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Oral Micronized Progesterone

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ABSTRACT

This review sought to examine the rationale for selecting an oral micronized progesterone formulation rather than a synthetic progestin for some of the main indications for progestogens. Unopposed estrogen use is associated with a high risk (relative risk, 2.1 to 5.7) of endometrial hyperplasia and adenocarcinoma, and it has been understood for some time that a progestogen must be added for at least 10 to 14 days per month to prevent these effects. However, the most commonly used synthetic progestins, norethisterone and medroxyprogesterone acetate, have been associated with metabolic and vascular side effects (eg, suppression of the vasodilating effect of estrogens) in both experimental and human controlled studies. All comparative studies to date conclude that the side effects of synthetic progestins can be minimized or eliminated through the use of natural progesterone, which is identical to the steroid produced by the corpus luteum. The inconvenience associated with the use of injectable, rectal, or vaginal formulations of natural progesterone can be circumvented by using orally administered micronized progesterone. The bioavailability of micronized progesterone is similar to that of other natural steroids, and interindividual and intraindividual variability of area under the curve is similar to that seen with synthetic progestins. A clear dose-ranging effect has been demonstrated, and long-term protection of the endometrium has been established. Micronized progesterone has been used widely in Europe since 1980 at dosages ranging from 300 mg/d (taken at bedtime) 10 days a month for women wishing regular monthly bleeding to 200 mg 14 days a month or 100 mg 25 days a month for women willing to remain amenorrheic. This therapy is well tolerated, with the only specific side effect being mild and transient drowsiness, an effect minimized by taking the drug at bedtime. The prospective, comparative Postmenopausal Estrogens/Progestin Intervention trial has recommended oral micronized progesterone as the first choice for opposing estrogen therapy in nonhysterectomized postmenopausal women. ***Key words:*** progesterone, synthetic progestins, artery-wall vasomotility, endometrial hyperplasia.

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INTRODUCTION

The immediate benefits of estrogen therapy in postmenopausal women include prompt relief of vasomotor symptoms, sleep disturbances, and vaginal dryness and, in the long term, reduction in bone loss, with a significant decrease in the risk of fracture.[1] Protection against myocardial infarction and a reduced risk of vascular mortality have also been observed in women currently using estrogen therapy compared with those who may or may not have used estrogen therapy previously.[2] However, in healthy, nonhysterectomized women, the use of estrogens alone is associated with development of endometrial hyperplasia and carcinoma, and the addition of a progestin is required to eliminate this risk.[3,4] Addition of progesterone or a progestin may also be beneficial for breast health.[5,6] A recent review of 51 published studies found no effect of progestins on breast cancer risk,[7] but several other studies have shown a better breast cancer prognosis in women treated with combined hormone replacement therapy (HRT).[8–11]

The progestins do, however, have a number of potential negative effects, particularly metabolic and vascular effects.[12–18] Although large observational studies have shown no harmful vascular consequences with the use of combinations of the available progestins and estrogens in postmenopausal women,[2] all randomized, controlled studies in animals and humans have consistently shown that the most popular synthetic progestins, including those with only weak androgenic activity (eg, medroxyprogesterone acetate [MPA]), induce significant disturbances in lipid levels, glucose metabolism, vasomotility, and histologic appearance of the artery walls.[12–18] Addition of a synthetic progestin is therefore suspected of having seriously reduced the potential long-term benefits of estrogen therapy in the first prospective, randomized trial of secondary cardiovascular prevention.[19]

In controlled animal studies and short-term human trials, however, no side effects were observed when circulating levels of natural progesterone were kept within the range seen during the normal luteal phase.[14,18,20–22] Therefore, natural progesterone may have a better risk-benefit profile than that of the synthetic progestins.

Daily injected, rectal, or vaginal administration of progesterone is poorly accepted for long-term treatment.[23] Chronic vaginal administration may even induce side effects specifically in postmenopausal women by creating a supraphysiologic local concentration of the antiestrogenic steroid, modifying vaginal mucosal histology and function, and increasing the incidence of various sexually transmitted and non–sexually transmitted infections.[24–26]

In the late 1970s it was shown that decreasing the size of progesterone particles through micronization substantially increased bioavailability of the hormone.[27] A micronized formulation of natural progesterone has been available in some European countries since 1980. The micronized formulation administered orally once daily has been shown to be as effective as the synthetic progestins for controlling endometrial growth but, according to consistent findings from short- and long-term prospective controlled human studies, has significantly fewer metabolic side effects.[3,4] This formulation was used in the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial and subsequently recommended by the PEPI investigators as the first choice for opposing estrogens

during postmenopausal HRT.[3,4,28] Furthermore, in premenopausal women with endogenous estradiol secretion but a short or insufficient luteal phase, oral micronized progesterone is effective in treating several consequences of progesterone deprivation, such as secondary amenorrhea.[29]

This paper reviews the pharmacology, clinical use, and tolerability of the oral micronized formulation of progesterone.

