Gynecologic and hormonal effects of raloxifene in premenopausal women

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Objective: To assess the effects of raloxifene on the ovaries, uterus, and serum hormone levels in premenopausal women.

Design: Prospective study comparing pretreatment findings with findings for those on treatment.

Setting: Government research hospital.

Patient(s): Thirty women 35 to 47 years of age who were at high risk of breast cancer and had regular, ovulatory menstrual cycles.

Intervention(s): Raloxifene (60 mg) and calcium (1,200 mg) daily for 2 years.

Main Outcome Measure(s): Sonographic evidence of ovarian stimulation (≥2 corpora lutea, or follicular cysts of >2 cm, or single follicular cyst of >3 cm). Changes in endometrial thickness, fibroid size, hormone levels, and menstrual-cycle length.

Result(s): Fifteen subjects developed some cycles with asymptomatic ovarian stimulation, and 9 developed benign endometrial polyps, compared with 2 subjects and 1 subject pretreatment, respectively. Uterine fibroid size was unchanged during raloxifene use in 16 subjects with fibroids. On treatment, E2 levels increased significantly only during the follicular phase, with peak E2 levels significantly higher in cycles showing ovarian stimulation compared with those without. Sex hormone-binding globulin increased, but levels of LH, FSH, P, DHEAS, and T did not. Endometrial thickness and cycle length were unchanged.

Conclusion(s): Premenopausal subjects receiving raloxifene showed sonographic and hormonal evidence of ovarian stimulation. Endometrial thickness, cycle length, and fibroid size were unchanged. Benign asymptomatic endometrial polyps developed in some.

Key Words: Raloxifene, premenopausal women, endometrium, ovary, hormones, breast cancer

Raloxifene, a selective estrogen receptor modulator (SERM) with potential as a breast cancer preventive agent, is currently approved for the prevention and treatment of osteoporosis in postmenopausal women. Tamoxifen, the SERM that currently is used for breast cancer prevention (1), has side effects that limit its acceptability, including endometrial hyperplasia, cystic myometrial changes, polyp formation (2–4), and less frequently, endometrial cancer (5–8). In premenopausal women, tamoxifen’s use causes ovarian stimulation, as evidenced by multiple ovulations or cyst formation (9). The resulting elevated E2 and P levels may contribute to myoma growth, endometrial hyperplasia, and cancer (10–13). In postmenopausal women, several studies have shown that raloxifene does not stimulate the endometrium (14–18); however, endometrial hyperplasia and endometrial polyps were reported after raloxifene use in three postmenopausal women (19, 20).

Few data are available regarding the gynecological effects of raloxifene in premenopausal women. In one small, short-term study by Baker et al. (21), endometrial biopsies in the follicular phase of the menstrual cycle showed a decrease in gland mitosis compared with baseline, indicating that raloxifene may not stimulate the endometrium of premenopausal women. In this study, short-term use of raloxifene did not affect the timing of ovulation or menstrual-cycle length, although its use was associated with a significant elevation in E2 and FSH levels.

The objective of our study was to examine the long-term gynecologic and hormonal effects of raloxifene in premenopausal women at increased risk of developing breast cancer.

MATERIALS AND METHODS

Subjects

Study participants were enrolled in an institutional review board–approved protocol, “A phase II trial of raloxifene in...”
premenopausal women at high risk for developing invasive breast cancer” at the Clinical Center of the National Institutes of Health, from December 1998 to January 2002. Each subject had an increased risk of breast cancer using at least one of the following criteria: Gail Model risk assessment of ≥1.7% over 5 years; a family history consistent with hereditary breast cancer (22); a diagnosis of lobular carcinoma in situ; or atypical ductal hyperplasia or locally treated ductal carcinoma in situ.

Subjects were of reproductive age and had to report a history of regular menstrual cycles for 6 months preceding study enrollment. Before starting raloxifene, premenopausal status and ovulation were verified by an FSH level of <20 mIU/mL on menstrual-cycle day 3 and by luteal-phase P levels (6.5–25 ng/mL); menstrual-cycle length of 26 to 35 days was confirmed over 1 to 2 months. Women who were not ovulatory or had irregular menstrual cycles were excluded. All women were protected from pregnancy by the use of condoms, spermicides, or sterilization. Any woman using other hormonal medications, including birth control pills, hormone replacement therapy, tamoxifen, P, or corticosteroids within 6 months of study entry was excluded. The clinical effects of raloxifene in this cohort have been described elsewhere (23, 24).

