PAPERS AND SHORT REPORTS

Treatment of the premenstrual syndrome by subcutaneous oestradiol implants and cyclical oral norethisterone: placebo controlled study

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Abstract

The hypothesis that the many non-specific changes normally associated with cyclical ovarian activity are the primary aetiological factors in the premenstrual syndrome was tested by suppressing ovulation with subcutaneous oestradiol implants. Sixty eight women with proved premenstrual syndrome were treated under placebo controlled conditions for up to 10 months in a longitudinal study. Active treatment was combined with cyclical oral norethisterone to produce regular withdrawal periods. Symptoms were monitored with daily menstrual distress questionnaires, visual analogue scales, and the 60 item general health questionnaire. Of the 35 women treated with placebo 33 improved, giving an initial placebo response rate of 94%. The placebo effect gradually waned, but the response to the active combination was maintained for the duration of the study. Analysis of the prospective symptom ratings showed a significant superiority of oestradiol implants over placebo after two months for all six symptom clusters in the menstrual distress questionnaire. Changes seen in the retrospective assessments were less significant but the trend was the same.

Treatment with oestradiol implants and cyclical progestogen was well tolerated and appears to be both rational and effective for severe cases of the premenstrual syndrome.

Introduction

All aspects of the premenstrual syndrome remain subjects of much controversy.[1] Nevertheless, in the confusion concerning definition, diagnosis, aetiology, and treatment five observations appear to be salient. The premenstrual syndrome is associated with cyclical ovarian activity and does not occur before puberty, during pregnancy, or after the menopause.[2] Menstruation itself is incidental, as cyclical symptoms continue after hysterectomy, provided that ovarian function is conserved.[3] Most healthy women report adverse symptoms before menstruation.[4] Extensive metabolic and psychological studies have failed to find a specific abnormality in the premenstrual syndrome.[1] Lastly, the condition shows a strong response to placebo.[5] While the factors concerned in responsiveness to placebo are extremely complex,[6] the evidence none the less suggests a primary role for cyclical ovarian activity in pathogenesis.

That the ovarian cycle is associated with such profound effects should not be surprising. Many physical, psychological, and behavioural changes affecting all body systems occur during the normal menstrual cycle.[7] Furthermore, the premenstrual syndrome is only one of many disorders that regularly fluctuate with ovarian activity; examples include migraine, epilepsy, rheumatoid arthritis, diabetes, and asthma.[7] The corollary of considering cyclical ovarian activity as fundamental in the aetiology of the premenstrual syndrome is that suppression of ovulation should abolish symptoms.[8] Anovulation may be achieved by subcutaneous implants of oestradiol (Organon Laboratories)[9] combined with cyclical oral progestogen to ensure regular withdrawal periods and prevent endometrial hyperplasia.[10] The benefits of that approach have been reported in a retrospective study.[11] This paper presents the results of a prospective randomised controlled study of oestradiol implants and cyclical oral norethisterone in the management of the premenstrual syndrome.

Patients and methods

Study design—As there is no standard treatment for the premenstrual syndrome and the condition shows a strong response to placebo,[1] the study treatment was compared against a placebo. A parallel study was appropriate, as subcutaneous oestradiol implants are long acting preparations with biochemical activity lasting over 12 months.[12] We find that the therapeutic benefit is maximal two to four months after implantation and that the response generally wanes after five to six months, when the implant is repeated.[12] Hence we planned to monitor treatment over two consecutive implants with special emphasis on months 2-4 and 8-10. Patients were

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reviewed every three months and given fresh implants when symptoms were returning. All those who were not sterilised were advised to use non-hormonal contraception throughout.

Patients—Women who fulfilled the following criteria were recruited from the premenstrual syndrome clinic at Dulwich Hospital: (*a*) age 25-45 with regular periods and a cycle length of 24-32 days; (*b*) not using drugs that affect ovarian function; (*c*) not suffering from other medical or psychiatric condition; (*d*) family complete; (*e*) normal pelvic organs on clinical examination; (*f*) agreeable to treatment with hormone implants; (*g*) prepared to monitor symptoms daily during the study; (*h*) a complaint of premenstrual distress for at least the past six months; and (*i*) confirmation of the diagnosis of the premenstrual syndrome on prospective daily symptom rating for at least one of the six symptom clusters studied. Of 132 consecutive patients referred to the clinic during the study period, 68 fulfilled these criteria and were entered into the study.

