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PREGNANEDIOL FOR TREATMENT OF PREMENSTRUAL SYNDROME

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This invention relates to compositions and treatments that are useful in alleviating distressing symptoms that are often associated with the rise and fall of ovarian activity. More specifically, the invention relates to the treatment of disorders that are related to the menstrual cycle in women, by the administration of small doses, 10 micrograms or less daily, of pregnanediol, or other metabolites of progesterone.

Certain conditions relating to the menstrual cycle have long been puzzling to clinicians. These conditions include pelvic (ovarian) pain or pelvic congestion, painful breasts, premenstrual tension, dermatoses such as acne, the so-called menopausal syndrome, and other distressing symptoms that vary with the rise and fall of ovarian activity. Since these conditions or disorders are not clearly limited, but merge one into the other, the term premenstrual syndrome may be employed to denote these conditions, or any such individual condition or group of such conditions.

A present common treatment for "premenstrual tension" is the administration of therapeutic doses of steroid. Male hormone is the one most commonly recommended, but some patients obtain greater benefit from estrogens and some from progestins. The mechanism of the beneficial effect of steroids is subject to speculation. The natural estrogens seldom cause responses that cannot be directly related to their estrogenic action. Synthetic estrogens, on the other hand, are apt to cause certain mild, untoward responses, especially when given orally. The most prominent of these are anorexia, nausea, vomiting, and mild diarrhea.

One object of the present invention is to provide a method of treatment of premenstrual syndrome, that will be convenient, simple, and effective in a great majority of cases.

Another and related object of the invention is to provide compositions that are effective in alleviating the distressing conditions that may be denoted as premenstrual syndrome, and which can be employed with confidence.

In studying premenstrual syndrome, it was observed that its occurrence cannot be explained on the basis of present concepts of the activity of hormones. Careful study indicated that the syndrome is an instance of endocrine allergy.

The necessary investigation occupied a period of years, and at an early stage, it was apparent that any separation of ovarian pain that is commonly associated with signs of ovarian insufficiency, from premenstrual tension or from the menopausal syndrome, was frequently arbitrary. Symptoms of all three conditions are often found simultaneously. Women who complain primarily of ovarian pain often have other symptoms which, if mentioned first by the patient, would prompt a diagnosis of premenstrual tension, or, particularly if she is around the age of 40, menopausal syndrome. Many patients who are troubled with tension, fatigue, and depression, also have typical, although perhaps mild, ovarian pain. A study of these cases indicates that premenstrual tension, the syndrome of ovarian pain and insufficiency, the congestion-fibrosis syndrome, and the menopausal syndrome are all manifestations of the same process. The term premenstrual syndrome is used here to designate the various manifestations of this process.

Characteristically, the premenstrual syndrome can be observed during the period of two weeks before menstruation. In this portion of the ovulatory cycle, the ovary produces progesterone.

Progesterone is metabolized or degraded in the body to other substances. Two such substances which appear in the urine and which are definitely known to be derivatives of progesterone metabolism are pregnanediol and pregnanolone.

During the premenstrual phase of the cycle, pregnanediol is excreted in the urine in amounts ranging up to 10 mg. during a twenty-four hour period. Pregnanediol is excreted in the conjugated form with glycuronic acid, as sodium pregnanediol-3(alpha), 20(alpha) glucuronidate.

I have discovered that the premenstrual syndrome is caused by the allergenic steroid metabolites that are produced in the body. Pregnanediol, when unconjugated with glycuronic acid, appears to be mildly toxic, since about 90 percent of all women experience some symptoms before menstruation; but pregnanediol is also allergenic, so that some women become sensitive, and have symptoms of varying severity, sometimes incapacitating.

Sensitivity to pregnanediol has been shown by me to the demonstrable by skin tests in a high percentage of patients with disorders that are related to the menstrual cycle. Women without these disorders are relatively insensitive, as shown, for example, in Tables 1, 2, and 3.

In the experiments that are summarized in Table 1, each adult female tested was injected with 0.05 mg. of pregnanediol dissolved in 0.05 ml. of bland oil, subcutaneously. The outer surfaces of the arms were always selected as the injection site, and the injection was made under the dense portion of the skin. Reactions were read in twenty-four hours.

The positive reactions were graded roughly, with a grading of slight to 4 plus. A "slight" reaction was one that was doubtful while nevertheless showing a minimal amount of tenderness and induration or redness. The "slight" reactions were nevertheless recorded, since individuals vary in sensitivity from time to time, and therefore the "slight" reaction might be significant. A 1 plus reaction was one of definite minimal induration, redness and tenderness; 4 plus, a wheal over 3 centimeters in diameter; 2 and 3 plus indicated intermediate grades. A control test of 0.05 ml. of oil alone was always given.