DESCRIPTION AND PHARMACOKINETICS

Oral micronized progesterone was first marketed in France in 1980 under the name Utrogestan® and more recently has been marketed in more than 35 countries under this name and as Progestan®, Prometrium®, and Lugesteron® (all, Besins-Iscovesco, Paris, France). It is synthesized from a naturally occurring precursor extracted from yams (*Dioscorea* sp) and is chemically identical to progesterone of ovarian origin (empiric formula, $C_{21}H_{30}O_2$; molecular weight, 314.47). The micronized formulation provides optimal progesterone bioavailability, which is dependent on both the size of the progesterone particles in suspension and the nature of the oily excipients.[30]

After oral administration of micronized progesterone, 50% to 60% of the dose is absorbed, as measured by urinary pregnanediol excretion.[31] A comparison between oral and injectable formulations determined that absolute bioavailability was 6% to 8%.[32,33] This is accounted for by a significant first-pass effect, which results in a large amount of the absorbed steroid circulating as metabolites, primarily pregnanediol, pregnenolone, pregnanedione, 20α-dihydroprogesterone, and 17-OH progesterone.[32,34] The bioavailability of progesterone after oral administration is comparable to that measured after oral administration of other natural steroids such as estradiol.[35]

The maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) of progesterone are substantially increased when micronized progesterone is administered orally with food rather than in the fasting state.[33] This effect is negligible when the drug is administered at bedtime as recommended. Steady-state plasma concentrations are rapidly reached after the second dose of oral micronized progesterone.[31] The AUC for progesterone shows a direct relationship to the dose of orally administered micronized progesterone (Table I).

Mean values for C_{max}, time to C_{max} (t_{max}), and AUC are relatively consistent between studies, although there is considerable interindividual variation.[27,32,33,36,37] Similar interindividual differences have been observed after administration of progesterone by the rectal, vaginal, and intramuscular routes[38] and after oral administration of other progestins, including MPA,[39] norethisterone,[40] desogestrel,[41] levonorgestrel, and gestodene.[42] In various pharmacokinetic studies, plasma levels of progesterone returned to baseline values within 12 hours after oral administration of micronized progesterone, and differences in AUC were small, whether measured at 10,[33] 24,[33] 48,[36] or 72 hours[33] after administration of the same dose of oral micronized progesterone. Also, the AUC over 24 hours was similar when the full dose was administered once daily or when half the dose was administered twice daily.[31,33] Despite these fluctuations in plasma progesterone levels, concentrations in the target tissue, the endometrium, are relatively constant throughout the day.[27]

Table I. Results (mean ± SD) of a dose-proportionality study.[33]

Variable	Daily Dose		
	100 mg	200 mg	300 mg
AUC_{0-24} (ng/mL/h)	46.9 ± 14.7	86.9 ± 44.7	148.4 ± 56.2
AUC (corrected)*	0.47 ± 0.15	0.43 ± 0.22	0.49 ± 0.19
C_{max} (ng/mL)	10.2 ± 8.4	19.9 ± 20.8	49.8 ± 3.19
C_{max} (corrected)*	0.10 ± 0.08	0.10 ± 0.10	0.17 ± 0.11
t_{max} (h)	2.7 ± 1.0	2.2 ± 1.0	2.0 ± 1.36
Mean plasma level (ng/mL)	1.9 ± 0.6	3.6 ± 1.8	6.18 ± 2.3

AUC = area under the progesterone absorption curve; C_{max} = maximum serum progesterone concentration; t_{max}= time to C_{max}.
*Normalized.

Pharmacodynamic Effects

Endometrial Cell Cycle

Mitotic activity in endometrial glands depends initially on estrogenic stimulation through specific nuclear estradiol receptors. Within a few days, unopposed estrogens increase the synthesis of estradiol receptors, then increase the number of cycling cells, and within a few months increase the incidence of endometrial hyperplasia.[43–45] Natural progesterone and the available synthetic progestins decrease the synthesis of nuclear estradiol receptors and then suppress estrogenic stimulation in the epithelial cells of the endometrium[46] without changing circulating levels of estrogens or their potential activity on other targets having different receptors (eg, bone). Several recent studies make it clear that optimal prevention of endometrial hyperplasia does not require reproduction of all the cytologic and histologic characteristics of a naturally occurring luteal phase.[45] Amenorrhea, related to a subatrophic or slightly proliferative endometrium, is far more acceptable than cyclic bleeding to a majority of postmenopausal women and may be safe in the long term, assuming that mitotic activity is low.[47]

