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Premenstrual Syndrome

A Double-blind Cross-over Study of Treatment with Dydrogesterone and Placebo

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A double-blind, cross-over, placebo-controlled study of dydrogesterone (10 mg b.d.) in the treatment of premenstrual syndrome is described. Two groups of women were studied: secondarily referred hospital clinic patients, and self-referred patients. Only one-third of patients screened completed the study. All patients showed significant improvements in symptom scores during the course of the study, the only significant difference between placebo- and dydrogesterone-treated patients being an increase in frequency of breast tenderness and a decrease in pain with menstrual bleeding in the latter.

Premenstrual syndrome describes a group of symptoms that women report as occurring before menstruation begins. Surveys of the literature describing treatments for premenstrual syndrome (Sampson & Prescott, 1981; Rubinow *et al*, 1984; Bancroft & Bäckström, 1985) identify several problems apparent in many studies of potential therapeutic agents. These include problems of definition, study design, lack of baseline pre-treatment data, and lack of placebo control. When this study was set up, some of the issues encountered in previous treatment studies of premenstrual syndrome with endocrine agents were taken into account. After the study commenced, further research findings (Lenton, 1984) indicated that yet more variables need controlling when assessing the effects of endocrine agents on premenstrual syndrome.

Dydrogesterone is a synthetic orally active progestogen (6-dehydro-retroprogesterone). It has been advocated for the treatment of premenstrual syndrome, and several studies have reported therapeutic effects (Taylor, 1977; Kerr *et al*, 1980; Strecker, 1981; Williams *et al*, 1983). There have been suggestions that women presenting to hospital clinics may differ from those presenting to general practitioners (GPs) complaining of premenstrual syndrome. This study compared the response to dydrogesterone in two groups of women; those attending a hospital-based premenstrual-syndrome clinic and those self-referring to a Family Planning Association clinic.

Method

The subjects were out-patients attending either a hospital-based established premenstrual-syndrome clinic (Royal Hallamshire Hospital) to which they were referred by either their GP or a hospital specialist, or a self-referral clinic (Family Planning Association), where they telephoned for an appointment. Both clinics were in Sheffield. Three female doctors conducted the study, and meetings were organised to ensure that they had as similar a 'style' as possible, in an attempt to standardise the effect of the doctor on the treatment. Patients always saw the same doctor throughout the study.

Subjects' first assessments were timed for 1 hour. A full menstrual, pregnancy, psychological, psychiatric, medical, personal, and family history was taken. Gynaecological examination was undertaken if appropriate. Subjects were asked to complete the Eysenck Personality Inventory (EPI; Eysenck & Eysenck, 1964). Subjects were given a menstrual chart to record bleeding, and a folder containing Moos Menstrual Distress Questionnaires (MDQ) (Moos, 1985). Each patient was instructed to complete a MDQ every evening describing how she had felt in the previous 24 h, date the form, and replace it in the folder. On the next day, she would use a new form. She returned her forms at each clinic visit.

The second assessment occurred at least one complete menstrual cycle later. Further history-taking and an initial 'naked eye' assessment of the daily MDQs allowed the doctor to make an initial assessment as to whether they considered, on prospective rating, that the patient's symptoms were related to the onset of menstruation. Women who were then considered to have premenstrual syndrome, and who consented, entered the study. Further exclusion criteria were: 1. current psychiatric illness; 2. current gynaecological illness; 3. pregnancy; 4. the taking of other hormonal agents, including oral contraceptives.

The treatment phase of the study consisted of 4 months of oral medication. The medication [identical amounts (10 mg) of placebo or dydrogesterone] was taken at 12-hourly intervals over a period of 14 days. The timing of treatment was determined by assessing the previous cycle length. In an average 28-day cycle, it was from day 12 to 26,

in a 26-day cycle from day 10 to 24, etc. The medication was given in a double-blind cross-over design consisting of 4 1-month treatment periods, two being active, two being placebo. This balanced two-treatment, four-period cross-over design allows for a test of significance and estimation of size of difference between drug and placebo effects, residual or carry-over effects of previous treatment periods, and 'between centre' effects (John & Quenouille, 1977). Those dropping out from the study were replaced by someone assigned a new code number with identical sequence allocation of medication. Patients were withdrawn if they developed exclusion criteria or suffered excessive breakthrough bleeding during treatment.

Data from the daily MDQs were marked to produce 8-symptom clusters. These were then plotted and analysed by fitting a sine wave to the daily symptom scores by the least-mean-square method of fitting sine waves (Sampson & Jenner, 1977), giving *A*, a measure of the amplitude of complaining in relation to menstruation. The diagnostic criteria for having premenstrual syndrome in this study was that a subject should have at least three significant *A* values (occurring between 210 and 330 degrees) in the symptom clusters of pain, concentration, behavioural change, autonomic response, water retention, or negative affect, in her initial cycle. Those subjects who were entered in the study after naked-eye analysis of graphs, and were found not to have three significant *A* values on later computer sine-wave analysis, were excluded as 'computer rejects' and replaced.

