Treatment of Common Gynecologic–Endocrinologic Symptoms by Allergy Management Procedures

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The technique of managing allergies by optimum-dose (provocative neutralization) testing and treatment using aqueous progesterone has been studied in 132 women having progesterone-related symptoms due to the menstrual cycle, pregnancy, or exogenous hormone administration. When extremely small doses of progesterone (0.0016 mg or below, up to a maximum of 2.5 mg) were administered following determination of specific dose requirement by skin testing, startlingly rapid and effective clearing of symptoms was observed. With these individualized doses, symptoms cleared completely or almost completely within 30 minutes in the majority of patients. A single-blind technique was employed to rule out placebo effect. Some common problems found to respond well to the procedure were nausea and vomiting during pregnancy (100%), premenstrual syndrome (96%), and dysmenorrhea (84%). ***(Obstet Gynecol 59:560, 1982)***

Startling, rapid, and unusually effective relief of progesterone-related symptoms was reported in 1974 by Miller,[1] who used injections of extremely small doses of progesterone. The dosages employed ranged from a high of 2.5 mg to a low of 0.004 mg or less, or .025 to .00004 times the dosage used in conventional progesterone therapy. Paradoxically, response to these extremely small neutralizing doses was found to be far superior to responses from conventional doses such as 100 mg. When dosage was individualized and precisely determined by skin testing, symptoms cleared completely or almost completely within 30 minutes.

The 2 main types of progesterone-related symptoms reported to respond were 1) adverse reactions or side effects secondary to exogenous administration of progesterone or progestogens, and 2) adverse responses to high or fluctuating levels of endogenous progesterone, including mid- and late-cycle problems such as ovulatory pain and premenstrual and menstrual exacerbations of allergic syndromes such as asthma, perennial allergic rhinitis, atopic eczema, urticaria, headache, and vertigo. Miller[1] reported that heavy menstrual flows often decreased toward normal, and that scant painful flows increased toward normal.

Similar responses have been reported with the neutralizing procedure using other material, including food and inhalant allergy extracts in patients with allergies to food and inhalants; *Monilia* extracts in patients with infections due to *Candida albicans;* and influenza virus vaccine in patients with influenza and herpesvirus infection.[2,3]

The report by Miller brought an end to a long gap in the medical literature concerning use of sex steroids in extraordinary small doses to treat gynecologic syndromes. In 1947 Zondek and Bromberg[4] demonstrated by skin testing the concept of endocrine allergy. Although they concluded that allergic endocrine conditions were not frequent, Heckel[5] in 1953 studied the same topic and reported that by using pregnanediol (a metabolic product of progesterone) rather than progesterone itself he could demonstrate positive skin whealing in approximately two thirds of patients who had common disorders relating to ovarian function. These included ovarian pain syndrome, menopausal symptoms, and premenstrual distress. Moreover, employing the concept that "the pelvic viscera are the shock organs of steroid allergy in these cases," Heckel was able to treat symptoms successfully in 84% of his series by subcutaneous hyposensitization using extremely small doses (dilutions) of pregnanediol. He therefore concluded that endocrine allergy was common rather than unusual and that unusually small doses of progesterone metabolic product were effective both in short- and long-term treatment.

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This is a report of a trial of Miller's progesterone procedure to determine if these reported results in gynecologic syndromes could be verified in gynecologic practice.

Materials and Methods

The product used in this study was Rucker Laboratories' Progesterone Aqueous Suspension, 50 mg/ml. The full-strength commercial material was designated as the stock bottle or concentrate. A series of 9 vials was prepared containing consecutively weaker 1:5 serial dilutions of progesterone aqueous suspension. To do this, 4 ml of diluent (sterile saline containing 0.4% phenol preservative) was added to each of the vials and the vials were labelled Progesterone no. 1, Progesterone no. 2, etc. Then, 1 ml of full-strength progesterone aqueous suspension (the concentrate) was added to the no. 1 vial, obtaining thorough mixing by 5 or 6 long push–pulls of the syringe plunger. Then, with the hypodermic needle still in the no. 1 vial, 1 ml of this suspension was withdrawn and added to the no. 2 vial. This procedure was repeated until all 9 vials were similarly mixed. The concentration and mg dosage of progesterone can be seen in Table 1.

