

1969

Psychophysiological tension in menstruation

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PSYCHOPHYSIOLOGICAL TENSION IN MENSTRUATION

by

Richard D. Schmidt

A THESIS

Presented to the Faculty of
The University of Nebraska College of Medicine
In Partial Fulfillment of Requirements
For the Degree of Doctor of Medicine

Under the Supervision of
Robert Messer, M. D.

Omaha, Nebraska
February 1, 1969

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PSYCHOPHYSIOLOGICAL TENSION IN MENSTRUATION

INTRODUCTION

This problem of menstruation is seemingly well known, but in reviewing the literature one is impressed with the scarcity of good information. At the present time, the greatest amount of information is descriptive in nature and usually goes under the name of "the premenstrual syndrome." The explanations for this syndrome, whether psychological or physiological, are numerous, but exploration of the problem has been of minor significance and incomplete. Information about attempts at treatment is scanty and conflicting. One major problem is the small scale of the previous investigations and the lack of coordinated studies. An attempt will be made in this paper to summarize the findings of previous investigations as reported in the literature in order that the overall complexion of the problem can be assessed.

DEFINITION AND OCCURRENCE

The term "premenstrual syndrome" was originally used by Frank in 1931, but in 1963 Coppen proposed the use of the term "cyclic syndrome."⁵ His reasons were: (1) It dispenses with restriction in time imposed by the word premenstrual; (2) It draws attention to the fact that it is more likely to be related to pituitary activity, and thus complex hypothalamic and endocrine multiglandular interaction than merely to a basically pelvic disturbance;

(3) It presents a concept of psychology rather than pathology with the inference that many features may occur which do not demand treatment. While no recent literature has disputed the term used by Coppen, the term premenstrual syndrome still prevails, probably by tradition.

The premenstrual syndrome is not just a given set of symptoms and signs which must be found in a person to classify them as having the premenstrual syndrome. It contains many signs and symptoms, only a few of which need be combined to qualify for the syndrome. It is not a rare academic syndrome, either. Estimates vary that from 25 to 100 percent of women have increased psychic and somatic disturbances during ovulation, premenstrually or menstrually.

One of the most commonly quoted figures for women having premenstrual tension syndrome is 70 per cent. This figure was obtained by Eichner, using a group of student nurses as controls in a questionnaire study.³ He found that 70 percent of the nurses had one or more of the common⁴ symptoms of premenstrual tension. Morton⁴ using a group of female prisoners found that 80 percent of 249 had premenstrual tension. As stated before, however, the figure varies from 25 to 100 percent, depending on which study is quoted and what definition of premenstrual syndrome is being used in that study.

In their study of the premenstrual syndrome, Coppen and Kessel used a questionnaire to obtain information from 150 nulliparas. Their data revealed that 76 percent

5
 had regular menses. The mean duration was 4.8 days and 54 percent contained clots. There was no pain reported in 17 percent, 47 percent reported pain in the premenstrum, and 66 percent had pain with menstruation. In the group with premenstrual tension, premenstrual pain was found in 12 percent, menstrual pain in 25 percent. Other common complaints menstrually or premenstrually are given in Table I.

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 Not all findings are subjective during premenstrual tension. Goldfarb, in a pamphlet on premenstrual tension, lists the following objective findings: glycemia, neutrophilia, lymphocytopenia, suppression of capillary resistance, digital sweating and increased sensitivity of the respiratory center. What the above shows is what Coppen, Dalton and others have come to agree on, that any combination of the above occurring cyclinically constitute what can be called "the Premenstrual Syndrome." See Table II.