The results of these injections are summarized in Table 1.

The "patients" were mature female who sought medical aid at various times during their cycle, and who complained of symptoms that were characteristic of the premenstrual syndrome. The "controls" were normal women who were free of the symptoms of the premenstrual syndrome. This same terminology is employed throughout.

Table 1

Subjects	No. of cases Tested	Total Reactions, Observed, Percent	Marked Reactions, 2+ or greater, Percent
Patients exhibiting symptoms characteristic of the premenstrual syndrome	182	81.8	39.2
Coatrols (normal women)	24	8.3	0

The data in Table 1 indicates that endocrine allergy is quite prevalent, since 81.8% of the patients, who were tested, exhibited a reaction; and 39.2% of the reactions were quite marked. By way of contrast, normal women, that is those free from the characteristics of premen-

strual distress, exhibited reactions in only 8.3% of the cases tested, and none of these women exhibited marked reactions.

The results of additional tests are summarized in Table 2. Except that the pregnanediol was administered in aqueous suspension, exactly the same procedure as that described above was followed in testing an additional number of patients. In each case, the injection comprised 0.1 mg. of pregnanediol and 0.1 ml. of water.

Table 2

Subjects	No. of cases Tested	Total Reactions, Percent	Marked Reactions, 2+or greater, Percent
Patients exhibiting symptoms characteristic of the premenstrual syndrome	120	97.5	55.8

This data indicates an even greater sensitivity to a higher dose of pregnanediol, in aqueous suspension. Of the 120 patients tested, 97.5% exhibited some reaction, and 55.8% exhibited marked reaction.

The pregnanediol, that was employed in conducting the experiments that are summarized in Tables 1 and 2, was subjected to chromatographic assay, and the assay indicated that the pregnanediol used contains approximately twice as much pregnanediol, 3-alpha, 20-alpha, as allopregnanediol 3-alpha, 20-alpha, and a small amount, about 3 to 5% by weight, of allopregnanediol 3-beta, 20-alpha. Any other isomeric forms, if present, were in amounts less than 1% by weight of the samples that were analyzed.

Several sensitive patients were skin tested simultaneously with the pregnanediol preparation whose analysis is given in the preceding paragraph, and with pure pregnanediol 3-alpha, 20-alpha. The reactions obtained were identical. The procedures followed were identical with those described above, and in making the tests, each injection consisted of 0.1 mg. of pregnanediol 3-alpha, 20-alpha in aqueous suspension in 0.1 ml. of water. The results are summarized in Table 3 below.

Table 3

Subjects	No. of cases Tested	Total Reactions, Percent	Marked Reactions, 2+or greater, Percent
Patients exhibiting symptoms characteristic of the premenstrual syndrome	79	82.3	40.5
Controls (normal women)	13	23.4	0

Since reliable authorities report that progesterone, and many other related steroids, definitely undergo metabolic transformation into pregnanediol 3-alpha, 20-alpha, the results in Table 3 are quite significant.

My invention consists in the treatment of the premenstrual syndrome by administering pregnanediol. The rationale of treating patients with disorders that are related to the menstrual cycle, with small doses of pregnanediol, is the same as the treatment of patients who are sensitive to exogenous substances such as pollens, foods, and the like, with small doses of the offending substance. The patient becomes hyposensitized, and develops a degree of immunity to the steroid metabolite that is manufactured in her own body.

There is some indication that it is the unconjugated pregnanediol, in the body, which initiates the allergy and is responsible for the later recurrence of symptoms. Analysis of the urine of a patient wtih recurrent symptoms, highly sensitive to pregnanediol, revealed that free as well as conjugated pregnanediol was excreted, and

that when the patient was experiencing symptoms, the amounts of free pregnanediol were greater.

That pregnanediol is the cause of the symptoms (premenstrual syndrome) is convincingly demonstrated by results of the tests that indicate that the symptoms are aggravated or produced by relatively large doses of pregnanediol (more than the sensitive patient can tolerate). In these tests, the pregnanediol is given orally, or by injection subcutaneously where so indicated. It is noted that aggravation or production of symptoms is seen more frequently with larger doses.

In making these tests, the pregnanediol was administered to patients at different dosage levels. Each dosage level was used at least once, and the reactions were noted. Seventy-five patients were treated in this way, each receiving a different number of doses. The data in Table 4 indicates the number of times that each dosage level was employed successfully, and also the number of times each dosage level produced a systemic reaction.

