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Comparison of Regimens Containing Oral Micronized Progesterone or Medroxyprogesterone Acetate on Quality of Life in Postmenopausal Women: A Cross-Sectional Survey

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ABSTRACT

A cross-sectional survey was conducted to examine quality of life (QOL) related to physiological, somatic, and vasomotor effects of changing progestogen treatment from medroxyprogesterone acetate (MPA) to micronized progesterone in postmenopausal women. Eligible women (n = 176) were currently using hormone replacement therapy (HRT) containing micronized progesterone for 1–6 months and had previously received HRT containing MPA. QOL was assessed via telephone interview using the Greene Climacteric Scale and the Women's Health Questionnaire. When compared with the MPA-containing regimen, women using micronized progesterone-containing HRT experienced significant improvement in vasomotor symptoms, somatic complaints, and anxiety and depressive symptoms. Women reported improved perceptions of their patterns of vaginal bleeding and control of menopausal symptoms while on the micronized progesterone-containing regimen. Approximately 80% of women reported overall satisfaction with the micronized progesterone-containing regimen. A micronized progesterone-containing HRT regimen offers the potential for improved QOL as measured by improvement of menopause-associated symptoms.

INTRODUCTION

ESTROGEN REPLACEMENT THERAPY during the menopause provides multiple benefits against physiological disturbances that occur following cessation of ovarian function. These benefits include protection from cardiovascular disease, treatment of some dyslipidemias, and prevention of osteoporosis. Another benefit, one that affects daily life, is relief of common but unpleasant menopausal symptoms that typically persist for more than a year in most menopausal women.[1,2] However, there are risks and side effects associated with estrogen therapy. When taken alone, estrogens produce vaginal bleeding in about three fourths of women and increase the risk of endometrial carcinoma.[3,4] The risk of endometrial carcinoma can be attenuated with the use of progestogens administered in a proper dose and over a sufficient period of time.[5,6] Therefore, the combination of estrogen and progestogen has become the cornerstone of treatment for women with an intact uterus who desire hormone replacement therapy (HRT).

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Progestogens used in HRT regimens are compounds with progesterone-like action and are grouped based on chemical structures that define their effect. These include C-21 compounds (e.g., medroxyprogesterone acetate [MPA], megestrol acetate) or 19-nortestosterone derivatives (e.g., norethindrone). The ideal progestogen in HRT should neither negate the beneficial effects of estrogen nor produce cyclic or irregular bleeding and, in addition, should be well tolerated. However, the addition of cyclic progestogens (providing progestogens for a limited number of days per month) results in the return of cyclic bleeding in at least 80% of women. An alternative method of progestogen administration, daily continuous progestogens, results in a high incidence of irregular bleeding.[7–9] Physical and psychological side effects, such as mood changes, bloating, and breast tenderness, have been reported with progestogen therapy.[10–12] Because the side effects of progestogen-containing regimens affect compliance and acceptability of treatment, it is not surprising that studies have revealed that acceptance rates are low in spite of a positive analysis of the benefits of HRT.[13,14]

Recent studies have focused on patient-perceived subjective advantages and drawbacks of HRT.[10–12] Although clinical study end points focus on practitioner-based assessments, it has been recognized that the patient's evaluation of therapy may differ greatly from that of the researcher or practitioner.[16] Patient-based quality of life (QOL) measures differ by definition and address specific measures targeted to the aspects of therapy and disorder under treatment. QOL assessments are well suited for menopausal studies, given the similar clinical efficacy rates of HRT regimens and noted problems of side effects and HRT acceptability. Generally, HRT appears to improve the QOL and is directly related to a reduction in the symptoms of menopause.[14,17] In addition, QOL surveys have demonstrated the advantages of different menopausal treatments.[12,13,18,19]

In 1998, micronized progesterone was approved for oral use in the United States, and it has been studied in HRT regimens designed to evaluate the prevention of cardiovascular disease in a large cohort of menopausal women.[15] In this study, micronized progesterone had the most favorable effect on lipoproteins associated with cardiovascular risk. However, there are few controlled studies that directly compare the effect of micronized progesterone on QOL with other progestogens. Therefore, this cross-sectional survey was conducted to examine QOL domains related to physiological, somatic, and vasomotor effects in women whose therapy was being changed from MPA to micronized progesterone. A secondary objective was to compare parameters associated with menopausal status, as measured from a standardized scale, between previous HRT and HRT-containing micronized progesterone. Finally, patient satisfaction with the different regimens was assessed.

