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Treatment of endometriosis with depot medroxyprogesterone acetate: a preliminary experience*

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Summary

The efficacy of depot medroxyprogesterone acetate in the treatment of endometriosis was assessed in 19 patients with severe diseases. Assessment was based on changes in subjective symptoms and signs at 4 weekly interval during treatment and after 52 weeks follow up, and changes in visible deposits and adhesions at laparoscopy before and after treatment.

There were significant reductions in mean total subjective and symptoms scores, mean total R-AFS adhesions and implants scores, and mean additive diameter of implant scores at the end of treatment and follow up. Treatment success occurred in 75% of the patients, majority (66%) of whom had complete resolution of deposits. Side effects encountered include menorrhagia, break through bleeding, excessive weight gain, myalgia, breast pain, acne and delay in return of menses.

It was concluded that DMPA an effective, cheap and readily available medication which is worth using in patients who can not afford the expensive alternatives.

Keywords: *Endometriosis, depot medroxy progesterone acetate, treatment, Nigeria.*

Résumé

L'efficacité du depot de medroxy progesterone acetate dans le traitement de l'endometriose a été évaluée chez 19 patients ayant une maladie sévère. L'évaluation était basée sur les changements dans les symptômes subjectifs et les signes à 4 semaines d'intervalle pendant traitement et un suivi de 52 semaines. L'évaluation avait aussi été faite basée sur les dépôts visibles et les adhésions à la laparoscopie avant et après le traitement.

Il y avait une réduction significative de la moyenne totale des scores de symptômes subjectifs, la moyenne totale des adhésions R-AFS et des scores de greffons. Les succès de traitements ont survécu chez 75% des patients. La majorité (66%) de ceux-ci avait eu la résolution complète des dépôts. Les effets secondaires rencontrés ont inclus: La ménorrhée, les saignements, l'excès de poids, la myalgie, la douleur de seins, les arthralgies et les retards de retour des menstruations.

Il a été conclu que la DMPA est efficace, moins chère et disponible à la medication des patients ne pouvant pas supporter le coût des alternatives chères.

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Introduction

Endometriosis remains one of the most frequently diagnosed gynaecological pathologies in the reproductive years among the Caucasians with a peak incidence between 30 and 45 years of age [1]. The prevalence is at least 1% and rising among women of reproductive age [2]. It has associated symptoms of cyclical pelvic pain, dysmenorrhoea, and infertility [3,4,5] which may be severe enough to warrant treatment, especially when these lead to deleterious social consequences. In the past, endometriosis was rarely diagnosed in Nigerians, so its reports in African literature is scanty. This is possibly due to inadequate diagnostic facilities or actual low incidence of the disease consequent to the multiparous nature of the native Nigerian woman who starts to procreate during adolescence. Thus her fertility is ascertained before endometriosis becomes well established while the closely spaced pregnancies discourages the disease progression. Very recently, some Nigerian women delay marriages and child bearing in order to attain formal education or vocational training. Therefore, endometriosis is increasingly becoming an important differential diagnosis in women with chronic pelvic pain and infertility in the country [6,7].

The treatment of infertility associated with endometriosis has been conservative surgery for over 50 years in both developed and developing countries. The dependence of endometriotic tissues on oestrogen for its continued growth [8,9] has evoked medical treatment aimed at inhibition of menstruation. Consequently, drugs like Danazol, progestogens and gonadotropin-releasing hormone agonists (GnRha) have been found useful [10-13]. Unfortunately, controversies persist regarding optimal therapy in terms of dosage and timing of therapy. The side effects of these drugs are not well tolerated by some patients while the cost is a hindrance to therapy in poor countries. Progestogens offer the cheapest therapy available [14,15]. Oral and injectable medroxy progesterone acetate (MPA) have been reported to be effective in improving symptoms and reducing endometriotic implants in Caucasians [16,17]. However their frequency of administration may not be convenient for the patients. The sustained slow release depot preparation of medroxy progesterone acetate (DMPA) is known to achieve consistent and greater degree of serum estrogen suppression than oral preparations. It is already in the Nigerian market for family planning purposes and has less gastro-intestinal side effects than oral tablets. These advantages of DMPA should be useful in treating endometriosis in this country.

The treatment of endometriosis in Ibadan had been mainly surgical or occasionally with Danazol, where patients were wealthy enough to obtain their drugs from abroad, and other progestogens. In December 1994, DMPA was added to the treatment choice of patients with endometriosis in Ibadan. This is a preliminary report on the efficacy of DMPA in the treatment of such patients.

