TREATMENT OF THE PREMENSTRUAL SYNDROME: A GYNAECOLOGIST'S VIEW

by

T. R. VARMA

SUMMARY

We studied 270 women with premenstrual symptoms (PMS) 7 to 14 days before the onset of the menstrual flow. All the 270 patients had ovulatory cycles. Of these 270 patients, 11 did not complete the different regimens and 9 patients moved out of our area. Each patient received placebo, Navidrex K (diuretic), pyridroxine (Vitamin B_6) and dydrogesterone (progesterone) alone and in different combinations of two or three drugs together from day 12 to 28 or up to the onset of menstrual flow. Placebo relieved symptoms in 26 per cent of patients. Pyridoxine relieved symptoms in 48 per cent of patients. Thirty per cent of patients were relieved of symptoms when they received Navidrex K alone. Dydrogesterone relieved symptoms in 62 per cent. Pyridoxine and Navidrex K together relieved symptoms in 58 per cent, combined dydrogesterone and pyridoxine regimen relieved symptoms in 76 per cent and dydrogesterone and Navidrex K helped 72 per cent of patients. However, we found when a combined regimen of dydrogesterone, pyridoxine and Navidrex K was given, 80 per cent had no symptoms and only 10 per cent remained symptomatic.

Introduction

Although recognised for centuries by clinicians, the distressing symptoms which occur cyclically in women prior to the menses were first described by Frank in 1931. Since then, considerable effort has been directed towards the clinical characterization and pathophysiological dilineation of this premenstrual syndrome (PMS). It has been maintained that premenstrual tension is the most common of the minor endocrinological diseases.

It has long been known that when women become irritable tense or depressed 7 to 14 days before the next menstrual flow. A temporary deterioration in their interpersonal relationships has been implicated in marital discord (Shabanah, 1963) baby battering and criminal behaviour (Dalton, 1980). Although the association between the PMS and intellectual impairment has not been clearly established there are an increased number of psychiatric admissions (Glass *et al* 1971), and suicide attempts (Glass *et al* 1971) in

From: Senior Lecturer, St. George's Hospital Medical School, Cranmer Terrace, London, SW17 ORE.

Accepted for publication on 18-5-83.

women during the premenstrual phase.

The term 'PMS' covers a wide range of psychic and somatic symptoms which occur during the post-ovulatory phase of the menstrual cycle. In the past, PMS was treated in a variety of ways, no single therapy emerging as the most generally accepted one. Because of the uncertain aetiology the treatment has been empirical and results obtained have been variable. This undoubtedly is due to the fact that the predominant symptom differs from patient to patient and that the treatment therefore must be individualised.

The treatment may have 4 different aims: influence of psychogenic factors, simple symptomatic treatment, dehydration of the patient and neutralization of the dominant oestrogenic influence. The lack of unanimity of opinion in the frequency and the value of treatment of PMS may depend largely on differences in diagnostic criteria. Selection of patients, assessment of symptoms, diagnosis of PMS and the variable nature of the conditions make it difficult to organize clinical trials in the treatment of PMS.

The aim of the present study was to evaluate the use of commonly administered drugs to patients with PMS.

Patients and Methods

Patients were referred to our special PMS clinic by other specialists or by their general practitioners. Vever few patients were seen at their own request. We studied initially 270 women with PMS who had ovulatory cycle and had symptoms 7 to 14 days before the onset of the menstrual flow which often relieved symptoms.

The median age was 31.8 years (range 19-46), the mean duration of the symptoms was 1.3 years (range 6-48 months) and the average number of pregnancies was 2.9 (range 0.5). Women did not take any medications, including contraceptive pills for at least 3 months prior to the study. All the patients had the serum progesterone and oestradiol levels estimated in the middle of the second half of the cycle to confirm ovulation. Patients were included in his study after confirming that they had an ovulatory cycle and PMS symptoms related to the luteal phase of the cycle were usually relieved by the onset of menstrual flow.

The main symptoms are shown in Table I.

TABLE I

Incidence of Different Symptoms in the Group of 250 Patients With Premenstrual Symptoms (PMS)

Symptoms	Patients (%)
Psychological symptoms	
Depression	90.6
Irritability and tension	88.2
Aggression	76.6
Anger	71.8
Nervousness	58.6
Tearful	31.2
Somatic Symptoms	
Weight gain/oedema	88.0
Breast tenderness	75.2
Headache	71.2
Abdominal distension + bloated feeling	66.8
Others	43.2

Ninety per cent of our patients complained of psychological symptoms of which irritability and depression were the commonest. Symptoms were also rated on a four-point scale from nil to severe (not present, mild, moderate and severe) on day 7. 18 and 26 of the cycle. Patients with moderate to severe symptoms were included in this study. Of the 270 patients who were chosen for this study, 40 per cent were housewives, 42 per cent were professionals and 18 per cent were doing other work. Of these 270 patients, 11 did not complete the

different regimen and 9 patients moved out of our area.

