Clinical Effects of Gestrinone for the Treatment of Pelvic Endometriosis in Infertile Patients

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Abstract

The clinical efficacy and side effects of oral gestrinone, 2.5 mg twice weekly, were evaluated in this prospective study involving 22 patients with laparoscopically confirmed endometriosis. All patients came to the hospital with infertility problem. After 6 months of treatment, 81 per cent of patients had amenorrhea. Dysmenorrhea and pelvic pain were reduced from 90.9 per cent to 14.3 per cent and 81.8 per cent to 9.5 per cent respectively. Pelvic tenderness and induration were improved from 55.6 per cent and 50.0 per cent to 15.8 per cent and 10.5 per cent respectively. Androgenic effects such as acne was founded in 18.2 per cent of the patients. Return of fertility was observed in 25 per cent (5 patients) after 30-254 days post treatment. No serious side effect was detected during the treatment. The results suggest that gestrinone may be considered an option for the treatment of endometriosis related infertility.

Key word : Pelvic Endometriosis - Infertile Patients - Gestrinone - Clinical Effect

Endometriosis is one of the commonest causes of female infertility. Several investigators have demonstrated that estrogen regulated the secretion of protein in endometrium and endometriotic tissue which may play a role in reproduction by modulating the uterine environment[1,2]. Medical treatment of endometriosis directed to interrupt ovarian estrogen production and/or interfere with the action of endogenous sex steroids at the level of target organs seem to improve clinical symptoms and fertility function. Gestrione (13ß-ethyl-17α-ethinyl-17-hydroxygona-4,9,11-trien-3-one; Roussel-UCLAF, Paris), a compound widely studied originally as a contraceptive[3-5], acts centrally by suppressing the midcycle peaks of the pituitary gonadotropins, possibly through a reduction of pituitary sensitivity to gonadotropin-releasing hormone, and blocks follicular development, thus decreasing estrogen synthesis. It also demonstrates an agonist-antagonist activity on progesterone receptors and

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an agonist action on androgen receptors, and it binds weakly to estrogen receptors, action as an antiestrogen[6]. Lastly, it possesses a high affinity for sex hormone-binding globulin (SHBG), the plasma levels of which fall markedly, leading to an increase in the concentration of free testosterone (T). Some studies have already demonstrated that gestrinone is effective in reducing endometriotic implants[7,8], but there are still no precise indications on its effect on the restoration of fertility, pain symptoms, androgenic side effects in medium-term follow-up especially in Thai women.

In this open-end trial we evaluated the efficacy and side effects of 2.5 mg of gestrinone for the treatment of infertile patients with endometriosis.

PATIENTS AND METHOD

The study was approved by the Faculty of Medicine Ethical Review Board.

Twenty two infertile patients with laparoscopic diagnosis of endometriosis volunteered participation in this study. They were in good health, sexually active, had regular menstruation, and did not have any other significant medical illness. No surgical therapeutic procedure was done during the initial pretreatment diagnostic laparascopy. All patients desired to become pregnant. They had at least one tube patent and their husband's semen analysis was in the normal range according to WHO standard[9].

A gestrinone tablet, dose 2.5 mg, was given continuously twice a week for 6 months, commencing on either day 2 or 3 of the menstrual cycle. The patients were asked to follow-up at 1, 3, 6 months after starting treatment. Associated symptoms including dysmenorrhea, dyspareunia, pelvic pain and side effects were recorded during each visit. Severity of dysmenorrhea, dyspareunia, and pelvic pain were graded on a categoric rating scale of none, mild, moderate, or severe on the basis of clearly delineated clinical experience, limitation, or functional impediment.

Statistical Analysis

The statistical significance of difference between baseline and treatment values was assessed by the Student's *t*-test for paired data. McNemar test was used to compare subjective symptoms pre and post treatment.

RESULTS

Twenty two patients aged between 23 and 41 years old (mean age ± S.D. : 33 ± 4.8 years), with duration of infertility ranging from 1 to 14 years (mean ± S.D. : 4.6 ± 3.7 years), were included in this study (Table 1).

The patients were classified as stage I, 8 ; stage II, 6 ; stage III, 6, and stage IV, 2 patients according to the Revised American Fertility Society Classification of Endometriosis (1985)[16] (Fig. 1). The body mass index of the volunteers was 20.4 ± 2.5 (range 16.8 - 26.0).