MATERIALS AND METHODS

Study design

This study was a cross-sectional survey of women who were currently being treated with HRT including micronized progesterone for a period of 1–6 months and had been treated previously with MPA. Sixty-two physicians located across the United States participated in identifying a total of 176 women to participate in this study. The Western Institutional Review Board and Mayo Foundation Institutional Review Board approved the survey protocol. The recruiting physician explained the survey to each subject, and patients provided information after written informed consent was obtained.

Participants provided information during a telephone interview. Demographic information and QOL assessments were collected using two validated scales. The Greene Climacteric Scale is a standardized 4-point ordinal scale consisting of 21 questions based on factor analytic studies of menopausal symptoms.[20] These factors include vasomotor, somatic, and psychological symptoms, further divided into anxiety and depression. The Greene Scale was developed to provide a standard measure of core climacteric symptoms that are experienced by the majority of menopausal women. The Greene Climacteric Scale is psychometrically sound and has high content validity and very high test-retest reliability coefficients. This instrument was administered twice during a single interview. Subjects described their symptoms during treatment with MPA (previous treatment) and with micronized progesterone (current treatment). All other scales were administered once during the interview.

The Women's Health Questionnaire (WHQ) is a reliable and validated scale consisting of 36 items covering 9 factors (somatic symptoms, depression, cognitive, anxiety, sexual functioning, vasomotor symptoms, sleep problems, menstrual symptoms, and attraction) experienced by perimenopausal and menopausal women and rated on 4-point scales.[21] Estrogen-related symptom improvements are detected by this scale.[19] The WHQ was developed to evaluate somatic and vasomotor symptoms and emotional changes during menopause. This scale identifies differences between premenopausal and postmenopausal women[22] and evaluates improvements in symptom-based QOL during estrogen replacement therapy.[18,19] The WHQ contains 36 questions related to somatic and emotional aspects of QOL. This instrument was administered only once and was used to assess current QOL using micronized progesterone.

To assess global patient satisfaction with current and previous HRT regimens, a Likert scale instrument containing 8 items using a 3-point ordinal scale (agree, neither agree nor disagree, disagree) was used initially in 35 interviews. This scale was modified to a 5-point ordinal scale (1, strongly agree; 2, somewhat agree; 3, neither agree nor disagree; 4, somewhat disagree; 5, strongly disagree) used in the majority of interviews (141 women). The scores were adapted to combine the 8-point and 5-point scales in order to conserve data from all participants and to use a sample size similar to that analyzed for the other scales. To combine the assessments from the 3-point and 5-point scales, a report of "agree" was assigned a value of 1.5 (between strongly agree and somewhat agree) and "disagree" was assigned a value of 4.5 (between somewhat disagree and strongly disagree). Questions 2 and 7 queried respondents about the effects of MPA-containing and micronized progesterone-containing regimens on menopausal symptoms (main aspects of satisfaction with HRT), and questions 3 and 8 made a similar comparison of vaginal bleeding (major dissatisfaction factor). These questions were used to compare mean scores for these two symptom complexes between MPA and micronized progesterone regimens. For all questionnaires, subjects were requested to choose from a comprehensive list of responses in order to collect analyzable group data. Few text comments, if volunteered, were not included in the analyses.

Data analysis

Frequencies and descriptive statistics were used to summarize the demographic and QOL variables. Comparisons between previous and current HRT regimens of QOL from the Greene Scale were made using paired *t* tests for continuous or near-continuous measures. To determine whether the use of micronized progesterone improved QOL, the WHQ was compared between this cohort of women and published data on 682 women between the ages of 45 and 65 years who had not received any kind of HRT.[22] A one-sample *t* test was used to determine whether the scores from this treatment group were significantly different from a population value. A paired *t* test was performed to determine differences in satisfaction with previous and current regimens for two questions relating to bleeding and menopausal symptoms.