Table 4

ANALYSIS OF DOSAGE

Dosage level in milligrams	Number of times dosage level was used successfully	Number of times dosage level produced a systemic reaction (aggravation or production of symptoms)
0.1	4	9
0.05	7	5
0.025	7	5
0.01	23	12
0.005	23	12
0.001	15	1
0.0005	15	1
0.0001	4	0
0.00001	5	1
1×10^{-5} (s.c.)	4	0
1×10^{-6} (s.c.)	3	2
1×10^{-7} (s.c.)	1	1
1×10^{-8} (s.c.)	0	2
1×10^{-9} (s.c.)	1	0
1×10^{-10} (s.c.)	1	0

Patients who received less than 0.0001 mg. were highly sensitive, as determined by previous skin tests, and hence, some systemic reactions were observed with dosage levels as low as 1×10^{-8} mg.

These tests show that this therapy is beneficial, but that systemic reactions occur in an undesirably large number at certain dosage levels.

An analysis of the results obtained in the treatment of the same seveny-five patients, from whom the data in Table 4 was obtained, indicated that in a large majority of patients, improvement can be obtained.

Table 5

Number of cases summarized	Number improved	Percent improved	Number of questionable results	Number of Failures
75	56	75	7	12

The foregoing data indicates conclusively that therapy based on the administration of pregnanediol is a successful and important treatment for alleviation of the premenstrual syndrome. Treatment with pregnanediol, and pregnanediol 3(alpha), 20(alpha), have been shown to be effective. Since systemic reactions are observed where the dosage level is too high, there remains the problem of selection of an optimum dosage level, that will be efficacious, yet sufficiently low to have the minimum number of systemic reactions. This optimum dosage level is about 0.1 microgram to about 10 micrograms.

In determining this optimum dosage level range, an analysis was made of the treatment of several patients to whom pregnanediol was administered. The results of this analysis appear below in Tables 6, 7 and 8. In

making this analysis, particular attention was paid to those cases in which a systemic reaction was observed.

The term "systemic reaction" is used to indicate the production or aggravation of symptoms that the patient has been experiencing, or the production of symptoms not previously noted by the patient. The analysis of the results of both oral and subcutaneous treatment reveals that systemic reactions occurred in all of the clinical categories, including premenstrual distress (tension), climacteric (menopausal syndrome), etc., and that they were proportional to dose; the larger the dose the more frequent and severe were the reactions.

Typical manifestations were as follows: The patient might feel worse about three hours after an injection, one or several symptoms such as pelvic pain, fatigue, dizziness and nausea would be increased. Within twenty-four hours, a local reaction might be apparent. Within twenty-four or forty-eight hours the patient might feel better than she had when the injection was given. Another reaction might be that symptoms, which the patient was not experiencing at the time, would be produced in a few hours. Tension and nervousness might predominate, with irritability and insomnia. This was most striking in cases of premenstrual distress treated early in the cycle.

Similar reactions were obtained when the administration of pregnanediol was oral and when it was subcutaneous, although with oral treatment, their appearance was less sudden and dramatic. New symptoms, those not previously noted by the patient, were usually those which are common in the syndrome. The more common in order of frequency were nausea, dizziness headache, pelvic pain, pain in the breasts, hot flashes, and nervousness. Occasionally a feeling of malaise was described.

Table 7

SUMMARY OF ORAL DOSAGE IN CASES IN WHICH IT WAS BENEFICIAL AND IN WHICH SUBCUTANEOUS TREATMENT WAS ALSO TRIED

[47 cases]

	Daily dose of Pregnanediol		
	1.0 mg.	0.5 mg.	0.1 mg.
Number of times dose was used	24	16	28
Number of times dose caused a systemic reaction	5	0	1

In these cases it was possible to evaluate oral treatment although subcutaneous injections were also given, usually initially as a test dose. All patients were relieved. Systemic reactions were proportional to the dose.

The foregoing data indicates that the occurrence of systemic reactions is a phenomenon that is somewhat unpredictable, and that at a dosage level of 0.1 mg., the number of systemic reactions that occur is undesirably high in proportion to the number of successful treatments.

For this reason, a broader spectrum of dosages was tried, and the results are summarized in Table 8. Sixty-four cases were treated successfully. The doses were administered orally above 0.0001 mg., and subcutaneously below that level.

Table 8

SUBCUTANEOUS DOSES USED IN HYPOSENSITIZATION AND FREQUENCY OF SYSTEMIC REACTIONS

	Daily dose of pregnanediol								
	0.1 mg.	0.01 mg.	0.005 mg.	0.001 mg.	0.0005 mg.	0.0001 mg.	0.00005 mg	0.00001 mg.	0.000005 mg.
Number of cases in which dose was used	6	28	5	13	3	5	1	2	1
Number of times dose produced a systemic reaction	19	8	1	4	0	0	0	0	0

An analysis of the results in Tables 6 and 7 reveals that the doses often were too large. Overdosage caused some of the failures.