Treatment—Eligible patients were treated under double blind conditions, such that neither the patient nor the assessing physician was aware of the allocation. Treatment was randomised by a second physician, whose role was to dispense the appropriate implant and progestogen. Allocation was based on random numbers, equating odd numbers with active and even numbers with placebo treatment. Blocking in groups of 10 was incorporated to minimise imbalance in allocation. Treatment was either a 100 mg subcutaneous oestradiol implant and 5 mg oral norethisterone for seven days per cycle (oestradiol group) or placebo implant and 5 mg placebo, identical in appearance with the active drug, for seven days per cycle (placebo group). Implants were inserted deep into the subcutaneous tissue of the anterior abdominal wall using the technique of Thom and Studd.[13] The timing of tablets was adjusted individually depending on the length of the menstrual cycle, such that the last tablet was taken two days before the next expected period. Implants were repeated if the assessing physician judged on interviewing the patient that symptoms were returning or had failed to respond to the first implant.

Assessment of symptoms—Symptoms before and during treatment were monitored using three parameters. Daily symptom ratings were obtained using a modified Moos menstrual distress questionnaire consisting of 34 adverse symptoms in six symptom clusters (pain, concentration, behavioural change, autonomic reactions, water retention, and negative affect) scored daily on a scale of 0-3 (no symptoms to severe symptoms).[14] While recognising that conclusions drawn from the analysis of symptom clusters cannot be applied directly to isolated symptoms, this approach is appropriate for a condition typically associated with numerous non-specific complaints, as it reduces the need for multiple statistical testing. A 100 mm visual analogue scale was also completed at each clinic visit to describe how the women had been feeling since their last attendance (0=very well to 100=very unwell).[15] Lastly, the 60 item general health questionnaire was applied at each visit as a non-specific screening tool for current psychiatric morbidity[16]; a score was obtained by counting the number of items for which morbidity was said to be increasing. Weight, blood pressure, menstrual pattern, changes in medication, side effects, complications, and reasons for stopping treatment prematurely were also recorded by the assessing physician.

Statistical methods—The total daily ratings for each of the six symptom clusters in the menstrual distress questionnaire during the pretreatment cycle and every second cycle after treatment (cycles 2, 4, 6, 8, and 10) were assessed by trend analysis.[17] This provides both qualitative and quantitative statistics concerning chronological data, in this case symptoms during the menstrual cycle. Records were analysed provided that no more than three days of values were missing in a cycle. Qualitative analysis of the pattern of symptom trends before treatment was used for diagnosing the premenstrual syndrome (eligibility criterion (*i*)); the syndrome was defined as a condition associated during the menstrual cycle with (*a*) significant ($p<0.05$) positive (worsening) symptom trends during the 14 days before menstruation and at no other time in the cycle; and (*b*) significant ($p<0.05$) negative (improving) symptom trends some time after the onset of menstruation and at no time after the presence of significant positive trends (fig 1). Quantitative analysis was used to provide three indices of the severity of symptoms before and after treatment—namely, the maximum and minimum exponentially smoothed averages, representing peaks and troughs in symptoms, and the mean symptom score during the cycle (fig 1). These indices were calculated for the six symptom clusters in the menstrual distress questionnaire and for all symptoms recorded. The effect of treatment on these three variables was assessed by the Kruskal-Wallis test (within groups) and, using the difference between scores before and after treatment, Wilcoxon's rank sum test (between groups). Data from the visual analogue scale (without transformation) and general health questionnaire were analysed by similar non-parametric techniques. Other variables were assessed using one way analysis of variance (within groups) and the unpaired *t* test and χ^2 test with Yates's correction (between groups). All statistics were two tailed. A significant difference was defined as $p<0.05$.

Power calculation—Trial size was estimated by considering that 90% of the cases would improve with active treatment and 50% with placebo and accepting a type I error of 5% and a type II error of 10%; with this calculation the required number of patients in each treatment group would be 23. Allowing for the length of the study and the pharmacokinetics of implant treatment, we decided to continue recruitment until roughly that number of cases had been treated for at least four months.