The effect of different doses of orally administered micronized progesterone on the endometrial cell cycle in postmenopausal women primed with estrogens has been the subject of several investigations.[46–48] Examination of endometrial biopsy specimens obtained 6 days after the administration of micronized progesterone 100, 200, and 300 mg OD showed a significant reduction in both nuclear estradiol receptors and thymidine-labeling index in gland cells; this reduction was similar to that previously observed with current progestin doses when micronized progesterone 200 and 300 mg/d was administered.[46] Examination of endometrial biopsy specimens taken at various times during the use of micronized progesterone 200 to 300 mg/d showed a progressive reduction in mitotic activity, with a maximum effect after 10 to 12 days.[47] Examination of endometrial biopsy specimens taken 21 to 25 days after daily administration of a 100-mg dose

of micronized progesterone revealed a striking reduction in DNA synthesis and the number of cyclic cells.[48]

Lipids

Currently used progestins combined with contraceptive doses of ethinyl estradiol in premenopausal women or with replacement doses of estrogens in postmenopausal women tend to decrease high-density lipoprotein cholesterol (HDL-C)—more specifically, HDL_2-C. This side effect is probably related to changes in hepatic lipase activity[49] and is considered potentially harmful by many investigators.[4,28,50] It has been the main impetus behind the search for a "third generation" of progestins.[50] Studies have shown that treatment with oral micronized progesterone alone[51] or its addition to estrogen therapy[4,28,52–58] induces significantly smaller changes in HDL-C metabolism than do synthetic progestins such as MPA, norethisterone, and norgestrel.

In one study,[51] 80 premenopausal women with dysfunctional uterine bleeding were randomized to treatment for 10 d/cycle with either oral micronized progesterone 300 mg/d or norethisterone 15 mg/d for 6 consecutive cycles. Endometrial hyperplasia was observed in none of the biopsy samples taken at the end of cycles 3 and 6 in either treatment group, compared with a diagnosis of endometrial hyperplasia in 51% and 10% of samples from the respective treatment groups taken before treatment and 3 months after cessation of treatment. HDL-C levels remained unchanged in the 40 women treated with micronized progesterone (1.36 vs 1.40 mmol/L), whereas a significant decrease was measured in those treated with norethisterone (0.65 vs 1.40 mmol/L; $P < 0.001$).

In postmenopausal women treated with estrogen, the effects on HDL-C levels of adding oral micronized progesterone 200 to 300 mg/d have been investigated in several studies lasting from 6 weeks to 3 years. The effects of using oral micronized progesterone plus estrogen have been compared with use of the same estrogen alone[4,53,56]; with untreated controls[57]; and with use of the same estrogen plus levonorgestrel 120 to 250 mg/d,[52,58] MPA 10 mg/d (cyclic)[4,58] or 2.5 mg/d (continuous),[4] or tamoxifen 20 mg/d.[54]

In a study by Moorjani et al,[56] a significant decrease in HDL-C levels was observed in users of estrogen plus micronized progesterone compared with hysterectomized users of estrogen alone. However, this was mainly due to change occurring during the first 2 cycles, and HDL-C levels largely returned to previous levels during the following 4 months. In other studies,[51–55,57,58] oral micronized progesterone induced no significant change in HDL-C metabolism, whereas levonorgestrel and MPA induced the expected significant decrease.

In the PEPI trial,[4] a total of 875 healthy postmenopausal women were randomly assigned in equal numbers to receive placebo, conjugated equine estrogens (CEE) 0.625 mg/d, CEE 0.625 mg/d plus cyclic MPA 10 mg/d for 12 d/mo, CEE 0.625 mg/d plus consecutive MPA 2.5 mg QD, or CEE 0.625 mg/d plus cyclic oral micronized progesterone 200 mg/d for 12 d/mo. This 3-year prospective study showed that adding MPA to the estrogen in both cyclic (10 mg/d) and continuous (2.5 mg/d) regimens significantly reduced HDL-C levels. HDL-C levels were significantly higher in the group treated with oral micronized progesterone than in both groups treated with MPA, both in the in-

tent-to-treat population[14] and in treatment-adherent patients.[28]

Glucose Metabolism

Synthetic progestins such as MPA induce significant disturbances in glucose metabolism in primates[59] and humans.[60] In the PEPI trial,[4,28] a significant increase in postchallenge glucose metabolism occurred in MPA users in comparison with the other groups using unopposed estrogen or estrogen plus oral micronized progesterone. This agrees with previous studies that found no deleterious effect of the use of oral micronized progesterone on glucose metabolism in postmenopausal women,[55] even when they had non–insulin-dependent diabetes mellitus.[57]

Blood Pressure

Because the serum ratio of deoxycorticosterone to progesterone is increased in women using oral micronized progesterone compared with those using the injectable formulation, there is some theoretical concern about blood pressure control, specifically in hypertensive patients.[32] However, progesterone is also a competitive inhibitor of aldosterone binding, and the dominant effect of oral administration of micronized progesterone on sodium metabolism is a significant increase in urinary sodium excretion similar to that observed with low doses of antialdosterone drugs such as spironolactone.[61]