A placebo study was done using the same serial progesterone dilutions alternating with normal saline (without phenol). The authors were not able to make a nonreactive placebo that looked identical to the progesterone suspension. Therefore the vials were completely encased in paper so as to hide the contents from vision.

In order to determine accurately the dose that relieved the natural symptoms under observation, patients were asked to come to the office when they were having symptoms relating to their menstrual cycle, pregnancy, or exogenous hormone administration. Testing was done to establish a therapeutic dose, which is defined as 0.05 ml of the strongest dilution that clears natural symptoms within 20 to 30 minutes of administration. According to Miller,[1] "The usual starting test dose is 0.05 ml/#1 administered subcutaneously. If this clears the symptoms within 20–30 minutes, as it often does, it is the treatment dose. If it does not, 0.05 ml of the concentrate is used next. If the symptoms worsen, remain unchanged, or improve only partially, 0.05 ml/#1 is used again, followed by consecutively weaker dilutions at 20 to 30 minute intervals as long as the symptoms become progressively better or at least do not worsen. If the symptoms improve or remain unchanged while going consecutively weaker, one should continue going weaker until the symptoms either clear completely or become worse. Worsening on a weaker dilution indicates that one has gone too far and should move consecutively stronger again. The rule is: While moving in a given direction, if symptoms are improving with each dilution, continue in the same direction; if symptoms worsen on a given dilution, change to the opposite direction. The neutralizing dilution is often bounded by a symptom-increasing stronger dilution and a symptom-increasing weaker dilution."

Table 1. Progesterone Dilutions Obtained by 1:5 Serial Dilution

Dilution	Concentration	Amount per 0.05-ml dose (mg)
Concentrate	50 mg/ml	2.5
No. 1 (1:5)	10 mg/ml	0.5
No. 2 (1:25)	2 mg/ml	0.1
No. 3 (1:125)	0.4 mg/ml	0.02
No. 4 (1:625)	0.08 mg/ml	0.004
No. 5 (1:3125)	0.016 mg/ml	0.0008
No. 6 (1:15,625)	0.0032 mg/ml	0.00016
No. 7 (1:78,125)	0.00064 mg/ml	0.000032
No. 8 (1:390,625)	0.000128 mg/ml	0.0000064
No. 9 (1:1,953,125)	0.0000256 mg/ml	0.00000128

One hundred patients were asked to participate in the initial phase of study. Thirty-two additional patients were treated with a single-blind technique employing normal saline as placebo in order to document the effectiveness of progesterone treatment doses versus possible placebo effect. In this group, usual testing procedures were carried out, the test material being serial dilutions of progesterone alternating with normal saline. The initial injection was test dose no. 1 (saline), followed by no. 2 (progesterone 1:5), followed by no. 3 (saline), followed by no. 4 (progesterone 1:25), and so forth.

Patients were asked to list the symptoms they were actually experiencing just before testing began. Many had more than 1 presenting symptom. At the completion of the test, they were asked to evaluate changes in each individual symptom as well as to assign an overall evaluation of symptom relief. The patients were asked to state the evaluations as: 1) Complete relief—100% better; 2) marked relief—75% or more improvement but with some symptoms remaining; 3) good relief—at least 50% better; 4) slight relief—25 to 50% improvement; or 5) no relief—less than 25% improvement.

After completion of testing, treatment was begun. Patients were issued multidose vials, each containing 1.0 ml of the treatment dilution. Detailed printed instructions and diagrams were sent home with the patient. Each patient gave herself the first subcutaneous treatment dose in the office under supervision. Patients were informed that a neutralizing dose could

