Chronic mental illness and the menstrual cycle

R. Gregory Lande, DO
Varsha Karamchandani, MD

The purpose of this study was to explore the relationship between chronic mental illness, menstrual cycle phases, and psychiatric hospitalization. A detailed menstrual history was obtained from each participating subject. Women who were pregnant, postmenopausal, or who were prescribed hormonal contraception were excluded from the study. Factors precipitating admission, such as a suicide attempt, were identified. All women had a documented history of chronic mental illness, defined in this study as two prior psychiatric hospitalizations. Based on the menstrual history, the phase of the women’s cycle at time of hospitalization was calculated. Diagnoses and the reasons for admission were correlated with the menstrual cycle phase.

Thirty-three women participated in the study. Seventeen (52%) of those women were admitted during the late luteal/early menstrual phase. Women with schizophrenia whose behavior precipitating the admission was characterized as nonsuicidal and nonaggressive were admitted exclusively during the postovulatory phase. On the basis of findings of this study, the authors conclude that the postovulatory phase of the menstrual cycle may be a time of increased risk for women with chronic mental illness, especially schizophrenia. Prophylactic interventions might minimize admissions.

(Key words: original contribution, mental illness, menstrual cycle)

Gender is an indisputable force shaping healthcare. Women, for example, access healthcare systems more frequently than men, have special medical needs, and are an important source of health education for the family. Gender can also have a more direct impact. Certain physical and mental disorders tend to occur more often in women. Substantial research efforts have focused on explaining this finding among patients with mental illness. This study, a clinical survey of women with mental illness, was done to determine whether there were relationships between the menstrual cycle and psychiatric hospitalization.

Many studies have considered the role of gender on mental illness. Clinical investigations have developed along several paths. Investigators have explored the relationship between crime and the menstrual cycle. In one study, a significant proportion of women were in the premenstrual phase of the menstrual cycle when they were arrested for shoplifting. A recent study suggested that “a significant excess of violent offenses were committed on the 28th day and the first day of the menstrual cycle.”

Epidemiologic studies have reinforced clinical observations. The prevalence of specific mental disorders has been estimated through careful study. Depression, for example, has an estimated prevalence rate of 10% among women and 5% among men. This 2:1 gender ratio survives across ethnic groups. Women are reported to have certain anxiety and pain disorders disproportionately more often than men. In addition, somatization, dissociative identity disorders, and eating disorders are more common among women. Paraphilias, pathological gambling, violence, and substance abuse are more common in men.

Emphasizing a correlation between mental disorders and gender can be controversial. Disagreements rarely challenge the accuracy of the clinical observation associating gender and specific mental disorders, but instead take aim at the interpretation. Explaining the apparent difference requires caution. A number of biobehavioral theories have been explored in an attempt to explain the difference with variations in hormone levels as an obvious focus.

The clustering of behavioral and physical symptoms around the premenstrual portion of the menstrual cycle suggests a potential hormonal dynamic. A role for hormone-mediated behavior is further supported by several findings. Emotional lability, for example, seems to congregate around certain phases of life. Adolescence, the postpartum period, and menopause all represent stages of life where hormonal changes may contribute to emotional upheaval. The exogenous administration of the sex hormones has long been known to affect emotions.

The modern concept of a premenstrual syndrome was described nearly 70 years ago. An “indescribable tension” was the chief premenstrual complaint. The original syndrome was defined by a constellation of physical, emotional,
and behavioral symptoms. Following that initial report, the premenstrual syndrome lost clarity as the number of eligible symptoms exponentially increased. The third edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) organized the criteria and reduced the number of symptoms. The syndrome also received a new name: late luteal phase dysphoric disorder. The diagnosis went through additional revisions a few years later and is currently designated the premenstrual dysphoric disorder.

Premenstrual dysphoric disorder is included in the appendix of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) under “Criteria Sets and Axes Provided for Further Study.” The research criteria for premenstrual dysphoric disorder require that symptoms be recorded through the use of “respectable daily ratings during at least two consecutive symptomatic cycles.” It is estimated that 3% to 5% of women will meet the research criteria of premenstrual dysphoric disorder.

The interrelationships between mood, ovarian hormones, and neurotransmitters may be reflected in higher admission rates at various times throughout the menstrual cycle. This study hypothesized that correlations between psychiatric admissions among patients with chronic mental illness and the phase of the menstrual cycle could be accurately identified through noninvasive means. It was further hypothesized that the normal fluctuations in female hormones that occurred during the menstrual cycle would produce the most instability (expressed in terms of higher admissions) when levels of estrogen and progesterone were lower during the late luteal/early menstrual phase.

### Methods

This study included women of reproductive age admitted to an urban inpatient psychiatric unit. Thirty-three patients were enrolled during the 6-month study. All study participants had chronic mental illness, defined in this study as two or more lifetime, documented psychiatric hospitalizations. Hospital records confirmed the admissions. All subjects had reportedly discontinued previously prescribed psychiatric medications. The time between medication noncompliance and hospital admission varied widely, from a few days to 2 months. None of the study participants was taking monoamine oxidase inhibitors.

