Effects of raloxifene hydrochloride on the endometrium of postmenopausal women

Susan M. Boss, BS,[a] William J. Huster, PhD,[a] Julie A. Neild, MTSC,[a] Michael D. Glant, MD,[b] Carol C. Eisenhut, MD,[b] and Michael W. Draper, MD, PhD[a]

Indianapolis, Indiana

OBJECTIVE: We evaluated subtle endometrial morphologic changes in postmenopausal women assigned to placebo, raloxifene hydrochloride 200 or 600 mg/day, or conjugated estrogens (Premarin 0.625 mg/day) according to a new estrogenicity scoring system. Raloxifene, a new selective estrogen receptor modulator, was not expected to stimulate the endometrium.

STUDY DESIGN: Baseline and end point endometrial biopsies were performed during this double-blind, placebo-controlled 8-week study. A scoring system that was based on standard glandular and stromal morphologic criteria was used to quantitate estrogen-induced effects. Baseline, end point, and baseline–to–end point changes were analyzed for treatment differences.

RESULTS: Treatment groups were similar at baseline with most women showing no estrogenic effects. At end point, statistically significant moderate and marked estrogenic effects were noted in 77% of estrogen-treated women versus 15% of placebo-treated women versus 0% of raloxifene-treated women.

CONCLUSIONS: As expected, estrogen treatment stimulated postmenopausal endometrium. In contrast, raloxifene did not induce histopathologic evidence of endometrial stimulation in healthy postmenopausal women. (Am J Obstet Gynecol 1997;177:1458-64.)

Key words: Raloxifene, endometrium, postmenopausal women, estrogen

An increasing number of postmenopausal women are being exposed to exogenous estrogen. Estrogen replacement is often prescribed for relief of menopausal and postmenopausal symptoms related to decreasing circulating estrogen and may have added benefits in preventing both osteoporotic fractures and atherosclerotic coronary artery disease.[1] Some postmenopausal women may be treated with tamoxifen, a mixed estrogen agonist and antagonist. Tamoxifen has become the standard for hormonal treatment of breast cancer. However, long-term exposure to unopposed estrogen or tamoxifen may increase the risk of endometrial cancer.[2-6]

Preclinical data indicate that raloxifene hydrochloride (Eli Lilly and Company, Indianapolis) may provide the therapeutic effects of estrogen without the stimulatory effects on the endometrium or on other reproductive tissues. Raloxifene (structural formula of [6-hydroxy-2(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]-phenyl] methanone hydrochloride and previously studied under the name keoxifene) is a compound derived from a benzothiophene series of antiestrogens and can be classified as a selective estrogen receptor modulator.[7-9] In an ovariectomized rat model raloxifene displays beneficial bone and serum lipid effects without significant uterine stimulation.[7] Raloxifene blocks uterotropic action in response to estrogen in the rat[7] and has an estrogen-comparable binding affinity for estrogen receptors in the uterus and breast.[7, 10]

On the basis of these preclinical studies, no stimulatory effects of raloxifene were anticipated in the endometrium of postmenopausal women. However, no scoring system had been devised that allowed classification of the full spectrum of estrogen-like effects that occur in the postmenopausal uterus. Standard descriptive pathologic diagnoses of the endometrium are based on *Blaustein's Pathology of the Female Genital Tract.*[11] However, this classification lacks discrete descriptive criteria for subclassifying within the proliferative category. To determine the effects of raloxifene on the postmenopausal uterus, quantifying subtle estrogenic effects on the endometrium was vital.

The purpose of this manuscript is to discuss the effects of raloxifene on the endometrium of healthy postmenopausal women participating in an 8-week clinical study. A new estrogenicity scoring system was developed for this study to quantify subtle morphologic changes in the

From the Lilly Research Laboratories, Eli Lilly and Company,[a] and the Diagnostic Cytology Laboratory, Inc.[b]
Supported by Eli Lilly and Company.
Presented in part at the Forty-third Annual Meeting of the Society for Gynecologic Investigation, Philadelphia, Pennsylvania, March 20-23, 1996, and at the Fall Annual Meeting of the American Society of Clinical Pathologists, New Orleans, Louisiana, September 16-22, 1995.
Received for publication October 29, 1996; revised June 10, 1997; accepted June 24, 1997.
Reprint requests: Michael W. Draper, MD, PhD, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center 2244, Indianapolis, IN 46285.

