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Antiproliferative effects of low-dose micronized progesterone*

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Objective: To study the pharmacodynamic effects of oral micronized P on endometrial maturation.

Design: This was a controlled, open, parallel group, pilot study.

Setting: The experiment was performed in an outpatient academic clinical research unit.

Patients: Twelve healthy, P-challenged, estrogen-primed, postmenopausal women participated in the study.

Interventions: Patients were given 300 mg micronized P daily (8:00 A.M.) or twice (8:00 A.M. and 4:00 P.M.) daily from study days 1 through 14 after estrogen priming for 30 days. Blood samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after the 8:00 A.M. dose on study day 1 and 14 and again at 8:00 and 9:30 A.M. on days 3 and 5 fasting, days 7 and 9 after a fatty meal, and day 11 after a high fiber meal. Endometrial biopsies were taken on day 1 and 14.

Main Outcome Measures: Progesterone concentrations were measured. Endometrial biopsies were studied for effects on histology, glycogen content of glands, ribosomal RNA, and nuclear estrogen receptors in glands, surface epithelium, and stroma.

Results: Day 1 and 14 P kinetics were similar for 8 hours. Dose-dependent increases in glandular glycogen, decrease in ribosomal RNA, and decrease in nuclear estrogen receptors were demonstrated.

Conclusions: Oral micronized P can induce antiproliferative changes in the human endometrium at doses lower than those required for transformation of the endometrium to a full secretory state. Fertil Steril 1996;65:323–31

Key Words: Antiproliferative, secretory, histomorphometric, progesterone, pharmacokinetics, pharmacodynamics, automated image analysis

As hormone replacement therapy (HRT) and assisted reproductive technologies (ART) assume greater importance in health care it is evident that an effective, convenient method to give natural P is needed. Progesterone is important in HRT to prevent hyperplastic-malignant changes in the endometrium stimulated by estrogen and is essential in the preparation of the endometrium for pregnancy and for the maintenance of early pregnancy.

Synthetic progestins may be problematic for HRT and ART despite a long history of safety and efficacy in oral contraceptives. The androgenic activity of

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synthetic progestogen may partially negate the beneficial effects of estrogen on lipoprotein metabolism and theoretically could have an adverse affect on cardiovascular health. The use of synthetic progestins during the luteal phase and in pregnancy may be unwise because of the threat of teratogenic effects and also may impose a heavier metabolic burden on the liver. Natural P does not have the androgenic activity that might compromise lipoprotein metabolism and certainly cannot be regarded as teratogenic given its essential contribution to pregnancy.

Natural P is delivered efficiently by injection or vaginal suppository (1–3) but these methods are inconvenient. Injections are painful and usually must be administered by trained medical personnel. Vaginal suppositories are difficult to place high in the vagina, may be aesthetically difficult or impossible for many individuals or cultures, and may lead to vaginal discharge. For long-term use these inconveniences are considerable. Oral intake is probably the most easily controlled and convenient method of drug delivery.

Oral natural P is metabolized extensively and rapidly in the intestine and liver, resulting in low bioavailability. Newer formulation technology uses micronized P, which enhances the bioavailability of natural P. This has stimulated increased interest in the development of oral dosage forms of P (1, 4–13).

Conversion of endometrium to a full secretory state is difficult with oral P even at a dose of 300 mg daily for 10 to 14 days (3, 12, 13). Higher doses of P also have sedative effects that may limit its use. Oral P is not used to prevent endometrial overgrowth that is the result of unopposed estrogen therapy because of the belief that secretory conversion of the endometrium is necessary for protection. The literature, however, has several studies that report no evidence of endometrial hyperplasia after long-term use of lower doses of oral P (14–16).

We designed this study to explore the differential threshold of the biologic endpoints of antiproliferation and secretory conversion of the endometrium by different regimens of oral micronized P (300 mg/d and 300 mg twice per day for 14 days). The pharmacodynamic effect was examined histologically (hematoxylin and eosin [H & E]) and immunohistochemically by measuring changes in glycogen content of endometrial glands, ribosomal RNA, and nuclear estrogen receptor content in endometrial surface epithelium, glands, and stroma. We examined the pharmacokinetics of P on days 1 and 14 to learn if there might be accumulation of P over this short period. Interval trough and peak measurements of P were performed to demonstrate nadir levels of drug and the effect of meals on P absorption and metabolism.