When the results in Table 8, and those in Table 4, are carefully considered, it can be seen that the optimum dosage level for the administration of pregnanediol is in the range of 1×10^{-10} mg. up to about 0.01 mg.

At dosages above about 0.01 mg., the number of times that the dosage level produces a systemic reaction is unfavorably large, percentage-wise, in comparison with the number of times that the dosage level can be employed successfully.

A detailed and careful analysis and appraisal of the dosages in the several foregoing tests indicates that the smaller doses are beneficial, without as much risk of systemic reactions.

Table 6

ANALYSIS OF DAILY ORAL DOSAGE OF PREGNANEDIOL

[108 cases treated with tablets alone]

	In cases improved on a constant dose			In cases improved in which the dose was changed			In cases where treatment failed on a constant dose			In cases where treatment failed although the dose was changed		
	1.0 mg.	0.5 mg.	0.1 mg.	1.0 mg.	0.5 mg.	0.1 mg.	1.0 mg.	0.5 mg.	0.1 mg.	1.0 mg.	0.5 mg.	0.1 mg.
Number of times dose was used	19	8	9	17	14	13	11	5	1	10	4	11
Number of times dose caused a systemic reaction	3	0	0	5	3	3	6	2	1	10	1	4

The figures show that systemic reactions (aggravation of symptoms or production of new symptoms) were proportional to the dose.

Tables were prescribed for at least a month. In some cases the dose was increased if there was no effect or decreased if a systemic reaction occurred.

If a systemic reaction was transient the same dose was usually continued.

As to toxicity, rabbits and guinea pigs become allergic to pregnanediol, as indicated by the occurrence of positive skin reactions, when they have been sensitized with pregnanediol plus suitable adjuvants. However, although allergenic, the toxicity is very low. The minimal lethal dose is greater than 2500 mg. per kilogram of body weight.

Pregnanediol may be administered orally or subcutaneously. Oral administration has the great advantage that it is convenient for this purpose. Tablets containing pregnanediol in a lactose vehicle are efficacious. Other satisfactory solid pharmaceutical carriers include corn starch and stearic acid. Subcutaneous injection may be employed for the most sensitive cases, in which case the dosage that may be used, in order to avoid systemic reactions, may be on the order of 0.000001 mg. Oral administration is not as reliable as subcutaneous administration, because, the digestive systems of different people affect the pregnanediol in different ways; however, oral administration is much more convenient and pleasant.

The treatment of the premenstrual syndrome with pregnanediol, in the amount of 0.1 microgram to about 10 micrograms, has been demonstrated to be efficacious in many cases.

In the light of the foregoing information, a common starting dose for this therapy is 0.000001 mg. This dosage can be altered as necessary to obtain a favorable reaction from the patient.

The "pregnanediol," referred to throughout, is the isomeric mixture whose analysis appears following Table 2.

While the invention has been described in connection with certain specific embodiments thereof, it will be understood that it is capable of further modification, and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice in the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as fall within the scope of the invention or the limits of the appended claims.

I claim:

1. A composition in dosage unit form comprising an amount not greater than about 10 micrograms of pregnanediol per dosage unit and a pharmaceutical carrier.

2. A composition in dosage unit form for alleviating the premenstrual syndrome comprising an amount not greater than about 10 micrograms of pregnanediol 3(alpha), 20(alpha), per dosage unit and a significant amount of a pharmaceutical carrier.

3. A composition in dosage unit form for alleviating the premenstrual syndrome comprising about 0.1 microgram to not more than about 10 micrograms of pregnanediol per dosage unit and a pharmaceutical carrier.

4. A tabletted composition in dosage unit form for alleviating the premenstrual syndrome comprising about 0.1 microgram to not more than about 10 micrograms of pregnanediol 3(alpha) 20(alpha), per dosage unit and a solid pharmaceutical carrier.

5. The process of alleviating a sign or symptom of the premenstrual syndrome in human beings, comprising administering to a living female an amount of from about 1×10^{-10} mg. to about 10 micrograms of pregnanediol in a pharmaceutical carrier.

6. The process of alleviating a sign or symptom of the premenstrual syndrome in female human beings, comprising administering to a living female an amount of from about 1×10^{-10} mg. to about 10 micrograms of pregnanediol 3(alpha), 20(alpha), in a pharmaceutical carrier.

7. A process comprising administering at daily intervals to a living female human being an amount from about 1×10^{-10} mg. to about 10 micrograms of pregnanediol in a pharmaceutical carrier.

8. A process comprising administering at daily intervals to a living female human being an amount of from about 1×10^{-10} mg. to about 10 micrograms of pregnanediol 3(alpha), 20(alpha), in a pharmaceutical carrier.

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