0002-9378/97 $5.00 + 0 ***6/1/84240***

endometrium. Healthy postmenopausal women were assigned to either placebo, raloxifene hydrochloride 200 or 600 mg/day, or conjugated estrogens (Premarin [Wyeth-Ayerst Laboratories, Philadelphia] 0.625 mg/day) and had endometrial biopsies performed at baseline and week 8. Biopsies were evaluated with an estrogenicity scoring system that was based on standard criteria of estrogen-induced proliferation in typical postmenopausal endometrium.[12-15] The methodologic development of the grading system is presented in a separate manuscript (Glant M, Eisenhut CC, Boss SM, Huster WJ, Neild JA, Draper MW. Unpublished observations.).

Material and methods

Study objectives. The primary objectives of this study were to evaluate the short-term effects of raloxifene compared with estrogen and placebo on biochemical markers of bone and lipid metabolism in healthy, postmenopausal women. A secondary objective was to evaluate the effects of raloxifene compared with estrogen and placebo on the endometrium of healthy postmenopausal women. The results of the effects of raloxifene on biochemical markers of bone turnover and lipids are presented elsewhere.[16]

Study population. A total of 251 healthy postmenopausal women were recruited from the community in 11 study centers throughout the United States.[16] After thorough explanation of the study, which had been approved by the appropriate institutional review boards, the subjects were invited to sign a written informed consent document.

Subjects were eligible for the study if they were in good health and free of any serious acute or chronic medical condition, were aged 45 to 60 years, had an intact uterus, and had been postmenopausal for >6 months but <6 years before beginning the treatment phase of the study. The date of menopause was defined as the subject's recall of the date of her last menstrual period. Postmenopausal status was confirmed by postmenopausal levels of serum estradiol (<120 pmol/L) and follicle-stimulating hormone (FSH) (>30 IU/L).

The following subjects were ineligible for the study: women who had been treated with estrogen within the 3 months before the study or who had ever been treated with fluoride, calcitonin, or bisphosphonate; women who were not eligible for therapy according to the Premarin package insert; women with clinically significant endometrial abnormalities, a history of cancer within the previous 5 years, any history of breast cancer, or undiagnosed abnormal uterine bleeding; or women with active thrombophlebitis or thromboembolic disorders or a history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use.

Study design. This was a phase 2, randomized, controlled, double-blind study consisting of three phases[16]: a screening phase, an 8-week double-blind treatment phase, and a 12-day posttreatment phase. Pipelle (Unimar, Wilton, Conn.) biopsy specimens were obtained at baseline and after 8 weeks of treatment.

Eligible women were randomized within the clinical centers to one of four treatment groups during the double-blind treatment phase, according to a randomization list generated and maintained by personnel at Eli Lilly and Company who were not involved in study management, as follows: placebo, raloxifene hydrochloride 200 or 600 mg/day, or unopposed conjugated estrogens (Premarin) 0.625 mg/day. At baseline and after 8 weeks of treatment, serum estradiol and FSH concentrations were measured in all women. Once treatment was completed, each subject received medroxyprogesterone acetate (Provera [The Upjohn Company, Kalamazoo, Mich.]) 5 mg/day for 12 days. Throughout the entire study (screening phase through posttreatment phase) all subjects received 520 mg/day of elemental calcium in the form of oral calcium carbonate (Eli Lilly). All study medications were taken once daily in the morning independent of meals.

Endometrial biopsy collection and evaluation. A single uterine biopsy specimen was obtained from each subject at baseline (week 0) and after 8 weeks of treatment with a Pipelle catheter.[17, 18] All tissue specimens were placed in 10% buffered formalin for processing at a central laboratory. Specimens were stained with hematoxylin and eosin, then examined for color, texture, consistency, and volume before being processed into paraffin blocks for histologic examination. A descriptive diagnosis of the prepared tissue specimens was made immediately by one of two pathologists and reported to the enrolling physician, so that only women with histologically normal uterine tissue were included in the study.