MATERIALS AND METHODS

Twelve postmenopausal females (no menses for >6 months and FSH > 40 mIU/mL; conversion factor to SI unit, 1.00), in good health and with intact uteri were enrolled in the study. Their ages ranged from 46 to 64 years (median 57.5 years) and all subjects' body weights were within ±20% of their ideal weight (17). Each subject had a thorough physical examination after a comprehensive medical history to ensure well being. Additionally, each subject had a Papanicolaou smear, screening blood chemistries (CBS 22; SmithKline Beecham Clinical Laboratories, Collegeville, PA), complete blood count (local laboratory), urinalysis, E_2, and FSH (Hormone Core Laboratory, The Jones Institute, Norfolk, Virginia). The Institutional Review Board of the Eastern Virginia Medical School approved the protocol. We obtained written informed consent from all participants before enrollment, and conducted the study from August 14 to November 20, 1992. Zetachron (State College, PA) supplied 300 mg oral micronized P tablets (66H0901) solubilized in polyethylene glycol at approximately 47% drug to excipient, in labeled containers of 14 or 28 tablets. Each subject was assigned to daily (8:00 A.M.) or twice daily (8:00 A.M. and 4:00 P.M.) treatment. A progestin challenge test was performed on each subject with 14 days of 10 mg/d medroxyprogestone acetate (MPA). Within 1 week after the last tablet of MPA, each subject took 1 mg of micronized E_2/d and continued through the remainder of the study. After approximately 30 days of E_2 treatment, women returned to the clinic in the fasting state (clear liquids only from at least 4:00 A.M.) for an endometrial biopsy and a baseline determination of serum P (day 1). At 8:00 A.M., the first P tablet was given with water. Blood samples (10 mL) for P were drawn again at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after dosing. This constituted the "day 1 pharmacokinetics." The subjects remained fasting except for clear liquids until 10:00 A.M. and then were allowed to resume a normal diet.

The subjects returned at 7:00 A.M. on days 3, 5, 7, 9, and 11 before medication in the fasting state. On days 3 and 5, fasting subjects took the P tablets at 8:00 A.M. after a blood sample was taken. They remained fasting until 1.5 hours later when another blood sample was taken. This constituted the trough and "peak" determinations in the fasting state. On days 7 and 9 after a baseline blood sample for P, the subjects were given their study drug immediately before eating a fatty meal. This meal (approximately 510 calories) was two eggs, toast (two slices with butter and/or jam), citrus juice (8 fluid ounces, or 204.56 mL, conversion factor to SI unit, 25.57 mL), and coffee or tea. Blood was taken again 1.5 hours

later. These trough and peak measurements demonstrate the effect of a fatty meal on P absorption. On day 11, the same procedures were performed but with a high-fiber meal (approximately 440 calories) of all bran (8 avoirdupois ounces, conversion factor to SI unit, 226.8×10^{-3} kg), milk, dry muffin, and coffee or tea.

On day 14, the subjects returned fasting for a follow-up endometrial biopsy and day 14 pharmacokinetics. The blood samples were taken on the same schedule as day 1.

Each subject was given a diary card to record bleeding, spotting, tablets taken, and any adverse experiences. An interim history and final physical examination were done 1 week after the subject completed the blood draws and final endometrial biopsy. Serum was frozen at −20°C and held for analysis (RIA) of P and E_2 at the completion of the study.

Serum E_2 (Pantex-Santa Monica, CA) and P (ICBN, Los Angeles, CA) concentrations were determined with commercial RIA kits. The E_2 assay had a sensitivity of 10 pg/mL (conversion factor to SI unit, 3.671) and intra-assay and interassay coefficients of variation of <7.6% and 9.1%, respectively. The P assay had a sensitivity of 0.2 ng/mL (conversion factor to SI unit, 3.180) and intra-assay and interassay coefficients of variation of <7.6% and 13.1%, respectively.

Endometrial biopsies were obtained from each subject before the morning dose of P on days 1 and 14. Endometrial biopsies were performed under aseptic conditions with topical endocervical anesthesia (2% Xylocaine gel; Astra USA, Inc., Westboro, MA) using Pipelle Endometrial Suction Curettes (Unimar, Wilton, CT). All endometrial biopsies were placed in 10% neutral buffered Formalin and analyzed at the Structural Research Center (Mobile, AL).

The tissues were dehydrated in a series of graded ethyl alcohols, cleared in xylene, embedded in paraffin, and sectioned at 5-μm thickness. Some sections were stained with H & E and were used to classify the biopsies. The remaining sections were used to demonstrate glycogen, ribosomal RNA, and nuclear estrogen receptors as described.