Table II shows the different regimen of treatment.

TABLE II
Regimens of Treatment

Regimen of treatment	Dosage	Duration of treatment
Placebo	2 tablets daily	From day 12 to onset of menstrual flow
Pyridoxine (Vitamin B_6)	50 mg twice daily (2 tablets)	,,
Navidrex K (Diuretic)	2 tablets daily	,,
Dydrogesterone (Progesterone)	10 mg twice daily (2 tablets)	,,
Pyridoxine + Navidrex K	50 mg twice daily 2 tablets daily (4 tablets)	,,
Pyridoxine + Dydrogesterone	50 mg twice daily 10 mg twice daily (4 tablets)	,,
Navidrex K + Dydrogesterone	2 tablets daily 10 mg twice daily (4 tablets)	,,
Placebo	4 tablets daily	,,
Navidrex K + Pyridoxine + Dydrogesterone	2 tablets daily 50 mg twice daily 10 mg twice daily (6 tablets)	,,
Placebo	6 tablets daily	,,

Figures in brackets shows the total number of tablets a patients received daily.

Each patient started with one of the regiment including the placebo and completed the whole course of treatment. Patients were not told the actions of each regimen. They were reassured of no side effects from the different drugs and they were included in this study with their informed consent.

Each regimen of treatment lasted for 2 months and the drugs were given from day 12 to 28 or until the menstrual cycle began. Patients were asked to record their symptoms and its severity in the menstrual calender. Each patient received placebo, Navidrex K (diuretic), pyridoxine (vitamin B_6), dydrogesterone (Duphaston) alone and in different combinations of two or three drugs together (Table II).

Patients were asked to record and rate their symptoms before they were included in the study and during each regimen of treatment during the second month on day 7, 18 and 26 on a menstrual calender.

Results

Table III shows the results of various regimens of treatment used for PMS.

TABLE III

Effect of Different Regimens of Treatment on Symptocytology of PMS Patients

Regimens of treatment	Patients Cured			Patients markedly improved			Patients with little or no improvement		
	Total (%)	Physical (%)	Psychic (%)	Total (%)	Physical (%)	Psychic (%)	Total (%)	Physical (%)	Psychic (%)
Single Medication (2 tablets)	—	—	—	—	—	—	—	—	—
Placebo	26	48	52	24	44	56	50	41	59
Pyridoxine	48	32	68	30	56	44	22	44	56
Navidrex K	30	52	48	36	51	49	34	48	52
Dydrogesterone	68	49	51	18	53	47	14	48	52
Combined Medication (4 tablets)									
Pyridoxine + Navidrex K	58	48	52	22	48	52	20	53	47
Pyridoxine + Dydrogesterone	76	54	46	12	46	54	12	49	51
Navidrex K + Dydrogesterone	72	56	44	16	44	56	12	42	58
Placebo	30	46	54	26	42	58	44	42	58
6 tablets Navidrex K + Pyridoxine + Dydrogesterone	80	51	49	10	46	54	10	52	48
Placebo	29	46	54	23	42	58	48	40	60

When we analysed the results, we had only 250 completed patient records since 11 patients discontinued the treatment for various minor reasons and 9 patients moved out of the area and could not attend the clinic.

Before entry into this study al the 250 patients had moderate to severe PMS symptoms. While they received placebo only 26 per cent had no symptoms and 74 per cent remained symptomatic and psychosomatic symptoms were more predominant.

When they received pyridoxine alone 48 per cent of patients had no symptoms, 30 per cent had mild symptoms of which physical symptoms were more common and 22 per cent continued to have mederately severe symptoms, mainly psychosomatic.

Navidrex K (diuretic) alone relieved symptoms in 30 per cent but 36 per cent of patients had mild symptoms and the remaining 34 per cent had moderate to severe PMS symptoms, both physical and psychomatic.

Dydrogesterone alone relieved symptoms in 62 per cent of patients, 18 per cent had only mild symptoms and 14 per cent continued to have moderatey severe symptoms.

When pyridoxine and Navidrex K were combined to treat PMS patients 58 per cent had no PMS symptoms, 22 per cent had mild symptoms and 20 per cent continued to have severe symptoms.

Combined dydrogesterone and pyridoxine therapy relieved symptoms in 76 per cent of patients, 12 per cent had mild symptoms and 12 per cent continued to have severe symptoms.

Combined dydrogesterone and Navidrex K relieved symptoms in 72 per cent of PMS patients, 16 per cent had ony mild symptoms and 12 per cent continued to have severe symptoms.

However, when all the three drugs, dydrogesterone, pyridoxine and Navidrex K were combined to treat PMS patients, 80 per cent had no symptoms, 10 per cent had mild symptoms and 10 per cent remained symptomatic.