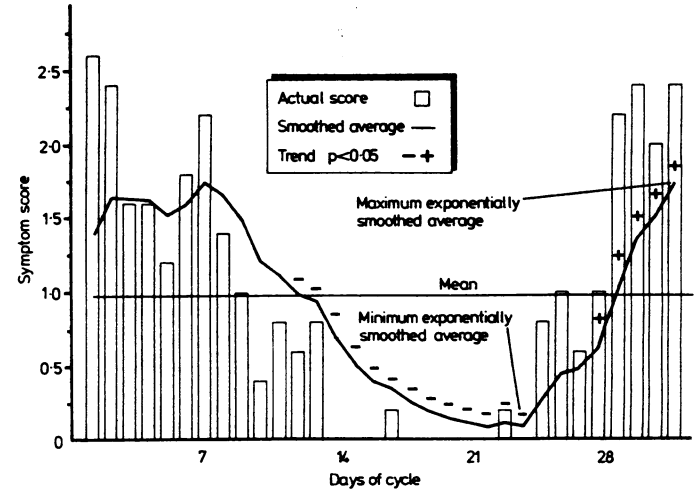

FIG 1—Trend analysis of symptoms during menstrual cycle. Symptoms scored 0-3 (none to severe). Trend analysis with smoothing constant of 0·25.[17]

Results

The characteristics of the two treatment groups, including baseline scores from the menstrual distress questionnaire, visual analogue scale, and general health questionnaire, were similar except for a significantly higher mean diastolic blood pressure in the placebo group (unpaired *t* test: df=66; $t=2.96$; $p<0.01$) (table I). The average duration of follow up was also comparable, with 5·5 (SD 3·2) and 4·9 (2·7) months respectively for the women treated with oestradiol and placebo. There were no drop outs from the group receiving oestradiol. Conversely, two women given placebo stopped treatment after three months because they thought that the implant had failed to help their symptoms, while a third failed to attend for follow up at six months.

Daily symptom ratings—Six of the 91 (6·6%) menstrual distress questionnaires in the oestradiol group and eight of the 81 (9·9%) in the placebo group were inadequate for analysis. Symptoms generally improved at the start of treatment with both oestradiol and placebo, as denoted by a fall in peak and mean daily ratings (figs 2 and 3). While the benefits of active implants were sustained, resulting in a significant improvement in all symptom clusters during treatment (Kruskal-Wallis tests: df=5; $12.9<\chi^2<40.5$;

TABLE I—*Characteristics of patients before treatment. Where relevant, values are mean (SD in parentheses)*

	Oestradiol group	Placebo group
No of patients	33	35
Age (years)	35·1 (3·5)	35·9 (5·0)
Married	26	24
Parous	30	28
Employed	20	23
Duration of premenstrual syndrome (years)	3·8 (4·4)	3·1 (2·8)
Length of menstrual cycle (days)	27·3 (2·5)	27·6 (2·7)
Reported duration of symptoms per cycle (days)	12·9 (5·1)	14·5 (4·9)
Previously treated for premenstrual syndrome	30	32
Weight (kg)	57·9 (6·5)	58·9 (9·1)
Systolic blood pressure (mm Hg)	118·6 (9·6)	123·4 (13·8)
Diastolic blood pressure (mm Hg)	72·9 (7·0)	78·6 (8·8)
Menstrual distress questionnaire:		
No of symptom clusters with trends for premenstrual syndrome	4·5 (1·5)	4·7 (1·5)
Maximum exponentially smoothed average	1·15 (0·4)	1·17 (0·5)
Minimum exponentially smoothed average	0·14 (0·1)	0·14 (0·1)
Mean daily score	0·56 (0·2)	0·58 (0·3)
100 mm Visual analogue scale	84·9 (13·0)	84·2 (14·6)
60 Item general health questionnaire:		
Mean score	17·2 (15·0)	15·6 (13·2)
Score >12	16	19