Glycogen was shown by the periodic acid-Schiff (PAS) technique. Glycogen was PAS-positive and diastase-labile (18). The area occupied by glycogen per 100 μm^2 of glandular epithelial cells was determined by automated image analysis with Bioscan Optimas (Bioscan, Edmonds, WA).

Ribonucleic acid was demonstrated by the pyronin method. Purified pyronin in acetate buffer was purchased from Rowley Biochemical Institute (Rowley, MA). Details of the procedure have been published (19, 20). Cytoplasmic (ribosomal) RNA was quantified as area of positive stain per 100 μm^2 of glandular epithelial cells by automated image analysis with Bioscan Optimas.

Nuclear estrogen receptors of epithelial cells and stromal cells were demonstrated by the Abbott ER-ICA Monoclonal Immunocytochemical Assay (Abbott Laboratories, Chicago, IL) (21, 22). Numbers of positive and negative nuclei in epithelial cells (glandular and surface) plus stromal cells were determined using automated image analysis with Bioscan Optimas. Rates of positivity were determined for epithelial cells, and positive cells per 200 μm^2 were evaluated for stromal cells.

All study data were entered onto case record forms. Elimination half-life ($T_{\frac{1}{2}}$ = 4, hours), maximum serum concentration (Cmax, ng/mL), time to Cmax (Tmax, hours), and area under the concentration-time curve (AUC, ng/h per mL for 0 to 8 hours) were estimated for days 1 and 14. Means ± SD of serum P at scheduled times were calculated for both regimens and compared by independent *t*-test (SPSS 4.0; SPSS Inc., Chicago, IL). The glycogen and RNA content of endometrial gland cells, the nuclear estrogen receptor content of superficial and gland epithelium, and stromal cells were compared by independent *t*-test for each regimen before and after treatment and between regimens.

RESULTS

There were no significant differences between the two groups in the matching variables of age, weight, height, or duration of menopause. The age of the subjects was 55.3 ± 2.2 and 59.5 ± 1.9 years (mean ± SEM); their weights were 158.7 ± 11.0 and 143.0 ± 11.2 lbs (conversion factor to SI unit, 453.59×10^{-3} kg), respectively, for the once per day versus the twice per day regimen.

For day 1, elimination half-life was approximately 2 hours by visual estimate. Tmax was 2.0 ± 1.6 hours (mean ± SD). Cmax was 62.7 ± 67.8 ng/mL (mean ± SD). The AUC estimated by the trapezoidal method was 164.4 ng/h per mL (conversion factor to SI units, 3.180). The pharmacokinetics for day 14 (once per day regimen) were not significantly different from those of day 1 (Fig. 1). There is minimal accumulation of drug with once per day dosing.

Nadir levels of serum P during days 3 through 14 were increased significantly compared with day 1 ($P < 0.05$). However, the increase of nadir levels did not meet statistical significance among matches from days 3 to 14. Women in the twice per day group showed five times higher nadir P levels (7.1 ± 4.7 versus 1.4 ± 1.8 ng/mL; mean ± SD, $P < 0.001$). Note, however, that the interval for subjects since last dose was only 16 hours for twice per day dosing versus 24 hours for the once per day dosing. Con-

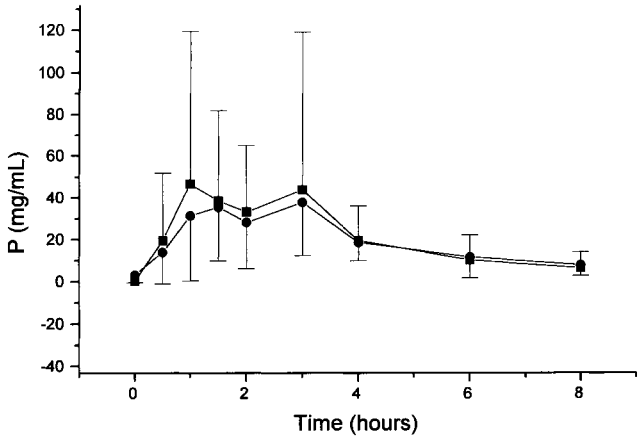

Figure 1 Serum P levels for 8 hours after 300-mg oral micronized P intake on day 1 (n = 12) (■, mean + SD) and day 14 (n = 6) (●, mean − SD) once per day regimen. Conversion factor to SI unit, 3.180.

sumption of either a high-fat or high-fiber diet dramatically increased absorption of P (Fig. 2). Fatty meals increased serum P by approximately 4.6 times and high-fiber meals increased serum P by approximately 3.2 times when compared with fasting.