Table 2. Results of Initial Testing—Patients' Self-Scoring

Clinical category	Subjects studied	Complete relief (100%)		Marked relief (75%)		Good relief (50%)		Slight relief (25%)		No relief (0)		Mean neutralizing dilution	Amount of progesterone (mg)
		No.	%	No.	%	No.	%	No.	%	No.	%		
Premenstrual syndrome	29	23	79	5	17					1	3	No. 4	0.004
Dysmenorrhea	31	21	68	5	16	1	3	4	13			No. 3	0.02
Pregnancy—nausea and vomiting	16	14	88	1	6	1	6					No. 4	0.004
Oral contraceptive side effects	11	9	82	2	18							No. 4	0.004
Climacteric	6	3	50					1	17	2	33	No. 6	0.00016
Ovarian pain, midcycle and residual ovary	7	7	100									No. 5	0.0008
Total	100		77		13		2		5		3		

change at any time, and that if such a change occurred, administration of the obsolete treatment dose could result in lessened effectiveness or even increased (but not dangerous) symptoms, and that retesting should quickly determine the new effective dose and provide prompt relief.

Results

This is a report of the first 100 patients studied plus the blind-study group. The test procedure was found to be simple and readily adapted to gynecologic practice. Initial testing in the progesterone group produced complete or marked relief in 90 patients (90%). Eight (8%) had little or no improvement (Table 2). Table 3 lists the major naturally occurring presenting symptoms (not diagnoses) in both groups and their response to the test procedure.

A total of 213 injections were given to the blind-study group. There were 120 progesterone and 93 placebo injections from which to choose an end point. Twenty-seven of the 32 patients picked a progesterone dilution as their neutralizing end point, and 5 picked the placebo. These results are highly significant, with a value of $P < .01$ (Table 4). The usual progesterone neutralizing dilution (no. 3) for those on the blind-study was similar to when blinding was not used (Table 5).

Table 3. Presenting Symptoms* and Response to Initial Minidose Progesterone Administration

	Basic study group (N = 100)			Blind study group (N = 32)			Total (N = 132)		
	No.	Marked or complete relief	%	No.	Marked or complete relief	%	No.	Marked or complete relief	%
Dysmenorrhea	37	32	86	6	4	67	43	36	84
Headache	29	26	90	10	10	100	39	36	92
Backache	14	13	93	11	10	91	25	23	92
Abdominal pain	11	10	91	9	8	89	20	18	90
Abdominal pressure, bloating	2	2	100	4	4	100	6	6	100
Neck, leg, and hip pain	4	3	75	6	5	83	10	8	80
Breast pain	2	2	100	5	5	100	7	7	100
Nausea	18	16	89	2	2	100	20	18	90
Nervousness, irritability, depression	26	25	96	18	17	94	44	42	95
Vertigo, dizziness	6	6	100				6	6	100
Fatigue, weakness	3	3	100	7	6	86	10	9	90
Flushing, hot flashes	1	1	100	3	2	67	4	3	75
Urticaria of pregnancy	1	1	100				1	1	100
Tinnitus	1	1	100				1	1	100

* Many patients presented with more than 1 complaint.

Table 4. Response to Blind Study

Clinical diagnosis	No. of patients	No response	Chose placebo	Chose progesterone
Dysmenorrhea	11*	0	3	8
Premenstrual syndrome	20*	0	2	18
Midcycle pain	1	0	0	1
Total	32	0	5† (15.6%)	27† (84.4%)

* Four patients in each group (total, 8) had documented endometriosis.

† Significant at $.01 > P > .001$ by McNemar test for paired alternatives.

Discussion

The symptoms responding to progesterone neutralizing therapy were many, and the response impressive. Many of the patients found that after 1 treatment cycle the following cycle or two were often without any significant symptoms. Even some of those patients who did not respond especially well or rapidly in the office noted significant delayed improvement, beginning an hour or more after treatment and extending through the following period. Many patients with longstanding symptomatology, after using neutralization therapy for 4 or 5 menstrual cycles, seemed to develop long-lasting improvement or freedom from cyclic symptoms.

Seventeen women in the combined study had documented endometriosis. Eight of these women were included in the clinical category of premenstrual syndrome. One was experiencing intolerance to oral contraceptives, 1 midcycle pain, and 7 were in the dysmenorrhea group. All but 1 patient had complete or marked relief of symptoms.