0·0001<p<0·05), the placebo response tended to wane during the study period and the overall effect was not statistically significant for any of the clusters (Kruskal-Wallis tests: df=5; 1·1<χ^2<9·0; p>0·1). Changes in trough symptom scores were variable after both treatments (fig 4), a significant and maintained reduction occurring only for negative affect after oestradiol implants (Kruskal-Wallis test: df=5; χ^2=11·9; p<0·05). Comparison of the two treatments showed superiority of the active combination over placebo at all times and for all variables (table II). The improvement in total scores in the menstrual distress questionnaire were consistantly significant after the first two months of the study for peak and mean daily symptom ratings (Wilcoxon's rank sum tests: 0·001<p<0·05). Differences in the minimum exponentially smoothed average were smaller and reached significance only at four months (Wilcoxon's rank sum test: p<0·01). Individual comparisons of the six symptom clusters showed that the efficacy of oestradiol applied to all complexes, with greatest benefit on pain, autonomic reactions, water retention, and negative affect (for example, Wilcoxon's rank sum tests 0·001<p<0·1 at four months for maximum exponentially smoothed average and mean daily ratings). Once more changes in the minimum exponentially smoothed average generally failed to reach the 5% level of significance compared with placebo.

Visual analogue scale—Irrespective of the treatment all but four women reported an improvement in symptoms throughout the study, scores on the visual analogue scale being reduced by on average 41-54% (table III). The exceptions included two members of the oestradiol group (one at six months and one at nine months) and two treated with placebo (both at three months). Overall, the reductions in visual analogue scores were significant for both oestradiol (Kruskal-Wallis test: df=3; χ^2=50·3; p<0·001) and placebo (Kruskal-Wallis test: df=3; χ^2=55·6; p<0·001). Although active treatment was associated with the greater fall in visual analogue scores at all times, the large interpatient variability in measurements and the relatively small number of observations later in the study meant that the comparison with placebo failed to reach statistical significance (Wilcoxon's rank sum tests: p>0·1).

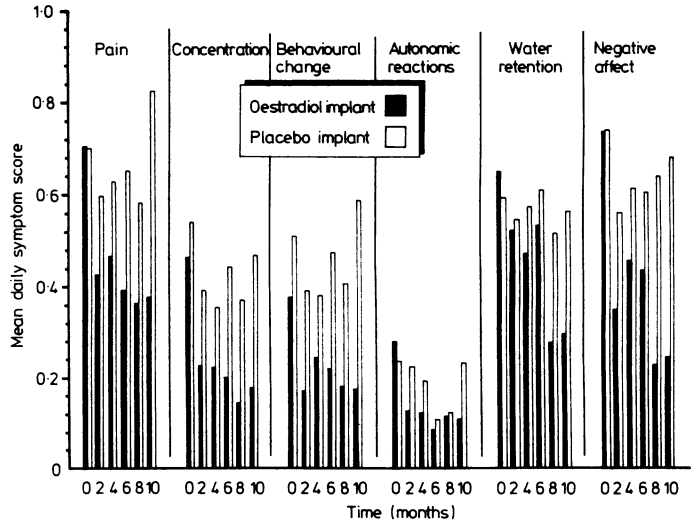

FIG 3—Effect of treatment on mean daily symptom scores.

TABLE II—*Changes in total menstrual distress questionnaire scores with treatment. Results expressed as mean (10th quantile, 90th quantile) difference between pretreatment and post-treatment scores per symptom*