An estrogenicity scoring system that was based on standard morphologic criteria (shown in Tables IA and IB) was used to quantitate estrogen-induced effects and identify subtle proliferative changes in the endometrium[19] (a full description of the system and its development is included in the unpublished observations of Glant et al.). Individual quantifiable morphologic features were considered because the endometrial effects of raloxifene in humans were undefined, and all women enrolled in the study were clinically and biologically postmenopausal. Evaluation of biopsy specimens was blinded to treatment assignment but not to temporal assignment (i.e., pathologists only had access to the date the specimen was obtained). Each sample was graded independently by both pathologist coinvestigators (M.D.G., C.C.E.) for specimen adequacy and glandular and stromal morphologic features.

Tables IA and IB summarize the estrogenicity scoring system. Briefly, scores for the individual glandular and

Table IA. Estrogenicity scoring system—Step 1: Score individual biopsy specimens according to eight morphologic features

Morphologic feature	*None (0)*	*Limited (1)*	*Higher (2)*
Glandular effects			
Shape	Small, tubular, straight	Open, straight	Open or cystic, tortuous
Nuclear/cytoplasmic ratio	Very high (>75%)	Moderate (75%-50%)	Low (<50%)
Pseudostratification	None	Limited	Diffuse
Mitoses	None	Rare	Scattered to many
Stromal effects			
Density	Compact or fibrous	Loosely cellular	Edematous
Mitoses	None	Rare	Few to many
Other effects			
Metaplasias*	None	Rare	Few to many
Tissue volume	Disrupted or scant intact	Moderate—Much being intact	Abundant—Intact

*Metaplasia includes tubular, eosinophilic, and squamous type.

Table IB. Estrogenicity scoring system—Step 2: Total morphologic feature scores and assign estrogen effect grade

Total score	*Estrogen effect grade*	*Description*
0-3	0	Typical postmenopausal endometrium with little or no estrogenic effect
4-6	1	Definite but limited estrogenic effect
7-10	2	Significant estrogenic effect
>10	3	Marked estrogenic effect

stromal or other morphologic features formed the basis of the scoring system. These individual scores were then combined for a total score for each sample, and finally, an estrogen effect grade was assigned to the sample on the basis of the total score. Estrogen effect grades ranged from 0, indicating little or no estrogenic effect typical of postmenopausal endometrium, to 3, indicating a marked estrogenic effect typical of proliferative endometrium. This article focuses on estrogen effect grade results. The companion manuscript (Glant et al. Unpublished observations.) compares the estrogenicity scoring system with descriptive diagnostic categories similar to those presented in the textbook *Blaustein's Pathology of the Female Genital Tract.*[11]

Statistical methods. Sample size and power calculations were based on two primary outcomes, osteocalcin and urinary hydroxyproline, which are biochemical markers of bone metabolism.[16] For the secondary outcome, the estrogen effect grade, the observed power was >80% to detect a treatment difference of ≥28% on the incidence of estrogen effect grades of 1, 2, or 3 versus the placebo incidence of 26% at end point.

Specimen adequacy was evaluated for between-treatment differences at baseline and end point with the χ^2 test and for within-treatment differences with McNemar's test.

Statistical analyses were performed on three indexes for each biopsy specimen: the estrogen effect grade, the glandular morphology score, and the stromal morphology score. Baseline and end point values were analyzed for treatment differences with Cochran–Mantel-Haenszel statistical techniques with an adjustment for investigator effects.[20] To correct the multiple-treatment comparisons, pairwise-treatment comparisons between each active treatment and placebo were performed only when the overall treatment difference was statistically significant (Fisher's protected least-significant-difference rule).[21]

Statistical significance was defined as $p < 0.05$, two-sided test.