All patients had significant improvement in dysmenorrhea and pelvic pain within 3 months of treatment and remained so until the completion of treatment (Table 2). Dysmenorrhea and premen-

Table 1. Demographic data of the volunteers.

Characteristics	(n = 22)
Age (year)	
Mean ± SD	33.0 ± 4.8
Min - Max	23.0 - 41.7
Height (cm)	
Mean ± SD	156 ± 5.5
Min - Max	145.0 - 166.0
Weight (kg)	
Mean ± SD	50.5 ± 6.8
Min - Max	41.2 - 68.8
BMI (kg/m^2)	
Mean ± SD	20.4 ± 2.5
Min - Max	16.8 - 26.0

Table 2. Symptoms of endometriosis before and after treatment (n = 22).

Symptoms	Before treatment	At 6 months of treatment	p-value
Dysmenorrhea	20/22	3/21	<0.001
Pelvic premenstrual pain	18/22	2/21	<0.001
Dyspareunea	5/22	3/21	0.625
Pelvic tendeness	10/18	3/19	0.016
Pelvic induration	9/18	2/19	0.016

Remark : McNemar test was used to compare statistical significant.

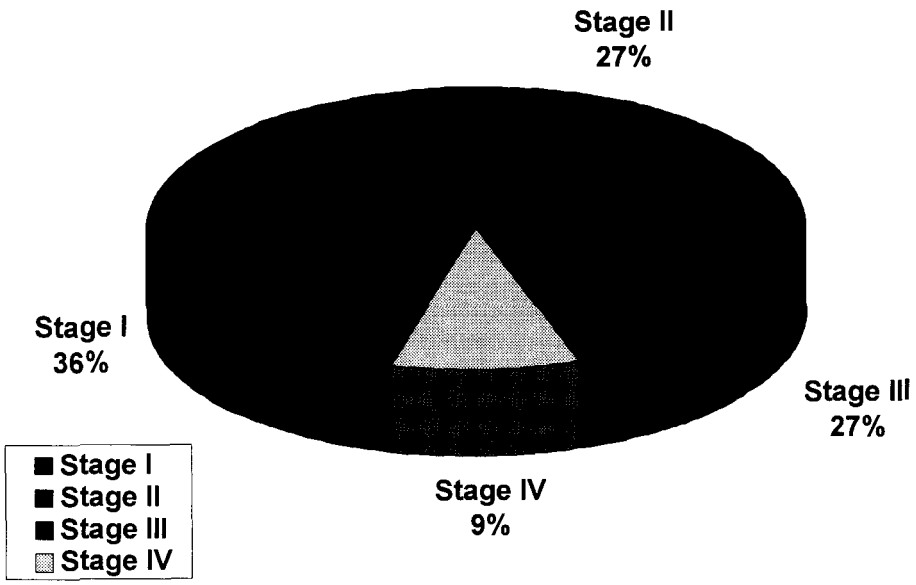


Fig. 1. Severity of Endometriosis (Revised American Fertility Society Score 1985).

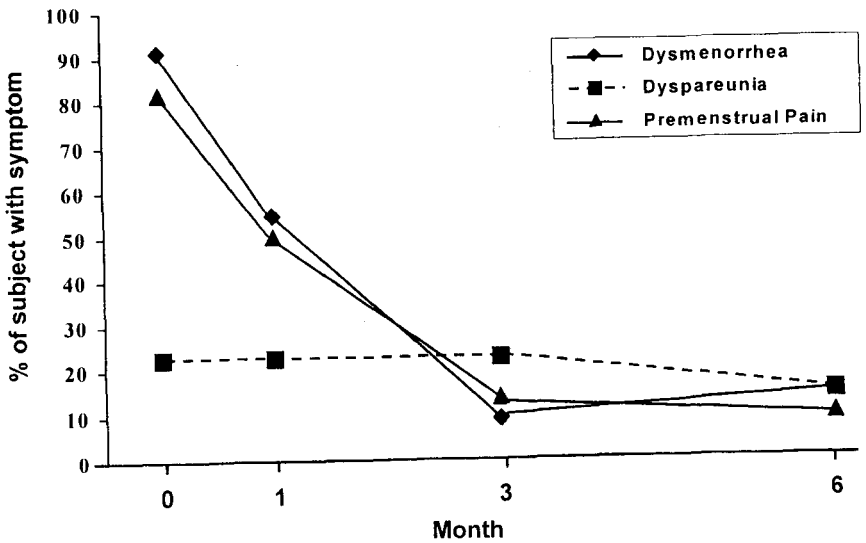


Fig. 2. Symptoms of endometriosis.