Some women also opted to enroll in a companion institutional review board–approved protocol, “Sonographic evaluation of the effects of raloxifene on the uterus and ovaries in premenopausal women at high risk for developing breast cancer,” to obtain more detailed evaluation of the ovaries and uterus by performing two or three transvaginal sonograms during the menstrual cycle, as described in Sonographic Evaluation.

Treatment Plan

Starting on the 1st day of menses, subjects self-administered raloxifene (60 mg) and calcium carbonate (1,200 mg) daily for 2 years. Calcium, obtained from commercial sources, was administered to ensure adequate intake of calcium (25). Compliance was assessed by interviews, subject-maintained calendars, and random serum drug levels.

Sonographic Evaluation

All patients had sonograms during the follicular phase of the menstrual cycle (usually cycle days 3–9) before receiving raloxifene as well as during the 1st, 3rd, 12th, and 24th months of raloxifene use. Those enrolled in the companion protocol also underwent sonograms during the luteal phase (usually cycle day 18–23) of the cycle to assess for multiple corpora lutea. They also had an additional sonogram performed in the periovulatory phase (cycle days 13–16) of the 3-month evaluation only. Gray-scale, color Doppler transvaginal sonography, and saline infusion sonohysterography were performed by one investigator (A.P.) with a multifrequency transducer (5–8 MHz) on an Acuson (Sequoia, Aspen, or 128xp) scanner (Acuson, Mountainview, CA). Those with abnormal findings at 2 years (n = 8) had another ultrasound 1 year after stopping raloxifene.

Ovarian measurements were obtained in three dimensions, and follicles and cysts were documented. An anechoic structure of <3 cm with a smooth, well-defined wall and good through transmission was considered a physiologic follicular cyst. Color Doppler was used to identify the typical vascularpattern surrounding a corpus luteum (26). Ovarian stimulation was defined as any cyst of >3 cm in diameter, two or more cysts of >2 cm in diameter, or more than one corpus luteum.

The endometrial thickness was measured in the midline sagittal plane on transvaginal sonography during the follicular and luteal phases. Saline infusion sonohysterography was performed in the follicular phase to examine the endometrial contour for polyps and other abnormalities. Endometrial thickness was measured separately from any polyps identified during SIS, in a region distinct from that of the polyps. If an endometrial polyp was noted, a hysterectomy and biopsy were performed as part of good clinical care.

The presence, location, and size of fibroids were documented with measurements taken in three dimensions. For those fibroids with shadowing from calcifications in which three dimensions could not be accurately measured, the maximum diameter of the fibroid and the plane in which it was measured were recorded for comparison in later ultrasounds.

Serum Sample Collection

Serum samples were drawn in the early follicular phase at baseline and at 3 and 12 months on the drug. Subjects had blood drawn on 11 days during the pretreatment menstrual cycle as well as during the 3rd and 12th month of taking raloxifene. Serum was collected on the 1st or 2nd day of the menstrual cycle, once during the early follicular phase (cycle days 3–7), daily for 6 days during the periovulatory phase (cycle days 10–15), and daily for 3 days during the luteal phase (cycle days 20–22). The protocol was amended to require fewer serum samples and subjects enrolled after September 2000 (n = 16) and had serum collected only during the early follicular phase (cycle days 3–7) of the pretreatment cycle and during the 3rd and 12th months of taking raloxifene. All samples were frozen at −70°C and run in batches of matched pairs.

Hormonal Assays

Early follicular-phase samples were used for all subjects to measure DHEAS, androstenedione, T, and sex hormone–binding globulin (SHBG). Estradiol, P, LH, and FSH were measured on each day for those with multiple samples per cycle and only once for those with a single sample. Both DHEAS and androstenedione were evaluated by RIA (Esoterix, Inc., Calabasas Hills, CA). Estradiol, P, SHBG, and T were assayed by the Immulite 2000 system (NIH Clinical
Statistical Analysis

Occurrence of ovarian stimulation was compared in the pretreatment and on-treatment scans by using a 1:M conditional matched odds ratio analysis, based on on-treatment occurrences that appeared to be independent. Endometrial thickness on treatment was compared with the patient’s pretreatment values by using a repeated measures analysis of variance and were presented as mean ± SE. The appearance of endometrial polyps on ultrasound was compared in pretreatment and on-treatment scans by using the McNemar’s test, assuming that the prevalence of polyps at baseline was equivalent to the incidence during the previous 2 years. Changes in fibroid size from baseline to 12 months showed no clustering by subject in an exact Kruskal-Wallis test and were therefore assessed by using the Wilcoxon signed rank test. The changes were compared with $E_2$ areas under the curve (AUCs), calculated by trapezoidal approximation over levels from baseline to 12 months, using the Spearman rank correlation method.