PSYCHOLOGICAL ASPECTS

To illustrate some of the psychological overtones associated with the menstrual cycle and menstruation in particular, Dalton divided a 28 day month into seven four-day periods. She then measured the time of admission of 276 female acute psychiatric patients. The expected probability was 14 percent during any four-day period. Dalton found 28 percent admitted during menstruation and 17 percent in the four days prior to menstruation. Of 36 attempted suicides, 39 percent were during menstruation and 14 percent were premenstrually. Depression accounted for

TABLE ICOMPLAINTS: MENSTRUALLY AND PREMENSTRUALLY

1) Cyclical acneform eruption	70%
2) Irritability	69%
3) Depression	63%
4) Swelling in some part of body	63%
5) Headache	32%
6) Constipation	20%
7) Dizziness	16%
8) Diarrhea	13%
9) Insomnia	5%
10) Spots before eyes	2%

The above list of symptoms has been confirmed numerous times although there may be variations in the frequency of occurrence of different symptoms. Greenblatt lists irritability, depression, insomnia, headaches, breast turgidity, premenstrual edema, and nausea as the seven most common symptoms.⁶

A study by Hood and Bond yielded the following
figures for premenstrual symptoms.⁷

TABLE II
SYMPTOMS OF PREMENSTRUAL SYNDROME

<u>Symptom</u>	<u>No. Of Patients</u>	<u>Percent</u>
Irritability	25	100
Headache	23	92
Bloating	22	88
Breast engorgement	21	84
Nausea	15	60
Abdominal cramping	14	56
Edema	11	44
Acne	9	36

185 patients, and, of this group, 33 percent were menstruating and 14 percent were premenstrual at the time of admission. Of 114 with an admitting diagnosis of schizophrenia, 26 percent were menstruating and 21 percent were premenstrual.^{9, 10}

In another study, Dalton found that of 156 female prisoners, 28 percent committed the crime while menstruating and that 22 percent of the crimes were premenstrual. A study using autopsy material revealed that of 22 Hindu women committing suicide by fire, 19 of the women were menstruating.¹² The amount of data could probably be endless in proving that there is often psychological tension associated with menstruation and in the premenstrual period, but the question is, why? The reasons given for the premenstrual syndrome range from strictly psychological to physiological, which most commonly involves hormonal studies.

The most commonly accepted psychological view "indicates that the perception of her menstrual flow intensifies a woman's pre-existing conscious and unconscious conflicts about pregnancy, having a child, castration fears, uncleanliness, lack of control of bodily functions, aggression, penis envy and masturbation. In the presence of a vulnerable ego structure; neurotic, psychotic or characterological reactions may occur. In most women the compensation for the deprivations associated with femaleness is the process of pregnancy and the bearing of a child. Hence, the common

psychoanalytic observation that a menstrual period is experienced as a "lost child."¹³

Some people, while realizing the above explanation and accepting it, have added to it more of the environmental aspects of life. Mary Chadwick, who wrote the book, The Psychological Effects of Menstruation, devotes one chapter to the common tribal taboos associated with menstruation. The book points up some interesting aspects which have not been fully studied, but which can be speculated about. An example was the fact that people in Brunswick thought "that if a menstruous woman assists at the killing of a pig the pork will putrefy."¹⁴ What effect did this have, and what effects do similar taboos of the past or present have on women today?

Some investigators have continued a step further and correlated the psychology with the physiology. One such study indicates that estrogen correlates to heterosexual tendency, masculine identification and infantile tendencies. Progesterone was correlated to homosexual tendency, narcissism, mother conflict, pregnancy and nursing tendencies. Low hormone levels were matched with dependence, depression and withdrawal, anal and genital elimination tendency and a destructive tendency.¹⁵

The most commonly studied psychological factor relates to neuroticism. Rees found that the premenstrual syndrome was associated more frequently with neurotic individuals and that neuroticism is also higher in women

with irregular periods. Rees made the following concluding statement, "It appears women who complain of premenstrual irritability are irritable at other times as well and it seems therefore, that menstrual symptoms are exacerbations of personality traits which in turn are related to neuroticism."¹⁶

To illustrate the above point, a study done by Irwin Perr¹⁷ serves appropriately. (Table III).

The major conclusion to be drawn from the preceding study was admirably stated by Suaiez-Murias when he wrote,¹⁸ "The psychologic aspect of premenstrual tension seems related largely to the manner in which the patient accepts psychically the menstrual function and also to the manner in which the patient unconsciously utilizes the menstrual function to express distress about pressing environmental situations of life, difficult interpersonal relationships, or about her own attitude concerning being a woman, or even about the fact of existence." In other words, personality type and environmental setting are the real factors in the psychologic manifestations of premenstrual tension. Israel,²⁰ one of the foremost writers on the premenstrual syndrome, stated this exact thought as follows: "Irrespective of the exacting mechanisms it cannot be denied; because of the nature of the symptoms, that emotional disturbances and psychogenic traumata not only aggravate the symptoms, but evoke additional ones."