Several studies have monitored the effect of oral micronized progesterone on the blood pressure of initially normotensive postmenopausal women.[4,54,57,58,62,63] None, including the PEPI trial, demonstrated any increase in blood pressure compared with untreated controls,[57] placebo-treated controls,[4] or groups treated with estrogen only,[4,63] progestins plus estrogen,[4,58,62] or tamoxifen plus estrogen.[54]

In a randomized, placebo-controlled, crossover study in 8 men and 4 postmenopausal women with mild-to-moderate untreated hypertension,[64] oral micronized progesterone caused a dose-dependent reduction in blood pressure that was significant at 200 mg/d compared with pretreatment and placebo values. An uncontrolled survey in 19 hypertensive postmenopausal women found that the addition of transdermal estradiol and oral micronized progesterone tended to improve the efficacy of participants' antihypertensive drugs.[65]

Hemostasis

No changes in hemostatic variables have been detected among users of oral micronized progesterone in short-[66,67] or long-term[4] studies. Unlike the progestins used in combination with ethinyl estradiol for contraception, those currently prescribed to postmenopausal women are not suspected of disturbing the hemostatic balance when used in combination with estrogens.[67–69]

EFFICACY

Premenopausal Progesterone Deficiency

Secondary Amenorrhea

A randomized, single-center, double-masked, placebo-controlled study[29] compared the efficacy and safety of 2 strengths of oral micronized progesterone (200 and 300 mg once daily for 10 days) in initiating bleeding in patients with secondary amenorrhea. The primary efficacy variable was initiation of bleeding, defined as any vaginal bleeding or blood-stained discharge from the beginning of progesterone therapy up to and including 1 week after

the final dose. The maximum period for a positive response was set at 16 days from the start of therapy. Each treatment group was compared with the placebo group with respect to induction of bleeding. The treatment groups were comparable in terms of mean pretreatment levels of follicle-stimulating hormone, luteinizing hormone, estradiol, progesterone, human chorionic gonadotropin–beta subunit, dehydroepiandrosterone sulfate, and testosterone.

This study found that 5 of 21 (24%) placebo recipients experienced bleeding, compared with 10 of 19 (53%) and 18 of 20 (90%) of those receiving micronized progesterone 200 or 300 mg/d, respectively. The mean (± SD) time to onset of bleeding was similar in each treatment group: 10.4 ± 4.7, 8.7 ± 2.7, and 10.7 ± 2.8 days, respectively. Both doses of micronized progesterone appeared to initiate bleeding in patients with secondary amenorrhea, but the difference from placebo was statistically significant only with the higher dose. Thus oral micronized progesterone 300 mg, taken once daily at bedtime for 10 consecutive days, was effective in inducing bleeding in secondary amenorrhea among patients with adequate endogenous estrogen production.

Endometrial Hyperplasia and Dysfunctional Bleeding

Eighty premenopausal women with dysfunctional bleeding disorders were randomized to treatment with norethisterone 15 mg/d or oral micronized progesterone 300 mg/d administered from days 15 to 24 of the menstrual cycle.[51] The diagnoses were metrorrhagia, hypermenorrhea, menorrhagia, and irregular menstruation in 39, 19, 15, and 7 cases, respectively. Histologic examination of the endometrium showed cystic glandular hyperplasia, proliferative endometrium, or incomplete maturation in 41, 30, and 9 cases, respectively. Endometrial biopsy samples were obtained from each patient during the last 3 days of the third and sixth treatment cycles and again during the third recovery cycle after cessation of treatment. No hyperplastic changes were detected at months 3 and 6 from either treatment group but were diagnosed in 51% and 10% of samples taken before and 3 months after cessation of treatment.

Thus oral micronized progesterone 300 mg/d given for 10 consecutive days during the second half of the cycle was effective in preventing a recurrence of endometrial hyperplasia, demonstrating a level of efficacy similar to that of high doses of the current progestins. In addition, 92% of patients had no recurrence of bleeding disorders during oral micronized progesterone treatment.

As an Adjunct to Postmenopausal Estrogen Therapy

The PEPI Trial

The PEPI trial[4,28,44] is the most important study of oral micronized progesterone use in postmenopausal women continuously treated with estrogens. This 3-year, multicenter, prospective, placebo-controlled trial compared the efficacy of micronized progesterone in preventing endometrial hyperplasia with that of placebo and two MPA regimens. Five hundred ninety-six nonhysterectomized postmenopausal women were randomized to 1 of the following treatments in a 28-day cycle: placebo; CEE 0.625 mg/d; CEE 0.625 mg/d plus MPA 2.5 mg/d; CEE 0.625 mg/d plus MPA 10 mg/d for the first 12 days; or CEE 0.625 mg/d plus micronized

progesterone 200 mg/d for the first 12 days. In the majority of patients (n = 2244), the endometrium was sampled during a scheduled visit for this purpose; other occasions on which endometrial samples were obtained included unscheduled biopsies (n = 174), curettage (n = 28), and hysterectomy (n = 14).

