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Efficacy and Tolerability of GnRH Analogues in the Treatment of Endometriosis

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자궁내막증환자에 투여된 GnRH Analogues의 치료효과 및 부작용

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= 국문초록 =

23~40세 (평균 연령 31.6세)의 자궁내막증 환자35명 (1기 7명, 2기 7명, 3기 14명, 4기 7명)을 대상으로 gonadotropin-releasing hormone agonist (Goserelin) 3.6 mg을 한달 간격으로 6개월 복부의 피하에 이식한 후 자궁내막증에 대한 치료 효과와 부작용을 알아보기 위하여 매달 호르몬 검사와 증상에 대한 설문조사를 시행하였다.

투여 1개월 후 혈청 estradiol농도는 30 pg/mL이었고 이후 치료중 10~20 pg/mL를 유지하였으며 투여를 중간한 1개월 후 50 pg/mL로 증가하였다. 혈청 LH농도는 치료 중 유의하게 감소하였으며 투여를 중단한 후 증가하였다. FSH는 투여 1개월 후 감소하였으나 2개월후부터 계속 치료전과 같은 농도를 유지하였다. 혈청 CA-125치는 19명중 10명에서 치료전에 35 mIU/mL이상으로 증가되었으며 치료 2개월 후부터 모두 정상으로 감소되었다. 월경곤란증은 치료 3개월째 완전히 소실되었고 성교통은 치료가 끝날 때까지 20%의 환자에서 지속되었다. 백혈구수, 혈색소, 전해질, 단백질, 빌리루빈 및 간효소는 치료중 모두 정상이었다. 혈압과 체중도 치료전, 치료중에 변화가 없었다.

투여후 86%의 환자가 안면홍조를 63%에서 질건조증을 20%가 두통, 우울을 호소 하였다. 이와 같은 부작용은 투여를 중단한 1개월 후 모두 소실되었으며 부작용 때문에 투여를 중단한 예는 없었다.

이상의 결과로 GnRH-a는 난소의 estradiol생산을 완벽하게 중단시키고 골반증상을 완화시켜 자궁내막증 치료에 효과적이라고 사료되며 안면홍조와 같은 부작용의 빈도가 높기 때문에 향후 호르몬 보충요법을 병행하는 것이 바람직 하다고 사료된다.

INTRODUCTION

Endometriosis affecting 2.5~15% of women of reproductive age (Guzick, 1989). The treatment of endometriosis very much depends upon the extent and the site of the disease process, the current severity and range of symptoms, the patient's future childbearing expectations. Medical treatment has an important role to play in the management of endometriosis. Progestogens, danazol and gestrinone have been proved to be efficacious to varying degrees. Recently, the use of GnRH analogues in the management of endometriosis has provided good clinical results, showing both an improvement in symptomatology and a reduction of endometriotic lesions. The introduction

of GnRH agonists has expended the physician's choices for effective therapy for endometriosis (Henzl *et al.*, 1988; Dlugi *et al.*, 1990). But it was not known whether the GnRH analogues have different effectiveness according to the race. Most of the previous data from English literature are results from white women. In this paper, we are trying to evaluate the efficacy of GnRH agonist (Goserelin) for the treatment of endometriosis in Korean women.

The adverse effects are significantly different between danazol and GnRH agonists. GnRH agonists causes hypoestrogenic symptoms and danazol induces androgenic and anabolic changes. Assuming equal effectiveness between danazol and GnRH agonists, as have been reported, the deciding factor in selecting a drug will be based on the degree of the patient's tolerance, lack of major side effects and the cost. Vasomotor instability, with hot flushes, is the most common side effect and can be expected in approximately 90% of patients with GnRH agonist administration (Henzl *et al.*, 1988). But the side effects associated with GnRH agonist in Korean women have not been well known. In our study we are trying to evaluate the tolerability of GnRH agonist (Goserelin) for the treatment of endometriosis in Korean Women.

MATERIALS AND METHODS

A total of thirty-five premenopausal women, 23~40 years of age (mean age + SD: 31.6 + 4.7 years) with endometriosis were selected for GnRH agonist treatment. Endometriosis confirmed by laparoscopy and laparotomy including biopsy, when appropriate, within one month prior to commencement of treatment. The degree of disease was assessed by the revised American Fertility Society (AFS) classification. Seven each were stage I, II and IV, and 14 were at stage III. All the patients had negative cervical smear test for malignancy within 12 months. Included patients were using non-hormonal contraception and showed a negative pregnancy test immediately prior to the study. Breast feeding, severe concurrent hepatic, renal and cardiac disease patients were excluded. Specific hormonal therapy such as danazol, gestagen or GnRH analogues during the past six months was also excluded. All subjects gave written informed consent.