Results

Study population. Of the 251 women enrolled, 208 (83%) had adequate biopsy samples at both baseline and end point. These 208 women form the population for this article. Mean baseline demographic characteristics, time since last menstrual period, and estradiol and FSH concentrations for these 208 postmenopausal women did not differ significantly among the four treatment groups (Table II). These results were similar to those for the entire study population of 251 women.[16]

Specimen adequacy. Forty-three women with biopsy specimens having no endometrial tissue at baseline (16 women), end point (16 women), or both time points (11 women) were excluded from analysis; these women were distributed evenly among the four treatment groups. Biopsy specimens that contained only surface epithelium but no intact glands or stroma were assigned an estrogen effect grade of 0. The treatment groups were similar at baseline in the occurrence of biopsy specimens that were assigned an estrogen effect grade of 0. Within each of the three active treatment groups (but not the placebo treatment group) there was a significant decrease from baseline to end point in the percentage of biopsy specimens that contained no intact glands or stroma. Conversely, all three active treatment groups showed a significant increase in the percentage of biopsy specimens that had intact glands or stroma. At end point, the percentage

Table II. Baseline demographic and hormonal characteristics of 208 postmenopausal women included in analyses

Characteristic	*Placebo (n = 53)*	*Raloxifene hydrochloride 200 mg (n = 54)*	*Raloxifene hydrochloride 600 mg (n = 54)*	*Estrogen (n = 47)*
Age (yr)				
Mean	53.5	52.9	53.3	52.8
Range	46.3-60.2	45.2-60.9	46.2-60.9	46.5-60.1
Height (cm)				
Mean	162.8	163.7	162.9	164.3
Range	135.9-172.7	139.7-175.3	149.9-175.3	153.7-180.3
Weight (kg)				
Mean	75.0	71.8	69.0	75.4
Range	43.1-125.6	46.0-121.6	49.4-117.9	50.8-128.8
Time from last menstrual period (mo)				
Median	38.0	33.5	26.5	31.0
Range	8-87	6-69	7-75	8-72
Estradiol level (pmol/L)				
Median	19	15	19	17
Range	0-118	0-85	0-105	0-112
FSH level (U/L)				
Median	91.0	93.5	101.5	95.0
Range	54-235	31-208	6-213	52-184

n, Number of subjects with adequate biopsy specimens at both baseline and end point.

Table III. Subjects with estrogen effect grade values at baseline and end point

Treatment	*Total No.*	*0*		*1*		*2*		*3*		*Statistical significance**		
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*vs Placebo*	*vs Raloxifene hydrochloride 200 mg*	*vs Raloxifene hydrochloride 600 mg*
Baseline grade												
Placebo	53	47	89	6	11	0		0		—	—	—
Raloxifene hydrochloride 200 mg	54	51	94	1	2	2	4	0		$p = 0.921$	—	—
Raloxifene hydrochloride 600 mg	54	49	91	3	6	2	4	0		$p = 0.844$	$p = 0.606$	—
Estrogen	47	40	85	4	9	3	6	0		$p = 0.313$	$p = 0.203$	$p = 0.281$
End point grades												
Placebo	53	39	74	6	11	8	15	0		—	—	—
Raloxifene hydrochloride 200 mg	54	45	83	9	17	0		0		$p = 0.012$	—	—
Raloxifene hydrochloride 600 mg	54	47	87	7	13	0		0		$p = 0.006$	$p = 0.567$	—
Estrogen	47	6	13	5	11	29	62	7	15	$p < 0.001$	$p < 0.001$	$p < 0.001$

Total No., Number of subjects with adequate biopsy specimens at both baseline and end point; *No.,* number of subjects with a particular grade in each treatment group.

**p* values are for pairwise treatment comparisons.

of biopsy specimens that contained intact glands or stroma was significantly higher in the raloxifene and estrogen treatment groups than in the placebo treatment group. In addition, the percentage of biopsy specimens that contained intact glands or stroma was significantly higher in the estrogen treatment group than in the raloxifene treatment groups.