Women excluded from the study were menopausal, pregnant, had irregular menstrual cycles, took hormonal contraception, or had a prior hysterectomy. All women had conditions diagnosed according to DSM-IV criteria, based on a routine clinical evaluation. Prior medical records documented evidence of an existing mental illness. An alcohol and drug history was obtained and was supplemented by a urine drug screen.

For purposes of data collection, subjects were broadly grouped into three diagnostic categories: schizophrenia, bipolar mood disorder, or current substance abuse as indicated by positive results of urine drug screen. In addition, the behavior immediately preceding the hospitalization was classified as assaultive, suicidal, reckless, hypersexual, or nonsuicidal nonassaultive schizophrenia. Nonsuicidal nonassaultive schizophrenia was manifested by a severe deterioration in functioning that alarmed the family or law enforcement, but lacked physical violence or suicidal expressions. Reckless behavior consisted entirely of subjects who ran in front of moving vehicles.

A detailed menstrual history was obtained from each participant and included date of the last menstrual period, length of cycles, duration of menstrual bleeding, pain, and intermenstrual bleeding. Menstrual history was further verified by noninvasive methods, such as staff observation of menses during the hospital stay, a second interview of the patient several days after admission, and corroboration of the history with a legal guardian, family members, or institutional caregivers.

The phase of the menstrual cycle was calculated as either late luteal/early menstrual, luteal, ovulatory, or follicular. Calculations were based on a 28-day cycle. Day 1 of the cycle commenced with the menstrual flow. The late luteal/early menstrual phase was defined as the period between days 1 to 3 and 25 to 28 of the menstrual cycle. The ovulatory phase was calculated as the time between days 14 and 15. The luteal phase was calculated between days 16 and 24. The follicular phase was between days 4 and 13. The broader measures of the menstrual cycle were the preovulatory phase, which was from days 1 to 13, and the postovulatory phase, which included the span between days 16 and 28.

### Results

Eighty-four patients were admitted to an urban hospital’s psychiatric unit during a 6-month period. From this group, 33 patients met the inclusion criteria for this study. Among those excluded, 16 were menopausal, 10 had a hysterectomy, 9 were uncooperative, 7 had irregular menstrual cycles, 5 were pregnant, and 4 were taking hormonal contraception.

Of 33 patients studied, 52% were admitted in the late luteal/early menstrual phase of the menstrual cycle. Among the remaining 16 patients, 24% were admitted in the luteal phase, 15% in the follicular phase, and 9% in the ovulatory phase. One subject who participated in this study tested positive for premenstrual dysphoric disorder.
phase (late luteal plus luteal phases) was considered, most suicide attempts (64%) and assaultive acts (67%) occurred during the latter half of the menstrual cycle (Table 3).

Discussion

A woman’s menstrual cycle can last 21 to 35 days. Many women have a predictable 28-day cycle. The first day of the menstrual period commences the cycle. The follicular phase occurs from days 2 to 13. During the follicular phase, the pituitary releases the follicle-stimulating hormone, which induces the ovary to produce a follicle and begin secreting estrogen. Estrogen stimulates endometrial tissue growth. Day 14 of the menstrual cycle is ovulation. The latter half of the menstrual cycle is termed the luteal phase. During this phase the pituitary releases luteinizing hormone. Luteinizing hormone converts the follicle into the corpus luteum, which in turn secretes progesterone. Progesterone further prepares the endometrium for implantation.

An interesting finding emerged when the behaviors preceding admission were correlated with the phase of the menstrual cycle. All 12 patients with schizophrenia manifesting nonsuicidal nonassaultive behavior were admitted in the postovulatory phase of the menstrual cycle. Of those 12 patients, 10 admissions occurred during the late luteal/early menstrual phase. The other behavioral reasons for admission, such as suicide attempt and assault, were more uniformly distributed across all phases. However, when the entire postovulatory phase (late luteal plus luteal phases) was considered, most suicide attempts (64%) and assaultive acts (67%) occurred during the latter half of the menstrual cycle (Table 3).

### Table 2
Menstrual Phase and Diagnosis

<table>
<thead>
<tr>
<th>Phase</th>
<th>Schizophrenia, No. (%)</th>
<th>Bipolar mood disorder, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late luteal/early menstrual</td>
<td>12 (63)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Follicular</td>
<td>2 (11)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Ovulatory</td>
<td>2 (10)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Luteal</td>
<td>3 (16)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Total</td>
<td>19 (100)</td>
<td>13 (100)</td>
</tr>
</tbody>
</table>