According to the initial evaluation of histologic findings,[4] women who were assigned to estrogen alone were more likely to develop simple (27%), complex (22%), or atypical hyperplasia (11%) than were those who received placebo (0.8%, 0.8%, and 0%, respectively). During follow-up, participants receiving one of the three estrogen-progestin regimens had rates of hyperplasia similar to those seen in women receiving placebo. Micronized progesterone 200 mg once daily at bedtime was as effective as the 2 MPA regimens in protecting the endometrium from hyperplastic changes associated with estrogen therapy. A later evaluation of the same endometrial samples[44] reached a similar conclusion.

Other Controlled Studies

In a 6-month prospective study,[63] 32 postmenopausal women were randomly assigned to oral micronized progesterone 200 mg once daily at bedtime in cyclic combination with either conjugated estrogen 0.625 mg/d or transdermal estradiol 1.5 mg/d for 14 days per month. None of the women who received either combination of micronized progesterone with estrogen showed hyperplasia on examination of endometrial biopsy specimens obtained after 24 weeks of treatment. Forty-four percent of cycles remained amenorrheic; 45% terminated with regular withdrawal bleeding, and 11% included some episodes of breakthrough bleeding during the study period.

A randomized trial compared the effects of micronized progesterone 200 mg/d and MPA 10 mg/d in 40 postmenopausal women receiving transdermal estradiol HRT for days 14 through 25 of 13 cycles.[70] Examination of endometrial biopsy specimens obtained before study entry and at the end of treatment revealed no hyperplasia. Based on daily records, there was significantly less bleeding and bleeding was of shorter duration in the women treated with micronized progesterone compared with those treated with MPA. Only 9 of 20 (45%) patients treated with micronized progesterone experienced regular withdrawal bleeding during the study, compared with 17 of 20 (85%) MPA recipients. The use of micronized progesterone in combination with postmenopausal HRT produced more desirable bleeding patterns for the patient and was comparable to MPA in terms of preventing endometrial hyperplasia.

In the study by Gillet et al,[71] 125 postmenopausal women received HRT with estradiol and micronized progesterone for 6 months. All women were prescribed a regimen of transdermal estradiol for either 21 of 28 days or 25 d/calendar month. The women were offered different schedules according to their willingness to experience withdrawal bleeding and the pattern of bleeding they considered most convenient. Of the 112 women who completed the 6-month study, 22 selected a cyclic schedule expected to induce regular bleeding, and 90 selected a schedule expected to maintain amenorrhea by combining estradiol and micronized progesterone 100 mg/d for 21 days per 28-day cycle (n = 11) or for 25 days per calendar month (n = 79). Examination of endometrial biopsy specimens showed no hyperplasia in any group. Sixty-four percent of

Table II. Long-term (>5 years) effects of hormone replacement therapy (HRT) combined with oral micronized progesterone.[47]

Effect	HRT Plus Oral Micronized Progesterone	
	300 mg/d for 10 d (%) (n = 23)	200 mg/d for 14 d (%) (n = 126)
Withdrawal bleeding	83	9
Recovery of endometrial tissue	100	18
Secretory changes	+	±
Macroscopic subatrophy	0	83
Hyperplasia	0	0

the women using the cyclic regimen experienced the expected withdrawal bleeding, whereas 90% of the women using the combined regimens were amenorrheic at the end of the study.

In a 5-year open survey,[47] 2 different regimens of micronized progesterone were compared by examination of endometrial biopsy specimens and hysteroscopic controls. Two hundred thirty-six postmenopausal women received a first prescription for micronized progesterone as an adjunct to HRT between January 1980 and December 1982. The initial prescription was 200 mg/d for 14 d/month, which was increased to 300 mg/d for 10 d/month in women willing to experience cyclic bleeding. Seventy-nine women stopped treatment for a variety of reasons during the following 5 years, none of them because of endometrial hyperplasia or carcinoma. Endometrial assessment was performed in the 157 patients who had received transdermal estradiol for 21 of 28 d/cycle in combination with micronized progesterone in a dosage of either 300 mg/d for 10 d/cycle (23 patients), 200 mg/d for 14 d/cycle (126 patients), or an intermediate dosage (8 patients) for at least 5 years (mean, 5.7 years). Endometrial tissue was available for histologic assessment from only 53 patients, whereas hysteroscopy showed uniform macroscopic atrophy of the endometrium in the remaining 104 women (Table II). HRT in which micronized progesterone 300 mg/d was added for 10 d/cycle after 11 days of unopposed estradiol was associated with more histologic secretory changes and with a higher incidence of withdrawal bleeding than the other regimen, whereas the addition of micronized progesterone 200 mg/d for 14 d/cycle after 7 days of unopposed estradiol was associated with the highest incidence of subatrophic endometrium and amenorrhea. No cases of endometrial hyperplasia or carcinoma were observed in either group. These findings suggest that endometrial secretory changes and regular withdrawal bleeding are not correlated with long-term endometrial safety.