strual pain was reduced from 90.9 per cent to 14.3 per cent and 81.8 to 9.5 per cent respectively (Fig. 2). Dyspareunia, however, was not significantly improved which might be due to vaginal dryness.

Amenorrhea was observed in 54.5 per cent of the patients after 3 months and increased to 81 per cent after 6 months of treatment. Spotting was reported in 22.7 per cent and 23.8 per cent after 3 and 6 months respectively. No menorrhagia was found. All patients returned to normal menses after cessation of medication ranging between 20 to 61 days (mean ± S.D. : 33.9 ± 10.1 days)

Pelvic tenderness and induration declined from 55.6 per cent and 50 per cent to 15.8 per cent and 10.5 per cent respectively during the treatment period. (Fig. 3)

Acne was found in 3 cases (18.2%). One patient (5%) was found to have hirsutism and seborrhea on the sixth month. Body weight of the patients increased by an average of 2.2 kgs.

No vascular complication was observed during and after treatment.

Two patients dropped out from the study due to transient elevation of liver enzyme during the third month of treatment. However, follow-up liver enzyme had returned to normal after discontinuation of treatment.

Six patients conceived spontaneously within six months after cessation of medication and delivered full term healthy neonates. One case, unfortunately aborted at 10 weeks of gestation (Table 3).

DISCUSSION

Endometriosis associated symptoms have classically been characterized as dysmenorrhea, dyspareunia, cyclic pelvic pain, and infertility. Our results suggest that gestrione is an effective treatment of endometriosis associated with infertility. The drug was well tolerated by the patients and was associated with fewer and less severe side effects.

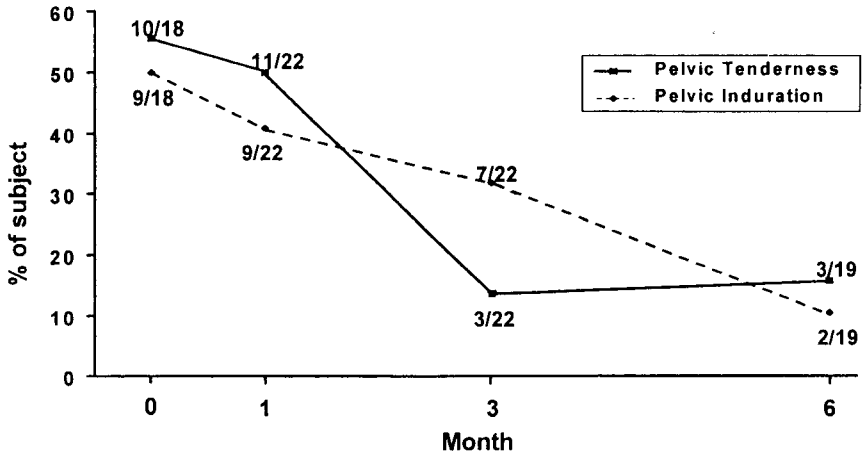
It is commonly accepted that gestrinone reduces ovarian estrogen production through the suppression of gonadotropin secretion. In fact, it has been proven to significantly inhibit LH and FSH levels in ovarectomized rats[10]. Besides inhibiting FSH and LH levels, gestrinone also decreases the pulse frequency of LH, and it may be this effect of gestrinone on the pulsatility of pituitary gonadotropins that is more crucial to its inhibition of ovulation and ovarian function[11,12]. A previous study

Table 3. Pregnancy results.

Six patients became pregnant after completion of medication. Five term delivery (5/20 = 25%) were observed.

Case#	Stage	Last date of drug	LMP	Total day
2	III	6/14/93	*	-
5	IV	12/6/93	2/8/94	64
6	I	12/21/93	2/13/94	54
10	II	1/29/94	6/22/94	144
19	III	5/29/94	2/7/95	254
20	I	6/18/94	7/18/94	30

Note : Total day = LMP - Date of last gestrinone medication
* Case No. 2 abort at 10 weeks gestation.