TABLE III
INCIDENCE OF PREMENSTRUAL TENSION
IN NORMALS AND NEUROTICS

<u>Degree of Tension</u>	<u>Normals (61)</u>	<u>Neurotics (84)</u>
None	78.7%	38%
Moderate	16.4%	30%
Severe	5.0%	32%

THE INCIDENCE OF PREMENSTRUAL TENSION RELATED TO
DEGREE OF NEUROTIC CONSTITUTION

<u>Degree of Neurotic Constitution</u>	<u>Degree of Premenstrual Tension</u>		
	<u>Nil or Mild</u>	<u>Moderate</u>	<u>Severe</u>
Nil	76%	17%	7%
Mild	56%	36%	8%
Severe	15%	48%	37%

PHYSIOLOGICAL ASPECTS

"That pathologic emotional findings are bio-chemically influenced is widely accepted. Speculations as to etiology are reviewed in Southam's article and include sodium and water retention, excess of aldosterone, allergy to progesterone and its metabolites, a menstrual toxin,²⁰ excessive antidiuretic substance and hypoglycemia.

An increase in mineral corticoids and glucocorticoids in relation to ovarian steroids, a high estrogen-progesterone ratio and effect of adrenocortical hormones in general² have also been suggested as etiologic factors.

The most widely accepted physiological explanation for tension during the menstrual cycle is sodium retention and its accompanying water retention. One study showed that of 42 normally menstruating women, 30 percent gained three or more pounds premenstrually. It is felt that the water and sodium retention secondarily may cause lowering of nerve activation thresholds and thus more nervous system irritability. The lowered threshold is manifested clinically by a weakening of ego controls according to the characteristics²¹ of the predisposing personality structures.

The increased fluid retention or increased steroids at various times during the menstrual cycle have also been thought to cause relative hypoglycemia and thus psychiatric symptoms. Common symptoms associated with hypoglycemia are depression, insomnia, anxiety, irritability, fatigue, sweating, headache and dizziness. The hypoglycemia may

be due to decreased glucose tolerance from increased glucocorticoids or other steroids, possibly estrogen,²² during the premenstrual period.

Thorn²³ in 1938, did the classical work in the area of menstrual edema. He did a study in which he showed that out of 50 normal women, 24 (48 percent) gained one kilogram or more premenstrually and that 38 (76 percent) gained one kilogram or more about the time of ovulation. Thorn postulated this was due to increased hormones, probably estrogen. Using dogs and injecting sex hormones, Thorn was then able to assay the salt retaining property of these hormones. He found that the following had salt retaining property: (They are listed in decreasing order of potency.) 1) Estradiol, 2) Progesterone, 3) Estrogen, 4) Pregnanediol, 5) Testosterone. It is very probable that estradiol accounts for much of the premenstrual fluid retention.

Morton experimentally verified this by studying²⁴ 29 patients with premenstrual syndrome. In these patients, he followed basal temperatures, endometrial biopsy, vaginal smears and urinary hormones, during the premenstrual phase in particular. Morton was unable to demonstrate an abrupt rise in temperature at midcycle, found proliferative or mixed endometrium, cornified vaginal cells and subnormal prenanediol excretion in 10 of 14 patients, indicating that estrogenic activity was much greater than progestational activity.

Estradiol peaks at ovulation and in the premenstrual²⁵ phase and is often given as the cause for water retention.

Morton suggests that it is actually the estradiol/progesterone²⁶ ratio that causes the water retention. In fact, the premenstrual syndrome has been induced in castrates and menopausal patients by large doses of estrogen.

The plausibility of the above theory is nicely explained in Drill's Textbook of Pharmacology 1965, and it also accounts for the implication that aldosterone is involved in the Premenstrual Syndrome. Drill states that, "Estrogens can promote sodium retention, with associated fluid retention and edema. This is more prone to occur only when high doses of estrogen are used. However, the effects of estrogen upon fluid retention are less severe than those seen after testosterone or glucocorticoid therapy. In all probability, it may be the decrease in progesterone level that is responsible for the fluid retention. Since progesterone displays anti-aldosterone activity, the lowered progesterone secretion level permits aldosterone, which increases at this time to induce fluid retention." Glucocorticoids have also been implicated because they have²⁷ many of the water retention properties of mineralcorticoids.