RESULTS

The majority of this population (75%) were between the ages of 45 and 59 years, were Caucasian (89%), and had at least some college education (79%). Of the 176 women surveyed, 147 (84%) gave a history of menopause and were included in the QOL analyses, and most women reported the duration of menopause as >3 years (65%). The remaining 16% who were premenopausal were probably receiving treatment for secondary amenorrhea. In this group, side effects were similar, and the overall number was small compared with the number of subjects on HRT.

Most women were healthy, as 65% reported no

Table 1. Reasons for Prescribing Micronized Progesterone (n = 176)

Indication	*Frequency*	*%*
Acute menopausal symptoms	111	63
Cardiovascular disease prevention	120	68
Osteoporosis prevention	119	68
Endometrial protection	87	49
Mental health	4	2
Other	8	5
Daily progesterone dose		
100 mg	98	56
200 mg	72	41
400 mg	2	1
Not reported	4	2

comorbid illness. Of those women with underlying illness, osteoporosis, hypertension, and cardiovascular disease were the major disorders reported, present in 6%, 15%, and 5% of this cohort, respectively. Previous HRT included the use of MPA and estrogen. The most frequently prescribed estrogen was conjugated equine estrogens (39%), followed by oral micronized estradiol (35%). Transdermal estradiol was used by 7% of the respondents.

The indications for HRT therapy are shown in Table 1. More than 63% of women reported using HRT for acute menopausal symptoms. Prevention of osteoporosis and cardiovascular disease was reported as a reason for use by 68% of women. Half of the women surveyed listed "endometrial protection" as an indication for combination HRT. The reasons for a woman's being switched from MPA to micronized progesterone are shown in Table 2. The most common reason was for the side effect profile, followed by belief in reduced long-term risks and inability to tolerate MPA. Perceived cardiovascular health benefits, including lipoprotein effects, were identified by 5% of the women as the reason for switching to micronized progesterone. The dose of micronized progesterone employed ranged from 100 to 400 mg/day. The percentages of women who used 100, 200, and 400 mg daily doses were 56%, 41%, and 1%, respectively.

The primary QOL assessment (Greene Climacteric Scale) is depicted in Figure 1. Women reported highly significant improvements in all somatic, vasomotor, and psychological scales when the regimen was changed from MPA to micronized progesterone (2-tailed paired t test, $p < 0.001$). The two subscales of depression and anxiety also demonstrated significant improvement. The percentages of women who reported improvement in each of the three major domains were 32%, 50%, and 45% for somatic, vasomotor, and psychological symptoms, respectively.

The mean scores for the WHQ survey results are shown in Figure 2. Compared with a historical population using no treatment, the use of micronized progesterone was associated with a significant improvement in 8 of 9 domains, including sleep disturbance, anxiety, depression, somatic symptoms, menstrual problems, cognitive difficulties, sexual functioning, and vasomotor symptoms.

The patient satisfaction profile is summarized in Table 3. The majority of respondents reported excellent satisfaction with a micronized progesterone regimen (80%). Over 65% of women thought that their current regimen containing micronized progesterone was better than any other previous regimen they had taken, and >70% of women surveyed believed that their current regimen would reduce future health risks.

Two special factors in the patient satisfaction instrument were examined separately: the effects on menopausal symptoms and vaginal bleeding. The mean scores indicated that there was a significant improvement in both bleeding (2.04 versus 2.63, $p < 0.001$) and control of symptoms (1.95 versus 2.95, $p < 0.001$) when the micronized progesterone-containing regimen was compared with previous therapy.

TABLE 2. REASONS FOR SWITCHING TO MICRONIZED PROGESTERONE (n = 176)

Reason[a]	*Frequency*	*%*
MPA intolerance	41	23
Better side effect profile	125	71
Reduced long-term use	62	35
Risk		
Cardiovascular health	5	3
Control bleeding	4	2
Other	19	11

[a]Percentages do not total 100; some subjects cited more than one reason.