Variable	Oestradiol group: No studied	Oestradiol group: Change in score	Placebo group: No studied	Placebo group: Change in score	R*	Z	p
Maximum exponentially smoothed average:							
0-2 Months	30	0·531 (0·04, 1·09)	30	0·300 (−0·36, 0·91)	815	1·47	<0·2
0-4 Months	23	0·422 (−0·10, 0·97)	25	0·175 (−0·36, 0·76)	510	2·10	<0·05
0-6 Months	14	0·458 (−0·08, 0·85)	10	−0·023 (−0·39, 0·37)	81	—	<0·01
0-8 Months	9	0·705 (0·22, 1·07)	8	0·162 (−0·46, 1·09)	48	—	<0·05
0-10 Months	9	0·651 (−0·10, 1·23)	5	0·005 (−0·25, 0·36)	19	—	<0·05
Minimum exponentially smoothed average:							
0-2 Months	30	0·033 (−0·14, 0·16)	30	−0·036 (−0·31, 0·17)	809	1·56	<0·2
0-4 Months	23	0·043 (−0·09, 0·25)	25	−0·068 (−0·34, 0·11)	484	2·64	<0·01
0-6 Months	14	0·047 (−0·06, 0·14)	10	−0·035 (−0·11, 0·02)	95	—	<0·1
0-8 Months	9	0·092 (−0·08, 0·42)	8	−0·008 (−0·19, 0·21)	57	—	>0·1
0-10 Months	9	0·103 (−0·04, 0·43)	5	−0·064 (−0·26, 0·16)	24	—	<0·1
Mean daily score:							
0-2 Months	30	0·252 (−0·01, 0·57)	30	0·115 (−0·26, 0·44)	821	1·38	<0·2
0-4 Months	23	0·206 (−0·05, 0·53)	25	0·035 (−0·34, 0·38)	495	2·41	<0·02
0-6 Months	14	0·236 (−0·15, 0·49)	10	−0·030 (−0·15, 0·11)	79	—	<0·01
0-8 Months	9	0·388 (0·04, 0·89)	8	0·030 (−0·34, 0·46)	47	—	<0·01
0-10 Months	9	0·378 (0·00, 0·92)	5	−0·084 (−0·23, 0·20)	18	—	<0·01

*Wilcoxon's sum of ranks test for comparison of treatment effect between groups.

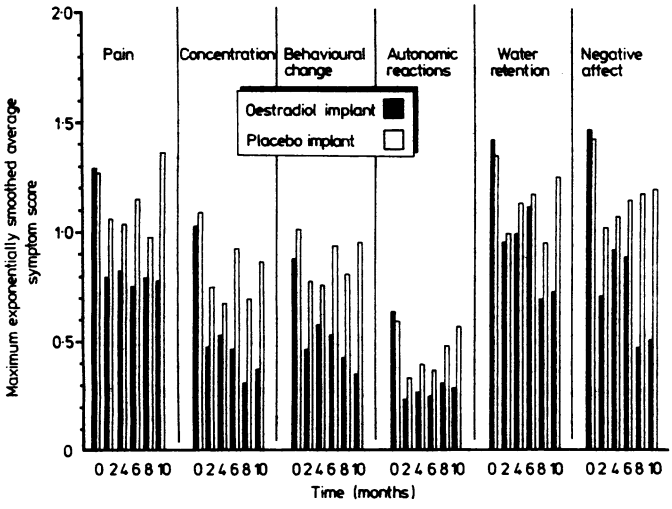

FIG 2—Effect of treatment on maximum exponentially smoothed average symptom scores.

General health questionnaire—Similar results were obtained from analysis of the 60 item general health questionnaire. Both treatments were followed by significant reductions in scores early on, but by nine months results in the placebo group were worse than before treatment (table III). Nevertheless, the treatment effects were not significantly different because of the large scatter of the data (Wilcoxon's rank sum tests: p>0·1).

Other variables—Of the women who had tried conventional treatments, 30 out of 30 receiving oestradiol and 27 out of 32 (84·4%) placebo considered implants to be more effective (Yates's χ^2 test: df=1; χ^2=1·92; p<0·2). The average number of implants dispensed during the study was similar for both treatment groups, being 2·1 (SD 0·51) for oestradiol and 2·0 (0·48) for placebo. For the 67 women who had more than one implant during the study the average interval between implants was 5·6 (SD 1·6) and 5·0 (1·6) months for oestradiol and placebo respectively (unpaired *t* test: df=65; *t*=1·5;

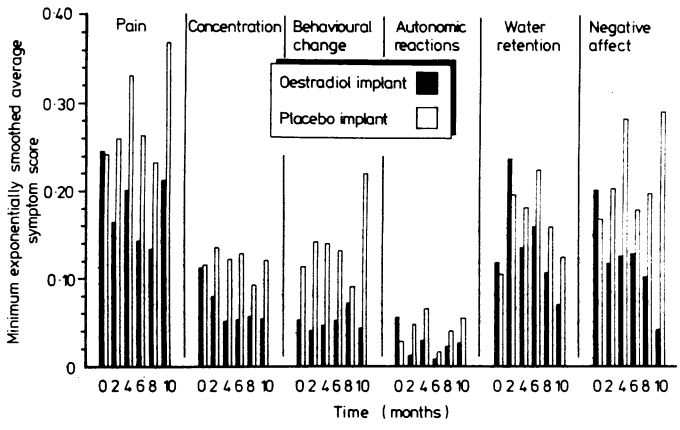

FIG 4—Effect of treatment on minimum exponentially smoothed average symptom scores.

