmerhorst FM. Steroidal contraceptives and bone fractures in women: evidence from observational studies. *Cochrane Database Syst Rev* 2012; 8:CD009849.