Estrogen effect grade. At baseline, the estrogen effect grades were similar among the treatment groups with most women having a grade of 0 (Table III). At end point the estrogen effect grades were significantly higher in the estrogen treatment group than in the placebo treatment group, whereas the estrogen effect grades in the raloxifene treatment groups were significantly lower than the grade in the placebo treatment group (Table III). At end point moderate and marked estrogenic effects (estrogen effect grades 2 and 3) were noted in 77% of estrogen-treated women, whereas only 15% of placebo-treated and none of the raloxifene-treated women showed moderate or marked estrogenic effects. An analysis of the estrogen effect grades, excluding the samples that were assigned an estrogen effect grade of 0 because they contained only surface epithelium and no intact glands or stroma, showed similar findings.

As noted previously, the baseline estrogen effect grade in the majority of women was 0. An increase of more than one estrogen effect grade occurred in a significantly higher percentage of women in the placebo and estrogen treatment groups compared with either raloxifene treatment group. No woman treated with raloxifene

Table IV. Mean and SE of values at baseline and end point and changes from baseline to end point for glandular and stromal morphology scores

	No.	Baseline	End point	Change	Statistical significance*: Comparison at end point†		
					vs Placebo	vs Raloxifene hydrochloride 200 mg	vs Raloxifene hydrochloride 600 mg
Glandular score							
Placebo	53	1.08 (1.43)	1.75 (2.12)	0.67 (2.10)	—	—	—
Raloxifene hydrochloride 200 mg	54	0.57 (1.30)	1.79 (1.23)	1.21 (1.51)	$p = 0.217$	—	—
Raloxifene hydrochloride 600 mg	54	0.68 (1.35)	1.72 (1.22)	1.05 (1.61)	$p = 0.383$	$p = 0.500$	—
Estrogen	47	0.88 (1.78)	5.60 (1.67)	4.71 (2.29)	$p < 0.001$	$p < 0.001$	$p < 0.001$
Stromal score							
Placebo	53	0.09 (0.20)	0.37 (0.71)	0.27 (0.67)	—	—	—
Raloxifene hydrochloride 200 mg	54	0.15 (0.56)	0.24 (0.47)	0.09 (0.63)	$p = 0.096$	—	—
Raloxifene hydrochloride 600 mg	54	0.13 (0.52)	0.20 (0.46)	0.07 (0.56)	$p = 0.073$	$p = 0.803$	—
Estrogen	47	0.23 (0.65)	2.09 (1.37)	1.85 (1.49)	$p < 0.001$	$p < 0.001$	$p < 0.001$

No., Number of subjects with adequate biopsy specimens at both baseline and end point.

*p Values are for pairwise treatment comparisons.

†No baseline differences were significant.

showed an increase of more than one grade from baseline. In the 7 women with a baseline estrogen effect grade of 2 or 3, only those treated with raloxifene showed a decrease to grade 0 at end point.

Scores for glandular and stromal morphologic features. No differences were observed among treatment groups at baseline in mean scores for the glandular morphologic features or the stromal morphologic features (Table IV). For the change from baseline–to–end point scores, those for the glandular and stromal morphologic features were significantly higher in the estrogen treatment group than in the placebo or raloxifene treatment groups. Compared with the placebo group, the raloxifene treatment groups showed similar changes in glandular morphologic scores and marginally significantly lower ($p = 0.096$ [raloxifene 200 vs placebo] and $p = 0.073$ [raloxifene 600 vs placebo]) changes in stromal morphologic scores.

Estradiol. No significant differences were observed among the four treatment groups at baseline in median serum concentrations of estradiol (range of medians, 15 to 19 pmol/L). Median estradiol concentrations in estrogen-treated women increased significantly ($p < 0.001$) from baseline to end point compared with values in women treated with placebo and raloxifene. Median estradiol concentrations increased 262 pmol/L in estrogen-treated women and 7.0 pmol/L in placebo-treated women. No change in median estradiol concentrations occurred in either raloxifene treatment group (median 0.0 pmol/L in both groups). The increase from baseline to end point in estradiol concentrations in the placebo treatment group was significantly greater ($p = 0.016$) than that in the raloxifene hydrochloride 200 mg treatment group and marginally significantly greater ($p = 0.053$) than that in the raloxifene hydrochloride 600 mg treatment group. The median estradiol concentrations for the total study population (251 women) were similar to those described for the 208 women.