Subject and methods

Between December 1994 and January 1998, twentytwo symptomatic patients presenting with laparoscopically confirmed endometriosis gave informed consent to use DMPA and be studied. Deep intramuscular injection of 150 mg DMPA was given to each woman weekly for 10 weeks or until amenorrhoea occurred (vaginal spotting was allowed initially). Subsequent interval between injections was increased to monthly until the 26th week of commencement of treatment. Patients were followed up until the 52nd week. Treatment was started on the 1st week (days 1 to 7) of menstrual cycle and within 2 weeks of initial diagnostic laparoscopy.

The exclusion criteria include (a) pre-treatment use of hormonal preparations within 8 weeks of recruitment, (b) use of anticoagulant, (c) Use of relevant drug for endometriosis within 26 weeks preceding treatment (eg., Danazol, MPA or GnRha), (d) hypertension or related medical diseases, (e) Obesity (Wt > 90 kg.) and hypersensitivity to DMPA. Due to ethical considerations all symptomatic patients were treated and no double blind study with placebo injections or non-treatment arm was carried out. The number of cases seen within the fouryear period was too small for a reasonable randomized comparative trial. The proven efficacy of Danazol made it the first choice in the medical treatment of endometriosis by many gynaecologists. It was too expensive to be used for a comparative trial in our setting.

Follow up was initially in 6 weeks followed by monthly visit till the end of the 52nd week. Each patient was questioned at each visit for pelvic symptoms (pelvic pain, dysmenorrhoea and dyspareunia) and examined for physical signs (pelvic tenderness and induration). These clinical features were separately graded as none (0), mild (1), moderate (2) or severe (3) accordingly. The scores of each of the three symptoms were added to give total symptoms score while those of the two physical signs gave the physical signs score. Total symptoms scores and physical signs scores were combined to give total subjective scores [1]. The degree of endometriosis was assessed according to the revised American Fertility Society classification [18] and the additive diameter for implant, in which a point score was given for every square millimetre of endometriotic implant visualised regardless of depth of invasion [1,10], at initial laparoscopy in all patients and at 2 months in 12 patients after treatment. Also at follow up, adverse drug effects, menstrual calendar, clinical evaluation (weight, vital signs and breast signs) were reviewed.

Differences in the mean scores at the beginning and end of therapy were compared using analysis of variance at 5% statistical significant level.

Results

The demographic characteristics of the patients is as shown on table 1. All women were in the child bearing age group and had received formal education. Only one patient had primary school education alone. Eighteen patients presented with infertility. Two patients were lost to follow up while one was withdrawn due to severe menorrhagia.

Table 1: Characteristics of the patients presenting with endometriosis.

Mean age	28.9 ± 3.6 (Range; 19-34) years
Mean weight	57.2 ± 5.8 (Range; 32-63) kg.
Mean parity	0.2 ± 0.01 (Range; 0-3)
Mean cycle length	28.6 ± 2.4 (Range; 21-36) days
<i>Blood pressure:</i>	
Systolic blood pressure	110 ± 4.8 (Range; 90-140) mmHg.
Diastolic blood pressure	67.6 ± 9.3 (Range; 60-80) mmHg.
<i>Educational status:</i>	
primary	1
secondary	
tertiary	13
Associated infertility	18

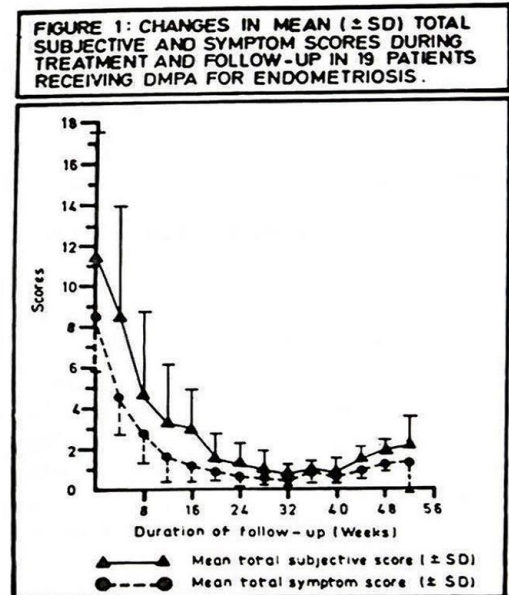
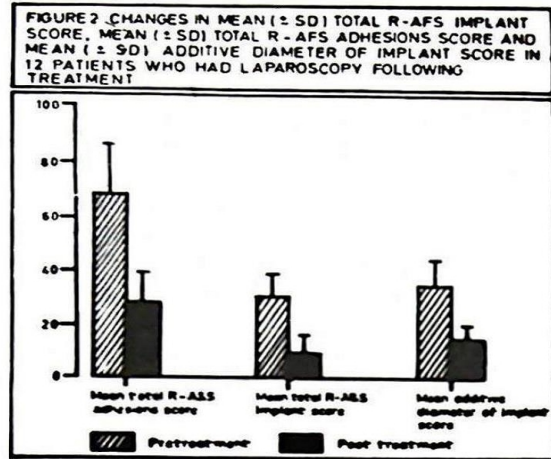


