complication it might be difficult to conclude which was the most significant risk factor for death. None the less, overall case fatality rate was highest among children with hyponatraemia.

The multiple linear regression model showed that deaths associated with hyponatraemia, hyperkalaemia, and hypoglycaemia were significant at the 0·10 confidence level, but the effect of confounding factors could not be measured.

In the logit regression model, which measures the effect of confounding factors, all the variables except serum sodium concentration and coma lost their effects. This observation that death was inversely related to serum sodium concentration supports our earlier findings that hyponatraemia is the most significant risk factor among children with complicated diarrhoea in Bangladesh.[4] We reported earlier that the incidence of hyponatraemia was directly related to the degree of malnutrition, but the results of the logit regression analysis did not show that malnutrition was a significant predictor of death. The reason for the direct relation of the incidence of hyponatraemia to the degree of malnutrition might be that serum albumin concentration carries a negative charge and is largely responsible for the normal anion gap by holding serum sodium in the intravascular space.[10 11] Although nutritional state was not found to be a predictor of death, the serum albumin concentration in these children was not run as a variable in the logit regression model owing to lack of data. None the less, hyponatraemia remained a significant predictor of death, though we do not have any satisfactory explanation for this. The direct relation between the incidence of hyponatraemia and the degree of malnutrition necessitates further, prospective studies to assess the effect of serum albumin concentration on the physiopathology of hyponatraemia.

The finding of coma as a predictor of death was not expected. As postmortem examinations were not performed we are unable to discuss the cause of the coma and its relation to death.

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Progesterone and the premenstrual syndrome: a double blind crossover trial

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Abstract

A double blind, randomised, crossover trial of oral micronised progesterone (two months) and placebo (two months) was conducted to determine whether progesterone alleviated premenstrual complaints. Twenty three women were interviewed premenstrually before treatment and in each month of treatment. They completed Moos's menstrual distress questionnaire, Beck et al's depression inventory, Spielberger et al's state anxiety inventory, the mood adjective checklist, and a daily symptom record. Analyses of data found an overall beneficial effect of being treated for all variables except restlessness, positive moods, and interest in sex. Maximum improvement occurred in the first month of treatment with progesterone. Nevertheless, an appreciably beneficial effect of progesterone over placebo for mood and some physical symptoms was identifiable after both one and two months of treatment.

Further studies are needed to determine the optimum duration of treatment.

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Introduction

Most women are aware of changes in their mood, behaviour, and body during the menstrual cycle. In some women these changes are severe enough to lead to presentation with complaints of premenstrual tension. Although a specific syndrome of premenstrual tension was described by Frank in 1931,[1] later authors added greatly to the symptomatology and length of

cycle affected, creating much confusion about the syndrome's criteria. More recently, several authors have highlighted the need to distinguish those women whose symptoms are present only in the premenstrual phase (the premenstrual syndrome) from those who seem to have an exacerbation premenstrually of psychiatric problems present throughout the cycle.[2,3]

The aetiology of the premenstrual syndrome remains controversial. The theory of an oestrogen-progesterone imbalance as the underlying basis for its symptoms has endured, although research evidence has often been inconsistent. Progesterone has been widely advocated as treatment for the premenstrual syndrome.[4] Whereas uncontrolled studies have reported favourable results,[5,6] most double blind studies have failed to show any efficacy of progesterone over that of placebo.[7-9] These studies have been criticised on the basis of the criteria used to select the sample and the methods of assessing change in symptoms.

In view of our recent findings of ovarian dysfunction with appreciably lowered pregnanediol concentrations[10] and the continued reports by clinicians of good clinical results with progesterone treatment we undertook a double blind trial to evaluate the effectiveness of an oral preparation of progesterone in alleviating symptoms of the premenstrual syndrome.

