Depression and heavy bleeding during the menopausal transition: adjusting our gaze

Researched published during the past three decades has explored the relationship between mood and menstrual bleeding. Investigators have established the relationship between cyclical mood symptoms and the menstrual cycle, characterizing perimenstrual symptoms, premenstrual syndrome (PMS), and premenstrual dysphoric disorder. Although each of these has been defined with respect to clusters of multiple symptoms (such as mood and fluid retention), severity, and interference with daily living, evidence supporting their relationship with endocrine fluctuation has been mixed. Data support associations between levels of estradiol and progesterone and perimenstrual symptoms and fluctuations in these same hormones.

Additional evidence supports the persistence of these cyclical symptoms in women after the age of 40 years and as women approach menopause. Hypotheses relating entrainment of mood symptoms to circannual (menstrual cycle) rhythm have been augmented by evidence supporting the relationships of the same symptoms and symptom clusters to the context of women’s lives, including their socialization about menstruation, relationships, and material stressors, and perceived stress.

As the oldest of the baby boomers began to enter the menopausal transition, the gaze of many researchers refocused on this birth cohort of women. Efforts to understand an increasingly irregular menstrual rhythm and its relationship to depressed mood once again examined levels of estradiol and variability in hypothalamic-pituitary-ovarian (HPO) axis hormones. To date, there have been studies on the relationship of menstrual cycle to the next.

To induce menses. In the absence of ovulation, progesterone levels remain low, and the endometrium does not continue to develop and is shed with menses. Indeed, progesterone withdrawal is used therapeutically to induce menses.

One of the perturbations that can suppress menses or ovulation is exposure to extreme stress. An early study of depression and menorrhagia among adult women not yet experiencing the menopausal transition (aged up to 42 y) linked depression to menorrhagia. Sixty percent of women experiencing menorrhagia experienced a severely stressful event within a year versus 40% of those without menorrhagia. Moreover, 50% of those with menorrhagia had experienced a severe loss versus only 17% of those without menorrhagia. In addition, 78% of the women with menorrhagia experienced menorrhagia after the loss experience. The more recent Harvard Study of Women’s Moods and Cycles revealed that a lifetime history of physical and sexual abuse was associated with elevated FSH levels and low estradiol levels, suggesting that exposure to violence, especially before adulthood, may lead to neuroendocrine disruption.

The impact of stress or shock on the endocrine system was described long ago by traditional Chinese medicine (TCM) scholars. Classic theory relates a feedback loop between the Heart Qi (including emotions, much as western culture also

* A capitalized organ name indicates the TCM physiological and/or anatomical concept of an organ. This differs from the biomedical physiological function of the organ.
Heart Qi is supposed to descend, thus promoting timely ovulation and menses. Shock or stress can disrupt this physiological function, causing Qi and Blood stagnation. Stagnation can lead to generation of Heat, which may result in depression, anxiety, and/or heavy bleeding (depending on the individual). Furthermore, this feedback loop between the Heart and the Kidneys involves several additional meridians (where Qi primarily flows), specifically the Conception, Governing, and Penetrating meridians. The physiological function of these meridians and organs closely parallels HPO axis physiology and anatomy. The pathology of HPO can therefore be understood in both biomedical and TCM theories.

The plausibility of the relationship between depression and menstrual bleeding is supported by the capacity of the hypothalamic-pituitary-adrenal (HPA) axis to modulate HPO axis functioning in ways that regulate reproductive function, including suppressing ovulation and menstruation under stressful conditions. Thus, explanations for the association of depression with heavy bleeding could include stress-induced effects on the HPA axis with perturbation of HPO axis functioning, resulting in both depressed mood and heavy bleeding.

A second contributing factor could be the influence of the menopausal transition on estradiol levels. In response to increasing FSH levels, some women experience episodes of hyperestrogenism, as described by Santoro et al, and these hyperestrogenemic episodes are associated with heavy bleeding. Variable levels of estradiol during these episodes, many of which may be anovulatory, may also trigger depressed mood through effects on neurotransmitters such as serotonin and norepinephrine. Women who are vulnerable to endocrine changes earlier in life, such as those experiencing PMS or postpartum depression, may also be troubled by heavy bleeding during perimenopause. Of interest is that when women undergo hysterectomy, with or without oophorectomy, they are less likely to experience depressed mood than women who experience natural menopause.

Indeed, there may be multiple periods in the life span during which hormonal dynamics increases vulnerability to both depression and heavy bleeding. In addition to the postpartum period and the menstrual cycle, depressed mood becomes more prevalent among girls making the pubertal transition. Angold et al’s study of girls in Tanner stages II and III revealed that depression was explained by changing estrogen levels. Of added interest was that morning salivary cortisol levels were 20% higher in Tanner stage II+ girls versus boys. Tanner stages II and III are the periods in pubertal development when the prevalence of depression increases markedly in young girls, but not in boys. In addition to changing estradiol levels during the menopausal transition, cortisol levels rise during the late menopausal transition stage, tracking with the rise of estrogen levels during the same stage. These relationships suggest the importance of the HPO-HPA axes in modulating both bleeding and depression.

Yet another explanation for the relationship between depression and heavy bleeding involves the role of depression in shaping one’s outlook. Heavy vaginal bleeding is generally regarded as a worrisome sign and is included as one of the warning signs for cancer. To a woman who is depressed or troubled by depression symptoms, heavy bleeding is both a sign and a symptom that requires an appraisal of seriousness and frequent attention to menstrual hygiene. Together, these contribute to a negative view of menses as a bodily function and may be perceived as interfering with activities of daily life. Heavy bleeding also is likely to rise quickly to conscious awareness and to stimulate stress arousal and symptom reporting.

In the SWAN MHS cohort, other risk factors for heavy bleeding included being in the early menopausal transition stage, having had more pregnancies, a higher body mass index (BMI), and a history of fibroids. BMI has been implicated in the extraovarian production of estrogen and in perturbations of the HPO axis function. Still another pathway may involve the effects of major depression on behavior, such as eating behavior, in turn increasing BMI, which is related to heavy bleeding.

Yet another explanation for the association of depressed mood with heavy bleeding can be found in the emergent view of depression as an illness with a myriad of correlates and consequences, including inflammatory, hemostatic, and lipid changes. Indeed, depression may also be regarded as a signal of physiological dysregulation, much as one regards heavy vaginal bleeding. It is possible that both are indicators of underlying perturbations that are unrelated to one another, except through their contribution to allostatic load.

The complexities of the relationship between depression and heavy bleeding will be best addressed by conducting research tracking women’s experiences during the reproductive life span and by incorporating a view spanning molecules to the organism. Women who experience both depression and heavy bleeding during the menopausal transition will be served best by researchers redirecting our gaze from only perimenopause to mood and bleeding patterns that women experience throughout their reproductive life. Moreover, re-focusing our view of depression as a discrete mental illness into an expression of loss of complexity in a highly ordered dynamic state, as informed by systems biology, will expand our understanding of depression and its myriad correlates. Such an integrative view prompts scientists to recognize that seemingly single phenotypic entities can have multiple etiologic and/or pathological processes. This integrative view is emblematic in TCM. Any given symptom is seen only in relationship to other symptoms. For this reason, women with heavy menses may be diagnosed and treated differently according to the cluster of symptoms and signs presented.

Moreover, taking a broader view of the phenomena reminds us that the defining feature of healthy functioning is the capacity to respond to unpredictable stimuli and that disease
is an expression of loss of complexity in a highly ordered dynamic state. The symptom patterns discussed here are thus likely to be local expressions of far-reaching global disturbances.

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