The average of all E_2 levels for early morning and 1.5 hours after P administration was 69 pg/mL (conversion factor for SI units, 3.671). Only 5 of 143 samples (3.5%) had a concentration of E_2 that fell below 30 pg/mL. Most subjects took their E_2 at bedtime, but this was essentially a random sampling of E_2 levels. This indicates that all subjects had relatively good compliance and sustained reasonable "follicular" levels of E_2 throughout the study.

Endometrial samples from all women were adequate to evaluate endometrial histology. Pretherapy endometrial biopsies in both groups showed moderate to markedly proliferative endometrium, and one subject had simple endometrial hyperplasia without atypia. This finding was unexpected because a "medical curettage" had been done a month earlier. This subject had no further evidence of hyperplasia on subsequent biopsies after once per day treatment for 14 days. The endometria of the once per day group showed incomplete secretory conversion in the second biopsy. The epithelial cells showed irregular vacuolization, and predecidual reactions were weak or absent. In contrast, five of six subjects on the twice per day regimen had full secretory conversion with suppression of mitotic activity and presence of predecidual reaction. The sixth patient had an incomplete secretory pattern similar to the once per day group. She was excluded from histomorphometric evaluation because of insufficient tissue for definitive evaluation.

The glycogen content of endometrial glandular cells (area of positive staining per 100 μm^2) was significantly increased in both groups, 124% (mean, $P < 0.01$) and 291% (mean, $P < 0.001$) for once and twice per day dosing, respectively. The difference between the groups also was significant (Table 1; $P < 0.001$)

The ribosomal RNA content of endometrial glandular cells (area of positive staining per 100 μm^2) was decreased in both groups; 50% (mean, $P < 0.05$) and 73% (mean, $P < 0.001$), respectively. The difference between the groups also was significant (Table 1; $P < 0.05$).

Two subjects in each group could not be evaluated for nuclear estrogen receptors in the superficial epithelium and stromal cells because of insufficient tissue. Generally, the nuclear estrogen receptors decreased significantly in every region of the endometrium in both groups. However, nuclear estrogen receptor decreases in the stroma of the once per day group did not reach significance possibly because of insufficient sample. Between the two regimens, an approximately twofold difference was present in the glandular ($P < 0.001$) and stromal cells ($P = 0.06$). The surface epithelia showed essentially equal percent decreases in both regimens (Table 1). One subject in each group had tissue insufficient for immunohistochemical evaluations. Two other subjects in each group had tissue samples that were insufficient for complete evaluation at all parameters.

A dose response to P in estrogen primed and maintained endometrium therefore was seen, especially in glycogen increase, RNA content decrease, and decrease of nuclear estrogen receptors in glandular epithelial and stromal cells. (One subject took her medi-

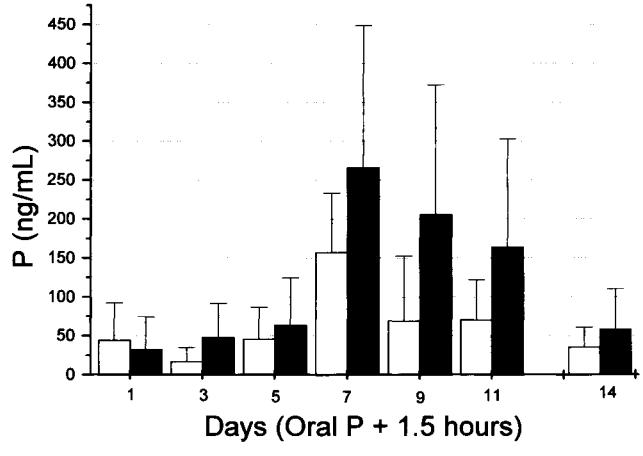

Figure 2 Serum P levels at 1.5 hours after 300-mg oral micronized P in fasting state (days 1, 3, 5, and 14) and postprandial states on days 7 and 9 (fatty meal) and day 11 (high-fiber meal). Mean of each day's values are presented for daily (□; n = 6) and twice per day (■; n = 6) regimens. Conversion factor to SI unit, 3.180.

