Norethisterone enantate in the treatment of premenstrual syndrome

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The aim of this prospective study was to assess whether norethisterone enantate can be recommended for use in patients with premenstrual syndrome (PMS) who also require effective contraception.

The subjects were 20 patients with severe PMS who required effective contraception. Premenstrual symptom scores on norethisterone enantate and oral contraceptives were compared.

Significantly fewer and less severe symptoms were experienced by patients on norethisterone enantate than those on oral contraceptives. Norethisterone enantate can therefore be recommended for use in patients with PMS who also require effective contraception.

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The aetiology of premenstrual syndrome (PMS) is unclear. Several theories exist and several agents have been advocated for its treatment. Most of these agents have not proved to be significantly better than placebo in double-blind controlled trials.[1,2]

It is known, however, that the symptoms of PMS do not occur during pregnancy or after menopause. There is a growing acceptance that PMS is a function of cyclical ovarian activity.[3] Alteration of this cycle through the use of anovulatory doses of subcutaneous oestradiol implants[4] and oestradiol patches[5] have been shown to be superior to placebo. However, when cyclical progesterone was added, some of the symptoms of PMS recurred.[4]

Norethisterone enantate is a depot progesterone injection used for hormonal contraception. Although its main actions are to impair sperm movement into the uterine cavity by alteration of the cervical mucus and to render the endometrium unsuitable for nidation by the production of morphological changes, ovulation is also suppressed by the antigonadotrophic effects of high plasma levels of norethisterone, particularly during the first 5 - 7 weeks after injection.

This study was conducted to ascertain whether these changes in cyclical ovarian activity would result in a reduction of PMS symptoms.

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Methods

Twenty patients who were using combination oral contraceptives and still complained of severe premenstrual symptoms were entered into the trial if they fulfilled the criteria outlined by Magos.[1] A prospective daily symptom diary was kept by the patients for 2 months. The five worst symptoms were listed and scored 0 - 3 according to severity. The total symptom score of the premenstrual week was compared with that of the postmenstrual week. PMS was diagnosed if the premenstrual score was more than double the postmenstrual score and the difference between the scores was greater than 10.

Patients were then given 200 mg norethisterone enantate by intramuscular injection and the oral contraceptive was stopped. The prospective daily symptom diary was kept for a further 2 months, and the symptom score of the premenstrual week on the oral contraceptive was compared with that on norethisterone enantate.

The study was approved by the Ethics Committee of the University of Cape Town and patients gave informed consent. Because of the effects of the depot progesterone on the menstrual cycle, a double-blind trial was not possible.

Results

The symptom scores of the 20 patients while on the oral contraceptive and on norethisterone enantate are shown in Table I. Because symptom scoring was subjective, the differences between the two treatment groups were analysed by means of the Kruskal-Wallis test.

Table I. Premenstrual symptom scores on an oral contraceptive compared with norethisterone enantate

Patient	Oral contraceptive	Norethisterone enantate
1	44	17
2	20	5
3	44	2
4	92	18
5	45	21
6	19	2
7	24	11
8	12	6
9	73	20
10	51	12
11	40	4
12	66	12
13	45	10
14	32	2
15	36	4
16	32	16
17	34	16
18	42	6
19	32	6
20	46	18

Significantly fewer and less severe symptoms were experienced by the patients on norethisterone enantate than by those on an oral contraceptive ($P < 0,005$).

Discussion

Many patients with premenstrual symptoms are treated with multiple agents, most of which are empirical or have only a theoretical basis for their use.[6] This is not only extremely expensive, but many patients only improve for the first few months, after which their symptoms recur. Since PMS is associated with cyclical ovarian activity, blocking ovulation is a logical way to reduce symptoms.[6]

This can be achieved by oestrogens alone but patients with an intact endometrium require cyclical progesterone to prevent endometrial hyperplasia if treated with oestradiol implants. This has, however, resulted in a partial return of their PMS symptoms.[3] Norethisterone enantate 200 mg as an 8-weekly intramuscular injection is inexpensive, easy to administer and effective in the management of PMS.

Because of the placebo effect, which has been extensively reported in trials involving PMS patients, a double-blind trial of norethisterone enantate versus placebo would be ideal. This would, however, exclude the many PMS patients who require reliable contraception. Furthermore, the alteration in the menstrual cycle, which occurs when long-acting progesterone injections are used, would make such a trial impossible.

REFERENCES

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Addendum

In the 12 months since this trial was completed, the patients were maintained on norethisterone enantate as follows.

The 9 patients whose symptom scores had been reduced to below 10 were continued on 8-weekly injections and all maintained their premenstrual score at below 10.

The 11 patients whose premenstrual scores were over 10 had the interval between injections reduced to 6 weeks. In 9 of the 11 patients, amenorrhoea and total cessation of symptoms occurred. In the remaining 2 patients, irregular periods persisted but their symptom scores were reduced to below 10.

In summary, all 20 patients treated with norethisterone enantate 200 mg every 6 - 8 weeks for 12 or more months, maintained their premenstrual symptom scores at below 10.