The Effects of Implanon in the Symptomatic Treatment of Endometriosis

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Objective: *To evaluate the efficacy of Implanon on treatment of symptomatic endometriosis*
Design: *An open clinical study without control group*
Setting: *Family Planning Clinic and out patient department, King Chulalongkorn Memorial Hospital, Bangkok, Thailand.*
Material and Method: *A total number of 50 women with symptomatic endometriosis who were diagnosed and confirmed by laparoscopy or whose symptoms recurred after surgical treatment were recruited in the study . These subjects were implanted Implanon subcutaneously at medial aspect of non-dominant forearm. The intensity of pain was assessed with Visual Analog Scale (VAS) before insertion and at 4^{th} and 12^{th} weeks after the insertion. The adverse effects were recorded by the patients in 4^{th} and 12^{th} weeks of treatment. The women evaluated their satisfaction on treatment at the end of study.*
Results: *50 women recruited in the study and all completed follow-up. Improvements of pain severity and menstrual symptoms were observed. The mean $\pm$ SD Visual Analog Scale score of dysmenorrheal were 7.08 $\pm$ 2.09 at baseline, 3.72 $\pm$ 2.04 at 4^{th} week, and 0.84 $\pm$ 1.67 at 12^{th} week of treatment. During the study period, regular menstruation, amenorrhea, spotting, and breakthrough bleeding were reported by 21(42%), 14(28%), 13(26%), and 2(4%). At final satisfaction evaluation, 6(12%) women were very satisfied, 34 (68%) were satisfied, and 10(20%) were uncertain. All of acceptors continued to retaining the implant after study.*
Conclusion: *Implanon, a sub-dermal progestin implant is an effective hormonal alternative for treatment of symptomatic endometriosis. However women should be carefully counseled regarding menstrual changes. It has the potential for providing long-term treatment of endometriosis. Nevertheless, the further study should be conducted to compare with other of modality of treatment.*

Keywords: *Endometriosis, Implanon, Dysmenorrhea*

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Endometriosis affects 6-20% of women in reproductive age[1] . Despite many theories, the exact aetio-pathogenesis is unknown. However the disease is known to be estrogen dependence[2]. Medical treatment, which is predominantly palliative, for symptoms commonly of dysmenorrhea, dyspareunia, non-cyclic pelvic pain, is based on hormone [3]. It aims at either inducing hypoestrogenism or antagonizing estrogen action [4]. The main goals of treatment are to alleviate symptoms and improve fertility. Disease progression is usually in 23-64% of women without treatment and nearly 20% of women with treatment[5,6]. For medical treatment various progestin, danazol and gonadotropin releasing hormone (GnRH) agonists are widely used[5-7]. They inhibit gonadotropin secretion and follicular development as well as suppress ovulation and menstruation. Side effects, however, are frequent and disturbing. Although these drugs are effective, their systemic side effects commonly affect compliance or long-term use. The need for regular follow up may further result in poor compliance. Anabolic, androgenic and metabolic side-effect, as well as untoward alteration of plasma lipids, are consequence of the use of

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danazol[8]. Hypoestrogenic symptoms such as hot flush, sweating and mineral bone loss limit the long-term use of GnRH agonists[9]. Abnormal uterine bleeding, mood change, breast tenderness and fluid retention have been associated with the use of progestin[10]. Progestins may exert an endometriotic effect by causing initial decidualization of endometrial tissue followed by atrophy[11]. These should be considered as the first choice for the treatment of endometriosis because they are as effective as danazol or GnRH analogues and have a lower cost and a lower incidence of side effects[11].

The synthetic steroid Implanon is a single-rod, progestogen only, non-biodegradable implant containing and releasing the desogestrel metabolite etonogestrel (ENG, 3-keto-desogestrel), which has been used for long-term contraception. It inhibits FSH activity resulting in ovulation inhibition. The implant provides long-term contraceptive efficacy during a period of 3 years. The earlier studies have shown that Implanon suppress follicular development and steroid production, producing hypoestrogenism[12]. Thus, patients with endometriosis may benefit from this kind of treatment. When endometriosis involves the ovaries and causes severe symptoms, surgery is indicated. After conservative surgery, there was a risk of persistent or recurrence disease with symptomatic endometriosis[13]. Medical therapy after a conservative operation may control painful symptom and eliminate the need for further surgical treatment[14].