A 3.6 mg dose of Goserelin was administered subcutaneously as an implant into the anterior abdominal wall every 28 days intervals over a period of 6 months following diagnostic laparoscopy. Therapy begins on the follicular phase of the menstrual cycle. Patients were questioned at each visit for pelvic symptoms (dysmenorrhea, dyspareunia, pelvic pain) and tolerance (hot flushes, night sweat, vaginal dryness, vaginal discomfort, depression, irritability, headaches). Each was graded as: 0, absent; 1, mild; 2, moderate; 3, severe. The scores for each of the three symptoms were summed to give a total pelvic score. Before, at monthly intervals during treatment, the subjects were questioned regarding symptoms and tolerance. Blood and urine samples were obtained for a variety of hematologic, biochemical, and endocrinologic assessments before and during therapy. The data were analyzed by t-test.

RESULTS

Efficacy of the GnRH analogues can be judged on the degree of ovarian suppression as assessed by the serum estradiol levels. After 4 weeks of therapy, mean serum estradiol levels decreased below 30 pg/mL and dropped to between 10 and 20 pg/ml for the duration of the study, but rose rapidly up to the 50 pg/ml two months after GnRH agonist

termination (Figure 1). It is clear that GnRH injection achieved complete ovarian suppression throughout out the treatment period. Mean serum LH values decreased during treat-

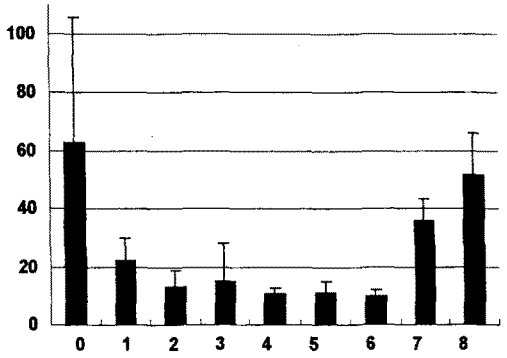

Figure 1. Mean serum estradiol values (pg/ml) during and after GnRH-a therapy.

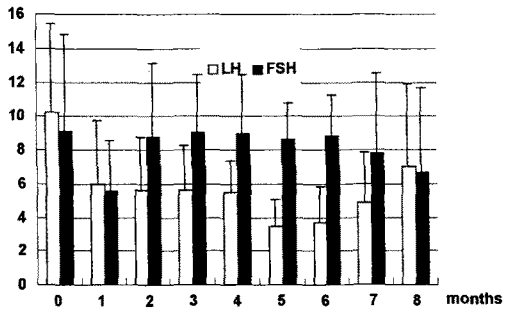

Figure 2. Mean LH and FSH values (mIU/ml) during and after GnRH-a therapy.

ment and increased at cessation. FSH levels initially decreased but, by the second month, had returned to pretreatment values where remained throughout (Figure 2). Mean serum CA-125 values were increased at base line in more than 50% (10 of 19) of patients. Mean levels decreased progressively during treatment and maintained after 2 month of therapy (Figure 3).

Pelvic symptoms such as dysmenorrhea, dyspareunia and pelvic pain reduced within 2 months of therapy. Further improvement was observed in the majority of patients until the fourth or fifth month of treatment, at which time, maximal overall response had usually been achieved. The mean total pelvic score was reduced as 94% at the end of therapy. Dysmenorrhea was totally abolished by the third month (Figure 4). Twenty-eight out of 35 patients complain dyspareunia before therapy and this symptom persist in 5 patients (20%)

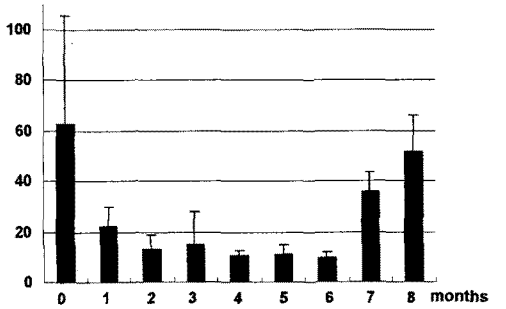

Figure 3. Mean CA-125 values (U/ml) during and after GnRH-a therapy.