Uncontrolled Studies

Two uncontrolled studies combined a low daily dose (100 mg) of micronized progesterone with estrogen replacement therapy for 21 or 25 days per 28-day cy-

cle or calendar month. In the study by Foidart et al,[48] 30 postmenopausal women received HRT consisting of estradiol plus micronized progesterone for 1 year. All 30 patients were prescribed percutaneous estradiol gel 1.5 mg/d with micronized progesterone 100 mg/d for 25 d/calendar month. All completed the study, and no case of hyperplasia was detected on examination of endometrial biopsy specimens at the end of the study. During the study period, 6 of 30 (20%) patients experienced at least one episode of irregular bleeding (defined as bleeding that began between days 3 and 22 of combined therapy); irregular bleeding occurred in 5% of the 362 observed cycles. No bleeding was recorded during the last 3 months of the study.

In a 1-year study by Marengo et al,[72] 112 postmenopausal women received HRT consisting of transdermal estradiol 1.5 mg/d combined with micronized progesterone 100 mg/d for 25 d/calendar month. No case of hyperplasia was detected on examination of endometrial biopsy specimens at the end of the study. Amenorrhea was recorded in more than 90% of the women during the last 3 months of the study.

Bleeding Pattern

The various dosages of micronized progesterone that have been studied—300 mg/d for 10 d/cycle, 200 mg/d for 12 to 14 d/cycle, and 100 mg/d for 21 to 25 d/cycle—have been equally effective in preventing endometrial hyperplasia in postmenopausal women treated with estrogens. Despite the similarities of these monthly dosages, they have strikingly different effects on bleeding pattern. The published studies show a large variation in the observed incidence of irregular bleeding, ranging from 0% to 40% of cycles or from 0% to >60% of HRT users.[47,48,63,70–77] Unscheduled bleeding that occurs during HRT may induce anxiety and lead to unpleasant and relatively expensive intrauterine examinations or even withdrawal from treatment.[75]

There are several possible explanations for the differences in the rate of irregular bleeding with similar HRT regimens reported in the literature. First, there are inconsistencies in the definition of irregular or abnormal bleeding in users of cyclic regimens. When the onset of bleeding is considered as the main end point, the reference period for "regular," "scheduled," or "withdrawal" bleeding may include from <25% to >50% of treatment days.[73,76,77] For example, using the actual day of progestin withdrawal as the limit for the onset of regular bleeding may double the apparent incidence of irregular bleeding in comparison with studies using a limit of 2 to 9 days earlier. However, in the latter case, the term "withdrawal bleeding" is inappropriate and may be misleading. The 1-year study by Archer et al[73] used a broad definition of regular bleeding as bleeding starting up to 9 days before progestin withdrawal and found that cyclic HRT employing the current progestins induced irregular bleeding in 16% to 19% of cycles. The 6-month studies by Dupont et al[63] and Gillet et al,[71] which used a more restrictive definition of regular bleeding as bleeding starting up to 3 days before progesterone withdrawal, found that cyclic HRT employing micronized progesterone produced irregular bleeding in 11% to 23% of cycles. Despite the small cohorts involved, these percentages do not suggest the existence of any specific problem of bleeding during micronized progesterone use.

Another possible reason for the differences in rates of irregular bleeding observed in the published studies is that the results may be based either on the number of patients experiencing bleeding during the entire study or only on those experiencing bleeding at the end of the study. The results may also include the number of observed cycles with bleeding during the study as a whole or only those with bleeding at the end of the study. Finally, the results may be based on the total number of days with bleeding or the mean duration of bleeding in each patient, and spotting may be differentiated from bleeding using varying definitions.

The duration of the study seems to have a great influence on the results. The incidence of irregular bleeding has been shown to decrease with time in several studies,[48,71,73] being higher during the first 6 months of HRT than during the following months. In the study by Moyer et al,[47] the incidence of irregular bleeding dropped to nil during the fifth year of cyclic HRT with micronized progesterone.

One explanation for the decreased incidence of bleeding with chronic treatment may be the high dropout rate often observed during the first year of HRT, with the women who remain compliant being more likely to be free of side effects.[74] The dropout rate is quite high in large multicenter studies[73] but can be dramatically reduced in studies involving a small number of motivated patients and physicians. The high dropout rate (40%) may have had a favorable influence on the results in MPA users in the study by Archer et al,[73] but the low dropout rate (0% to 11%) in other studies[47,71,72] is not likely to have had a significant influence on the high incidence of amenorrhea observed in users of micronized progesterone.

Another explanation for the decreased incidence of bleeding with chronic treatment is the potential for patients to customize their HRT during the first months, selecting their own optimal doses. This option was offered to women participating in the studies by Gillet et al[71] and Moyer et al.[47] Although neither explanation proves that the incidence of irregular bleeding improves over time with any fixed HRT regimen, together they suggest that the apparent improvement stems mainly from individuals' adaptation of doses, if allowed, or, if not allowed, from patient dropout.