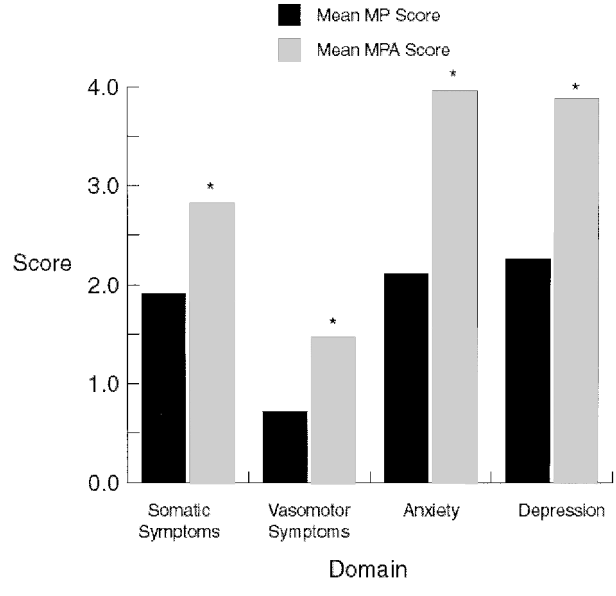

FIG. 1. Greene Climacteric Scale, which assesses QOL. A lower score indicates improvement. MP, micronized progesterone, MPA, medroxyprogesterone acetate. *$p < 0.001$.

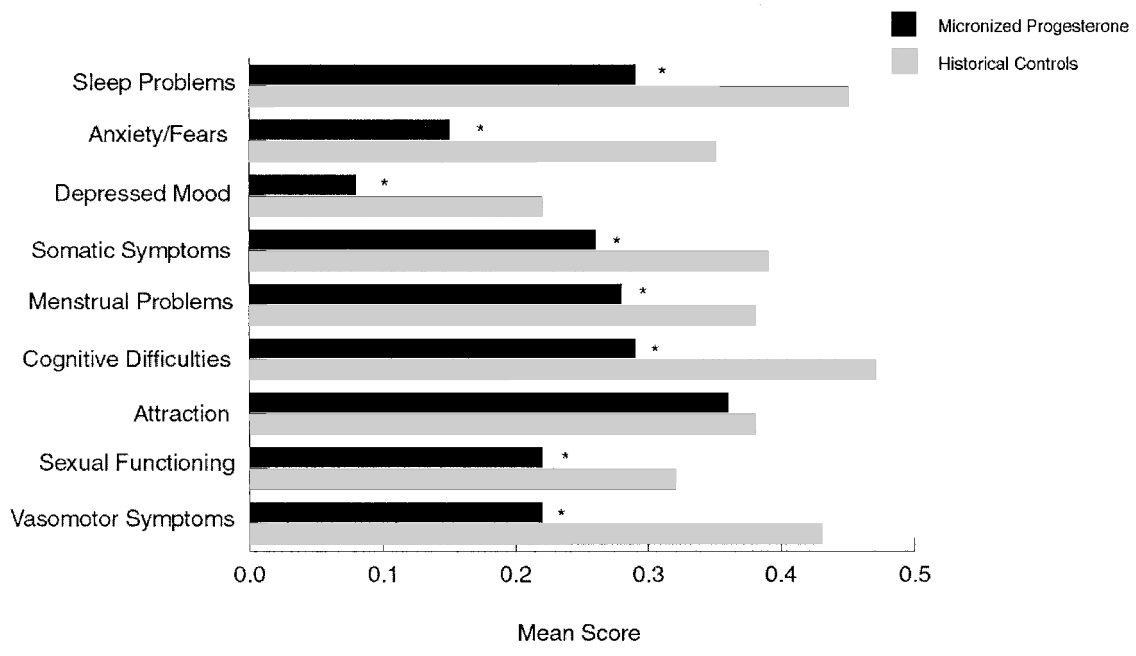

FIG. 2. Women's Health Questionnaire mean scores in micronized progesterone users and historical controls. Lower scores indicate improvement in QOL. *$p < 0.001$.

