

Effects of Etonogestrel implants on pelvic pain and menstrual flow in women suffering from adenomyosis or endometriosis

Results from a prospective, observational study

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Abstract

Adenomyosis and endometriosis are common causes of pelvic pain in women of reproductive age. Furthermore, adenomyosis is a major cause of menorrhagia. This study aimed to evaluate the effects of Etonogestrel implants on pelvic pain and menstrual flow in women requiring long-acting reversible contraception and suffering from adenomyosis or endometriosis.

One hundred women with adenomyosis or endometriosis and asking for contraception with Etonogestrel implants were enrolled in this study and were followed-up for 24 months. Patients were interviewed on pelvic pain by visual analog scale (VAS) pain score, menstrual flow by the number of sanitary napkins, menstrual bleeding pattern, weight gain, breast pain, and any other treatment side effects.

Seventy four patients who were treated with Etonogestrel implants completed the 24-month follow-up in which we found a significant decrease in pelvic pain VAS scores comparing baseline scores to 6, 12, and 24 months (baseline: 6.39 ± 2.35 to 24-month: 0.17 ± 0.69 , $P < 0.05$). The menstrual volume decreased significantly compared with that at baseline (40.69 ± 30.92 %, $P < 0.05$). However, vaginal bleeding, amenorrhea, weight gain, and acne occurred after treatment in some patients.

Etonogestrel implants were effective in reducing pelvic pain and menstrual flow of adenomyosis or endometriosis.

Abbreviations: BMI = body mass index, GnRH = gonadotropin-releasing hormone, LARC = long-acting reversible contraception, LH = luteinizing hormone, LNG-IUS = levonorgestrel intrauterine contraceptive system, SD = standard deviation, VAS pain score = visual analog scale pain score.

Keywords: adenomyosis, endometriosis, Etonogestrel implants, menorrhagia, pelvic pain

1. Introduction

Adenomyosis and endometriosis are chronic estrogen-dependent gynecological diseases characterized by the presence of endometrial glands and stroma outside the uterine cavity. They occur in 2% to 20% of women of reproductive age.^[1,2] And 15% to 40%

of adenomyosis combined with endometriosis.^[3,4] Chronic pelvic pain represents one of the most common symptoms of adenomyosis and endometriosis. In addition, the common clinical manifestations of adenomyosis include increased menstrual flow and prolonged menstrual period. And uterine adenomyosis is the one of most common causes among the structural causes of abnormal uterine bleeding in Chinese women.^[5] Furthermore, among women suffering from adenomyosis or endometriosis, chronic fatigue syndrome, which manifests with widespread myalgia and arthralgia, cognitive difficulties, and other somatic and mental symptoms, are more often found. Women with adenomyosis or endometriosis are exhausted and tend to react more strongly to stressors. So, adenomyosis and endometriosis are medical, emotional, and sociological problems.^[6]

The management of adenomyosis and endometriosis includes both surgical and medical treatments. On one hand, surgery can remove the uterus or visible lesions in the pelvic cavity. However, since surgery can not affect the pathogenic mechanisms of adenomyosis and endometriosis, it is unable to prevent the diseases from recurrence. On the other hand, medical treatments, including gonadotropin-releasing hormone (GnRH) agonists and analogs, high-performance progestogen, compound oral contraceptive, androgen derivative, approach aims to suppress ovulation, and menstruation. To achieve a therapeutic effect, these treatments should be administered in a continuous regimen and for long period.^[7,8] However, most of the available therapeutic options are burdened by considerable systemic side

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The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

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effects, like climacteric symptoms, osteoporosis, elevated liver enzymes, and weight gain. Inconvenience in usage and side effects affect treatment compliance and preclude long-term use.