Patients and methods

SELECTION OF PATIENTS

The women studied were attending a premenstrual tension clinic at a Melbourne teaching hospital. Some were referred by their own doctors; others responded to publicity about the study. Women selected for evaluation reported:

(1) complaints of mood and physical changes in the seven to 10 days before menstruation;

(2) complaints of sufficient severity to incapacitate the woman's normal functioning in terms of her occupation or relationships, or both;

(3) complaints alleviated within three days of the onset of menses with a symptom free phase of at least one week;

(4) regular menstruation and regular occurrence of symptoms over the previous six menstrual cycles;

(5) no current psychiatric disorder;

(6) no concurrent psychotropic or hormonal drugs;

(7) age between 18 and 45 years.

EVALUATION BEFORE TREATMENT

Questionnaire—Before attending the clinic women completed a questionnaire at home in which they gave detailed demographic information and were invited to list their complaints, together with duration and association with the menstrual cycle.

Interviews—Medical, gynaecological, and psychiatric histories were obtained at the initial interview in the follicular phase of the cycle (days 5-7). During the assessment cycle that followed 24 hour urinary total concentrations of oestrogens and pregnanediol were measured, symptoms were self rated daily, and women were interviewed during the follicular phase (days 5-7) and premenstrual phase (days 22-26 approximately).

Psychometric tests—Scales were administered at both interviews and included: Moos's menstrual distress questionnaire[11]; Beck *et al's* depression inventory[12]; Spielberger *et al's* state anxiety inventory[13]; and the mood adjective checklist.[14] Ten symptoms were also scored daily on a rating scale (daily symptom record; see tables II and III). Patients were asked to record on going to bed whether they felt these symptoms during the day: not at all (1), very little (2), moderately (3), a fair bit (4), or a great deal (5). The symptoms included common premenstrual complaints, positive feelings of wellbeing, and two variables not often linked with the menstrual cycle by patients—hot flushes and sexual thoughts or interest. The means for each symptom were obtained for the last seven premenstrual days.

Outcome of assessment—Observation during the month before treatment confirmed reports of symptoms in 24 women. All had total scores to Moos's menstrual distress questionnaire in the premenstrual phase that were at least 30 units greater than scores obtained in the follicular phase. These women were then invited to participate in the clinical trial, and written informed consent was obtained. One woman dropped out of the study after a month of treatment because she was under increasing pressure from her other commitments. She was 43, had five children, and was the principal of a primary school. She had taken one month of placebo and reported feeling worse than she usually did premenstrually. The remaining 23 women completed the drug trial.

TREATMENT

During the four months of treatment women were interviewed in the premenstrual phase of each cycle. All psychological tests were completed at these four interviews. Daily ratings of symptoms continued throughout the four months. Means for each symptom were obtained for the last seven premenstrual days of each month.

ADMINISTRATION OF DRUGS

Oral drugs were chosen because of complaints of discomfort with rectal and vaginal administration. Micronised progesterone combined with oil in soft gelatine capsules (Utrogestan) was used. Previous studies had shown satisfactory blood concentrations and determined that 300 mg/day was necessary to produce adequate morphological and biochemical end organ response.[15] Matching placebo and progesterone capsules were supplied by the manufacturer in the form of a randomised double blind crossover study, so that each woman received two months' continuous treatment with each drug. A crossover design was chosen because a highly significant interpatient variability had been shown in response to steroids.[16,17] There was no tablet free cycle between phases of treatment. Women were instructed to take one 100 mg capsule in the morning and two 100 mg capsules at night as there had been reports of drowsiness of short duration. Treatment was prescribed for 10 days of each menstrual cycle starting roughly three days after ovulation. In each cycle ovulation was confirmed by determinations of urinary 24 hour pregnanediol and total oestrogen concentrations.

STATISTICAL ANALYSIS

Psychometric test data were summarised for each subject to obtain scores for the premenstrual visits during assessment and in each month of treatment. Analyses of variance were carried out to determine whether change occurred during the study from pretreatment levels in any of the variables. Further statistical tests[18] were used to determine whether the observed changes reflected pharmacological effects of the drug or the non-specific effects of treatment.