Comment

Treatment with raloxifene hydrochloride in doses of 200 and 600 mg/day for 8 weeks did not stimulate the endometrium of healthy postmenopausal women. When raloxifene-treated women were compared with placebo-treated women, no significant increases in estrogen effect grade or glandular and stromal morphologic scores were observed. In fact, the estrogen effect grade was significantly lower in raloxifene-treated women than in placebo-treated women. In contrast, estrogen treatment had an expected highly proliferative effect on endometrial tissue as evidenced by a significant increase in the estrogen effect grade and the glandular and stromal morphologic scores.

In ovariectomized rats treated with raloxifene a slight increase in uterine body weight was observed.[7, 22] It is possible that the effect of raloxifene on uterine weight is related to a slight hypertrophy of the myometrium and endometrial stroma, which in previous work had been attributed to water retention.[7, 23]

In this study both raloxifene and estrogen treatment resulted in greater specimen adequacy when compared with placebo, as evidenced by a significantly higher percentage of biopsy specimens that had intact glands and stroma at end point. The explanation for this finding in the raloxifene treatment groups is not obvious, given the lack of endometrial proliferative effects noted during the study. This may reflect a treatment effect on the uterine body caused by edema or other

nonproliferative effects of the myometrium, as has been previously noted in ovariectomized rats. One hypothesis to explain this effect derives from observations of stromal edema in the ovariectomized rat model.[7, 22] In raloxifene-treated women nonendometrial effects, such as a slightly edematous myometrium, might result in a larger cervical os or a larger internal surface area, which in turn might lead to easier catheter insertion or greater sample adequacy. Adequate biopsy specimens were obtained even more frequently in estrogen-treated women.

It is interesting to note that placebo-treated women showed a slight but significant increase in estrogen effect grade from baseline to end point compared with both raloxifene treatment groups. There is no obvious explanation for this clinically insignificant change, but it could have involved an artifact such as instrumentation effect in the uterus. The fact that the estrogen effect grade did not increase in the raloxifene groups may be a further example of the raloxifene antagonistic effects on endometrial stimulation.

Estradiol concentrations in the placebo and estrogen treatment groups increased slightly during this study. These changes were statistically significant but too small to have clinical impact. The small number of study subjects and short duration of the study complicate interpretation of this result. Changes in estrogen levels are currently being investigated in larger, long-term studies.

An early study in postmenopausal women established that normal postmenopausal endometrium is not completely atrophic or static.[13] Few subsequent studies have described the normal postmenopausal endometrium, and none has quantified changes. In our study subjects the baseline state of the endometrium varied from exhibiting no estrogenic effect to demonstrating moderately proliferative changes, confirming that some biochemically postmenopausal women still demonstrate proliferative signs in the endometrium.

Other techniques, such as transvaginal ultrasonography, are useful for detecting gross uterine abnormalities (e.g., enlarged uterus, thickened or cystic endometrium, polyps, frank hyperplasia, neoplasia), but the grading system developed for this study provides a quantifiable assessment of subtle stimulatory effects on the endometrium and is highly correlated with the descriptive diagnostic system.[24] Additional raloxifene studies now in progress may determine whether the subtle changes assessed by this scoring system can be correlated with gross abnormalities detected by ultrasonography or can be used to predict risk for developing clinical abnormalities. These studies might also indicate whether short-term histologic changes can be correlated with long-term development of clinical pathologic conditions.

In summary, 8 weeks of treatment with raloxifene hydrochloride 200 and 600 mg/day did not induce histopathologic evidence of endometrial stimulation in healthy postmenopausal women, as assessed by a new estrogenicity scoring system. In contrast, estrogen treatment produced highly stimulatory endometrial effects. The mean estrogen effect grades in the raloxifene treatment groups were marginally or statistically significantly lower than those in the placebo treatment group. The data in this short-term study could suggest that raloxifene exerts estrogen antagonistic effects in the endometrium of postmenopausal women.