Hormone measurement values for DHEAS, androstenedione, T, and SHBG are expressed as mean ± SD, and comparisons were made by using the exact Wilcoxon signed rank test. Hormone values for $E_2$, P, FSH, and LH were evaluated by menstrual-cycle phase. Follicular phase included measurements up to and including the respective $E_2$ and LH peaks, as well as the luteal-phase values after the LH peak. The AUC for follicular and luteal-phase levels was calculated by trapezoidal approximation, adjusted for interval length, and the changes in the measurements were analyzed by the Wilcoxon signed rank test, comparing the 3-month level to the baseline. The $E_2$ AUC was used for the analysis, because the maximum $E_2$ levels were not consistently available.

Cycle length for the baseline period and for the first 12 cycles on study drug were calculated as the median of documented cycles before or during treatment. Cycles of >40 days on treatment were censored from this comparison because perimenopausal women may have irregular cycles, or cycles >40 days may represent an undocumented cycle rather than a longer one. The intrasubject change in cycle length over the study duration was determined by using the Wilcoxon signed rank test. Irregular cycles were defined as a change in cycle length on study drug of >5 days (longer or shorter) from a subject’s baseline cycle length (27). The percentage of irregular cycles and the number of women with cycles of >40 days and <21 days while on raloxifene also were determined.

RESULTS

Of 37 subjects volunteering to participate, 30 women (mean age, 43 y; range, 35 to 47 y) started the study drug, and 7 were ineligible. Twenty-seven of these 30 completed 2 years. The analysis included available data from those who discontinued study participation as well as from the 1st year of one subject who experienced menopause at 12 months on raloxifene. Fourteen subjects had more frequent ultrasound evaluations.

Ovarian Findings on Sonography

In all, 15 of 30 subjects showed sonographic evidence of ovarian stimulation on raloxifene, compared with 2 at the baseline cycle ($P=.04$, Table 1 and Fig. 1). Nine of 14 subjects with follicular- and luteal-phase ultrasounds showed ovarian stimulation, and 6 of 16 subjects with only follicular-phase ultrasounds showed ovarian stimulation. One patient had a solid ovarian lesion with the typical appearance of a benign dermoid cyst at baseline and elected not to remove it. The ovarian mass neither changed in appearance nor size with 2 years of raloxifene use.

Uterine Findings on Sonography

Endometrial thickness did not change with raloxifene therapy. The mean endometrial thickness in the follicular phase was $5.4 ± 0.5$ mm at baseline, compared with $5.4 ± 0.5$ and $5.4 ± 0.4$ mm at 3 and 12 months, respectively. Similarly, the mean endometrial thickness in the luteal phase ($n = 16$) was $9.1 ± 0.8$ mm before treatment, compared with $9.5 ± 0.8$ mm and $9.9 ± 1.0$ mm at 3 and 12 months, respectively.

An endometrial polyp was seen in one subject on the baseline hysterosonogram. Nine others who had a normal baseline exam developed polyps while on raloxifene (risk, 30%; 95% confidence interval, 15%–49%; $P = .02$; Fig. 2 and Table 2). All were asymptomatic at presentation, and all polyps ($n = 8$) were benign. After polypectomy, new polyps were seen on follow-up hysterosonogram in two subjects. Two other subjects with new polyps at 24 months did not have polyps 12 months later, after stopping raloxifene. There was no association between elevated $E_2$ levels and polyp incidence.

Uterine fibroids were present in 16 of 30 subjects at baseline; each had one to three fibroids, for a total of 37 fibroids. No decrease in fibroid size was observed on raloxifene. Ten of the 16 subjects with fibroids had at least one fibroid increase in size >1 cm in 1 year (range, 1 to 2 cm). Three subjects had minimal increase in fibroid size (0.5–1 cm), and the other three had no change in fibroid size. The mean increase in size of all fibroids was $0.49 ± 0.65$ cm; range, −0.5 to 1.9 cm. There was no correlation between changes in fibroid size and $E_2$ levels.