Table 1 Endometrium: Comparison of Immunohistomorphometric Parameters

Group†	Glandular glycogen (n = 5)	Glandular RNA (n = 5)	Nuclear estrogen receptors		
			Gland cells (n = 5)	Surface cells (n = 4)	Stromal cells (n = 4)
	% increase	*% decrease*		*% decrease*	
1	124 ± 19‡	50 ± 6§	33 ± 2‖	48 ± 7§	49 ± 11¶
2	291 ± 26‖	73 ± 2‖	87 ± 4‖	48 ± 6‡	89 ± 2§

* Values are means ± SD.
† Group 1, once per day regimen; group 2, twice per day regimen.
‡ Significantly different before and after treatment, $P < 0.01$.
§ Significantly different before and after treatment, $P < 0.05$.
‖ Significantly different before and after treatment, $P < 0.001$.
¶ Not significantly different before and after treatment.

cation only when she came to the clinic for blood draws. Her nadir P concentrations were below detectable limits on each visit except 48 hours after the fatty meals [days 9 and 11] when P concentrations were 0.68 and 0.65 ng/mL, respectively. Her responses were not different from those of the subjects who took P once every day.) Although there was a substantial decrease in nuclear estrogen receptors in surface epithelial cells that line the uterine cavity, no dose response could be demonstrated. Representative micrographs by each staining technique are shown in Figures 3 and 4.

No subject experienced withdrawal bleeding after the initial 10-day exposure to 10 mg/d MPA, indicating that they were all relatively estrogen deficient. Eight of 12 subjects had breakthrough bleeding or spotting during the study and all subjects experienced withdrawal bleeding after P. The bleeding patterns almost certainly were confounded by the endometrial biopsies.

Eleven of 12 subjects reported sleepiness with medication at some time during the study, particularly after taking medication with a meal. Three subjects reported mild dizziness, and another five women complained of moderate or severe dizziness with or without staggering and giddiness at some time during the study. These symptoms were new to all of the subjects and were noticed mainly after food or coffee but disappeared completely after 2 to 3 hours of onset. No other significant side effects appeared.

DISCUSSION

The 300 mg formulation of micronized P used in this study provides blood levels and kinetic patterns similar to previously studied oral formulations (1, 2). Because of rapid absorption and metabolic clearance, we observed maximal plasma P levels 1 to 3 hours after administration of this dose regardless of the number of doses per day or the day of observation (Fig. 1). The kinetic profiles demonstrate that both regimens provided equivalent serum P levels of 6 to 7 ng/mL (19 to 23 nmol/L) 8 hours after ingestion. However, the twice a day regimen produced 4.5 times higher nadir levels. These higher nadir levels may reflect the shorter interval between doses in this group. The elimination half-life of oral micronized P is short compared with IM or intravaginal administration (1, 2), so multiple daily oral dosing may be required for successful decidualization of the endometrium.

We standardized the timing and type of meals to further objectify the impact of food intake on P absorption (Fig. 2). Food may influence drug absorption by increasing splanchnic blood flow and gastrointestinal secretion or by reducing gastric emptying time. Food also may alter the metabolism of P by inducing liver enzymes that compete for breakdown of the drug, thus prolonging the serum half life. In this study, consumption of a 500-calorie high-fat meal increased serum P levels approximately four times and a high-fiber meal increased it approximately three times. Fat may bind P, take it directly into the lymphatics, and thus protect it from liver metabolism thus increasing its availability and prolonging its elimination half-life (23). These findings are in agreement with Simon et al. (1) who found Cmax increases of approximately two times with concomitant food ingestion. Our subjects with very high P levels during the first 2 hours of the kinetic evaluations may have ingested food or coffee. We feel that diet is a major factor in the absorption of P and may indeed aggravate the sedative hypnotic symptoms seen. Delayed absorption of P in some of the subjects could have been due to a decrease in splanchnic blood flow secondary to the endometrial biopsy. None of these subjects experienced vasovagal reactions that were detectable however. These subjects also may have needed the boost of the meal given at 10:00 A.M. to enhance absorption. In contrast, meals decrease circulating steady state P levels by increasing metabolic clearance rate (24).