REFERENCES

1. Cummings SR. Evaluating the benefits and risks of postmenopausal hormone therapy. Am J Med 1991;91(Suppl 5B):145-85.
2. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 1992; 117: 1016-37.
3. Brinton LA, Hoover RN. Estrogen replacement therapy and endometrial cancer risk: unresolved issues. Obstet Gynecol 1993;81:265-71.
4. van Leeuwen FE, Benraadt J, Coebergh JWW, Kiemeney LA, Gimbrere CH, Otter R, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. Lancet 1994; 343:448-54.
5. Wolf DM, Jordan VG. Gynecologic complications associated with long-term adjuvant tamoxifen therapy for breast cancer. Gynecol Oncol 1992;45:118-28.
6. Kedar RP, Bourne TH, Powles TJ, Collins WP, Ashley SE, Cosgrove DO, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. Lancet 1994;343:1318-21.
7. Black LJ, Sato M, Rowley ER, Magee DE, Bekele A, Williams DCRF, et al. Raloxifene (LY139481 HCl) prevents bone loss and reduces serum cholesterol without causing uterine hypertrophy in ovariectomized rats. J Clin Invest 1994;93:63-9.
8. Sato M, Glasebrook AL, Bryant HU. Raloxifene: a selective estrogen receptor modulator. J Bone Miner Metab 1994; 12(Suppl 2):S9-20.
9. Kauffman RF, Bryant HU. Selective estrogen receptor modulators. Drug News Perspect 1995;8:531-9.
10. Miller MA, Katzenellenbogen BS. Characterization and quantitation of antiestrogen binding sites in estrogen receptor-positive and -negative human breast cancer cell lines. Cancer Res 1983;43:3094-100.
11. Kurman RJ, editor. Blaustein's pathology of the female genital tract. 4th ed. New York: Springer-Verlag; 1994.
12. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. Fertil Steril 1950;1:3-25.
13. McBride JM. The normal post-menopausal endometrium. Br J Obstet Gynaecol 1954;61:691-7.
14. Morphological changes induced by exogenous gestagens in normal human endometrium. In: Dallenbach-Hellwag G, editor. Functional morphologic changes in female sex organs induced by exogenous hormones. New York: Springer Verlag; 1980. p. 95-100.
15. Buckley CH, Fox H. Biopsy pathology of the endometrium. New York: Raven Press; 1989. p. 47-55.
16. Draper MW, Flowers DE, Huster WJ, Neild JA, Harper KD, Amaud C. A controlled trial of raloxifene (LY139481) HCI: impact on bone turnover and serum lipid profile in healthy, postmenopausal women. J Bone Miner Res 1996;11:835-42.
17. Johannisson E, Parker RA, Landgren B-M, Diczfalusy E. Morphometric analysis of the human endometrium in relation to peripheral hormone levels. Fertil Steril 1982;38:564-71.
18. Stovall TG, Photopulos GJ, Poston WM, Ling FW, Sandles LG. Pipelle endometrial sampling in patients with known endometrial carcinoma. Obstet Gynecol 1991;77:954-6.

19. Glant M, Eisenhut C, Boss S, Draper M. A scale for assessing postmenopausal endometrial proliferation in response to potential or known selective estrogen receptor modulators [abstract]. Am J Clin Pathol 1995;104:341-2.
20. Landis RJ, Heyman ER, Koch CG. Average partial association in three-way contingency tables: a review and discussion of alternative tests. Int Stat Rev 1978;46:237-54.
21. D'Agostino RB, Massaro J, Kwan H, Cabral H. Strategies for dealing with multiple-treatment comparisons in confirmatory clinical trials. Drug Info J 1993;27:625-41.
22. Fuchs-Young R, Rippy MK, Dorr FA, Short LL, Glasebrook AL, Termine JD, et al. Raloxifene diminishes the uterotrophic effects of tamoxifen in treated ovariectomized rats [abstract]. Breast Cancer Res Treat 1994;32:199.
23. Szego C, Roberts S. Steroid action and interactions in uterine metabolism. Recent Prog Horm Res 1953;8:419-68.
24. Huster WJ, Boss SM, GIant MD, Eisenhut CC, Neild JA, Draper MW. Raloxifene does not cause endometrial proliferation in postmenopausal women [abstract]. J Soc Gynecol Invest 1996;Suppl 3:142A.