Suicide and the Menstrual Cycle

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> "And arbitrary blackness gallops in. . ."
> —"Mad Girl's Love Song," by Sylvia Plath

In this issue, Ross et al. (1) describe the results of a rigorously conducted study showing that suicidal ideation and suicidal planning vary in a menstrual cycle phase–dependent fashion in concert with many affective symptoms. The article serves to highlight different approaches used to study the role of reproductive physiology in behavior and stimulates a number of questions.

Why Would We Think That Suicidal Ideation, Suicidal Planning, and Affective Symptoms Would Be Related to Menstrual Cycle Phase?

Almost 180 years ago, von Feuchtersleben noted that "the menses in sensitive women is almost always attended by mental uneasiness, irritability, or sadness" (2). This observation helped introduce two critical ideas: the menstrual cycle (and not the uterus, as per Hippocrates) could be a modulator of behavior, and some factor(s) generated susceptibility to increase the likelihood of behavioral disturbance in a menstrual cycle phase–related fashion.

Interest in the first idea—menstrual cycle as a modulator of behavior—was advanced by Robert Frank's description of the premenstrual tension syndrome in 1931 (3). By the time Greene and Dalton's article "The Premenstrual Syndrome" was published in 1953 (4), well over 100 symptoms had been reported as part of the premenstrual syndrome (PMS), as had observations of the clustering of crimes of violence, psychiatric hospital admissions, and suicide attempts during the paramenstruum (4 days before to 4 days after menses). Dalton reported that 53% of suicides occur during these 8 days of the cycle, although she opined that depression was usually at work in concert with menstrual cycle phase (5). Although many explanatory hypotheses were generated, the potential mediators of the symptoms observed in PMS remained unknown.

The Categorial Approach: Do Reproductive Hormones Play a Causal Role in Menstrual Cycle–Related Behavioral Symptoms?

The year before Dalton's 1953 article appeared, the APA published DSM-I (6), the first attempt in U.S. psychiatry to follow the Kraepelinian model of categorizing psychiatric illnesses. Studies of PMS did not immediately benefit from these efforts, and it would be more than 60 years before PMS in the form of premenstrual dysphoric disorder (PMDD) would be officially included in DSM-5. Over the next few decades following the release of DSM-I, much was published about PMS, with diagnoses made idiosyncratically on the basis of self-report—which, unfortunately, was shown to be notoriously inaccurate and highly subject to expectancy bias. Because PMS was a time-based diagnosis (i.e., symptoms appearing in the luteal phase and not present after menses) rather than a specific symptom-based diagnosis, several of us developed criteria for PMS that required prospective documentation of symptom confinement to the luteal phase (7). Documentation was critical, given the observation that retrospective self-reported symptoms were disconfirmed by prospective ratings in two-thirds of cases. These criteria allowed for the selection of subjects who were similar with respect to the defining characteristic (luteal phase–restricted symptoms), and there followed a series of replicable observations regarding the treatment and underlying biology of PMS: selective serotonin reuptake inhibitors were efficacious (8); the hormonal events of the mid to late luteal phase had nothing to do with PMS (9); women with PMS had normal hormone levels (10), indicating that PMS was not an endocrinopathy; and PMS represented an abnormal behavioral response to normal changes in reproductive steroids in a subgroup of susceptible women (11). The source of this "susceptibility" (reminiscent of von Feuchtersleben's "sensitive women") and the means by which physiological changes in reproductive hormones trigger a dysphoric mood state in women with PMS are yet undetermined. Nonetheless, a direct role for gonadal steroids in PMS was established, because the syndrome could be precipitated or prevented through blinded manipulation of gonadal steroids in most women with PMS. Notably, roughly one-third of women with prospectively documented PMS were not affected by hormone manipulation, which meant that their affective syndrome, although tied to the menstrual cycle, was not affected by suppression or replacement of ovarian steroids. Thus, these

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women could not be called "hormone sensitive," despite the confirmed linkage of their symptoms to the luteal phase. So how, then, might the menstrual cycle influence the appearance of behavioral symptoms?

The Dimensional Approach: Does the Menstrual Cycle Decrease the Threshold for Suicidal Ideation and Planning?

As part of a rigorous attempt to understand the relationship between menstrual cycle phase and suicidal cognitions, Ross et al. obtained multiple prospective behavioral ratings over at least two cycles in a transdiagnostic sample who experienced suicidal thoughts in the preceding month. They observed that suicidal ideation and suicidal planning were highly associated with increased severity of depressive symptoms (depression, hopelessness, rejection sensitivity, and anhedonia), all of which worsened during the paramenstruum. These observations are important for several reasons.

First, they provide data on an enormously important problem. Let's face it, we know all too little about suicide despite the fact that it is the 10th leading cause of death in the United States (>48,000 deaths per year), with rates having increased by 35% from 1999 to 2018 (12). Suicide, like depression, is a complex phenomenon, comprising a variety of different but related cognitions and behaviors: suicidal thoughts, ideation, intentions, plans, gestures, completions, and equivalents (13). How are impulsive acts of suicide different from planned and very deliberate acts of suicide? How do we understand the difference between someone who is chronically suicidal and someone who is only momentarily suicidal in relation to a stressful event that feels overwhelming? What we know with certainty is that we are lousy at predicting when suicidal ideation turns into suicidal behaviors.

