To determine the relationship between the timing of a hysterectomy performed during the menstrual cycle phase and the postoperative complication rate in women who had undergone surgery for dysfunctional uterine bleeding, the authors examined the charts of 24 patients for the 3-month period immediately after the hysterectomy. Twelve of the women were in the follicular phase, and 12 were in the luteal phase at the time they had undergone the hysterectomy. Patients were classified by operative pathology report. No significant differences (P ≤ 0.05) were found between the two groups with respect to age, weight, para status, pathology, preoperative and postoperative hemoglobin levels, operation time, blood loss, days before return to full functioning, days in hospital, and uterine morphology. Further prospective studies with longer follow-up time are needed to obtain more conclusive indications regarding the optimal timing of hysterectomy during the menstrual cycle.

(Key words: Endometrium; hysterectomy; menstrual cycle; luteal phase; follicular phase; receptors, estrogen; receptors, progesterone)

The timing of breast cancer surgery during the menstrual cycle may affect outcome, according to some studies. In this current study, the results of which are reported herein, we examined the effect of menstrual cycle phase on the rate of postoperative complications from hysterectomy performed for dysfunctional uterine bleeding.

Literature review
Breast cancer surgery outcome and menstrual cycle phase
Veronesi and colleagues concluded that breast cancer surgery performed during the follicular phase on node-positive patients confers a higher risk of relapse than surgery done in the luteal phase. In contrast, Senie and Kinne found that patients who had had surgery during the luteal phase had a greater risk of relapse than did those patients who had had surgery during the follicular phase.

One explanation for the effect of the menstrual cycle phase on breast cancer surgery outcome is that unopposed estrogen secretion during the follicular phase of the menstrual cycle promotes metastases, possibly because estrogen depresses killer T-cell activity. However, the mechanism remains controversial. Giglio and coauthors think that "no clear correlations between specific in vivo endocrine patterns and immune system function have been demonstrated." Palumbo and colleagues found that proliferative response to the mitogen Con A was greatest during the early and midfollicular phase. This finding implies that T-cell activity is as high in the follicular phase as in the luteal phase, if not higher. Morrell hypothesized that the female immune system is most responsive during unopposed estrogen secretion, which occurs in the follicular phase.

Some studies found that the timing of breast cancer surgery during the menstrual cycle has no effect on the rate of breast cancer relapse. The most recent of these studies by Holli and coinvestigators, which had included the largest number of patients, found that menstrual cycle phase at breast cancer surgery had no effect on outcome. Thus, the impact of the menstrual cycle phase on outcome of breast cancer surgery remains controversial.

Of all the studies of breast cancer surgery and menstrual cycle phase, only four investigations examined the impact on outcome related to the hormone level, the most reliable indicator of the menstrual cycle phase. Moreover, we are not aware of any prospective studies of the timing of breast cancer surgery in the menstrual cycle phase being linked with outcome. Because the conclusions of many retrospective studies examining the impact of menstrual cycle phase on breast cancer surgery outcome differ, a prospective study is crucial to further clarify the relationship between those variables that define menstrual cycle phase based on measured hormone levels.

To the best of our knowledge, little or no work has been done to determine the effect of the menstrual cycle phase on postoperative gynecologic surgery complications. In the current retrospective study, we examined the possible effect of...
the timing of hysterectomy surgery during the menstrual cycle on postoperative complications.

The breast cancer surgery literature implicates a deficiency of killer T cells in the follicular phase as one cause of poor breast cancer surgery outcome.

**Hysterectomy outcome and menstrual cycle phase**

The hysterectomy literature proposes alternative mechanisms. Hysterectomy for leiomyoma is complicated by possible estrogen secretion by the tumors themselves. In this case, the impact of menstrual cycle phase on estrogen levels is not as critical as it may be for other types of surgery. Dysfunctional uterine bleeding requiring hysterectomy may result from a similar mechanism: autocrine estrogen secretion by the endometrial tissue. Thus, the impact of the menstrual cycle on estrogen secretion may not be an important determinant of outcome.