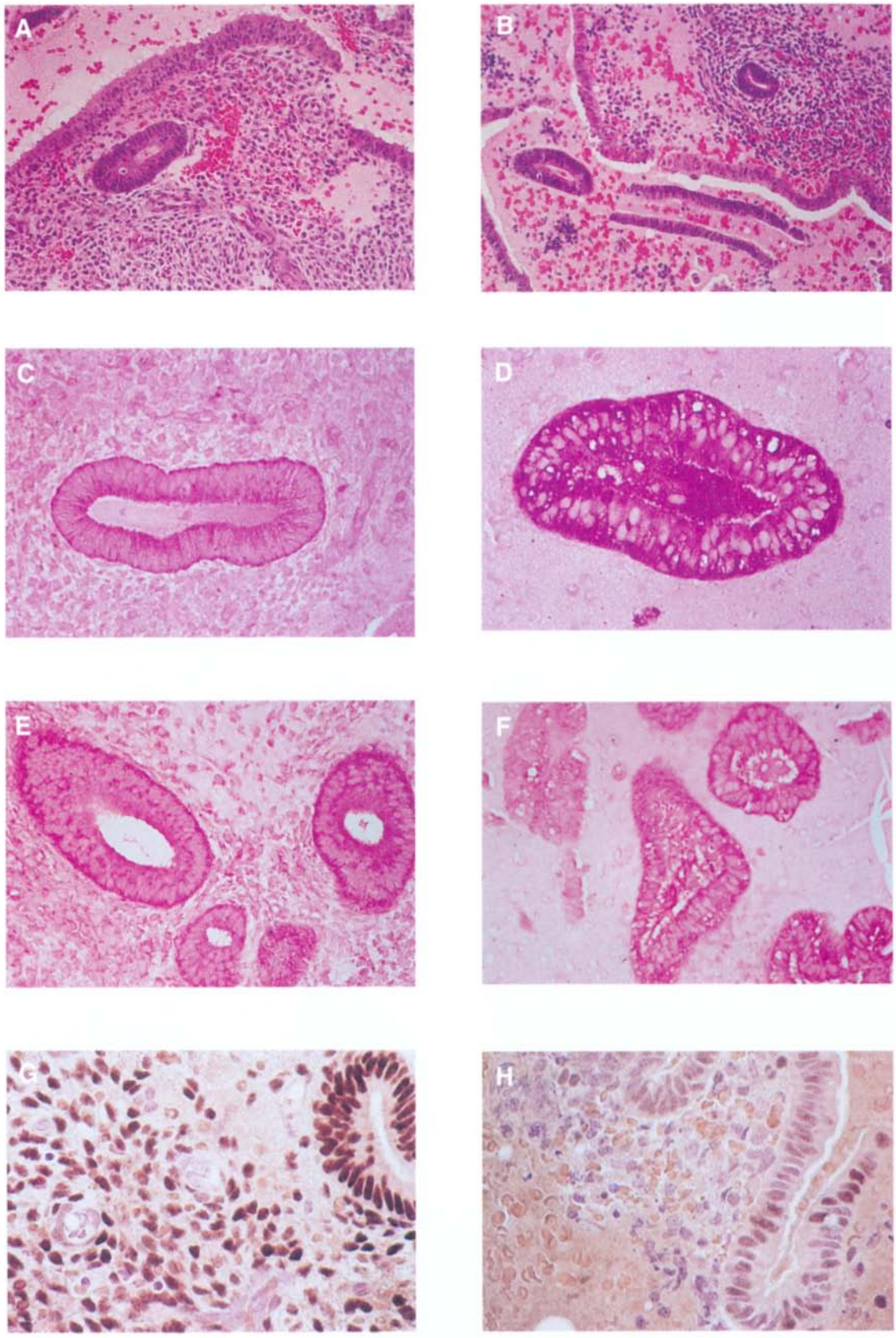

Figure 3 Photomicrographs of endometrium before (*left*) and after (*right*) once per day regimen of 300-mg oral micronized P. (**A** and **B**), H & E (×50); (**C** and **D**), glandular glycogen by the PAS method (×440); (**E** and **F**), ribosomal RNA by the pyronin method (×440); (**G** and **H**), nuclear estrogen receptors by monoclonal antibody immunohistochemistry (×440) (See Table 1 for statistics).