DISCUSSION

These survey data indicate that micronized progesterone administered to postmenopausal women led to significant improvements in QOL based on specific menopausal symptomatology when compared with an MPA-containing regimen. Included were improvements in vasomotor symptoms, somatic complaints, anxiety, and depressive symptoms. Previous studies using a 200-mg oral dose of micronized progesterone at bedtime to menopausal women demonstrated improvement of mood.[23] In a double-blind, crossover trial, micronized progesterone was also effective in women with complaints of premenstrual mood changes.[24] These data support the observations in this survey and suggest that micronized progesterone may exert superior effects on mood compared with MPA-containing regimens.

There are several potential shortcomings of this study. First, the lack of a parallel control group might raise some doubts about the possibility of a placebo effect. However, the symptoms of

TABLE 3. PATIENT SATISFACTION PROFILE MEAN SCORES (SD) IN CURRENT MICRONIZED PROGESTERONE USERS[a]

Item	*Mean*	*SD*	p *value*
1. Very satisfied with current HRT regimen	2.06	1.28	
2. Satisfied with overall quality of life on current HRT	1.79	1.11	
3. Compared with all previous HRT, current regimen is the best	2.14	1.27	
4. Feel satisfied that current HRT will reduce future health risks	1.86	1.00	
5. Satisfied how last HRT controlled my symptoms	2.95	1.50	<0.001
6. Satisfied how current (micronized progesterone) HRT controls my symptoms	1.97	1.19	
7. Satisfied how last HRT controlled breakthrough bleeding	2.66	1.53	<0.001
8. Satisfied how current (micronized progesterone) HRT controls breakthrough bleeding	2.06	1.27	

[a]Based on a scale of 1–5, where 1 = strongly agree and 5 = strongly disagree. Tests of statistical significance were done by comparing scores of previous HRT use (questions 5 and 7) with satisfaction scores for current HRT (questions 6 and 8). No comparison data were available for questions 1–4.

menopause are usually of sufficient severity to allow comparison of two effective regimens. For example, a placebo-controlled study examining the benefits of oral MPA for treating menopausal symptoms identified a 25% reduction in vasomotor flushes during placebo treatment; however, a 74% decline in menopausal symptoms was observed in the active treatment group, and crossover from active treatment to placebo resulted in a significant proportion of women with immediate worsening of symptoms.[25] Other studies using SSRI for treatment of postmenopausal hot flashes indicate a 20%–25% reduction in symptoms due to a placebo effect.[26] A second potential shortcoming, the lack of randomization into this study, may introduce either recall bias or a period effect. The possibility of recall bias is not likely given the short duration of time between the change to micronized progesterone and the assessment time of 1–6 months. Whether there was improvement in QOL parameters as a time-dependent phenomenon is unknown. Again, the period of time between previous MPA treatment and initiating micronized progesterone was short and would be unlikely to influence the recall of menopasual symptoms on previous treatment. The dose of progesterone used was generally 100–200 mg, with only 1% of subjects on a larger dose and 2% unreported. Thus, although the dose of micronized progesterone varied, this reflects current practice standards and is similar to the varying doses of MPA (2.5–10 mg) used clinically for HRT. An additional potential bias is the fact that most participants were highly educated and Caucasian. This reflects compliance and satisfaction issues associated with HRT. These results may not be easily extrapolated to minority groups, where different QOL issues may exist.

A rationale for using QOL assessments to evaluate menopausal treatments is that the treatments may have roughly equivalent clinical efficacy, yet one may have clear QOL benefits over the other.[27] Comparisons of micronized progesterone and MPA are excellent candidates for such QOL surveys in postmenopausal women. Both compounds are equally effective in preventing estrogen-induced endometrial proliferation, but micronized progesterone produces significantly greater beneficial effects on high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol than do MPA regimens[28] and may confer the same benefits on QOL.

Overall, women using micronized progesterone were satisfied with the beneficial effects of this regimen, and, on average, the respondents thought that a regimen containing micronized progesterone would reduce health risks associated with menopause. In addition, the better average score for women's perception of vaginal bleeding, menopausal symptom control, and side effects for micronized progesterone when compared with MPA suggests that QOL effects of natural progesterone are superior to those of MPA-containing regimens. These benefits, combined with the positive effects on lipoproteins, suggest that a micronized progesterone regimen may offer a wider spectrum of benefits for postmenopausal women.

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