

## Chronic Inflammation and Premenstrual Syndrome: A Missing Link Found?

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**P**REMENSTRUAL SYMPTOMS ARE highly prevalent among women of reproductive age. Population-based studies suggest as much as 85%–90% of women regularly experience one or more physical, emotional, or behavioral symptoms before the onset of menses.<sup>1</sup> For the majority of women, symptoms are relatively mild and do not adversely impact quality of life. For 15%–20% of women, symptoms are severe enough to impair regular functioning and are consistent with clinical criteria for premenstrual syndrome (PMS).<sup>2</sup> Approximately 3%–8% of women with severe emotional symptoms may also meet criteria for premenstrual dysphoric disorder. Despite extensive research, the etiology of premenstrual symptoms and PMS remains poorly understood. Fluctuations in sex steroid hormones are undoubtedly important, but studies have not identified clear differences in levels of estradiol, progesterone, or other hormones between women experiencing and not experiencing premenstrual symptoms. Neural, psychosocial, and behavioral factors are also likely to influence the type and severity of symptoms experienced, but few contributors have not been conclusively established.

There is emerging interest in determining whether chronic inflammation contributes to premenstrual symptoms and PMS. The immune system plays an important role in many aspects of female reproductive function, including follicular recruitment, ovulation, implantation, and endometrial repair.<sup>3</sup> In premenopausal women, plasma and endometrial levels of inflammatory factors including C-reactive protein (CRP), interleukin (IL)-6, IL-1 $\beta$ , and tumor necrosis factor- $\alpha$  increase after ovulation and are highest during menstruation.<sup>4</sup> The magnitude of cyclic changes in immune markers differs measurably between women; it is plausible that variations in immune function that promote chronic systemic inflammation contribute directly to premenstrual symptom expression.

Extensive work has linked chronic inflammation to psychiatric and somatic disorders sharing common features with PMS, including depression, anxiety, migraine headache, and irritable bowel syndrome.<sup>5–8</sup> Very few studies to date have directly evaluated the association of inflammation and premenstrual symptoms or PMS, but results are remarkably consistent. Puder et al. (2006) reported that CRP levels were positively associated with symptom severity in 15 healthy women, with associations strongest for mood and pain symptoms.<sup>9</sup> In a recent study of 277 younger women, both emotional

and physical premenstrual symptom scores were positively associated with levels of several inflammatory factors, including IL-2, IL-4, IL-10, IL-12, and interferon-gamma.<sup>10</sup> Levels of IL-12 and interferon-gamma were more than twice as high in PMS cases versus controls, even after adjustment for body mass, smoking, and other PMS risk factors.

Because previous work in this area is so limited, new work by Gold et al. presented in this issue of the *Journal of Women's Health* contributes importantly to knowledge of chronic inflammation and PMS.<sup>11</sup> Using data from the large, multiethnic Study of Women's Health Across the Nation, the authors assessed the association of elevated CRP levels with premenstrual symptom severity among 2939 premenopausal and early perimenopausal women. At baseline (1996–97), women reported the presence or absence of each of eight symptoms in the week before menses or during menses, and whether symptoms ended within 1–3 days of menses onset. Factor analysis was used to identify five distinct symptom groups from among reported symptoms. Women provided a fasting blood sample, assayed for hsCRP; women with levels >3 mg/L were classified as having elevated CRP. After adjustment for important demographic and behavioral factors including body mass index and level of social support, elevated CRP was associated with significant 26%–41% higher odds of four of the five symptom groups evaluated: anxiety/jittery/nervous, and mood changes; abdominal cramps and back/joint/muscle pain; increased appetite/craving and weight gain/bloating; and breast pain/tenderness. In contrast, elevated CRP was not associated with odds of headache.

This is not only the largest but also the most racially and ethnically diverse study of inflammation and premenstrual symptoms conducted to date. Importantly, observed associations did not vary by race or ethnicity, supporting the wide generalizability of this association. Participants in the Study of Women's Health Across the Nation are older than women previously studied (mean age of participant at baseline was ~46), demonstrating that inflammation is involved in premenstrual symptom expression in older premenopausal as well as younger premenopausal women.

Additional questions are raised by these findings and set a path for ongoing research. The temporality of relations remains unclear, as all studies on inflammation and premenstrual symptoms conducted to date have been cross-sectional. It is unknown whether immune dysfunction contributing to

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chronic inflammation actually precedes the onset of premenstrual symptoms. The alternative is also plausible: treatments for premenstrual symptoms, behavioral changes in response to symptoms, and/or symptoms themselves could potentially alter inflammatory factor levels. Prospective studies directly evaluating levels of inflammatory factors versus timing of premenstrual symptom onset or worsening will be required to fully understand how these are etiologically related. Prospective evaluations will also be necessary to determine whether treatments targeting inflammatory pathways have the potential to improve symptom severity.

Determining a causal relationship between chronic inflammation and premenstrual symptoms could also put PMS in a larger context. PMS may plausibly share a common etiology with conditions related to chronic inflammation that tend to occur later in the life course, such as hypertension, coronary heart disease, and type 2 diabetes. This possibility is supported by results from a recent prospective study suggesting that women with PMS have a higher risk of subsequently developing hypertension than control women.<sup>12</sup> Establishing PMS as an inflammatory condition suggests that PMS may be a useful sentinel of future chronic disease risk, allowing for earlier identification of women at elevated risk and thereby enhancing prevention options. This intriguing possibility also suggests that treatment of premenstrual symptoms with therapies targeting inflammation could have positive impacts on long-term chronic disease risk.

A better understanding of how immune dysfunction and chronic inflammation contribute to premenstrual symptoms could have important implications for primary prevention and provide new avenues for treatment. As millions of women are adversely affected by PMS on a monthly basis, continued research in this area is essential.

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