Discriminant analysis examined the collective influence of a set of variables in differentiating between progesterone and placebo treatments. To test directly the differential effects of progesterone or placebo on each variable means for all variables for all subjects were calculated for the two months with placebo and the two months with progesterone and a series of paired t tests performed. In addition, the scores obtained in the first month of each treatment were compared for each variable.

Results

The median age of the women in the sample was 34·5 years. Eighteen (80%) were married or in de facto relationships. Median parity was two (with a maximum of four), and only two (10%) were nulliparous.

Table I gives details of the symptoms spontaneously reported by women in questionnaires completed at home before attending the clinic. Symptoms had been present for between one and 24 years with a median of 9·5 years.

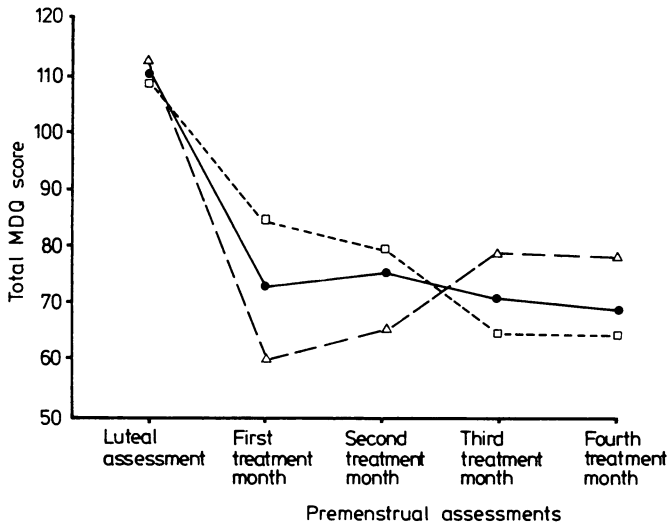
EFFECT OF TREATMENT ON SYMPTOMS

Analyses of variance found significant differences in the means for all variables except arousal (menstrual distress questionnaire) and sexual thought or interest (daily symptom record). To illustrate the differential effects of placebo and progesterone the mean total scores to the menstrual distress questionnaire for all patients were plotted

for the five premenstrual assessments (figure). The figure shows a large drop in scores in the first month of treatment followed by a general levelling out over the four months of treatment. When the patients' scores were divided according to the order in which the drugs were received the beneficial effects of progesterone over placebo were clearly shown. The shapes of the graphs of the various menstrual distress questionnaire subscales were strikingly similar to that of the total mental distress questionnaire score, except for arousal.

Discriminant analysis showed that after only one month of treatment those receiving progesterone could be clearly distinguished from those receiving placebo on measures of stress (mood adjective checklist), state anxiety (state anxiety inventory), and concentration (menstrual distress questionnaire) (discriminant analysis: $Rc = 0{\cdot}79$; $p < 0{\cdot}002$; 85% accurately classified). Tables II and III show the findings of the paired t tests. Table II lists the results of paired t tests when the scores for each variable were obtained for the first month of progesterone treatment and compared with those for the first month with placebo. Mean scores for each variable were obtained for the two months of each type of treatment. Paired t tests were again calculated, and table III gives the results.

Of the many pairs of means analysed by t test, the only premenstrual complaint not consistently in the direction favourable to the use of progesterone was arousal (menstrual distress questionnaire). For arousal (mood adjective checklist) small and non-significant differences were reversed; arousal levels for the first month of progesterone treatment were higher than for the first month of placebo, but the mean for the months with placebo together (30·18) was higher than the mean for the months with progesterone together (30·02).



Comparison of total scores in menstrual distress questionnaire (MDQ) (transformed) for all subjects (●—●) and subjects grouped according to order of treatment (progesterone followed by placebo: △—△; placebo followed by progesterone: □- - -□).