Subjects entering the study were seen after each menstrual cycle. At each visit, MDQs were collected. Patients were asked to recall 11 specific symptoms in the previous cycle; these were rated in terms of severity (0–4), and frequency (the number of days each symptom was present). Cycle length, a global rating of therapeutic response (1–4), and the presence of side-effects were elicited; and assessment was made of whether symptoms had interfered with work, home, or social life.

Results

A total of 215 patients were initially assessed; 110 at the Royal Hallamshire Hospital, and 105 at the Family Planning Association. Of these, 108 patients entered the study (47 from Royal Hallamshire Hospital, 61 from the Family Planning Association), and 69 satisfactorily completed it. As the design required a balanced set of patients in matched blocks of four, a response to treatment data was analysed for 64 patients, although for other data, all 69 completing patients were used. Of the 108 patients entering the study, the mean age was 35.48 with an age range of 24–50, 84 were married, and 64 patients reported experiencing painful menstruation before the age of 18. The majority (95%) of the group were parous; the mean number of live births per woman was 1.89. Seventy-seven of the subjects had used oral contraceptives at some time prior to entry in the study. The mean age of onset of premenstrual symptoms was 27.14 years; the mean duration of premenstrual syndrome symptoms before entering the trial was 8.34 years. Of 108 women entering the study, 19 had recognised premenstrual syndrome before the age of 18 years, while six women were over 40 years before symptoms began.

TABLE I
Means of Y–C scores for untreated and treated cycles

Moos syndrome cluster	*Cycle treatment*		
	Untreated	*Placebo*	*Dydrogesterone*
Pain	3.08	2.00**	2.02**
Concentration	4.03	1.77**	2.07**
Behavioural change	2.39	1.26**	1.31**
Autonomic response	0.37	0.03*	0.08*
Water retention	2.77	1.78**	1.90**
Negative affect	4.50	1.99**	2.38**
Arousal	1.15	0.53*	0.47*
Control	0.42	0.37	0.36

Levels of significance comparing treatment with untreated cycles: *$P<0.05$; **$P<0.001$.

Thirty-nine patients dropped out or were rejected after commencing the study. Of 13 at the Royal Hallamshire Hospital, three were 'computer rejects', four failed to continue attending, two developed side-effects, and four left for other reasons. Twenty-six dropped out at the self-referral Family Planning Clinic; ten were 'computer rejected', nine (including some 'computer rejects') failed to continue attending, three developed side-effects, and a further nine left for varying reasons.

Analysis of the daily MDQ ratings for the untreated and four treated cycles of 64 patients was undertaken, using Y–C values for each of the 8-symptom clusters of the MDQ. The means of patients taking dydrogesterone in a particular month against those taking placebo that month were compared, as were the means of the 16 patients in the same sequence each month. The data was assessed to show a direct treatment effect and a carry-over effect from the previous month's treatment on the month being assessed. The data was also assessed using results from all 69 completed patients, to see whether the addition of these five patients would change the results. Table I shows the means of the Y–C scores for the untreated and the treated cycles. The figures indicate that all symptoms except 'control' show an improvement in treated cycles (both dydrogesterone- and placebo-treated), although for the 'arousal' scale this implies a diminution in well-being. The carry-over effects for both placebo and dydrogesterone treatment for each symptom were estimated, and the symptom clusters 'pain', 'concentration', and 'negative affect' showed a beneficial carry-over effect for dydrogesterone, although this was not significant.

Table II indicates the incidence of reporting a symptom retrospectively at interview in at least one treated cycle. It also gives the mean duration and severity of symptoms as recalled by patients at their monthly visits. There were significantly lower scores for severity ($P<0.001$) and frequency ($P<0.05$) of pain associated with menstruation in dydrogesterone-treated cycles compared with placebo-treated cycles. The analysis for the severity of breast tenderness showed a significant carry-over effect of dydrogesterone at the 5% level, and some suggestion of

TABLE II
Mean duration and severity of symptoms as recalled by patients

Symptom	*Number of patients with symptoms in at least one treated cycle (n = 64)*	*Mean duration of symptom (days)*		*Mean severity of symptom*[1]	
		Placebo	*Dydrogesterone*	*Placebo*	*Dydrogesterone*
Tension	64	6.80	8.10	1.64	1.72
Irritability	64	6.70	7.66	1.61	1.77
Depression	62	6.04	7.24	1.43	1.52
Loss of energy	61	6.33	7.70	1.62	1.67
Bloated feeling	60	6.29	6.54	1.45	1.41
Difficulty concentrating	59	5.19	5.87	1.16	1.27
Headache	56	3.57	3.73	0.96	1.12
Loss of libido	53	5.87	5.87	1.13	1.19
Tender breasts	52	4.27	5.83**	1.05	1.23
Pain with bleeding	49	1.21	0.82**	1.02	0.77*
Pain before bleeding	40	1.18	1.21	0.56	0.52