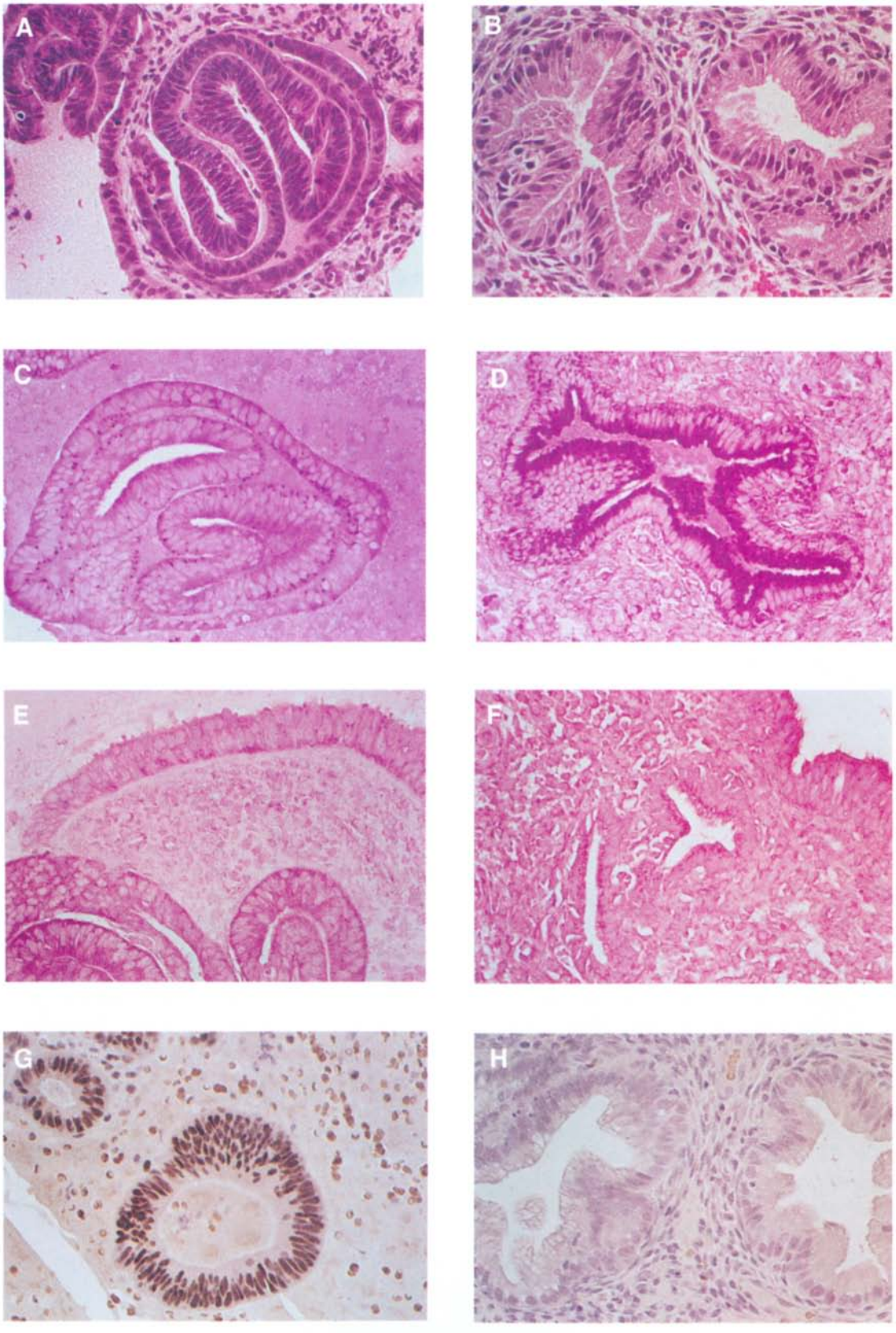

Figure 4 Photomicrographs of endometrium before (*left*) and after (*right*) twice per day regimen of 300-mg oral micronized P. (**A** and **B**), H & E (×50); (**C** and **D**), glandular glycogen by the PAS method (×440); (**E** and **F**), ribosomal RNA by the pyronin method (×440); (**G** and **H**), nuclear estrogen receptors by monoclonal antibody immunohistochemistry (×440) (See Table 1 for statistics).

Because Hargrove et al. (6) demonstrated that the extent of absorption and bioavailability of oral P could be influenced significantly by both particle size and vehicle for delivery, micronization and delivery in lipid vehicles have been studied to enhance P delivery by mouth. Additionally, increases in dose and frequent dosing have been used. Peak mean serum levels are dose dependent under fasting conditions (1) and 200 to 300 mg doses meet or exceed the mid-luteal P levels of spontaneous ovulatory cycles at least with regard to Cmax (3, 12, 13). Oral P still is not appreciated as a reliable clinical implement particularly because these daily doses failed to demonstrate full secretory maturation of estrogenized endometrium (2–4, 6–10). The incomplete secretory conversion raises a fundamental question as to whether or not oral P can protect the endometrium from hyperplastic lesions.