Second, the authors' findings call attention to a potentially modifiable risk factor for the exacerbation of suicidal ideation and planning—the paramenstruum. The identification of clear periods of time representing increased risk can inform behavioral strategies (e.g., avoiding particularly stressful interactions or recognizing that one's reactions might be state dependent). As noted below, however, menstrual cycle phase–related emergence of symptoms does not necessarily entail mediation by effects of gonadal steroids on the brain.

Third, the authors embrace a polythetic or dimensional approach to suicide, recognizing that many different factors can contribute to risk. The categorical approach to PMS—its presence or absence on the basis of timing and severity ratings—undoubtedly advanced our understanding of PMS. But the criterial thresholds were arbitrary: is there a difference between individuals with 25% versus 30% (typical threshold value) increases in symptoms? The same is true for the five-of-eleven symptom requirement for PMDD (there is no evidence that four symptoms are any less predictive of course or treatment response than five). It makes sense to try to identify groups that are similar enough to permit acquisition of biological insights or to develop therapies with high likelihood of success. But categories can also be blinders and may not capture the complexity and variability of mental health conditions, because many individuals experience symptoms that do not neatly fit into predefined categories. (One may also wonder about the coherence of some diagnostic categories, such as depression, in which there are hundreds of unique ways of meeting diagnostic criteria [14].) Our criterion-based nosology can lead to ignoring or rejecting information that doesn't fit the model. The diagnosis then may become the end of our inquiry and prevent us from listening effectively. In contrast, but similarly, the dimensional approach illustrated by the Research Domain Criteria framework and employed by Ross et al. has value, but it has its own set of problems. It may be valuable for research, but it is complex and of questionable clinical utility; when it is applied rigidly, it may tell us about processes but not about the illnesses that we are attempting to understand and treat.

How Might the Menstrual Cycle Influence the Emergence of Suicidal Ideation?

The first and most immediate answer is that some of the hormone constituents of the menstrual cycle (i.e., sex steroids) act directly as pluripotent regulators of CNS activity. The good news (and the bad news) is that sex steroids and their receptors regulate everything: all types of polymerases, signal transduction pathways, the synthesis and metabolism of virtually all neurotransmitters and their receptors, and so on. Such global impact doesn't really get us much closer to understanding the specific potential biological contributions to suicidal behavior or to understanding why only some individuals are affected.

A second possibility is that suicidal ideation and planning are aspects of a transient behavioral state, with ovarian steroids affecting or mediating the transition into that state. Most affective disorders can be viewed as disorders of the process by which we change mood states. In this regard, states can be considered transient, coherent, replicable, and self-organized assemblies of thoughts, associations, memories, cognitions, and perceptions (15). In essence, states are filters or programs for interpreting and interacting with our environment. There are several advantages of viewing psychiatric disorders through the lens of states rather than seeing them as collections of symptoms. One is that this approach suggests that pathology may exist at the level of the process by which we change states, the process that regulates state change, and the kinetics that underlie state change. Depression could be considered a stuck state; bipolar disorder is characterized by at least two very distinct states; panic anxiety reflects the sudden intrusion of an anxious state; and PMDD could be seen as an obligatory transition into a dysphoric state during the luteal phase (followed by a sudden switch out of the state). In each case, it is the kinetics at least as much as the specific symptoms that define the disorder. Another advantage is that states are a product of the interactions of brain networks that we already know display

disturbed interactions in certain conditions (for example, depression involves disruptions in the default mode, salience, and hedonic networks). Notably, each of these networks is regulated by estradiol. Affective disorders, then, can be viewed at a mesoscopic level, not as collections of symptoms but as integrative dysfunction within and across networks, influencing state content and transitions. Gonadal steroids are "designed" to change state and regulate network selection (16), as without the ability to motivate reproductive behavior hedonically, the species would likely die out. Indeed, dysphoric behavioral states associated with PMDD can be precipitated or prevented through hormone manipulation.

A third scenario may be that gonadal steroids influence mood state changes indirectly. For example, suicidal ideation and planning might be more likely if irritability consequent to the discomfort of premenstrual somatic symptoms led to fractious interpersonal interactions. In that case, gonadal steroids would be involved in mediating suicidal ideation and planning through somatic side effects, not through direct regulation of brain networks.

What Is the Take-Home Message From These Data?

First, our field remains dependent on both categorical and dimensional approaches if we are to better understand physiology in the service of increased diagnostic precision. We can measure a lot, but we still know less than we think we know. Hence, we need both categorical and dimensional approaches to understand behavioral disorders.

Second, we should ask our patients about menstrual-related alterations in symptoms. Whether or not such information is actionable, it is important in helping us understand our patients. To state the obvious, our patients have lives and experiences outside of our offices: their lives are not static but rather dynamically fluctuate across different states, and information that might help us to better understand our patients may be found in the states and the transitions between them.

Third, to say that someone has a menstrual cycle–related increase in suicidal ideation is not to say that gonadal steroids are directly involved, an inference that can only be confirmed experimentally. For example, the menstrual cycle may indirectly choreograph mood state changes (e.g., through expectancy or increased irritability due to premenstrual somatic symptoms or insomnia). Nonetheless, the evidence for the relevance of gonadal steroids in mood regulation is strong, as seen in PMDD, postpartum depression, and perimenopausal depression. These disorders are almost unique in psychiatry in that we have identified the physiological trigger that precipitates them. But what the article by Ross et al. suggests is that the menstrual cycle, whether through the direct involvement of gonadal steroids or not, is a relevant source of symptom exacerbation in women with nonreproductive-related disorders.

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