A third explanation has to do with the amount of time that has passed since menopause. The longer this time, the lower the possibility of residual irregular ovarian activity that can induce irregular bleeding independent of HRT. This may partially explain the low rate of bleeding observed in the studies by Marengo et al[72] and Moyer et al,[47] in which the mean ages of the study populations were 61 and 59 years, respectively.

Nonetheless, the major influence on bleeding pattern comes from the addition of progestogens to estrogen. The highest rate of regular cyclic bleeding (>80% of cycles) is obtained with the cyclic addition of micronized progesterone to estrogen, allowing an unopposed estrogen phase of ≥10 d/cycle.[29,47,70] Reducing or suppressing the unopposed estrogen phase markedly reduces the rate of regular cyclic bleeding and increases the incidence of amenorrhea in 60% to 94% of cycles.[47,48,71,72] A randomized study comparing micronized progesterone and MPA combined with the same estrogen on the same dosing schedule also showed that different progestogens induce different bleeding patterns; oral progesterone in-

duced significantly less bleeding for a shorter duration, with more amenorrheic cycles, than did MPA.[70]

Because a relatively high incidence of irregular bleeding (>30%) has been reported with continuous daily combined estrogen-progestin therapy,[73-75] this schedule has not been investigated using micronized progesterone. Obviously the withdrawal of progestogen, estrogen, or both is not the only mechanism of bleeding induction, since almost 50% of women bleed before any interruption of treatment.[29,76,77] In these cases, bleeding is probably triggered through the angiogenic process, probably through continuous stimulation by progestogens and mediated by vascular endothelial growth factor.[78]

SAFETY AND TOLERABILITY

No unusual or serious adverse events have been attributed to the use of micronized progesterone in clinical trials. The most frequently reported adverse reactions are dizziness or drowsiness, which are probably related to the mild sedative effects of the pregnenolone metabolites[34] but unrelated to vasoactive changes.[79]

Two controlled studies arrived at inconsistent results for the incidences of dizziness, sleepiness, and vertigo reported by patients receiving placebo, various doses of oral micronized progesterone, or injectable progesterone. A pharmacokinetic study[33] observed none of these side effects after injectable progesterone or oral micronized progesterone 100 mg/d was administered in the morning to volunteers with estradiol levels <30 pg/mL. Three of 18 subjects experienced short-lasting side effects after receiving micronized progesterone 200 mg while fasting, compared with 4 of 18 subjects receiving the same dose with food. Seven of 18 subjects experienced side effects after receiving micronized progesterone 300 mg, with 1 subject experiencing symptoms for the entire day.

In contrast, during the "secondary amenorrhea" study by Shangold et al,[29] in which 43 patients with estradiol levels >50 pg/mL received micronized progesterone 200 or 300 mg at bedtime, there was no difference in side effects between those who received placebo (21 patients) and those who received micronized progesterone (22 patients). Similar percentages of patients felt sleepy or dizzy at bedtime after receiving placebo or one of the doses of micronized progesterone (figure).

The difference in results between these two studies may reflect the fact that plasma estrogen levels were low in the postmenopausal volunteers, whereas higher plasma estrogen levels were present to oppose the effects of progesterone in the premenopausal patients. In the study of postmenopausal volunteers, administration of micronized progesterone in the morning may also have contributed to the higher incidence of side effects in the treatment groups, whereas feeling sleepy at bedtime is a normal and even desirable occurrence. Because there is no doubt that daytime dizziness and drowsiness are potential side effects, micronized progesterone should be taken once daily at bedtime.

Somewhat different results were obtained in a randomized, double-masked, crossover trial of micronized progesterone (2 months) and placebo (2 months) conducted by Dennerstein et al[80] in patients complaining of premenstrual mood disturbances. None of the patients experienced sleepiness. Improvements in anxiety, depression, and stress were reported with the use of micronized progesterone