That aldosterone is indeed elevated in the luteal phase of the menstrual cycle has been demonstrated by Strausfeld. He demonstrated that aldosterone secretory rates range between 100 μ g during the follicular phase in females, while during the luteal phase the range is between 230 μ g^r and 350 μ g. The rates in the luteal phase were all outside the normal range for a male. In one woman with premenstrual tension, the luteal secretory rate was five times that

found in the follicular phase.²⁸ An additional cog in the wheel is the fact that emotional stress can activate the adrenal cortex in man, thus increasing steroid levels in the peripheral blood.²⁹ The question arises, however, as to how much stress menstruation causes?

One last hormone should be mentioned as a possible cause of fluid retention, i.e. antidiuretic hormone (ADH). Although ADH has not commonly been discussed as a cause for premenstrual tension, Pendergrass³⁰ did an interesting experiment involving irradiation of the posterior pituitary in humans. He felt that ADH may cause premenstrual tension and therefore he irradiated the pituitary glands of women with fluid retention premenstrually. Initial success was noted in approximately 50 percent of his cases. One-third of the cases had no ADH substance in the urine following irradiation. A point not fully explained in this study is the method or feasibility of destroying only the ADH producing center. What else may have been involved?

Of final significance in the etiology of premenstrual tension is the theory of Macht and others who feel that the pathology is caused by a toxin, "the menotoxin."³¹ Macht felt the "menotoxin" was toxic to both plant and animals and was found circulating in the blood at the time of the menses. He proposed that the "menotoxin" was closely related pharmacologically to the phenanthrene derivatives, cholesterol and oxysterol, although it was a separate entity. The possibility that the "menotoxin" was a breakdown product of the steroid hormones was included as a possible origin.

TREATMENT

Treatment of the premenstrual syndrome has been aimed mainly at the problem of fluid retention. Low salt diets, diuretics and lithium have been used, but they do not seem to be of significant value. Progesterone may be one of the most useful preparations in the premenstrual syndrome because of its action as an antagonist of aldosterone. Other ideas which have been tried but which showed little promise are androgen, vitamins, and oophorectomy.

The best studied of the therapeutic regimens for the premenstrual syndrome seems to be the so called "multi-demsional" approach. This is a preparation (Pre-Mens^R) composed mainly of ammonium chloride as a diuretic, homatropine and a number of vitamins, Vitamin B complex being the main vitamin. Vitamin B. complex deficiency supposedly affects the ability of the liver to destroy estorgens which are probably an important causative factor in premenstrual tension. Homatropine acts as an antispasmodic.

Morton's study of 249 female prisoners with premenstrual tension indicated that:

- 1) 15 percent of inmates reported improvement when given placebos.
- 2) 30 percent of inmates reported improvements with placebos and high protein diet.
- 3) 61 percent of inmates given Pre-Mens^R only improved.
- 4) 79 percent of inmates improved when given Pre-Mens^R plus high protein diet.

Thus, from this study, Pre-Mens^R seem to be quite effective. Eichner and Waltner demonstrated 50 percent of 86 women had a complete relief of congestive symptoms with Pre-Mens^R.³² Many had partial improvement.

Although ammonium chloride is thought to be the main functional chemical in Pre-Mens^R, Eichner has shown that the "multidimensional" tablet is superior to ammonium chloride alone.³³ Pre-Mens^R has also produced improvement of the acne associated with the Premenstrual Tension Syndrome. In one study, 42 of 50 patients improved; 33 improved markedly. Pre-Mens^R worked three times better than ammonium chloride³⁴ alone.

