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DSM-V and reproductive-related psychiatric disorders: a closer look at windows of vulnerability

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As the discussions on how to reformulate the Diagnostic and Statistical Manual of Mental Disorders (DSM) approach a crucial moment, it would be pertinent to take a closer look at the predictive value and clinical significance of reproductive-related psychiatric events. As it stands in its current edition, the DSM fails to help clinicians and researchers to consider these events while conceptualizing clinical diagnoses or establishing therapeutic strategies for psychiatric disorders, particularly mood and anxiety disorders in women. Such omission is inconsistent with robust epidemiologic and clinical evidence gathered over the past decades that sub-populations of women present with a heightened susceptibility to develop mood disorders during periods of intense hormonal fluctuations such as the puerperal period or the menopausal transition. Based on accumulate evidence, some have hypothesized that sub-groups of women would be exposed to "windows of vulnerability" for depression throughout their lifespan (Rubinow et al. 1998; Bloch et al. 2000). The basic premise is that a heightened brain's sensitivity to *changes* in levels of reproductive hormones—rather than exposure to absolute hormone levels (e.g., low estrogen concentrations)—could constitute the trigger for reproductive-related mood disorders. By recognizing the existence of these 'windows', the new DSM could not only promote a better conceptual framework and advance research on the biological underpinnings of mental disorders but also help clinicians to tailor clinical interventions for female-specific mood disorders with novel hormonal and non-hormonal strategies.

Animal studies and clinical data further support the hypothesis of 'windows of vulnerability' by documenting the effects of reproductive hormones—particularly estrogen—on various neurochemical pathways linked to depression. For example, estradiol β receptors are present in significant number in areas of medial amygdala, hippocampus and limbic system that are intimately involved in mood regulation. Estrogen regulates the expression of targeted genes and modulates the synthesis, release, and metabolism of monoamines; increases the number of serotonergic receptors and the transport and uptake of this neurotransmitter; increases synthesis of serotonin, up-regulates 5-HT1 receptors, down-regulates 5-HT2 receptors, influences the binding affinity for 5-HT receptors and decreases its metabolism via monoamine oxidase activity. In addition to its effects on 5-HT circuitry, estrogen augments noradrenergic (NA) activity by increasing NA turnover and decreasing NA reuptake, and decreasing the number and sensitivity of dopamine D2 receptors (Stahl 2001; Bethea et al. 2002; Kugaya et al. 2003; Soares et al. 2003).

Clinical trials that examined the antidepressant properties of estrogen provide further support of the existence of 'windows of vulnerability'—for that, the menopausal transition constitutes an elucidative example. The use of transdermal estradiol has shown to be efficacious in treating major depressive episodes in perimenopausal (Soares et al.

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2001; Schmidt et al. 2000) but not in postmenopausal women (Morrison et al. 2004) suggesting that timing for its use may be decisive. Estrogen also regulates the hypothalamic thermoregulatory center, where core body temperature control is a result of a fine balance of peripheral, neurochemical and vascular signals. During the menopausal transition and early postmenopausal years, the occurrence of vasomotor symptoms may imply dysregulation of one or more of these inputs; since estrogen fluctuations can affect the serotonergic and noradrenergic circuitry, it unlikely that the occurrence of vasomotor symptoms prior to or concomitant with the development of depressive disorders in menopausal women is merely accidental (Stahl 2009). Moreover, various psychotropic agents with serotonergic and noradrenergic properties seem to promote relief of both depressive and vasomotor complaints reinforcing the importance of taking into consideration hormonal and non-hormonal treatments for symptomatic, menopausal women (Joffe et al. 2007).

The argument used by some investigators that depression during female-specific critical times occurs due to a host of environmental changes and stressors (e.g., changes in family or professional roles during the perinatal period, physical illnesses and aging parents during the menopausal transition) shouldn't be seen as contrary to the 'critical window' hypothesis. Instead, based on the epigenetic model, it would be plausible to consider the occurrence of mood disorders during 'windows of risk' as a result of complex, modulatory effects of reproductive hormones and environmental stressors on vulnerable conditions (Payne et al. 2009). In addition, earlier exposure to stressful events (e.g., childhood trauma, abuse or neglect) and presence of psychiatric history could characterize a *continuum* of risk for some sub-populations, leading some to be at even greater risk for developing depression while facing these critical windows in life.

The challenges to integrate these concepts into the current format of DSM are substantial but it seems imperative that a revised DSM recognizes the contribution of sex hormones and reproductive staging to the development and/or susceptibility of psychiatric disorders. This way, we can continue disentangling the biologic, psychological and neurochemical aspects of these critical windows while better tailoring our treatment algorithms.

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