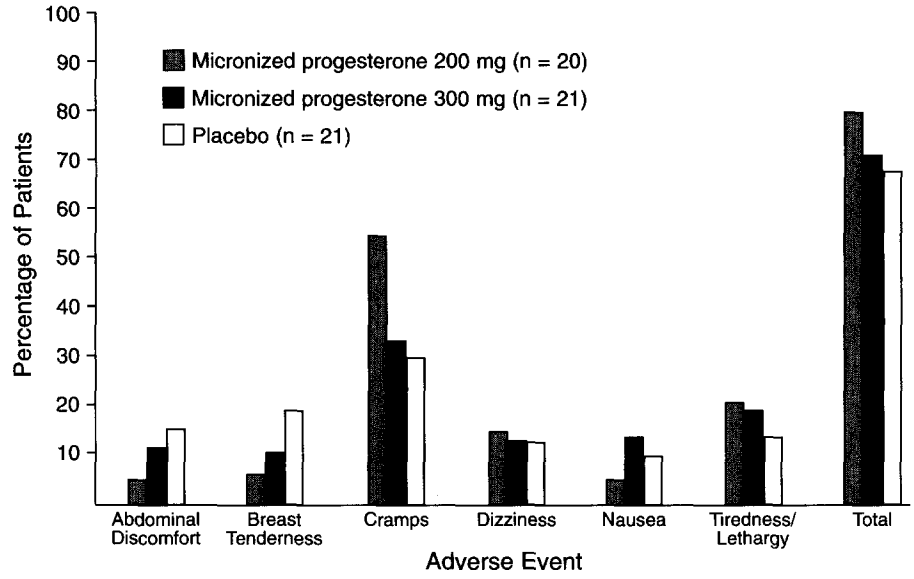

Figure. Adverse experiences reported during the Secondary Amenorrhea Study.[29]

100 mg in the morning and 200 mg at bedtime, in contrast with results reported with the current synthetic progestins, which tend to worsen such symptoms.[81] Similar improvements in mood have been observed in postmenopausal women taking micronized progesterone 200 mg at bedtime,[82] suggesting that favorable central nervous system effects can also be achieved when most of the dose is ingested at bedtime.

Because the deoxycorticosterone-to-progesterone ratio is higher after oral administration of micronized progesterone than after injection of progesterone, Ottosson et al[32] expressed some concern about the potential for disturbance of sodium metabolism. However, Corvol et al[61] demonstrated the antimineralocorticoid effect of oral administration of micronized progesterone, which is related to progesterone's competitive inhibition of the aldosterone receptors. No increase in blood pressure has been observed in normotensive postmenopausal women using micronized progesterone,[4,62] and a slight decrease in blood pressure has been observed in initially hypertensive women.[64,65]

Unusually high doses of micronized progesterone (>600 mg/d) administered to pregnant women to avoid premature labor[83,84] have been suspected of increasing the risk for intrahepatic cholestasis during pregnancy in women who are genetically predisposed.[85,86] However, these doses are far higher than the doses recommended for any of the approved indications of micronized progesterone. Despite widespread use of micronized progesterone in Europe since 1980 (>500,000 current users in France), no specific side effects have been reported.[31]

CONCLUSIONS

The micronization of progesterone increases the efficiency of its oral absorption

and circumvents the more problematic and less desirable routes of delivery (eg, intramuscular, rectal, and vaginal). Gastrointestinal absorption is rapid as a result of micronization, which increases the amount of surface area of the steroid that comes in contact with the mucous membrane. Dispersion of the progesterone in oil also favors gastrointestinal absorption.[30]

Several pharmacokinetic studies have shown relatively consistent AUC, C_{max}, and t_{max} values.[31,33,36,37] AUC is directly related to the dose of orally administered micronized progesterone.[33] Progesterone concentrations measured in the endometrium during treatment are significantly higher than those measured in untreated controls, do not follow serum fluctuations during the day, and reach levels compatible with efficacy.[27]

Administration of micronized progesterone 300 mg once daily for 10 days is effective in inducing withdrawal bleeding in women who have been diagnosed with secondary amenorrhea. In one study,[29] after oral administration of micronized progesterone 300 mg, 90% (18/20) of patients experienced regular withdrawal bleeding, compared with 53% (10/19) and 24% (5/21) of those receiving micronized progesterone 200 mg and placebo, respectively. The proportion of patients experiencing withdrawal bleeding in the 300-mg group was significantly greater than in the placebo group ($P < 0.001$). Administration of micronized progesterone 300 mg/d for 10 days is as effective in treating endometrial hyperplasia in premenopausal women as are high doses of norethisterone, with fewer effects on lipid metabolism.

Administration of oral micronized progesterone as part of a regimen of HRT in postmenopausal women is effective in preventing estrogen-dependent endometrial stimulation. There is a choice of several regimens, depending on the patient's preference for remaining amenorrheic or experiencing the return of regular bleeding. Dosages of 300 mg/d for 10 days,[46,47] 200 mg/d for 12 to 14 days,[44–47,63,70] or 100 mg/d for 21 to 25 days[48,71,72] have all been shown to be effective.

The results of published clinical studies show minimal or no changes in lipid profile, blood pressure, or carbohydrate metabolism during treatment with oral micronized progesterone.[28] This safety profile contrasts with the reported negative effects of some synthetic progestins, including adverse effects on lipid metabolism and glucose tolerance. Several studies, including the 3-year prospective PEPI study,[4,28] have shown that oral micronized progesterone significantly improves metabolic tolerance compared with such progestins as MPA.[52,54,58]

Only minor adverse events have been reported in association with oral micronized progesterone therapy in clinical trials. Dizziness and sleepiness are the primary adverse reactions reported.[33] However, these side effects can be suppressed by administering micronized progesterone once daily at bedtime.[29] Oral micronized progesterone is therefore an effective and well-tolerated form of progestogen replacement in premenopausal and postmenopausal women.

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