highly effective in the management of the syndrome. Though the retrospective ratings (visual analogue and general health questionnaire scores) failed to distinguish between the treatments, their infrequent application necessarily means that they represent the weakest index of treatment effect. Conversely, the improvement seen in daily symptom ratings with oestradiol was statistically superior after the first two months, and this difference applied to all symptom clusters. To our knowledge this is the first treatment subjected to a large scale controlled study to have been found to be successful in relieving the typical complaints of the syndrome. Our results support those of the pilot retrospective study, which, in addition, showed that the treatment was well tolerated after prolonged use.[11] In that study lower doses of oestradiol were generally dispensed after the initial 100 mg pellet without loss of effect, and this is to be recommended in the long term to avoid hyperoestrogenaemia.

We attribute the efficacy of our treatment to suppression of cyclical ovarian activity by the oestrogen rather than any effect of

TABLE III—*Changes in visual analogue scale and general health questionnaire scores with treatment. Results expressed as mean (10th quantile, 90th quantile) difference between pretreatment and post-treatment scores*

Variable	Oestradiol group: No studied	Oestradiol group: Change in score	Placebo group: No studied	Placebo group: Change in score	R*	Z	p
Visual analogue scale:							
0-3 Months	33	46·1 (15, 78)	35	35·2 (0, 63)	1017	1·50	<0·2
0-6 Months	15	40·2 (0, 71)	12	37·6 (13, 67)	169	—	>0·1
0-9 Months	10	45·3 (7, 82)	8	42·4 (4, 78)	60	—	>0·1
General health questionnaire:							
0-3 Months	33	13·6 (−1, 33)	35	10·3 (−7, 31)	867	0·56	<0·6
0-6 Months	15	5·3 (−14, 24)	12	5·8 (−10, 27)	182	—	>0·1
0-9 Months	10	7·3 (−20, 34)	8	−7·3 (−45, 22)	52	—	>0·1

*Wilcoxon's sum of ranks test for comparison of treatment effect between groups.

p<0·2). There were no significant changes in weight or blood pressure during the study.

Side effects—Both treatments were well tolerated and side effects were usually mild and transient. Most common complaints in the oestradiol and placebo groups included mastalgia (nine and two cases respectively), nausea (three and four), weight gain (five and none), and headache (two and three). Menstrual pattern remained unchanged or improved for most women. In particular, there was a tendency for period pain and flow to decrease with active treatment. Only two women receiving oestradiol and four placebo reported episodes of irregular bleeding.

Discussion

Several important observations are evident from our study. Firstly, even carefully selected women suffering from the premenstrual syndrome usually show a significant response to placebo, certainly early in treatment. The immediate response to placebo in our study was 94%, all but two of the 35 women receiving a placebo implant reporting improvement during the first three months. This is much higher than the often quoted 50-60% and, indeed, larger than the maximum rate reported (89%).[5] The duration of the response varied, but on average the daily symptom ratings, which are generally considered to be the most accurate index of symptoms, returned to pretreatment scores by six months. The response to the subsequent placebo implant appeared to be weaker and of shorter duration (figs 2-4). Though the "surgical" nature of the treatment may in some way account for such a potent placebo response, we must assume that psychosocial factors play an important part in this condition. Many of these patients admit to problems with personal, family, and sexual relationships in particular, and it is this aspect of their distress that we believe responds to placebo.

Despite the extent of the placebo response, subcutaneous oestradiol implants with cyclical oral norethisterone proved to be the progestogen. Controlled studies have failed to find that norethisterone, or indeed other progestogens, are successful for any but isolated symptoms of the premenstrual syndrome.[1] Conversely, implants of 100 mg oestradiol have been shown to be contraceptive—though not immediately, as pregnancies may occur during the first six months.[9] We have also found that follicular activity and luteinisation continue in some cases during the first few months (unpublished observations). Incomplete suppression of ovulation early on may partly explain the inferior response at two months.