Implanon, a single rod Etonogestrel implant produced by N.V. Organon containing 68 mg Etonogestrel that is slowly released for up to 3 years, provides an alternative way of delivering progestogens. It is a subcutaneous progestogen-releasing device that achieved contraceptive action mainly by inhibition of the secretion of luteinizing hormone (LH) and ovulation. Among the previously published studies, several researchers reported a comparable average decrease in pelvic pain after the treatment with Etonogestrel implants in patients suffering from endometriosis.^[9–11] Nevertheless, fewer studies were found in patients affected by adenomyosis, and all these studies were limited in sample size and follow-up time.^[12] So, it did not allow us to draw a firm conclusion about the topic.

Therefore, this multicenter observational prospective self-controlled study aimed to further evaluate the effect of Etonogestrel implants on pelvic pain and menorrhagia in women requiring long-acting reversible contraception (LARC) suffering from adenomyosis or endometriosis.

2. Materials and methods

2.1. Subject

From May 2014 to October 2015, we screened a population of 400 women asking for long-term reversible contraception with Etonogestrel implants at the Women's Hospital, School of Medicine, Zhejiang University and Zhejiang province Lin'an District Maternal and Child Health Care Center. All the 400 patients were part of the clients from the contraceptive counseling clinic. And after counseling and exclusion of contraindications, they choose Etonogestrel implants. Then, we included 100 women affected by adenomyosis or endometriosis, mean age, 33.81 ± 5.24 years (range 20–45 years), with a clinical history of pelvic pain or menorrhagia. The inclusion criteria for this observational clinical study were women >18 years-of-age, confirmed adenomyosis or endometriosis (diagnosed by clinical symptoms and signs, transvaginal ultrasound,^[13,14] serum CA125 level), ineligibility, or patient refusal for surgery or other hormonal treatment. We excluded patients with uterine fibroids, endometrial polyps, and other gynecopathy except adenomyosis and endometriosis; cardiovascular, hepatic, renal impairment, or any other contraindications and special warnings for treatment with Etonogestrel.

Fifty-six of the 100 women were adenomyosis patients and 44 were endometriosis patients. All the patients suffered from different degrees of pelvic pain and 26 patients suffered from menorrhagia. Twenty-six patients suffered from severe pelvic pain and needed to take a pain killer. Twelve of the 56 adenomyosis patients had a previously use of Levonorgestrel intrauterine contraceptive system (LNG-IUS, Mirena).

The study was approved by Ethics Committee of Women's Hospital, School of Medicine, Zhejiang University (20180125). All the patients were well informed regarding the procedures that they underwent and signed consent forms.

2.2. Methods

Before subcutaneous implantation of the Etonogestrel implants, all patients underwent pelvic examinations, breast examinations,

blood routine tests, blood biochemistry tests, blood coagulation function tests, cervical cytology, breast ultrasound, and transvaginal ultrasound to exclude liver and renal dysfunctions, blood diseases, gynecological cancer or breast cancer, or recent reproductive tract infection. Between days 1 to 5 of the menstrual cycle, subcutaneous implantation was performed by trained clinical staff, and implantation was confirmed to be successful for each study participant.

All the patients were followed up by trained specialized clinical personnel at 1, 6, 12, and 24-month after subcutaneous Etonogestrel implantation. A specially designed chart was used for follow-up consultations for all patients. Pain symptoms were interviewed by investigators using a VAS pain score (0–10).^[15] The 0-point was for no pain, and 10 for the strongest unbearable pain. A decrease of more than 2-point of the VAS score meant the remission of the pelvic pain. Menstrual flow was estimated through the number of sanitary napkins used in the menstrual period according to the FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding.^[16] The baseline (before implantation) was defined as 100%. Record the ratio after implantation by comparing it to baseline.

In addition, changes in the bleeding pattern (bleeding, spotting, amenorrhea, and oligomenorrhea) according to World Health Organization (WHO)-recommended definition,^[17] and other adverse reactions were interviewed and recorded.