Serum Hormone Levels

Fourteen subjects had multiple blood draws over the course of the menstrual cycle. Sixteen had serum hormone levels drawn only in the early follicular phase. Serum $E_2$ AUC increased significantly in the follicular phase of the menstrual cycle on raloxifene. The mean change in follicular-phase $E_2$ AUC was 115 pg/mL per day (median, 63 pg/mL; $P = .0059$). There was no significant change in midluteal-phase $E_2$, P, FSH, and LH AUCs in cycles on raloxifene.
when compared with baseline. Twelve of 15 subjects with evidence of ovarian stimulation on ultrasound had concurrent hormone values for the cycles in which ovarian stimulation was observed. Ovarian stimulation noted on ultrasound was associated with significantly higher E<sub>2</sub> levels in months 3 and 12 compared with the baseline (P = .0011 by repeated measures analysis of variance of the log-transformed E<sub>2</sub> peaks).

Hormone levels for DHEAS, androstenedione, T, and SHBG were available for 24 subjects at baseline and for 20 subjects after 3 and 12 months on raloxifene. Sex hormone–binding globulin increased significantly from baseline at 3 months, for a mean increase of 22% (P = .0002). There was no significant change in DHEAS at 3 or 12 months from pretreatment levels, with a mean of 93/38 and 97/44 ng/dL at baseline, compared with 91/26, 89/19, and 93/29 ng/dL for the respective cycles. The mean level for T could not be calculated because the values were reported as <50 ng/dL for more than half of the subjects. Although subjects’ levels changed to both above and below 50 ng/dL, more than half of the subjects constantly had values of <50 ng/dL, indicating that there was no change overall.

**Cycle Length**

Cycle length did not significantly change with raloxifene therapy (26.3 d pretreatment [range, 20–31 d] vs. 26.7 d on raloxifene [range, 24 to 31 d]). Eighteen percent (70 of 393) of observed cycles were ≥5 days longer or shorter on raloxifene than the baseline cycle length. These 70 abnormally long or short menstrual cycles occurred in 16 women. Of these 16 women, 5 (including 1 who became menopausal) reported only having at least one long cycle (>40 d; range, 1 to 3 cycles per subject), 7 had at least one short cycle (<21 d; range, 1 to 3 cycles per subject), and 4 had at least one long as well as one short cycle.

**DISCUSSION**

In this study, we detected sonographic evidence of asymptomatic ovarian stimulation with corresponding elevated E<sub>2</sub> levels in a cohort of premenopausal women taking raloxifene (60 mg/d), similar to effects described elsewhere for tamoxifen and clomiphene citrate (10, 12, 28). Our results were similar to those of Baker et al. (21), who studied short-term use of raloxifene in premenopausal women and noted an increase in E<sub>2</sub> AUC and SHBG levels. Baker et al. (21) also observed an increase in FSH AUC and therefore hypothesized that raloxifene mainly exerted a direct effect on the pituitary, similar to the case of clomiphene citrate and tamoxifen, as well as some effect on the ovary. Unlike Baker et al. (21), we saw evidence for asymptomatic ovarian stimulation on ultrasound without an increase in FSH AUC. However, because we did not measure daily hormone levels, it is possible that the study methodology was not sensitive enough to detect a change in FSH AUC.

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<sup>a</sup>In this cycle only, in addition to early follicular and midluteal ultrasound, midcycle ultrasound was performed.

<sup>b</sup>More than one corpus luteum.

<sup>c</sup>Either one cyst of >3 cm or two cysts, each of >2 cm.

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TABLE 1. Ultrasound evidence of ovarian stimulation with raloxifene.

Similar to reports of postmenopausal raloxifene use (18, 29, 30), we did not find any evidence of endometrial stimulation, as measured by increased endometrial thickness, in this cohort of premenopausal women; however, endometrial polyps developed during raloxifene therapy. Endometrial polyps are more frequent with increasing age and have been reported with the use of tamoxifen (5, 31, 32). A hyperplastic polyp with surrounding atrophic endometrium was reported by Maia et al. (19) in a postmenopausal woman on raloxifene. Tsalikis et al. (20) also reported the polyp development in one postmenopausal woman as well as endometrial hyperplasia in a second one; both women were on raloxifene. None of the polyps that we detected were hyperplastic. Our study is the first report of polyps detected in premenopausal women taking raloxifene. The higher rate of detection of polyps also could be related to the use of saline sonohysterography for diagnosis (33).

The factors influencing the recurrence of polyps in this cohort are unclear but could be a result of an age or treatment effect. Because the incidence of endometrial polyps increases with age, the higher rate of polyps on raloxifene may be influenced by the women’s taking raloxifene after an observation period and their thus being older when the polyps were noted. Two subjects had recurrent polyps after polypectomy; two others had spontaneous regression of polyps after treatment was stopped. This pattern of recurrent polyps differs from the findings of Berliere et al. (34), who found that 80% of those who developed an endometrial abnormality on tamoxifen had a pretreatment abnormality and were asymptomatic at baseline.