Figure 1 Shows the changes in mean total subjective scores (pelvic symptoms and physical findings) during treatment and follow up. There was a rapid decrease in mean total subjective scores initially during treatment which tailed off towards the end of follow up. The mean total subjective score at the end of treatment was significantly lesser than the pretreatment score ($P < 0.05$). This score remained low beyond the time of treatment in those who remained amenorrhoeic but gradually rose towards the end of the 52nd week once periods resumed mainly due to recurrence of symptoms to varying degrees in 4 patients. However, the mean symptoms score by the 52nd week was significantly less than those of the pretreatment value (9.6 ± 2.8 vs 1.3 ± 1.9 ; $P < 0.05$).

All the 22 patients had severe endometriosis with the mean total R-AFS score of 103 ± 15.4 and mean total R-AFS adhesions score of 63.8 ± 22.7 pretreatment. The pretreatment total R-AFS implant score was 32.4 ± 15.6 . Amongst the 12 women who had second look laparoscopy, a

significant fall in mean total R-AFS implant score from 30.9 ± 9.6 to 9.7 ± 6.2 ($P < 0.05$) was noted. This fall was less with adhesions (68.3 ± 18.55 vs 28.4 ± 11.2) as seen in figure 2.



The changes in mean additive diameter of implant scores was equally significant statistically posttreatment compared with pretreatment (36.4 ± 9.7 vs 10.6 ± 7.2 ; $P < 0.05$).

Treatment success (i.e., $\geq 50\%$ decrease in total R-AFS score) occurred in 9 (75%) of the 12 patients who had second look laparoscopy. Six of these had complete resolution of deposits. Seven pregnancies, one of which was an ectopic, were reported amongst the 22 patients.

Patients' complaints and side effects of treatment were as shown on table 2. Majority (54%) of them had no complaints but excessive weight gain was the most common complaints. Majority of those who complained had more than one complaint. The longest delay of menstruation was 6 months.

Table 2: Complaints by patients on DMPA for endometriosis.

Complaints	Number of patients with complaints
Menorrhagia	1
Break through bleeding	4
Excessive weight gain	6
Myalgia	5
Breast pain	2
Acne	3
Delay in return of menses	2
No complaints	12

Discussion

The basic principle in the medical management of endometriosis is to suppress the proliferative effect of oestrogen on the ectopic endometrial tissues. The effectiveness of various medications (e.g. Danazol, GnRha

and progesterones) for the treatment has been reported in terms of indirect parameters such as improvement in symptoms, changes in laparoscopic extent or histological appearance of the disease and pregnancy [1,10,17,19], and direct parameters such as suppression of isolated proliferative phase endometrial stroma cells [20]. Antimitotic effects of progestogens on oestrogen primed endometrium has been reported [21] but data on effects of progesterone and progestins alone are somewhat conflicting [22, 25]. The use of secretory as opposed to proliferative phase endometrial cells in the later two reports [24, 25] would account for the differential results. In order to take advantage of the suppressive action of progestogens on the growth of proliferative endometrium, DMPA therapy was started in this study during menstrual or early proliferative phase of the cycle (days 1-7). This report shows a marked improvement in both objective ($>50\%$) and subjective scores for endometriosis with DMPA. The revised AFS scores used to classify endometriosis and record these changes is subjective and arbitrary but the use of additive diameter of implants to assess the responses adds credence to the results obtained. Additive diameter of implant scores demonstrated a reduction in mean size of the implants relative to the revised AFS scores. The fact that the scores were estimated by the same observer will validate the results which are comparable to those reported with other medications for endometriosis else where [1,10,11,16]. The induction of sustained hypoestrogenic state is a critical factor in the treatment of endometriosis [10,14]. Once the critical level of hypoestrogenism is achieved, additional reduction below this threshold has no additional benefits [1]. Therefore, the use of expensive drugs or those with unwanted side effects may not necessarily be the best treatment in this environment. DMPA is an anabolic steroid and can induce effects such as weight gain, myalgia, acne, hirsutism, breast pain and changes in cholesterol and lipid levels with prolonged use [13,15,17]. Fortunately, no deleterious side effects were seen in this study and only one patient was withdrawn as a result of the use related events encountered. The pretreatment disease severity and the degree of tubal damage may be responsible for the low pregnancy rate following treatment in this study. At the moment DMPA is commonly being used as a family planning agent and is readily available in the country. Its introduction into treatment armamentarium of endometriosis may be worthwhile.

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