2.3. Statistical analysis

Statistical analysis was performed using SPSS 19.0 software (SPSS Inc. Chicago, IL, USA). Descriptive data were shown as the mean \pm standard deviation (SD). The significance of compared differences was tested using the paired *t*-test for measurement data and chi-square test for numeration data. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Pelvic pain

All the 100 participants suffered from varying degrees of pelvic pain before implantation of the Etonogestrel implants. And 26 of them required pain killer, including indomethacin, ibuprofen, and acetaminophen, to relieve pelvic pain.

At the 6-month follow-up after implantation, 5 patients removed the Etonogestrel implants. Eighty-one of the rest 95 patients reported milder pelvic pain. At the 12-month follow-up after implantation, another 8 patients removed the Etonogestrel implants. And 73 of the rest 87 patients reported a complete remission of pelvic pain. At the 24-month follow-up after implantation, a total of 26 patients removed the Etonogestrel Implants. And 66 of the rest 74 patients reported a complete remission of pelvic pain.

The VAS score significantly decreased, from 6.39 ± 2.35 pre-implantation to 0.59 ± 0.37 at 6 months after implantation ($P < 0.01$) (Table 1).

3.2. Menstrual flow

All the participants had normal menstrual cycles before subcutaneous Etonogestrel implantation, without irregular vaginal bleeding or amenorrhea. Following subcutaneous Etonogestrel implantation, the menstrual flow of the patients

Table 1
VAS scores before and after implantation of Etonogestrel implants.

	cases	Pelvic pain (VAS)	t	P
Baseline	100	6.39±2.35		
6 months	95	0.59±0.37	11.383	.000
12 months	87	0.44±0.86	5.067	.000
24 months	74	0.17±0.69	2.439	.017

VAS=visual analog scale.

who continuously used the Etonogestrel implants decreased obviously from 100±0.00 pre-implantation to 56.32±36.21 at 6 months after implantation ($P < 0.01$) (Table 2).

At the 6-month, 12-month, and 24-month follow-up after implantation, the amenorrhea/oligomenorrhea incidence rate was 54.73% (52/95), 57.47% (50/87), and 58.11% (43/74).

3.3. The rate of continued use and side effects

A total of 26 patients had the implants removed, and the 6-month, 12-month, and 24-month continuation rate were 95.0%, 87.0%, and 74.0%. Seventeen of adenomyosis patients (30.4%) and 9 of endometriosis patients (20.5%) had their implants removed, but there was no statistically significance between the two groups ($\chi^2 = 1.256, P = 0.262$).

The main reasons for implants removed included vaginal bleeding (16/26 patients, 61.54%), amenorrhea (5/26 patients, 19.23%), weight gain (2/26patients, 7.69%), planned pregnancy (2/26patients, 7.69%), and severe constipation (1/26patients, 3.85%). Most of the patients reported spotting or irregular vaginal bleeding. However, 2 adenomyosis patients reported mass vaginal bleeding at 6 and 7 months after implantation. The two young patients, with uterus as large as 2 and a half months of pregnancy, had been unwilling to undergo hysterectomy. But due to unsuccessful treatment of Etonogestrel implants, subtotal hysterectomy had been taken at the end.

Among all the participants, changes in vaginal bleeding patterns (72/100patients) were most common. The other side effects included weight gain (19/100patients), acne (13/100patients), breast tenderness (10/100patients), arm itching, rash, numbness (2/100patients), mood changes (3/100patients), hyposexuality (2/100patients), sleep disorder (2/100patients), skin pigmentation (2/100patients), and constipation (1/100patients). No patient was pregnant.

3.4. Implantation following failure treatment of LNG-IUS

Twelve of the 56 adenomyosis patients, who were suffered from both pelvic pain and menorrhagia, had a previously use of LNG-IUS. However, the devices were expelled due to an obviously enlarged uterus and excessive menstrual flow. For unwillingness

Table 2
Menstrual flow before and after implantation of Etonogestrel implants.