The relationship between outcome and timing of hysterectomy for malignant tumor also remains equally unclear. One study found lymphoid tissue proliferation in the uterine endometrium throughout the menstrual cycle, but with a possible shift toward T-cell proliferation in the follicular phase. Another study found substantial lymphoid tissue with a high concentration of T cells in the uterine endometrium in the luteal phase. Another investigation discovered almost equal concentrations of killer and suppressor T cells in the endometrium during both the follicular and luteal phases of the menstrual cycle. If the immune response of the killer T cells is the critical factor in determining outcome, the results of these aforementioned studies are ambiguous. If lymphoid tissue in the endometrium is an important determinant of hysterectomy surgery outcome, then the effect of the menstrual cycle phase on surgery outcome remains uncertain. Tabibzadeh, as well as Bonatz and colleagues, found that lymphoid tissue is present or proliferates equally rapidly throughout the menstrual cycle.

The immunologic state of the cervix and the vagina appears to differ from that of the endometrium. The effect of estrogen on uterine endometrium and cervical and vaginal tissue differs. Any influence timing of hysterectomy during the menstrual cycle may have, therefore, must be separately investigated for tumors of the cervix, vagina, or uterus.

Studies performed on tissue obtained from women who had undergone hysterectomy for subjectively diagnosed menorrhagia or who had had laparoscopy or laparotomy for endometriosis showed no difference in epidermal growth factor receptor (EGFR) concentrations during differential menstrual cycle phases.

Conversely, Oliver and Ingram found increased EGFR concentrations in the follicular phase in the breast tissue of patients about to have breast cancer surgery. This association was thought to correlate with the poorer prognosis of patients who had surgery in the follicular phase. Troche and coauthors studied normal premenopausal women and uncovered a similar result for EGFR in the uterine endometrium. Investigations examining results of tissue taken from women who had undergone hysterectomy for subjectively diagnosed menorrhagia and from women who had laparoscopy or laparotomy for endometriosis showed no difference in EGFR concentrations during different phases of the menstrual cycle. These two studies indicate that the timing of hysterectomy for menorrhagia or endometriosis is irrelevant to outcome.

In our study, we specifically examined the outcome of hysterectomy and any complications, which may have ensued, with the timing of this procedure during the menstrual cycle for women who had dysfunctional uterine bleeding.

**Materials and methods**

The charts of 24 patients for the 3-month period immediately after hysterectomy were selected from two gynecology offices and were reviewed retrospectively. Twelve women underwent hysterectomy during the follicular phase, with the remaining population undergoing this procedure during the luteal phase of the menstrual cycle. Classification was made by operative pathology report. Variables examined included age, weight, para status, pathology, preoperative and postoperative hemoglobin levels, operation time, blood loss, days required before return to full functioning, days in the hospital, and uterine morphology.

Normality, equal variance, and t-test analyses were used to assess change in hemoglobin levels, blood loss, operation time, and age. The chi-square test was used to compare fever among women in the two groups.

**Results**

Comparison of results of women who had undergone surgery in the follicular phase with those in the luteal phase showed no difference at the $P < 0.05$ level in any of the variables examined. The equal variance and normality tests for change in hemoglobin levels, blood loss, operation time, and age were passed with a $P$ value $> 0.14$, and the t-tests were passed with a $P$ value $> 0.16$. With regard to days spent in the hospital and weight, the data failed the normality tests. Results from the t-tests were not statistically significant: the differences between the two groups had a $P$ value $> 0.26$. When the chi-square analysis was performed for fever, the two groups did not differ statistically ($P = 0.8132$).

**Discussion**

In our retrospective review, the timing of hysterectomy during the menstrual cycle had no apparent effect on the postoperative complication rate. Thus, the theoretical basis seems less compelling for the proper timing of hysterectomy during the menstrual cycle for an optimum outcome than it does for breast surgery outcome. Further prospective studies are needed with longer follow-up time to obtain more conclusive indications of optimal timing of gynecologic surgery. The conclusions of our study are preliminary, because the sample size was small; the powers of the statistical analyses were well below the desired level of probability of 0.800 at an alpha
level of 0.05; the reasons for performing hysterectomy were not studied separately; the study was retrospective in design; and the postsurgical period was limited to 3 months.

Comment
Based on the findings of this study, we cannot definitely rule out the impact of menstrual cycle phase on hysterectomy outcomes. These findings would indicate no need to time hysterectomy surgeries to a specific menstrual cycle phase. However, given the high volume of hysterectomies performed, prospective studies are warranted.

Acknowledgement
The authors thank the medical editing department at Kaiser Foundation Research Institute (Oakland, Calif) for their assistance in preparing this article.

References