Table 1. Blood pressure and body weight changes during GnRH agonist treatment

Month	Diastolic (mmHg)	Systolic (mmHg)	Body weight (Kg)
0	66.6±7.6	110±11	54.7±5.0
1	68.0±10.4	108±11	54.3±5.2
2	68.4±9.4	109±10	54.0±5.3
3	68.9±9.3	109±12	54.1±5.3
4	67.4±9.1	108±10	54.2±5.1
5	67.9±8.0	109±11	54.2±5.0
6	68.0±8.8	110±11	54.5±5.2

to the end of therapy. The laboratory parameters examined including white and red blood cell count, hemoglobin, hematocrit, sodium, potassium, chloride, urea, creatinine, bilirubin, total protein, albumin, AST were maintained in normal range throughout the treatment period. No significant changes in blood pressure (systolic or diastolic) were recorded during treatment. Initial body weight (54.7±5.0 kg) were not changed throughout the therapy (Table 1).

Hot flushes, the most frequently reported subjective side effects, were experienced during the treatment by 86% of patients, 63% complained of night sweats and a similar number of vaginal dryness. Vaginal discomfort, headaches, depression and irritability were also reported in less than 20% of patients. Vaginal dryness developed at the end of therapy (Figure 5). The side effects had almost disappeared two month after the last injection; no patients withdrew due to an adverse events. A local

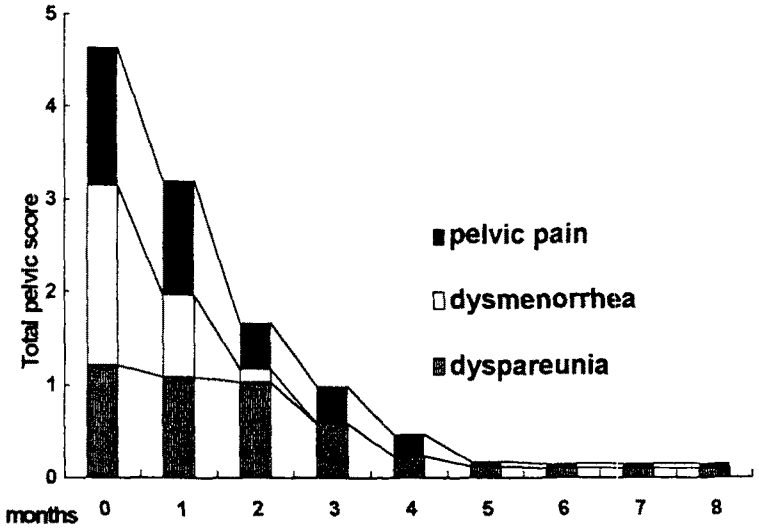

Figure 4. Total pelvic score during and after GnRH-a therapy.

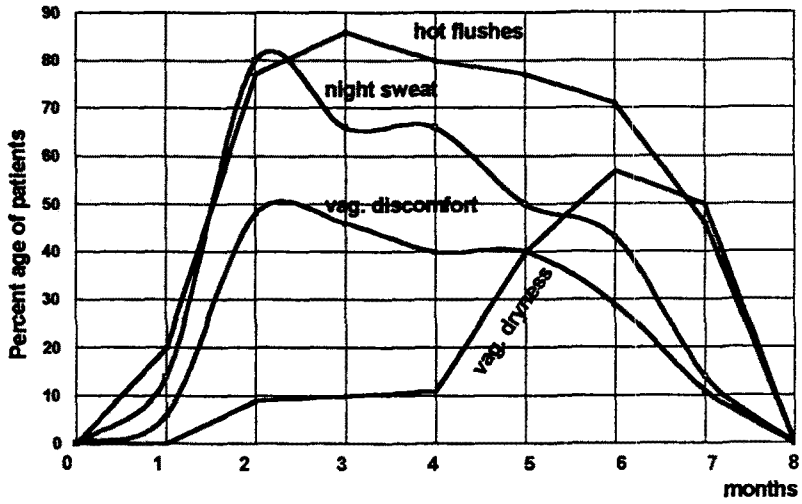

Figure 5. Percentage of incidence of side-effects during GnRH-a therapy.

reaction, such as erythema at the injection site was not noted.

DISCUSSION

Surgical oophorectomy has been thought to be the most effective overall treatment for endometriosis. This treatment, however, is usually reserved as the final resort in patients who no longer contemplate further pregnancies. A reversible means of achieving a medical oophorectomy by the repetitive administration of GnRH agonist would offer many advantages in younger women with endometriosis.