	Cases	Menstrual flow (%)	t	P
Baseline	100	100.00±0.00		
6 months	95	56.32±36.21	9.562	.001
12 months	87	41.12±32.45	12.964	.002
24 months	74	40.69±30.92	11.962	.003

of hysterectomy, subcutaneous implantations of Etonogestrel implants were performed after being fully informed. The decreased menstrual flow and alleviated or eliminated pelvic pain were observed in 10 of the 12 patients. The rest 2 patients removed the implants for failure treatment of Etonogestrel implants during the study period. Two-year continuation rate was 83.3%.

4. Discussion

In this study, Etonogestrel implants were confirmed effectively in reducing pelvic pain and menstrual flow of adenomyosis or endometriosis.

The treatment of adenomyosis and endometriosis has been a clinical challenge, considering the high recurrence rates of these two diseases. Even if surgical treatments have been performed, most of the patients still need long-term medical treatments to reduce the recurrent chance, especially among patients with pelvic pain. According to the available evidence, there are no major differences in terms of efficacy between various medical treatments, including the use of GnRH agonists and analogs, high-performance progestogen, compound oral contraceptive, androgen derivative.^[7,8] To achieve therapeutic effect, all these treatments should be used in a continuous regimen. Therefore, easy-to-use, long-acting, tolerable medicine or systems may be more favorable in improving patients' compliance and better in preventing adenomyosis and endometriosis from recurrence.

Progestins have been reported to reduce or eliminate pelvic pain effectively in patients affected by adenomyosis and endometriosis. For instance, a retrospective study evidenced a marked relief from adenomyosis associated menorrhagia and pain can be obtained with the use of norethindrone acetate.^[18] Dienogest has been shown effective in reducing adenomyosis-associated pelvic pain as well as serum CA-125 and CA19-9 levels.^[19] The efficacy and safety of Esmya, Duphaston, and Dienogest treatment were compared in a clinical trial, showing a significant reduction in lesion size and weight of endometriosis. However, upon treatment cessation, lesion growth rebound in all the 3 groups.^[20] Furthermore, the LNG-IUS is an effective treatment for adenomyosis and endometriosis particularly on dysmenorrhea and heavy menstrual bleeding.^[21,22] The LNG-IUS treatment longer than 5 years is an effective and feasible method for patients diagnosed with adenomyosis.^[23] In a prospective randomized clinical trial, Ozdegirmenci et al compared the LNG-IUS with hysterectomy in adenomyosis patients. LNG-IUS demonstrated significant and comparable improvements in hemoglobin levels and seemed to have superior effects on patients' psychological and social lives.^[24]

Etonogestrel is the main component of Implanon which is an effective progestin-only contraceptive and inhibits the secretion of LH and ovulation. Its contraceptive effect can be quickly achieved after insertion, and last for at least 3 years. Etonogestrel might affect the lesions of adenomyosis or endometriosis both directly, through progesterone receptors in the heterotopic endometrium and interstitial cells, and indirectly, inhibiting ovulation, and thus eliminating the ovulatory peak of estrogen and reducing the average estrogen levels during the menstrual cycle,^[25] thereby alleviate the symptoms of adenomyosis and endometriosis.

In the present study, we investigated the effects of Etonogestrel implants on pelvic pain and menstrual flow in women with adenomyosis or endometriosis. The effect of treatment with the

Etonogestrel implant on pelvic pain was evaluated using the VAS pain scoring method.^[15] We found a significant reduction in VAS score from baseline to 6, 12, and 24 months after treatment. And respectively 89.19% (66/74) of patients experienced a remission of pain within 24 months after treatment. One previous study has suggested that Etonogestrel implants may reduce the uterine volumes of adenomyosis patients.^[12] However, according to data gathered in this study, we did not find any significant change in uterine volumes after treatment.

Menorrhagia is another common clinical manifestation of adenomyosis. And it is one of the main reasons for hysterectomy. In this study, the amount of menstrual flow was estimated through the number of sanitary napkins used in the menstrual period according to the FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding.^[16] The baseline (before implantation) was defined 100%. The mean relative ratio of napkins used was decreased to (40.69 ± 30.92) % within 24 months after treatment.