TABLE I—*Number of women reporting various premenstrual complaints*

Complaint	No of women (n = 23)
Irritability	21
Depression	17
Tender breasts	17
Aggressiveness	11
Weight gain	10
Tension	9
Lethargy	8
Headache or migraine	8
Tiredness	7
Bloated stomach	6
Pimples	5
Insomnia	5
Mood swings	4
Breast swelling	4
Indecision	4
Clumsiness	4
Blurred vision	3
Backache	2
Concentration difficulty	2
Constipation	2
Pain	2
Craving for sweets	2
Hot flushes	1
Increased appetite	1
Suicidal feelings	1
Loss of interest in sex	1

RESPONDERS

To determine which women responded to progesterone difference scores were calculated for daily symptom record and menstrual distress questionnaire total scores for the two months of placebo and the two months of progesterone. Twelve women clearly responded to progesterone for both measures and four clearly responded to placebo.

SIDE EFFECTS

Women's spontaneous reports of side effects of treatment were noted at the monthly premenstrual interviews (table IV). The only

TABLE II—*Related t tests: comparison between symptoms during first month of placebo and symptoms during first month of progesterone*

Variables	Placebo	Progesterone	Difference	Standard deviation	t	Level of significance	Direction of change
Interview:							
Comparison with original	4·05	4·64	0·59	1·53	1·81		+
Symptoms improved	2·35	2·78	0·43	1·47	1·42		+
Symptoms worsened	1·91	1·30	0·61	0·99	2·95	0·007	+
Clinicians overall assessment	3·68	4·23	0·55	2·19	1·16		+
Menstrual distress questionnaire:							
Pain	12·13	10·96	1·17	5·11	1·10		+
Concentration	20·56	17·30	3·26	10·80	1·45		+
Behavioural change	12·91	10·26	2·66	6·97	1·83		+
Autonomic	5·96	5·52	0·43	3·1	0·67		+
Water retention	10·70	8·78	1·91	4·69	1·95	0·05	+
Negative affect	23·22	17·83	5·39	13·41	1·93		+
Arousal	14·52	14·04	0·48	4·89	0·17		−
Control	10·89	8·22	1·87	3·67	2·44	0·02	+
Total	81·25	65·26	16·00	39·97	1·92		+
Mood adjective checklist:							
Stress	43·59	33·36	10·22	23·80	2·02	0·05	+
Arousal	28·09	31·63	3·55	11·67	1·42		−
Affective tests:							
Beck depression	12·70	7·13	5·56	13·45	1·98		+
Spielberger anxiety	47·43	35·35	12·09	23·01	2·52	0·02	+
Daily symptom record:							
Restlessness	2·05	1·94	0·11	0·74	0·69		+
Headache	1·62	1·49	0·13	0·56	1·03		+
Breast discomfort	2·93	2·30	0·63	1·53	1·84		+
Depression	2·19	1·74	0·45	0·99	2·04	0·05	+
Active aggression	2·00	1·75	0·25	1·00	1·08		+
Hot flushes	1·31	1·25	0·06	0·67	0·38		+
Wellbeing	2·81	3·03	0·22	0·88	1·13		+
Irritability	2·65	2·26	0·39	0·92	1·90		+
Sex interest	2·22	2·18	0·04	1·14	0·17		−
Swelling of abdomen, hands, legs	2·60	2·01	0·58	0·94	2·74	0·01	+
Total	2·29	1·93	0·36	0·58	2·82	0·01	+

+ = Improved; − = worse.

TABLE III—*Related t tests: comparison between mean scores obtained during first month of placebo and those obtained during first month of progesterone*