Pelvic tenderness and induration were improved from 55.6 %, 50.0 % to 15.8 %, 10.5 % respectively.

Fig. 3. Gynecological examination.

has shown that gestrinone induces anovulation and a low level of circulation estrogen and progesterone by acting on central and peripheral steroid receptors[11]. Short term therapy with gestrinone can induce a degree of cellular inactivation and regression in peritoneal endometriotic implants. Cellular involution and degradation are seen in approximately 25 per cent of the implants[8].

Side effects of gestrinone are usually associated with its androgenicity. Coutinho found seborrhea and acne in 70 per cent of the patients[13] while Fedele found 21 per cent[14]. However, these symptoms are less frequent among Thai patients.

A variety of mechanisms have been suggested to explain endometriosis-associated infertility, including prostaglandin-induced tubal and ovulatory dysfunction, spontaneous abortion, luteinized unruptured follicles syndrome, alterations in the immune system, and intraperitoneal inflammation. Although all of these mechanisms emphasize different pathophysiologic events, they all rely on the presence of ectopic endometrial implants as the basis for infertility. Therefore, eradication of implants should restore fertility to normal. It is interesting to note that the menses returned to normal within 60 days after cessation of treatment. Our result showed a pregnancy rate of 25 per cent. Because these women in general have had several years of infertility prior to seeking medical advice, it has been assumed that all pregnancies resulted from treatment. Although this encouraging result of conception was based on the open-trial, it confirmed the return of fertility function which has been studied in a randomized double-blind control trial[15].

SUMMARY

Gestrinone treatment for pelvic endometriosis in Thai patients was well accepted and was associated with fewer and less severe side effects. Androgenic side effects were less common than those reported in Caucasian patients. The patients with pelvic pain experienced an almost complete remission of pain symptoms during the treatment. Spontaneous recovery of fertility within 6 months after the 6 month treatment was found in one-fourth of the patients. For its efficacy and good tolerance, gestrione may represent an option for the treatment of endometriosis related infertility.

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ผลทางคลินิกในการรักษาภาวะเยื่อบุโพรงมดลูกอยู่ผิดที่ในอุ้งเชิงกรานในผู้ป่วยที่มีบุตรยากด้วยยาเกสตริโนน

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การศึกษาแบบไปข้างหน้าเพื่อประเมินผลการรักษาและผลข้างเคียง ในการรักษาภาวะเยื่อบุโพรงมดลูกอยู่ผิดที่ในอุ้งเชิงกราน โดยการใช้ยา gestrinone ชนิดรับประทาน 2.5 มก. สัปดาห์ละ 2 ครั้งในผู้ป่วยที่มาพบแพทย์ด้วยปัญหาการมีบุตรยาก 22 คน ซึ่งได้รับการส่องกล้องภายในอุ้งเชิงกรานเพื่อยืนยันการวินิจฉัย พบว่าภายหลังการได้ยา gestrinone เป็นเวลา 6 เดือน ร้อยละ 81 ของผู้ป่วยจะมีภาวะไม่มีระดู อาการปวดระดูและอาการปวดในอุ้งเชิงกรานลดลงจากร้อยละ 90.9 เป็น 14.3 และร้อยละ 81.8 เป็น 9.5 ตามลำดับ อาการกดเจ็บบริเวณอุ้งเชิงกรานพบว่าดีขึ้น จากร้อยละ 55.6 เป็น 15.8 ผลข้างเคียงของการแสดงออกคล้ายแอนโดรเจน เช่น การมีสิว พบร้อยละ 18.2 ผู้ป่วยร้อยละ 25 (5 ราย) พบว่าสามารถตั้งครรภ์ปกติได้เองภายหลังการรักษา 30–254 วัน ไม่พบภาวะแทรกซ้อนที่เป็นอันตรายระหว่างการรักษา

คำสำคัญ : ภาวะเยื่อบุโพรงมดลูกอยู่ผิดที่ในอุ้งเชิงกราน – ผู้มีบุตรยาก – เกสตริโนน – ผลการรักษา

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