1. 0 = absent; 1 = mild; 2 = moderate; 3 = severe.
*$P<0.05$, **$P<0.001$, comparing placebo and dydrogesterone cycles.

a direct effect of dydrogesterone. However, this was not large enough to be statistically significant. The analysis of the frequency of breast tenderness showed a higher frequency with dydrogesterone than with placebo ($P<0.05$). There were no other significant differences between placebo and dydrogesterone cycles, but there were significant differences between centres for a number of symptoms. For the symptoms 'loss of energy', 'difficulty concentrating', 'severity of depression' and 'irritability', the scores of the hospital clinic were higher than those of the self-referral clinic. 'Tension' was the symptom noted as 'most severe' in both groups, but this showed no inter-centre difference.

The mean cycle length for the dydrogesterone months was longer than for placebo (mean for dydrogesterone, 27.5 days; mean for placebo, 27.3 days). There was, however, a significant carry-over effect, suggesting that in the months following dydrogesterone treatment, the cycle lengths were shortened, but although significant, the difference was less than 1 day. When patients gave their own global rating of therapeutic improvement, both the direct and carry-over effects favoured placebo over dydrogesterone, but neither was large enough to be significant. Only four patients failed to report any improvement in at least one of the four treated cycles.

Patients were asked to rate whether symptoms affected their work, home, and social life. There was an inter-centre difference, in that the hospital-clinic patients rated symptoms more highly than self-referred patients. There was also a trend for fewer patients to be affected by symptoms as the trial proceeded, there being no difference between dydrogesterone- and placebo-treated cycles.

Of the 108 patients entering the study, 73 complained of side-effects. The commonest side-effect was breast tenderness, which 28 patients reported, 20 of these in dydrogesterone-treated cycles, and eight on placebo. Of 23 patients reporting nausea, 14 were on dydrogesterone cycles, 9 on placebo. Twelve reported changes in bleeding pattern, 12, urinary frequency, and 10, headache. These latter occurred equally often in placebo and dydrogesterone cycles. The presence of side-effects did not depend on the order in which medication was given, nor did it relate to the likelihood of dropping out. Some patients dropped out of all cycles, irrespective of treatment. There was a significant reduction in side-effects with time (34 patients complaining in month 1, 18 in month 4). More patients complained of side-effects at the hospital centre. Eysenck Personality Inventory scores were no different from the two referral groups: mean N = 15.705 (s.d. 4.422); mean E = 11.24 (s.d. 3.98); mean L = 3.02 (s.d. 15.83).

Discussion

Premenstrual-syndrome research highlights many of the problems encountered in assessing syndromes that as yet have no universally agreed definition, no accepted aetiology, and no proved therapy. Any study using daily symptom records for approximately half a year will cover many life-events. It is impressive that so many women did show a significant periodicity of symptoms in relation to their menstrual cycle. Several factors influenced these symptoms, especially 'giving a treatment' and 'time' (as reflected by further months of diary-keeping and clinic visits). Both of the 'given treatments' significantly diminished negative symptoms as assessed by prospective and retrospective rating; symptoms of well-being in the follicular phase of the cycle ('arousal') were also diminished.

Only two retrospectively reported symptoms showed any significant difference between placebo- and

dydrogesterone-treated cycles. Dydrogesterone significantly reduced the severity and number of days of pain with menstrual bleeding; it has been used for many years as a therapeutic agent for dysmenorrhoea, and our findings confirm its efficacy (Ayder & Coleman, 1965; Fairweather, 1965). Dydrogesterone was significantly worse than placebo in reducing the number of days for which symptoms of breast tenderness were present; however, there was no difference between the two treatments in effect on severity of breast tenderness. Of those patients reporting this side-effect, 20 (71%) did so in dydrogesterone cycles and 8 (29%) in placebo cycles. These two findings suggest that dydrogesterone may have some direct effect upon breast symptoms.

Dydrogesterone was administered in a treatment regime (days 12–26) initially developed from an aetiological hypothesis of progesterone deficiency in the luteal phase of the cycle. Recent work (Lenton, 1984) has demonstrated the differing endocrine response when dydrogesterone is given at different times in the menstrual cycle in relation to ovulation. Day 12, as used in this study, could have been pre-, peri-, or post-ovulatory; if the therapeutic effect of dydrogesterone is related to its altering an endocrine state, the time of commencing treatment in this study is unhelpful in elucidating its therapeutic effect.

The study found no major difference between self-referred and secondarily referred patients in terms of demographic data, prospective ratings, or response to placebo or dydrogesterone. The hospital-clinic patients complained more retrospectively, but equally, prospectively. These results are in keeping with most other double-blind cross-over studies of therapeutic agents compared with placebo in premenstrual syndrome, in that there is a significant diminution of symptoms in both placebo- and actively treated cycles.

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