The first 100 patients in this study represent a difficult patient population as evidenced by 33% having experienced previous pelvic surgery. Fifteen had previous bilateral tubal ligation, 8 previous major pelvic surgery, and 8 dilatation and curettage and/or laparoscopy. One pregnant patient had previous ovarian cystectomy, and another pregnant patient had previous conservative endometriosis surgery. Ten (37.5%) of the 29 patients assigned to the premenstrual syndrome category had previous postpartum or interval tubal sterilization performed.

In addition to the placebo study, suggestion would seem to be ruled out by the fact that most tests require several doses, some of which may not change the symptoms whereas others can make the symptoms worse. Furthermore, after relief has been achieved, symptoms can be made to return by administering a different dilution and can be made to clear by readministering the neutralizing dilution in a single-blind manner.

Zondek and Bromberg[4] noted that about half their patients gave evidence of allergies to food and/or inhalants. Heckel[5] demonstrated common allergic disease such as allergic rhinitis, recurrent hives, and eczema to respond to hormonal treatment. And Phillips[6] found that not only premenstrual distress but also symptoms of recognized allergic disease such as asthma responded to hormonal treatment. Moreover, the present authors have been impressed that the women in their practice who have premenstrual and/or menstrual difficulties also have a high incidence of allergic syndromes, just as Miller was impressed by the high incidence of premenstrual and menstrual problems in his allergy practice.

Increased size and congestion of pelvic organs and endometrial nodules secondary to edema could presumably cause pain due to stretching of organ capsules or through pressure on adjacent tissues, blood vessels, and nerves. Increased capillary permeability may be an important factor even though there is no direct evidence that these hormonal problems are IgE-mediated. Symptom response and palpable change in size of endometrial nodules with therapy suggest the possibility that allergic angioedema of the ovaries and other pelvic tissues may cause organ dysfunction.

Table 5. Response to Blind Study—Patient Evaluation of Effectiveness by Self-Scoring

Injection chosen as neutralizing injection	Complete relief (100%) no.	Marked relief (75%) no.	Good relief (50%) no.	Slight relief (25%) no.	No relief (0%) no.	Total no.
Saline placebo	1	2		2		5
Concentrate (2.5 mg)		1				1
No. 1 Progesterone (0.5 mg)	1	1		2		4
No. 2 Progesterone (0.1 mg)	1	6		2		9
No. 3 Progesterone (0.02 mg)	2	5		2		9
No. 4 Progesterone (0.004 mg)						
No. 5 Progesterone (0.0008 mg)		3				3
No. 6 Progesterone (0.00016 mg)						
No. 7 Progesterone (0.000032 mg)				1		1
Total	5	18		9		32

Prostaglandins may be of great importance in the association of gynecologic and allergic syndromes. Prostaglandins have been found in the mucous membrane and smooth muscle coats of the uterus, in the ovary and fallopian tube, and in menstrual fluid. Prostaglandins are believed to be key participants in the ovulatory process at the hypothalamic–pituitary level and locally at the ovary. Dysmenorrhea, with its accompanying lower abdominal pain, headache, and menstrual and premenstrual gastrointestinal effects such as nausea and diarrhea, has been reported to be caused by release of prostaglandins from the uterus into the peripheral circulation.[7–10] The 2 primary cells of the immune system, the lymphocyte and the macrophage, have been shown to be very active pharmacologically and to actually make and respond to prostaglandins,[11] which themselves may have a regulatory role in allergic histamine release.[12] Additionally, histamine, serotonin, and bradykinin have received attention in ovarian function[13] and are also important factors in some immune disorders. These biochemical, immunologic, and endocrinologic associations could explain effectiveness of minidose progesterone in relieving premenstrual allergic manifestations as well as gynecologic symptoms.

The widely used method of provocative neutralization first described by Lee[14] and elaborated upon, systematized, and extended into gynecologic, viral, and other fields by Miller, would appear to be a simple and safe procedure in gynecology as it employs minute amounts of standard products. It is the authors' impression that only the surface has been scratched using this technique to solve hormonal problems. Although the mechanism of action has not been studied, it seems clear that some facet of the host response mechanism with an interplay of immunologic and endocrinologic phenomena is involved. This may or may not include antibody interaction but undoubtedly still falls into the general concept of allergy/immunology as an altered immune response following the broad definition originally proposed by Von Pirquet.[15]

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