In a 3-year study on the contraceptive efficacy and tolerability of Implanon demonstrated that it was well tolerated and had excellent, reversible, contraceptive efficacy[15,16]. Over 85% of women with dysmenorrhea at baseline noted an improvement at the end of treatment[15,16]. Implanon has been extensive evaluated for contraceptive purposes, but never formally evaluated for the treatment of endometriosis. Given this background, we set out to evaluate the effectiveness and tolerability of Implanon in the treatment of women with symptomatic endometriosis. The objectives of this study were to determine degree of symptoms relief and assess patient's satisfaction after 3-month period of Implanon treatment on symptomatic endometriosis.

Material and Method

This open-labelled clinical study was undertaken at the family planning clinic and gynecologic out patient clinic, Department of Obstetrics and Gynecology, Chulalongkorn Memorial Hospital, Bangkok, Thailand from July 2003 to April 2004. The protocol was approved by the ethics committee of the institution. Women with symptomatic endometriosis who were previously diagnosed and previously confirmed by laparoscopy or whose symptoms recurred after surgical treatment were recruited in the study. The exclusion criteria were age <18 years or >45 years, any hormonal therapy in preceding 3 months, a desire to conceive within 3 months, the usual contraindication for progestin therapy, unwillingness to tolerate menstrual change or other adverse effects of Implanon, and unable to follow up.

At the time of recruitment in the clinic, general physical and gynecological examination was performed. Subjects were asked to keep a menstrual diary record card and marked the severity of their endometriosis-related pelvic pain (dysmenorrheal and/or non-cyclic pelvic pain) on a 10 cm visual analog scale (VAS) and possible side effects at pre-treatment. The implant was inserted subcutaneously into the medial aspect of upper forearm within 5 days of onset of menstruation. The insertion technique was the same as describe by the manufacturer[24]. Follow-up visit were at 4 and 12 weeks after the implantation. The duration of treatment was completed in 12 weeks. At the end of study, subjects were requested to rate their overall degree of satisfaction with treatment, which assessed by using a 4-point verbal rating scale (very satisfied, satisfied, uncertain, dissatisfied). At this point, those who requested the discontinuation had the implant removed.

The outcome measures included severity of pain relief which was assessed by using a VAS, amount and frequency of bleeding by using a menstrual diary card and degree of satisfaction of the patients.

Data Analysis

SPSS version 11.0 was used to record and statistically analyze data. Values at time of Implantation of the Implanon were compared with those at different time points after implantation using repeated ANOVA with Bonferroni correction. Additionally, perception by the patient on the efficacy of the implant in pain control was evaluated at 0, 4th, and 12th week using a Visual Analog Scale, as well as overall satisfaction with treatment (taking in to account the undesirable side effects) as indicated on a 4-point verbal rating scale.

Results

Fifty women were recruited and all completed the study. Thirty-one patients were confirmed diagnosis by previously laparoscopy and 19 had previous

conservative surgery. Significant (P<0.001) improvements in severity and menstrual symptoms were observed. In the changes in the mean VAS for pain severity during the study period, there was a significant fall from 7.08±2.09cm pre-treatment to 3.72+2.04 at 4 weeks post-Implanon implantation (P < 0.001) and to 0.84+1.67 at 12 weeks of therapy (P < 0.001). During the study period, regular menstruation, amenorrhea, spotting, and breakthrough bleeding were reported by 21(42%), 14(28%), 13(26%), and 2(4%) women. At final evaluation, 6(12%) women were very satisfied, 34 (68%) were satisfied, 10(20%) were uncertain. All were willing to continue treatment with the implant after the end of the study.