Variables	Placebo	Progesterone	Difference	Standard deviation	t	Level of significance	Direction of change
Comparison with original	4·23	4·56	0·34	0·98	1·63		+
Symptoms improved	2·52	2·65	0·13	1·14	0·55		+
Symptoms worse	1·78	1·59	0·20	0·94	1·00		+
Clinician's overall assessment	3·75	3·89	0·14	1·73	0·37		+
Menstrual distress questionnaire:							
Pain	12·02	10·67	1·35	5·06	1·28		+
Concentration	19·35	18·61	0·74	7·13	0·50		+
Behavioural change	11·50	10·83	0·67	5·00	0·65		+
Autonomic	6·33	5·52	0·80	2·02	1·91		+
Water retention	10·04	8·54	1·50	3·26	2·21	0·04	+
Negative affect	21·26	19·41	1·85	10·31	0·86		+
Arousal	14·26	13·50	0·76	3·23	1·13		−
Control	10·09	8·17	1·93	3·11	3·09	0·05	+
Total	76·87	68·37	8·50	32·21	1·27		+
Mood adjective checklist:							
Stress	42·02	36·59	5·43	18·91	1·35		+
Arousal	30·18	30·02	0·16	8·46	0·09		
Affective tests:							
Beck depression	10·45	8·13	2·32	8·40	1·29		+
Spielberger anxiety	46·26	40·65	5·61	17·75	1·54		+
Daily symptom record:							
Restlessness	1·96	2·07	0·11	0·58	0·85		−
Headache	1·66	1·56	0·10	0·53	0·80		+
Breast discomfort	2·69	2·29	0·40	1·03	1·68		+
Depression	2·13	2·02	0·10	0·75	0·59		+
Active aggression	1·86	1·83	0·03	0·69	0·17		+
Hot flushes	1·47	1·24	0·22	0·45	2·13	0·05	+
Wellbeing	2·83	2·86	0·03	0·66	0·22		+
Irritability	2·37	2·36	0·01	0·73	0·07		+
Sex interest	2·08	1·97	0·11	0·60	0·82		−
Swelling of abdomen, hands, legs	2·48	2·05	0·42	0·67	2·77	0·01	+
Total	2·16	2·02	0·14	0·44	1·33		+

+ = Improved; − = worse.

TABLE IV—*Number of women (n=23) reporting side effects of placebo or progesterone treatment*

Side effect	Placebo	Progesterone
Drowsiness	7	10
Insomnia	1	
Night terrors	1	1
Fatigue	2	1
Dizziness	1	2
Increased appetite	1	1
Nausea, diarrhoea	1	2
Altered taste in mouth		1
Dry mouth	1	
Dry skin		1
Itchy nipples	1	
Pimples		1
Ringing in ears		1
Hot flushes	1	
Loss of interest in sex	1	
Migraine		1

serious side effect reported was by a 36 year old woman who developed a migrainous attack premenstrually while taking progesterone during the last month of the clinical trial. This did not recur after stopping treatment. She had a history of migraine while taking the oral contraceptive pill and while taking hormones to stop lactation. She had not complained of headache or migraine as a presenting symptom.

Discussion

Our findings confirm descriptive reports of beneficial effects of progesterone on the symptoms of premenstrual tension. Improvements were attained both in mood symptoms such as anxiety, depression, and stress and in the physical complaints of swelling and hot flushes. Although not all variables reached a significant level of improvement, the direction of change for premenstrual complaints, with the exception of arousal, was always in favour of progesterone treatment. There was considerable variability of the sample with consequent large sampling error. With a larger sample more variables might have achieved significant levels of change.

Taken together the analyses also show the general positive effects of treatment. There was a trend to general improvement in almost all the physical and psychological variables over the four months of treatment, an improvement even more appreciable for the months of progesterone treatment alone. The greatest improvement occurred during the first month of treatment with progesterone. Nevertheless, the discriminant analysis and the tests comparing the different treatments were still able to show significant effects of progesterone over the general placebo effect.

We noted that significant changes were also found in the control subscale of the mental distress questionnaire. The control symptoms included feelings of suffocation, chest pains, ringing and tingling in the ears, blind spots, and fuzzy vision. All these symptoms occur in severe anxiety and are included in many anxiety rating scales. The mental distress questionnaire was originally evaluated in a non-patient population of college students' wives, a much younger age group than our patients. As few of this sample would be expected to suffer from premenstrual tension the more severe accompaniments of anxiety would not be expected and this may be why these symptoms showed little change over the cycle in the group of non-patients.

The only variables showing no discernible benefit from progesterone during the study were sexual thoughts or interest (daily symptom record), arousal (mental distress questionnaire and mood adjective checklist), and restlessness (daily symptom record). The arousal subscale of the menstrual distress questionnaire measures feelings of wellbeing, activity, affectionate feelings, orderliness, and excitement. Positive moods were thus not helped by the treatment, suggesting a different aetiology than for negative moods.