Ovulation may be suppressed by other therapeutic manoeuvres. The combined oral contraceptive pill may not only be contraindicated in this age group but, though the definitive study has still to be done, is probably effective in only half or so of cases.[1] The reason may be that the benefits of anovulation secondary to the oestrogen component are negated by progestogenic side effects which are similar to the typical complaints of the premenstrual syndrome.[18,18a] Furthermore, the cyclical nature of the pill regimen is itself associated with hormonal swings. Crystalline implants of "natural" oestradiol not only provide a continuous source of oestrogen but do not have the potential cardiovascular complications of "synthetic" oestrogens; implants are already widely and safely used for the treatment of climacteric complaints.[19] Giving norethisterone for a shorter duration each cycle may account for the better tolerance with our treatment, though we have seen women who are extremely sensitive to progestogen. Such patients may improve with reduced dosage or other progestational agents.

Ovarian function may also be inhibited by danazol. Recent trials have reported favourably on certain symptoms (D H Gilmore *et al*, paper presented to 11th World Congress of Gynecology and Obstetrics, West Berlin, 1985). Danazol, however, appears to be poorly tolerated and is associated with a considerable drop out rate because of androgenic and other side effects. Gonadotrophin

releasing hormone agonist has been used to produce reversible "medical ovariectomy" and relief of premenstrual distress but, as pointed out by the authors, the low levels of oestradiol release induced precludes its long term use.[20] Oestradiol implants are both well tolerated and also maintain plasma oestrogen concentrations in the normal to high follicular range.[11]

In conclusion we have shown that subcutaneous implants of oestradiol combined with cyclical oral norethisterone is of definite benefit for the premenstrual syndrome. Taken in conjunction with the degree of placebo responsiveness shown by these patients, we hypothesise that the primary event in this condition is ovarian activity with its associated physical, psychological, and behavioural changes, which, in this group of women, are amplified secondary to psychosocial factors or as yet undetermined central mechanisms. Despite arguments about the importance of "reproductive biology" in the genesis of psychiatric morbidity[21,22] there seems little doubt that the hormonal and other changes associated with the ovarian cycle have profound effects on both the soma and the psyche, effects that may logically be controlled by manipulating ovulation.

We thank all our colleagues who helped in the premenstrual syndrome clinic, including Laila Hanna, Tim O'Dowd, Maggie Blott, and Julia Montgomery. We are also grateful to Linda Abbott and Trish Waghorn, whose administrative and secretarial work was essential; and, finally, to Sister P A Fryer and other members of the nursing staff who prepared the implant sets for the clinic. This work was supported by a grant from King's Voluntary Research Trust.

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Associations between symptoms of irritable colon and psychological and social conditions and lifestyle

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Abstract

In a survey of risk factors for coronary heart disease 14 102 middle aged men and women answered a questionnaire on lifestyle, diet, and health, including symptoms of functional abdominal disorders. The overall prevalence of reports of one or both of the abdominal symptoms of "bloating and rumbling" or "cramping abdominal pain" was 28% in men and 35% in women. Only a weak negative association between age and prevalence of reported pain was found in both sexes. Women reported abdominal symptoms, especially cramping abdominal pain, significantly more commonly than men. In a multiple regression analysis abdominal symptoms were much more strongly associated with symptoms of mental stress such as depression, sleeping difficulties, problems of coping, and the use of analgesics than with lifestyle, dietary, and social variables together. The association was stronger in subjects reporting both symptoms.

This strong and consistent association between functional abdominal disorders and psychological and social problems suggests that action other than prescribing drugs, diets, or radiography is required.

Introduction

Of the more common aches and pains, abdominal complaints make up a large share,[1,3] leading to more patients consulting their general practitioner and the use of costly high technology examinations. A quarter of those who report abdominal symptoms eventually consult a doctor,[1,2] and a third to a half of outpatients in gastroenterological departments are classified as having functional disorders.[4,5] Common symptoms of bowel disorders are bloating, rumbling, cramping pain, and obstipation or diarrhoea, or both, which, when occurring without signs of organic disorders, constitute the irritable bowel syndrome.

The aetiology of this syndrome remains obscure. Both psychological conditions and diet are considered to contribute, though they are not established as causal. The great variation in treatment regimens reflects the lack of consistent knowledge about provoking

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