When dydrogesterone was given the relief in physical symptoms were better, whereas when pyridoxine was given it had very little effect on physical symptoms, as compared with the effect on psychosomatic symptoms.

When dydrogesterone was part of the regimen 4 per cent of patients had breakthrough bleeding and slight alteration from their original menstrual cycle. Three per cent of women also complained of breast tenderness or increase in the tenderness they had before. There were no side effcts when Navidrex K or pyridoxine was given alone.

Discussion

Few aspects of the syndrome are clearly understood. This is probably due to several factors, including failure to define it, failure to conduct adequate controlled trials and the complexity of the sydrome. Katherina Dalton first suggested a relationship between progesterone and premenstrual syndrome and has since written many papers and a monograph on the subject.

Literature is full of uncontrolled clinical trials in a syndrome where the placebo effect is so well established. While there are reports of no response to placebo treatment of PMS (Shabanah, 1963) others have reported a response rate of 15 per cent (Morton, 1950) and 58 per cent (Mattsson and Schoultz, 1974).

A renewed interest in Vitamin B_6 therapy occurred with the discovery that this vitamin acts as a co-enzyme (Pyridoxial phosphate) in the final step of biosynthesis of dopamine and serotonin. Aberrant metabolism of these brain mono amines has been implicated both in disorders of hypothalamic-pituitary function and in a variety of disorders of mood and behaviour. The mechanism of action of vitamin B_6 is still not fully established, but this drug was

found to be useful in PMS by Day (1979). Day (1979) and Taylor and James (1979) reported that PMS symptoms were relieved by pyridoxine in 63 per cent and 55 per cent respectively. We found vitamin B_6 alone relieved symptoms in 48 per cent and when combined with a diuretic Navidrex K, symptoms were relieved in 58 per cent of patients with PMS.

Taylor (1977) and Day (1979) reported that the PMS symptoms were relieved by dydrogesterone in 70 to 76 per cent respectively. This was confirmed by Taylor and James (1979) and found 70 per cent of patients with PMS symptoms was relieved by dydrogesterone (Duphaston). Our results were similar to that of the above workers. However, Sampson (1979) did not find a significant difference in the relief of symptoms with the use of progesterone as compared with the placebo treatment.

A variety of diuretic agents were employed and were alleged to relieve PMS symptoms (Greene and Dalton, 1953; Jungck *et al* 1952). O'Brien *et al* (1979) used spironolactone and reported that psychological symptoms were reduced in more than 80 per cent of the symptomatic group When we used Navidrex K alone only 30 per cent of patients had complete relief of symptoms. Recently Wood and Jakubowicz, (1980) stated that mefenamic acid significantly improved mental symptoms, but was not effective for breast symptoms.

We found the combined regimen using dydrogesterone vitamin B_6 and diuretic were most useful in treating PMS symptoms and the side effects were minimal.

Our study suggests that both dydrogesterone and vitamin B_6 helped in relieving mental and physical symptoms significantly as compared with the effect produced by placebo. When oedema was a predominant feature or oedematous feeling was one of the symptoms, diuretic was helpful. We now prescribe the combined regimen of progesterone, diuretic and vitamin B_6 cyclically and the results are encouraging.

Acknowledgements

I wish to thank all the medical and nursing staff for their help in completing this study.

References

1. Frank, R. T.: Archives Neurol. Psych. **26: 1053, 1931.**
2. Shabanah, E. H.: Obstet. Gynec. **21: 49, 1963.**
3. Dalton, K.: Lancet, **2: 1070, 1980.**
4. Glass, G. S., Heninger, G. R., Lansky, M. and Talan, K.: Am. J. Psych. **128: 705, 1971.**
5. Morton, J. H.: Am. J. Obstet. Gynec. **60: 343, 1950.**
6. Mattsson, B. and Schoultz, B. U.: Acta. Psychiatr. Scand. Suppl. **225: 75, 1974.**
7. Day, J. B.: Current Medical Research and Opinion **6, Suppl. 5, 40, 1979.**
8. Taylor, R. W. and James, C. E.: Current Medical Research and Opinion. **6: 46, 1979.**
9. Taylor, R. W.: Current Medical Research and Opinion. **4: 35, 1977.**
10. Sampson, G. A.: B. J. Psych. **135: 209, 1979.**
11. Greene, R. and Dalton, K.: Brit. Med. J. **I: 1007, 1953.**
12. Jungck, E. C., Barfield, W. E. and Greenblatt, R. B.: J. Am. Med. Assoc. **169: 96, 1952.**
13. O'Brien, P. M. S., Craven, D., Selby, C. and Symonds, E. M.: B. J. Obstet. Gynec. **86: 142, 1979.**
14. Wood, C. and Jakubowicz, D.: B. J. Obstet. Gynec. **87: 627, 1980.**