Other diuretic preparations have also been used to treat the premenstrual syndrome, although none have been so well studied as ammonium chloride. Of the other diuretics, the thiazides have been best studied, but much more information is needed. One of the few studies available was done by Bushnell.³⁵ In this study the author gave 36 patients with symptoms of premenstrual tension 5 to 7.5 mg. of methyclothiazide each day during the ten day period prior to the onset of menses. After continuing treatment over a one to five year period, the author observed that symptomatic response was excellent in 15 patients; good in 20; and fair in one. Similar results may be found in the works of Winshel and Shabanah.^{36, 37} Shabanah recorded weight losses of from two to ten pounds in 72 hours. Taking these reports

into account, the thiazide diuretics may be as good as ^RPre-Mens and better than ammonium chloride. It should be noted that while the diuretics often totally relieved symptoms of premenstrual tension, they were best at relieving the symptom of pelvic congestion.

The second major group of agents used to treat the premenstrual syndrome are the hormones. Many have felt that they are the answer, since very probably estrogen is a causative factor in premenstrual tension. It now becomes apparent that they are only partially the answer. Even the proposed cause of the syndrome, estrogen, has been tried as a method of treatment, and with reported success. In a number of cases they seem to be of help. Greenblatt feels that simple estrogens, like estriol, help but complex estrogens such as estradiol may aggravate the condition.⁶ No well planned experiments have been carried out to investigate this problem.

Progesterone has been studied much more than estrogen as a method of treatment for the premenstrual syndrome. Although it has not been proven conclusively, that women with premenstrual tension are relatively deficient in progesterone, this is a generally accepted theory. Hence, people have used progesterone as treatment.

^REnovid (norethynodrel with added ethinyl estradiol) has been one of the best studied progestational agents. Heller and Hood have both confirmed that ^REnovid relieves

the premenstrual syndrome.^{38, 7} Hood studied 25 patients with premenstrual tension, each receiving Enovid^R as treatment. The usual symptoms were noted and Enovid^R was used in the prescribed method. Of the 5 patients, 21 obtained at least partial relief. Side effects were high, however. Nausea with the first treatment cycle was experienced by 22 patients, nausea in subsequent cycles by 8, breast engorgment in 22, and delayed menses in 11. Although Enovid^R is of benefit in a high percentage of cases, Hood made the following comment in summarizing his study, "There appears to be no advantage over other therapeutic agents for the control of premenstrual tension." In fact the Food and Drug Administration has found this to be quite true and does not recognize Enovid^R as treatment for premenstrual tension. (Refer to letter from Searle & Co. at the end of paper).

Testosterone is the last of the hormones to be tried. Once again adequate studies have not been done, and one must follow impressions only. Enough has probably been said if one mentions that Greenblatt and Freed have both had good results with testosterone, although they found it may aggravate water retention.^{39, 40}

Many other agents and methods for treating premenstrual tension have been recommended over the years. In most cases these agents have been adopted empirically for use in premenstrual tension after studies have shown their value in relieving the same symptom when not associated with

the premenstrual syndrome. Examples of this are the minor analgesics such as aspirin, the tranquilizers such as reserpine or the phenothiazines. All have been used in treating premenstrual tension and are often successful in relieving a specific symptom. Other drugs have been mentioned for treating the premenstrual syndrome such as Vitamin B to increase liver destruction of estrogen (studied by Biskinds). Bellergal^R an autotomic depressant and anti-spasmodic drug, which has been studied by Craig has also⁴² been used.

The best overall summary of the results of treatment using many of the drugs discussed in this paper can be found in two charts from an article on the premenstrual syndrome by Edward Eichner.³³ A copy of the charts from this paper can be found on the following page.

SUMMARY

The premenstrual syndrome, while being a common problem, is also a bothersome one. The entity is well described and reduplicated in the literature, but as with many human functions, it is complex. Its causative factors are probably an interaction of psychic aspects and hormonal-physiologic functions. Because of the complexity of the syndrome no one cause will probably be found and no one treatment will be the answer.