### Table 3
Menstrual Phase and Behavioral Reason

<table>
<thead>
<tr>
<th>Phase</th>
<th>Nonsuicidal nonassaultive behavior, No. (%)</th>
<th>Suicide attempt, No. (%)</th>
<th>Assautive, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late luteal/early menstrual</td>
<td>10 (83)</td>
<td>4 (37)</td>
<td>3 (34)</td>
</tr>
<tr>
<td>Follicular</td>
<td>N/A</td>
<td>3 (27)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Ovulatory</td>
<td>N/A</td>
<td>1 (9)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Luteal</td>
<td>2 (17)</td>
<td>3 (27)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Total</td>
<td>12 (100)</td>
<td>11 (100)</td>
<td>9 (100)</td>
</tr>
</tbody>
</table>
tors spurred speculation that hormones played a role in regulating mood and behavior.10

The precise mechanism by which the sex steroids alter neurotransmitter function is unclear. Animal studies suggest several possible mechanisms. The gonadal steroid hormones act directly on the striatum and the nucleus accumbens affecting dopamine concentration. In rats, the levels of dopamine fluctuate across the menstrual cycle.11

Sex steroids may influence monoamine metabolism by altering the action of monoamine oxidase (MAO). Estrogen seems to decrease MAO activity; progesterone exerts the opposite effect.12 A variation in MAO activity across the menstrual cycle has been reported in women.12 None of the study participants was taking MAO inhibitors.

The ovarian hormones probably have an effect on serotonergic system. The effectiveness of serotonin receptor inhibitors in alleviating the symptoms of premenstrual dysphoric disorder is indirect proof.13 Whole blood serotonin levels are lower in the postovulatory phase of the menstrual cycle.14 From animal research it appears that estrogen and progesterone affect the serotonergic system at multiple points.15 Estrogen replacement therapy promotes a sense of well-being, possibly mediated through serotonin.16

Exogenous estrogen administration increases dopamine turnover.12 Estrogen may partially account for the fact that schizophrenia develops in women at a later age than in men.17 The ovarian hormones affect other neurotransmitters and messenger systems, such as gamma-aminobutyric acid, glutamate, endorphins, and prostaglandin.12

In this study, carefully selected women with a documented clinical history of two or more psychiatric hospitalizations were studied in terms of menstrual phase admissions. Although the cohort size was small (n = 33), this study found that the greatest risk for admission was during the 6 days of the late luteal/early menstrual phase, during which time slightly more than half of the women were admitted. Three fourths of the admissions occurred during the 14-day postovulatory phase of the menstrual cycle.

The predominant influence of the postovulatory phase on admissions was intriguing. Although no single explanation can account for this finding, speculation would include a hormonal etiologic factor. The postovulatory phase of the menstrual cycle corresponds with increasing levels of progesterone. The increase in progesterone might result in serotonergic and dopaminergic dysfunction in a manner that mimics the neurotransmitter changes. The decline in estrogen during the postovulatory phase could, by acting through the serotonergic system, contribute to anxiety and social isolation. Other factors, such as the fluctuating ratio of estrogen to progesterone, may be more important than the individual changes in estrogen or progesterone levels. Not all explanations may be biological. The onset of premenstrual symptoms, for example, may launch a cascade of psychological conflicts resulting in deterioration. Another possibility involves the older antipsychotic medications and their propensity to elevate prolactin levels. Theoretically, discontinuance of these medications might alter the menstrual cycle through a reduction in prolactin levels. Excluding women who had irregular or changing menstrual histories minimized that potentially confounding variable in this study.

Our study also classified behaviors that immediately preceded admission. Neither suicidal behavior nor assaults clustered around the late luteal phase of the menstrual cycle. These two behaviors did congregate in the longer postovulatory phase. The overwhelming but small sample (N = 12) of women admitted with nonsuicidal nonassaultive behavior during the late luteal/early menstrual phase was notable. These admissions were characterized by a severe nonaggressive, nonsuicidal mental disorganization that precipitated the hospitalization. If replicated in future studies, this finding might suggest that a different mechanism underlies the production of nonsuicidal nonassaultive psychotic behavior in women. The study also has implications for postmenopausal women with chronic mental illness. The loss of estrogen, with its purported dopamine blocking activity, could signal heightened vulnerability to relapse, particularly in schizophrenia. Clinically, this is sometimes manifested by a decreased responsiveness to antipsychotic medicine. Whether the clinician should respond with an increase in antipsychotic medication or simply add estrogen is an area ripe for research.

Conclusion
The findings of this study indicate a menstrual phase influence on psychiatric admissions. Even without understanding the exact mechanism underlying the phenomenon, certain preventive practices could be empirically adopted. Clinical appointments, for example, could be adjusted to the postovulatory phase of a woman with chronic mental illness. Perhaps this would heighten outpatient interventions, obviating a psychiatric admission. Patients with a history of frequent admissions might benefit from a record review aimed at identifying temporal trends. Medications could be prophylactically increased if a pattern documented a higher proportion of admissions occurred during the postovulatory phase. In the postmenopausal woman who begins relapsing more frequently, the risks of increasing antipsychotic medication or offering estrogen replacement need to be discussed openly.

Our findings developed from careful clinical observations. Greater certainty will come from studies that obtain hormone levels, examine ratios, and include testosterone in the analysis.

References