Table 1. Patient characteristics

Variables	N = 50
Age (years)	
Mean ± SD	34.5 ± 4.6
Min	23
Max	45
Status	
Single	22 (44%)
Married	26 (52%)
Widow	1 (2%)
Separated	1 (2%)
Parity	
0	34 (68%)
1	8 (16%)
2	5 (10%)
3	6 (3%)

Table 2. Side effects observed during the study period

Side effects	N = 50
Amenorrhea	14 (28%)
Spotting	13 (26%)
Breakthrough	2 (4%)
Allopecia	2 (4%)
Acne	5 (10%)
Melasma	2 (4%)
Breast tenderness	8 (16%)
Headache	4 (8%)

Table 3. Pain symptom score (VAS) in patients with endometriosis before and during therapy

Baseline	Month 1	Month 3
7.08 (5.2-10)	3.72 (0-8.2)	0.84 (0-5.4)*

* P < 0.05

Discussion

The present study indicated that Implanon has a positive effect on endometriosis-related symptoms and may prevent recurrence of ovarian endometriotic lesion. Although bleeding and spotting were common adverse effects, no patients discontinued the treatment. However, the women should be carefully selected and specifically informed of inevitable variations in menstrual patterns.

Implanon may also be a choice for long-term treatment of endometriosis in order to alleviate symptoms and prevent repeated surgery. Because medical therapy for endometriosis should be considered non-cytoreductive. Long-term therapy with progestin appears to be more favorable than with GnRH analogues. The limitation of GnRH analogues and danazol treatment were due to their side effects and could not use in long-term course due to risk of menopausal symptoms and osteoporosis. One of the advantages from Implanon comparing to DMPA is that the patients return their fertility function more rapidly after discontinuation, since the ENG levels decreased to level less than the detection limit of the assay (20 pg/ml) within 1 week[12,17].

In conclusion, Implanon offers good result in symptom alleviation with tolerable side effects in selected patients with symptomatic endometriosis. Overall nearly 80% of the women were satisfied after 3 months of treatment. Implanon is an option for long-term medical treatment and should be more extensively evaluated for this indication in comparison with other medical treatment. The long-term study should also be conducted to evaluate the effectiveness and recurrence of the disease after implant removal.

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ผลการรักษาภาวะเยื่อบุโพรงมดลูกเจริญผิดที่ด้วยยาหลอดฝังคุมกำเนิด Implanon

จิราวัตร พลภักดี, สุรศักดิ์ ฐานีพานิชสกุล

ภาวะเยื่อบุโพรงมดลูกเจริญผิดที่ พบได้ในสตรีวัยเจริญพันธุ์ร้อยละ 6-20 ภาวะเยื่อบุโพรงมดลูกเจริญผิดที่นี้สามารถรักษาด้วยวิธีต่างๆ ทั้งการรักษาโดยการผ่าตัด การใช้ฮอร์โมนเพศ และการใช้ยารักษา ผู้วิจัยได้ทำการศึกษาผู้ป่วยสตรีที่เป็นภาวะเยื่อบุโพรงมดลูกเจริญผิดที่ที่มีอาการจำนวน 50 ราย โดยใช้ ยาหลอดฝังคุมกำเนิด Implanon โดยประเมินอาการปวดระดู ปวดท้องน้อย และลักษณะระดู ภายหลังจากฝังยา 4 สัปดาห์ และ12 สัปดาห์ ผลการศึกษาพบว่าสตรีที่เข้ารับการศึกษา มีอาการปวดระดูและปวดท้องน้อย โดยใช้การวัดความเจ็บปวดด้วย Visual Analog Scale (VAS) มีคะแนนเฉลี่ย 7.08±2.09 ก่อนการฝังยา และค่า VAS ลดลงเป็น 3.72±2.04 เมื่อ 4 สัปดาห์ภายหลังการฝังยา และ 0.84±1.67 เมื่อ 12 สัปดาห์ภายหลังการฝังยา ผู้ป่วยมีความพึงพอใจในการใช้ยาฝังคุมกำเนิด Implanon ร้อยละ 80 และร้อยละ 20 ไม่แน่ใจ ผู้ป่วยทั้งหมดยังคงใช้ยาหลอดฝังคุมกำเนิดภายหลังเสร็จสิ้นการศึกษาแล้ว การใช้ยาหลอดฝังคุมกำเนิด Implanon นับว่าเป็นวิธีการรักษาภาวะเยื่อบุโพรงมดลูกเจริญผิดที่ที่ได้ผลดีและมีผลข้างเคียงน้อย