Schally et al first indentified GnRH in 1971. Shortly afterward, a synthetic GnRH became available for use in clinical investigation. Continued administration of GnRH agonist results in desensitization or down regulation of the pituitary GnRH receptor, with a resultant reduction in circulating serum gonadotropin concentrations and a secondary inhibition of ov-

arian steroidogenesis. The induction of a sustained hypoestrogenic environment has been thought to be a critical factor in the treatment of endometriosis. Meldrum and colleagues first reported the use of a GnRH analogue in the treatment of endometriosis (1982). Efficacy of the GnRH agonist can best be judged on the degree of ovarian suppression as assessed by the serum estradiol levels. Serum estradiol levels increased immediately after GnRH analog administration due to initial agonist induced release of LH and FSH. But estradiol falls to within menopausal range one week following therapy (Steingold *et al.*, 1987; Show 1988). In our study, GnRH agonist therapy effectively achieved complete ovarian suppression within four weeks since the serum estradiol levels fell to concentrations consistent with menopausal state. These findings are similar to those of Caucasian women (Show, 1988; Shaw, 1992; Rock *et al.*, 1993). The objective response to the therapy, changes in second look laparoscopy, were not measured in present study, significant reduction in subjective symptom scores had been achieved by 2 months (treatment, and the score continued to fall u the 4~5 months assessment.

Although serum CA-125 measurement could not to be a clinically useful diagnostic test, there have been a number of reports that CA-125 levels are increased in women with endometriosis (Patton *et al.*, 1986; Kauppila, *et al.*, 1988). It have been reported that the serum CA-125 levels decreased after surgical reduction of endometriosis (Kauppila *et al.*, 1988) and may offer a useful method of monitoring disease progress (Moloney *et al.*, 1989). In our study, serum CA-125 values were increased at baseline in more than 50% (10 of 19) of patients. Mean levels decreased progressively during treatment and maintained after 2 month of therapy.

Because of the chronic nature of endometriosis, the average symptomatic patients will probably require and receive several courses of medical therapy during her reproductive life. Some women will unquestionably exhibit side effects to one drug, others will be unresponsive or intolerance. The availability of several drugs enables the physician to select the most suitable medication for the patients at any given time. The selection of the drug of choice is based on several factors including effectiveness, response of the patients, side effects, and the last, but not the lesser, the cost. The adverse effects, which may be predicted during GnRH agonist usage, are menopausal-like symptoms. Hot flushes is the most frequently reported adverse effect. With regard to menopausal hot flushes, the incidence is quite lower in Asian population (Oldenhaven *et al.*, 1993; Chung *et al.*, 1996) and Korean women (Lee *et al.*, 1995) than those from Caucasian women (Barlow *et al.*, 1991). According to these reports, It might be expected that the incidence of GnRH agonist induced hot flushes also lower in Korean women. But 86% of treated premenopausal women reported hot flushed and this findings are similar to those of other studies from western countries (Shaw *et al.*, 1992). The proportion of patients who discontinued therapy because of them may best judge the relative severity of the adverse symptoms. In one study, the number of drop-outs in patients receiving GnRH agonist was only 1% (Schweppe *et al.*, 1990), and no one discontinued therapy due to side effects in current study, although the number of participants are small. This indicates that the hypo-estrogenic adverse effects induced by GnRH agonists are perhaps well tolerated. However, prolonged sustained estrogen deprivation in premenopausal women has a significant impact in accelerating the loss of trabecular bone. Using dual-energy X-ray absorptiometry measurement technique, a mean reduction of -5-6% of bone mineral density within the lumbar spine as early as 3 months after GnRH agonist

therapy occurs in patients being treated for endometriosis (Fogel *et al.*, 1994; Dawood 1994). This side effect is the key issue that limits the duration of therapy to a period of 6 months. It should be emphasized that the bone loss form GnRH agonist treatment of endometriosis has not produce any immediate clinical effect and the patients remain asymptomatic. However, such a loss among premenopausal women who, for the most part with endometriosis, have a recurrent disease and may require medical interventive treatment could induce repetitive reduction in bone mineral density without complete replacement. It would thus have a cumulative effect with a postulated negative impact on peak bone mass when entering menopause. For this reason, strategies to avoid or prevent such bone loss have been developed. These include multi-agent add-back therapy to counter act the bone depletion effects of GnRH agonist. Howell (1995) reported that the addition of hormone replacement therapy to GnRH agonist for the treatment of endometriosis did not reduce the efficacy of treatment, and adverse hypoestrogenic effects were decreased, although not abolished. Bone mineral density was not measured in our study but add-back steroid treatment with GnRH agonist should be considered in women with high risk for osteoporosis especially, reduced body mass index, low dietary calcium intake.

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