There are many possible explanations for the positive findings in the present study when compared with those of other double blind trials. In the present investigation the sample was studied prospectively before admission to the clinical trial. Although this reduced the size of the sample, there was objective evidence that the sample included in the clinical trial suffered from a discrete premenstrual syndrome. Great care was taken during the study to interview patients and have questionnaires completed each premenstruum rather than relying on retrospective accounts, which might have reduced the sensitivity of rating scales.

Effects of treatment can best be evaluated if the measuring instruments are valid, reliable, and sensitive to change. For this reason several rating scales were used. Previous trials have administered progesterone by vaginal or rectal routes. It is possible that administration by mouth may have produced more beneficial results than alternative routes. Further studies are needed to clarify whether this is so and to determine whether

similar plasma concentrations of progesterone and its metabolites occur with each method of administration. Of interest would be the 5B reduced metabolite, pregnanolone, which appears to be responsible for the well known hypnotic effect of progesterone.[19]

Some measure of patient preference for progesterone was indicated from interview data; women had been asked to rate change from their original (pretreatment) condition (table II). More change was detected during treatment with progesterone than during placebo. Women also reported that more symptoms grew worse while they were taking placebo. More patients were clearly shown to respond, according to both the menstrual distress questionnaire and the daily symptom record, to progesterone than to placebo.

Many women requested to continue treatment with progesterone and told others about it. We were unable to continue the treatment outside the clinical trial approval granted. There was no significant difference between progesterone and placebo in the incidence of side effects. The large incidence of reported drowsiness may have been related to the patients being told that this was a reported side effect of progesterone.

This study showed that an oral formulation of micronised progesterone was effective in alleviating many premenstrual complaints including those of anxiety, stress, depression, hot flushes, swelling, and water retention. Although these results indicate a beneficial pharmacological effect of progesterone, they do not necessarily imply that progesterone deficiency is the cause of the premenstrual syndrome. Further studies are needed to determine the optimum duration of treatment.

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Effect of seat belts on injuries to front and rear seat passengers

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Abstract

Data on 2520 occupants of cars involved in accidents were analysed in relation to injury and the severity of the crash to investigate the effect of rear seat passengers on injury to restrained and unrestrained front seat occupants and vice versa. Unrestrained front seat occupants showed a higher incidence of serious injury when there were rear seat passengers. The presence of a rear seat passenger did not affect significantly the overall incidence of injury among restrained front seat occupants within the range of crash severity considered. Unrestrained rear seat passengers behind unrestrained front seat occupants showed a higher incidence of moderate injury and a lower incidence of no injury than those behind restrained front seat occupants.

It is concluded that legislation on seat belts has not greatly increased the risk of person to person injury.

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Introduction

Concern has been expressed about injuries to people in the front seats of cars caused by passengers in the back seat being thrown forward in collisions and directly or indirectly injuring the front seat occupant.[1 2] Front seat occupants may not, therefore, be receiving full benefit from the use of a seat belt, and more active encouragement or even legislation for the installation and use of rear seat belts may be required.[3] Complementary to this possibility that rear seat occupants injure front seat occupants is that they themselves may be injured in collisions with front seat occupants. Unrestrained rear seat passengers might be at greater risk of injury in collisions in which the front seat occupant is held in position by a seat belt.

In this study the severity of injuries sustained by restrained and unrestrained front seat occupants in cars with and without rear seat passengers was compared. Similarly, the injuries sustained by unrestrained rear seat passengers were assessed in relation to the use or non-use of seat belts by the person directly in front.

Patients and methods

The investigators were members of a medical and an engineering team. A total of 2520 car occupants involved in accidents over 30 months before the use of seat belts became compulsory (on 31 January 1983) were included in the sample. All car accidents that occurred within the catchment area of the John Radcliffe Hospital, Oxford (roughly,