Biological Psychiatry: Celebrating 50 Years

Premenstrual Dysphoric Disorder: From Plato to Petri Dishes

Erica B. Baller and David A. Ross

Gradually my whole concept of time changed until I thought of a month as having twenty-five days of humanness and five others when I might just as well have been an animal in a steel trap.
– Florence King

Fascination with the mysterious workings of the female body has been the topic of scientific and political debate since as early as 1900 BC in Egypt, when women were believed to be eliminating impure elements and were banned from temples during menstruation. The Old Testament similarly prescribed a monthly trip to the mikvah 7 days after the end of a woman's menstrual cycle to restore her to a state of "purity." No one was as colorful in their musings as Plato in 360 BC, who compared a woman's uterus to a creature that "wanders throughout a woman's body, blocking passages, obstructing breathing, and causing disease" (1). In modern times, women's biological differences—and specifically the impact of reproductive hormones on mood and behavior—have been used as a cultural weapon. For example, in the lead-up to the 2016 presidential election, the *Sun Gazette* (Williamsport, PA) published a letter to the editor stating: "They call us sexist just because we are critical of Hillary Clinton and her health. What if that time of month comes and she is sick at the same time?" (2). Buried within this toxic misogyny there is also a sad irony: while this physical attribute ostensibly renders women to be unfit to perform even basic tasks, until recently the medical establishment has largely neglected this aspect of women's health. Before the 1980s there was virtually no research exploring the condition that we now refer to as premenstrual dysphoric disorder (PMDD), which affects approximately 1 in 20 women.

It was not until 1984 that a group led by David Rubinow became the first to rigorously and prospectively study mood and behavioral fluctuations in PMDD (3). An interesting pattern emerged: women were in their usual state of health until about 1 week before menses, when they would have at least a 30% increase in depressive symptoms. As soon as they started their period they would feel better and return to baseline. The timing of the symptoms was striking, with the peak of symptoms coinciding with the luteal phase when estradiol and progesterone are naturally at their highest.

As with other endocrine conditions, the obvious explanation was that PMDD symptoms were a result of abnormally high hormone levels. To test this hypothesis, Rubinow *et al.* (3) serially tracked women's hormone levels for months to see if they correlated with symptoms. The results were clear—and surprising: women with PMDD had absolutely normal estradiol and progesterone levels throughout the menstrual cycle.

Rubinow was fascinated by this unexpected result. And so, in the early 1990s, Rubinow teamed up with Peter Schmidt to explore it further: was it possible that women with PMDD, rather than having higher hormone levels, might be differentially sensitive to the same signals? To test this hypothesis as precisely as possible they devised a clever experimental paradigm. Their team enrolled cohorts of regularly menstruating women, both with and without PMDD. They then gave all of the women a medication (leuprolide) that induced an artificial temporary menopause, thereby eliminating any cyclical hormone changes. The researchers then separately and sequentially added back estradiol and progesterone, thereby enabling the careful observation of how the women responded to each specific hormone independently. Throughout all three phases of the study, participants kept a daily record of their mood and behavior. Not surprisingly, the women in the healthy control group did not manifest symptoms in any of the conditions. The women with PMDD, however, responded differently. Just like the control subjects, they were asymptomatic when they had neither estradiol nor progesterone in their systems. However, during both of the hormone add-back conditions, they experienced a recurrence of PMDD symptoms (4).

This finding was a landmark for the field of psychiatry. Foremost, the study clearly demonstrated a causal biological mechanism that could explain patients' symptoms—a rarity in psychiatry, even today. Moreover, it was one of the first instances in which researchers demonstrated the ability to predictably and consistently control both the onset and the remission of a major psychiatric condition. Astonishingly, these (and related) data were not enough to warrant the inclusion of PMDD into the main body of the DSM-IV-TR; despite the overwhelming evidence, it was relegated to the appendix as a "condition requiring further study."

It is easy to imagine that researchers might have found this marginalization of women's health to be demoralizing—but, nevertheless, they persisted. Several groups continued to explore how differential sensitivity to sex hormones could lead to cognitive and affective symptoms. Their work was facilitated by the rapid advances in modern neuroimaging techniques that took place in the late 1990s and early 2000s. A range of studies showed, at a circuit level, that women with PMDD had differences in functioning of the prefrontal cortex. This was especially interesting because the prefrontal cortex is rich in hormone receptors and rapidly develops during puberty—thereby enhancing strong face validity for the model (5–7). Critically, many of these studies also showed that functional imaging data were well correlated with clinical measures of PMDD, opening