CHART 1
DIURETIC TREATMENT FOR PREMENSTRUAL TENSION


<i>Rx</i>	<i>Dosage</i>	<i>No. Patients</i>	<i>Satisfactory Results</i>	<i>Ill Effects</i>
Acetazolamide (Diamox®)	0.125 - 1.0 Gm. Daily to Relief, Start with Symptoms	62	33.9	12.9
Ammonium Chloride, Plain-coated	4.0 Gm. Q.I.D. for 4 Days, Start with Symptoms	38	28.9	13.1
Hg - Theophylline Compd:				
(Cumertilin® Inject.)	1 - 2 cc. Intragluteal, Once at Onset	15	40.0	6.7
(Cumertilin® Oral Tab.)	2 Tabs. Q. AM to Relief, Start with Symptoms	30	26.6	10.0
Aminometramide (Mictine®)	1 Tab. Q.I.D. 3 Days (less is inadequate)	5	20.0	60.0
Aminoisometradine (Relicton®)	1 Tab. Q.I.D. 2 Days, Then 1 Tab. B.I.D. 15th Day Cycle to Onset of Flow	23	39.1	8.7
Ethoxzolamide (Cardrase®)	62.5 - 250 Mg. Daily 3 Days Starting with Onset of Symptoms	5	40.0	40.0
	62.5 - 250 Mg. Q.2.D. Starting 18th D.	9	33.3	22.2
Hydrochlorothiazide (Hydrodiuril®)	1 Tab. B.I.D. 15th Day to Onset of Flow, or Duration Symptoms	7	57.2	28.6
TOTAL OF DIURETICS:		194	33.5	14.4

CHART 2
TREATMENT OF PREMENSTRUAL TENSION

<i>Rx</i>	<i>Dosage</i>	<i>No. Patients</i>	<i>Satisfactory Results</i>	<i>Ill Effects</i>
DIET: - Hi-Protein, Lo Sodium	(200 Mg. Na Daily) Starting 15th Day of Cycle	347	15.3	0.0%
ALL DIURETICS	Variable - See Chart 1	194	33.5	14.4
POLYPHARMACAL MEDICATION:				
Premens® Plain	Schedule Constant for All Types	242	84.3	5.0
Premens with Amphetamine®	2 Tab. T.I.D. Starting with Symptoms.	28	64.3	42.8
Premens with Reserpine	Discontinue with Relief or in 5 Days.	121	81.0	6.6
Placebo Control	Restart SOS c Symptoms.	45	8.8	11.1
Diamox Compound* "A", "B", "C"	1 - 2 Caps. Daily Starting 7 - 10 Days Before Expected Onset of Flow	26	61.5	24.6
Ethisterone Compound*	1 - 2 Tabs. Daily Starting 7 - 10 Days Before Expected Onset of Flow	14	57.1	42.8
SYNTHETIC STEROIDS				
Ethisterone Compound	See Polypharmacal Medication-Ill Effects Primarily Heavy or Prolonged Bleeding			
Delalutin®	250 - 375 Mg. I.M. 15th - 18th Day Cycle	9	22.2	22.2
Enovid®	1 Tab. 5th thru 25th Day Cycle, or	7	42.9	28.6
	1 - 2 Tabs. Daily 15th - 25th Day Cycle	10	50.0	40.0
Braxorone	2 - 6 Tabs. Daily 5th thru 25th Day	5	20.0	40.0
	2 - 6 Tabs. Daily 15th - 25th Day Cycle	6	50.0	33.3

*Series incomplete

From Eichner, E., Premenstrual Tension Syndrome and Primary Dysmenorrhea, W. Virg. Med. J., 56:1-8 1960.

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January 2, 1969

Mr. Richard D. Schmidt
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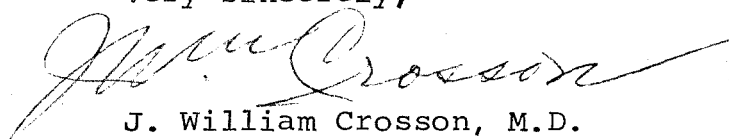
Dear Mr. Schmidt:

Many thanks for your letter of December 12 in which you request information concerning the use of Enovid for treatment of patients with premenstrual tension.

Enclosed are several published reports in which you will be interested. Sometime ago, however, the Food and Drug Administration withdrew approval for recommending this clinical application of Enovid and our only current claims for this preparation are those described in the enclosed information leaflets for Enovid 10 mg, Enovid 5 mg and Enovid-E.

I hope you will find this material to be of assistance.

Very sincerely,



J. William Crosson, M.D.
Assistant Medical Director

JWC:vz

enc.

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