In this study, none of the estrogen-primed endometrium exposed to 300 mg P daily for 14 days showed secretory conversion. This confirms previous reports that showed 300 mg P per day will not produce full secretory endometrium (3, 12, 13). In contrast, all but one of the subjects who were given 300 mg P twice per day had full secretory endometrium. The immunohistochemical histomorphometric analyses of glycogen, ribosomal RNA, and nuclear estrogen receptors indicate that complete secretory conversion may not be necessary to prevent the proliferative effects of estrogen. Even the subject who took 300 mg P every other day demonstrated increases in glycogen and decreases in mitotic activity that were not significantly different from the response of the subjects who took 300 mg daily. Therefore, a "no response dose" for antiproliferative activity was not identified. A dose response was identified in all parameters between the once per day versus twice per day regimens with the exception of the reduction of estrogen receptors in surface epithelium. In that instance, the minimal dose given induced maximal response.

Two previous long-term studies that used 200 or 300 mg oral P for 1 year (14) and 5 years (15) reported no evidence of endometrial hyperplasia or adenocarcinoma. In the 1-year study, endometrial histology showed quiescence and atrophy after continuous micronized E_2 (0.7 to 1.05 mg/d) and P (200 to 300 mg/d). Our histomorphometric results are consistent with Lane et al.'s (13) biochemical results, which showed a dose response of oral P with the suppression of DNA synthesis and nuclear estrogen receptors. They also showed induction of E_2 17-β-dehydrogenase activity with small doses of P. Moyer et al. (15) assert that endometrial secretory transformation requires larger doses of P but that secretory conversion does not provide additional benefit for the prevention of hyperplasia. Furthermore, higher doses of P are rather likely to induce withdrawal bleeding, which may not be acceptable to most postmenopausal HRT users.

Our findings support previous studies that used ≥600 mg oral micronized P per day for luteal phase support after IVF (8) or to synchronize the endometrium in ovum donation cycles (9). The latter study reported that pregnancies were established in two patients with ovarian failure with oral micronized E_2 and P; one case with 400 mg P three times per day and the other with 200 mg four times per day, after GIFT or transfer of donated oocytes. Frishman et al. (Frishman GN, Klock SC, Luciano AA, Nulsen JC, abstract) demonstrated that 200 mg of oral P three times per day could correct luteal phase defects more efficiently than IM or intravaginal P. In this study, 300 mg P twice per day maintained serum nadir levels at >7.2 ng/mL (22.9 nmol/L), which are comparable to mean P levels of 7 to 12 ng/mL (22.3 to 38.2 nmol/L) achieved by vaginal administration of 100 or 200 mg three times per day. The 4.5-fold difference in nadir levels between the two regimens may be a clue to understanding why the twice per day dosing induced full secretory conversion and the once per day dosing failed.

The question of sedative hypnotic effects of oral P remains, especially with high doses orally. It is known that high levels of P and its metabolites have short-lived anesthetic and hypnotic effects (25). Unfortunately, it is impossible to substantiate this side effect in our study because we did not have placebo controls. Mild dizziness and sleepiness were clustered mainly after meals and were self-limiting. The potential effect of sleepiness could be neutralized if the drug were taken at bedtime.

This study demonstrates a dissociative endometrial effect between the two regimens of oral micronized P. Antimitotic effects are seen with 300 mg/d oral micronized P (and even 300 mg "every other day"). Decidualization requires an oral dose of ≥300 mg twice per day (or 200 mg three times per day) (26). Sustained low concentrations probably are sufficient to inhibit endometrial overgrowth, hyperplasia, and/or cancer. In conclusion, our study supports the view that, with oral P, prudent selection of drug regimen can tailor endometrial responses to individual needs. The responses range from significant reduction of mitotic activity (15) to production of a full secretory endometrium capable of supporting embryo implantation (9). Further studies to determine the lowest effective dose of P needed to prevent endometrial overgrowth from unopposed estrogen are needed. For long-term therapy (HRT), the use of low-dose oral P would have many advantages, including the reduction of synthetic progestin side effects such

as irritability, scheduled and unscheduled bleeding, and the effects on lipoprotein metabolism. The hypnotic and sedative effects of oral P can be minimized by dose and time adjustments.

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