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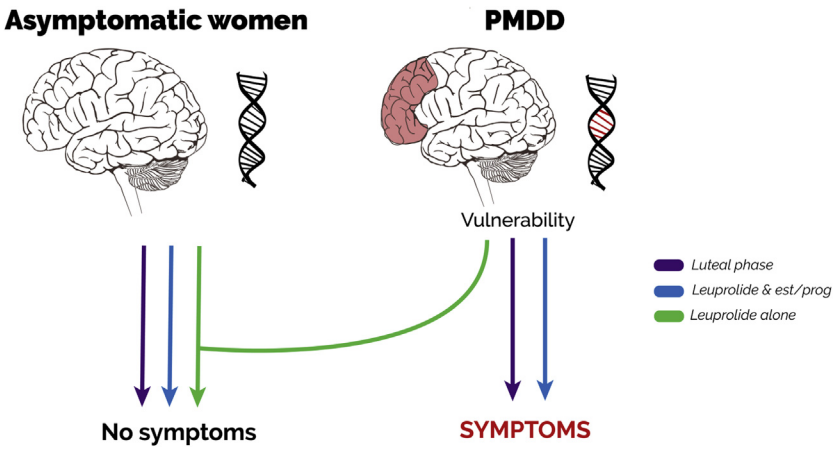

Figure 1. Schematic of the relationship between hormones and symptomatology. Premenstrual dysphoric disorder (PMDD) is a condition in which women with regular menstrual cycles experience mood, behavioral, cognitive, and affective symptoms during the luteal phase of the menstrual cycle, when estradiol (est) and progesterone (prog) levels peak. Symptoms remit with the onset of menses. In the leuprolide experiment by Schmidt *et al.* (4), cohorts of healthy women and women with PMDD underwent a three-phase hormone manipulation protocol. In the first stage, women were administered leuprolide alone to induce temporary menopause and abolish the cyclical hormone fluctuations associated with menses. In the second and third phases, estradiol and progesterone were added back separately and sequentially to the leuprolide to allow scientists to study the independent effects of each hormone condition. Healthy women did not experience symptoms during any of the three hormone conditions. The women with PMDD experienced symptoms during add-back with either estradiol or progesterone but, during the leuprolide alone condition, showed remission of their symptoms and were indistinguishable from the healthy control subjects. Further studies suggested that women with PMDD have an underlying neural and genetic vulnerability that is triggered by estradiol and progesterone.

the door for their use as one of the most cutting edge approaches in psychiatry: brain-based biomarkers.

Given the mounting evidence of circuit-level differences, Schmidt teamed up with geneticist Neelima Dubey and colleagues and they turned their focus to understanding the central question of *how* these differences might emerge in the first place. While PMDD was known to be highly heritable, it was clear from the beginning that genetics alone did not fully explain the risk of developing the condition. Rather, it seemed that gene–environment interactions were likely playing a crucial role. To probe these interactions, the team used a new technique involving culturing white blood cells. Recent work had shown that messenger RNA expression from peripheral leukocytes roughly correlated with gene expression from neurons. By applying this method to an adaptation of the Rubinow protocol described above, Dubey *et al.* (8) were able to compare gene expression between asymptomatic women and individuals with PMDD in the presence of leuprolide alone or in one of the add-back conditions with estradiol or progesterone. They made two big discoveries. First, across all conditions, the women with PMDD overexpressed the gene complex *ESC/E(Z)* that is known to regulate epigenetic responses to the environment, including sex hormones. Second, hormone add-back differentially affected the transcription of four other key genes (including one involved in the transcription of the androgen receptor). These data suggest that, even at a cellular level, women with PMDD have an underlying vulnerability and a different susceptibility to the effect of sex hormones (8). This study represented a new frontier for translational psychiatry: it was one of the first instances in which scientists were able to conduct basic science research in human beings with a defined clinical syndrome. Moreover, it helped link the previous findings together: women with PMDD have a genetic and neural vulnerability that, when acted upon by circulating estradiol and progesterone, leads to altered messenger RNA expression and altered brain network activity, resulting in clinical symptomatology (Figure 1).

What is critical to the conversation—and too often omitted—is that despite being a highly prevalent disease with considerable morbidity, PMDD is also highly treatable. The first-line treatment is selective serotonin reuptake inhibitors, which work in about half of patients with major depressive disorder but are effective in up to 85% of women with PMDD—a better rate of treatment success than that of antibiotics for pneumonia (9). An intriguing aspect of these data is that women do not need to take these medications consistently: they do just as well if they take them during the luteal phase alone. This suggests that they may be acting via a novel mechanism—a possibility that is currently under investigation. Moreover, understanding of the underlying neurobiology is pointing to a range of additional treatment options should first-line treatments fail. Martinez *et al.* (10) have had success pharmacologically altering progesterone metabolism to treat women with PMDD (10). Leuprolide itself can be used as a treatment for PMDD. In extreme cases, ovariectomy is curative for women with treatment-resistant illness. To date—and for the foreseeable future—this is the only psychiatric disease for which we can achieve a 100% cure rate.

So why is it that, despite all of this research, many clinicians have no idea that PMDD (an official DSM-5 diagnosis as of 2013) is an actual condition? The real mystery is how we manage to underscreen and undertreat a condition that affects 5% of all women and accounts for 14.5 million disability-adjusted life-years lost in the United States each year (5). Perhaps we are still wedded to our societal values regarding the validity of the condition. Or perhaps women are generally resilient enough to accomplish what they need to despite the toll PMDD takes on their personal and emotional lives.

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