The prevalence of fibroids in nearly 60% of our cohort is similar to the peak prevalence of >75% in this age group (35, 36). In previous studies of raloxifene, uterine leiomyoma size did not change in premenopausal women (37) but decreased in postmenopausal women (38). Jirecek et al. (39), using a higher dose of raloxifene (180 mg/d) compared with a no-treatment group, showed an inhibition in fibroid growth in premenopausal women. Contrary to these findings, in our study, the fibroid size increased at a low rate of growth and was variable, with some fibroids growing and others not, in the same subject. This low rate of growth is similar to the findings of DeWaay et al. (31), who showed that in asymptomatic premenopausal women, fibroids grew an average of 1.2 cm in 2.5 years.

Menstrual cycle length, in our study, did not change on treatment, similar to the findings of Baker et al. (21). Despite a normal menstrual-cycle length and premenopausal FSH levels at baseline, a few women occasionally had irregular cycles (40).

Studies of the effects of tamoxifen use on hormonal levels and menstrual-cycle length have yielded similar results to this study of raloxifene. In a small study of premenopausal

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**FIGURE 1**

Ovarian stimulation. (A) Transvaginal sonogram with color Doppler shows bilateral corpora lutea. (B) Large bilateral ovarian cysts seen in a subject on raloxifene.

**FIGURE 2**

Uterine polyps. Saline infusion sonohysterogram at 12 months after raloxifene shows multiple endometrial polyps (arrows).
women with fibroids (N=6; mean age, 40 y), tamoxifen taken for ≥3 months lengthened the luteal phase by about 4 days (12.5 to 16.9) and increased urinary estrogen and P metabolites as well as luteal-phase FSH levels (41). Premenopausal women with breast cancer who received tamoxifen had high 17β-E2 levels with persistent ovarian cysts (42). Premenopausal women treated with tamoxifen for mastalgia had elevated levels of SHBG and total E2 with a slight increase in free E2 when compared with the placebo-treated group (43). These effects of tamoxifen appear similar to the effects that we saw with raloxifene in premenopausal subjects.

A strength of the study is that 90% of subjects complied with the complex series of evaluations. This very thorough gynecological evaluation with nearly daily hormone measurements in an at-risk population provides very important data that are difficult to obtain.

Our study was somewhat limited by the relatively small sample size and by not having a concurrent age-matched
control group taking placebo to determine whether the long-term changes were caused by the effects of raloxifene and/or age. However, performing baseline scans and hormonal levels before starting raloxifene enabled us to compare the changes seen on treatment with the subject’s own baseline status. The menstrual-cycle changes that we observed do not appear to be clinically significant in a cohort of women in their 40s, because with increasing age, menstrual cycles are known to become more irregular, with impaired folliculogenesis (40). Thus, it is difficult to determine whether cycle irregularity was related to raloxifene or to increasing age. Similarly, because endometrial polyps occur at a higher rate with increasing age, it is unknown whether the development of polyps was related to raloxifene use or to increasing age. The development of endometrial polyps in this cohort, albeit difficult to interpret without a placebo group, suggests a need for further study regarding polyps in this age group of women who are at higher risk of breast disease and are likely to be treated with hormonal agents.

The number of women with ovarian stimulation may have been underestimated because of our study design. Follicular-phase ultrasounds, performed on all subjects on cycle day 3 to 9, were optimal for detecting endometrial abnormalities but often were too early to detect a dominant follicle. Sixteen subjects did not have luteal-phase ultrasounds, which precluded detecting multiple corpus lutea. The single midcycle scan, which was performed once in 14 women in the 3rd month, was scheduled according to cycle day and did not consistently correlate with the timing of the growth of the dominant follicle.

We report on the first long-term study of the gynecologic effects of raloxifene use in premenopausal women. The ovarian and hormonal stimulatory effects of raloxifene appear to be similar to those with tamoxifen in premenopausal women, but endometrial hyperplasia that was detected with tamoxifen was not observed with raloxifene. Raloxifene did not inhibit fibroid growth, nor did it appear to cause significant changes in menstrual-cycle length. Endometrial polyp formation, an interesting observation, should be examined in a larger cohort. Given the important use of both tamoxifen and raloxifene for breast cancer risk reduction, it is important to consider the gynecologic effects of these agents, perhaps with larger randomized studies.

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