The LNG-IUS is an effective treatment for adenomyosis and endometriosis particularly on dysmenorrhea and heavy menstrual bleeding, and now is used as a first-line medical treatment for adenomyosis and endometriosis. However, a previously published study showed that most of the patients with adenomyosis had abnormally enlarging of the uterus, and the uterine cavity was too large to place the LNG-IUS.^[26] In the present study, 12 of the 56 adenomyosis patients had a previous use of the LNG-IUS. However, the devices were expelled due to obviously enlarged uterus and excessive menstrual flow. For refusing to hysterectomy, subcutaneous implantation of Etonogestrel implants was performed in these 12 patients. The decreased menstrual flow and alleviated or eliminated pelvic pain were observed in 10 of the 12 patients. The rest 2 patients removed the implants for failure treatment and underwent a subtotal hysterectomy. This result might indicate that Etonogestrel implants can be used as an alternative to LNG-IUS and hysterectomy for some adenomyosis patients due to heavy menstrual flow.

A total of 26 patients had the Etonogestrel implants removed. The primary reason for Etonogestrel implants removed was vaginal bleeding (16/26 patients, 61.54%), which is consistent with the previous study.^[27] The mechanism of the change of menstrual bleeding pattern is not very clear, and the individual menstrual bleeding pattern is also hard to predict.^[28] In addition, the amenorrhea/oligomenorrhea incidence rate was 58.11% after 24-month treatment in the present study, which is similar to Mansour's report at 55.8%.^[29] Amenorrhea is an inevitable result of long-term simple progestin treatment. But even full consultation given by trained specialized clinical personnel was taken, some patients still had chosen to remove the Etonogestrel implant for amenorrhea (5 patients). The other adverse events, including weight gain, acne, breast tenderness, arm itching, rash, and so on, in the present study are comparable to those observed in the previous studies.^[11,17]

No pregnancy and no severe adverse events were observed during the study. However, 2 adenomyosis patients with uterus as large as 2 and a half months of pregnancy and unwilling to undergo hysterectomy reported mass vaginal bleeding at 6 and 7 months after implantation of Etonogestrel implants. As a result of the unsuccessful treatment of Etonogestrel implants, a subtotal hysterectomy had been taken.

In this study, we confirm the favorable effects of Etonogestrel implants to counteract pelvic pain and reduce menstrual flow in women with adenomyosis or endometriosis. As a LARC,

Etonogestrel implants are safe in use, good in tolerance and compliance, low in cost, and might be an alternative treatment to current therapeutic options. Especially, the results of the study have shown that the use of Etonogestrel implants provides an alternative treatment approach for women who are not suitable for placement of LNG-IUS due to enlarged uterine cavity or heavy menstrual flow which may lead to the expulsion of LNG-IUS. However, the side effects of Etonogestrel implants, such as vaginal bleeding, amenorrhea, oligomenorrhea, weight gain, acne, breast tenderness, arm itching, rash, numbness, mood changes, hyposexuality, sleep disorder, skin pigmentation, and constipation should also be noted. All the patients who are going to accept the implantation of Etonogestrel implants should be fully informed about these side effects to improve treatment compliance.

Several limitations of the present study should be taken seriously. First, the sample size of this observational clinical study was still not large enough to draw a definitive conclusion. Second, since all of the patients had not undergone surgical treatment in this study, we could not rely on histological confirmation of adenomyosis and endometriosis. Although transvaginal ultrasound has been confirmed to have high sensitivity and specificity for adenomyosis and endometriosis,^[13,14] we should still take into consideration the possibility of misdiagnosis. Third, we have not evaluated the body mass index (BMI) of the patients. Since BMI influence the stage of endometriosis, the symptoms and the fertility treatment outcomes, the effects of Etonogestrel implants on a patient with different BMI should be discussed.^[30] Henceforth, this study design was based on a single-arm (no controls with placebo or other drugs).

In view of the above-mentioned facts, randomized controlled trials on a large population are needed to further confirm our results.

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