Partnered sexual activity moderates menstrual cycle–related changes in inflammation markers in healthy women: an exploratory observational study

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Objective: To examine differences in inflammation markers in sexually active versus abstinent women and observe changes in inflammation markers across the menstrual cycle. Cycle-related immune fluctuations may have evolved to reduce interference with conception. If so, reproductively active (i.e., sexually active) women should show the most variability in cytokine expression.
Design: Participants provided serum samples at menses and ovulation (from which cytokines were assayed) and saliva samples at menses and during follicular, ovulation, and luteal phases (from which C-reactive protein [CRP] was assayed). Participants self-reported intercourse frequency during the study.
Setting: Academic research laboratory.
Patient(s): Thirty-two healthy, naturally cycling premenopausal women (sexually active, n = 15; abstinent, n = 17).
Intervention(s): Observational study.
Main Outcome Measure(s): Levels of proinflammatory cytokines (interleukin-6 [IL-6], interferon γ [IFN-γ], tumor necrosis factor-α [TNF-α]), an anti-inflammatory cytokine (interleukin-4 [IL-4]), and a marker of total inflammation (CRP).
Result(s): Sexually active women had higher levels of all of the immune markers measured, including both pro- and anti-inflammatory cytokines, than abstinent women. Relative to sexually active women, abstinent women had less change across the menstrual cycle in levels of CRP. Among sexually active women, higher intercourse frequency predicted greater midcycle decreases in CRP, IL-6, and IFN-γ and midcycle increases in IL-4.
Conclusion(s): Sexual activity may stimulate a complex interaction between pro- and anti-inflammatory cytokines that subsequently drives midcycle declines in inflammation. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Inflammation, sexual activity, menstrual, C-reactive protein, interleukin-6, cytokine, interferon-γ, tumor necrosis factor-α, interleukin-4

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Inflammation is a critical process in the immune response, as it is the first-line defense against pathogens, tissue healing or remodeling, and toxin containment and removal. Variations in inflammation drive variations in symptoms such as fatigue (1), pain (2), and depression (3). In premenopausal women, inflammation varies significantly across the menstrual cycle (4). Several studies have documented midcycle decreases in markers of inflammation, with higher levels at menses (5, 6) and a nadir around ovulation (4, 7). Such variation has important implications for research and the clinical interpretation of inflammation biomarkers. One study examined values of C-reactive protein (CRP), a marker of inflammation commonly used to index heart disease risk, and found that failure to account for menstrual cycle–related variability

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doubled the chances of misclassification of heart disease risk in a large sample of healthy women (8).

The curvilinear pattern in CRP has been attributed to a fundamental trade-off between reproduction and immune response: for conception to occur, the female immune system must provide a conducive environment for sperm and conceptus. Local inflammation can impair sperm motility (9) and make the uterine environment more hostile to implantation (10). More broadly, inflammation in general circulation can interfere with conception in two significant ways. First, systemic inflammation can signal a potential infection or injury, which would divert energetic resources from reproduction to somatic maintenance or defense (11–13). Second, the female reproductive tract uses inflammatory signals such as cytokines to coordinate ovulation and implantation (14); in the presence of high systemic inflammation, however, these small, local inflammation signals fail to appropriately trigger the processes that lead to ovulation or implantation (10, 15)—potentially leading to poorer rates of conception.

Thus, it is argued, a midcycle decrease in systemic inflammation—corresponding to peak fertility—may have evolved to reduce potential disruption of reproduction (11). If so, it would follow that these effects would be most critical (and most subject to evolutionary selective pressure) in individuals who are reproductively active, that is, regularly engaging in sexual activity. Indeed, several studies suggest that immune parameters, including inflammatory cytokines, differ in sexually active versus abstinent women (16–18), with sexually active women showing more variation in immune markers across the menstrual cycle than abstinent women (13, 19, 20). Thus, we would expect that inflammation would differ significantly across the menstrual cycle in sexually active but not in abstinent women.

We examined this hypothesis by comparing changes in pro- and anti-inflammatory cytokines as well as CRP across a menstrual cycle in women who were abstinent and women who were sexually active with a partner. We assessed four primary cytokines: interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-4 (IL-4). The first three are commonly measured as an index of inflammation signaling (21, 22), while IL-4 is considered an "anti-inflammatory" cytokine (23). We included an anti-inflammatory cytokine as there is some work suggesting sexual activity may influence inflammation through shifting T-helper cell profiles (20). In addition to their important roles in coordinating inflammation, IFN-γ, TNF-α, and IL-6 interact with the central nervous system, supporting a suite of behavioral effects related to sickness (e.g., loss of appetite, decreased motivation for social interaction) (24). More specifically, IFN-γ is predominantly produced by natural killer cells and cytotoxic T cells (25) and is a potent activator of macrophages, which in turn induce local inflammation (26). TNF-α is produced primarily by activated macrophages and mast cells and stimulates the release of histamines and other inflammation-causing agents (27). Both TNF-α and IFN-γ have been identified as particularly predictive of early pregnancy loss (28, 29) owing to their role in stimulating natural killer cells in the uterus (28). Thus, suppressing these proinflammatory cytokines could improve the chances of sexual activity leading to offspring. IL-6 is widely used by a variety of immune actors such as T-cells and macrophages and is an important mediator of inflammation and acute phase response (see, however, Schindler et al. [30] for discussion of IL-6's anti-inflammatory effects via suppression of IFN-γ-producing cells). Finally, CRP is an acute phase protein induced by the liver in response to cytokines such as IL-6 and has a relatively short half-life ($\sim$48 hours); as such, it is a good index of total current inflammation across the body (13).

There have been several studies investigating menstrual variations in cytokines and CRP. In healthy nonpregnant women, higher levels of IL-4 have been observed in the luteal phase relative to the follicular phase (20, 31). Studies of IFN-γ, TNF-α, and IL-6 have had more mixed findings, with some studies documenting decreases from early to mid- or late cycle (32–34) and others increases (35, 36) or no change (37). Similarly, studies of menstrual cycle variations of CRP have been mixed, with some showing a midcycle nadir and others a midcycle peak or no change (4, 6, 7, 38, 39). The variability in findings may be due to lack of consideration of the timing (or even occurrence) of ovulation. The largest and best-controlled study to date, which accounted for differences in luteal phase progesterone (P_4) in ovulatory and anovulatory cycles, found that markers of inflammation were lowest at ovulation and rose during the luteal phase (4). Similarly, confusion across studies may occur due to lack of consideration of sexual activity. A recent study found that among women with ovulatory cycles, being sexually active (dichotomized as yes/no) was associated with a U-shaped pattern of serum CRP, while sexual abstinence was associated with no significant change across the cycle (13); unfortunately, this study did not measure the frequency of sexual activity or cytokine concentrations.

In the present study, our primary analysis compared women by sexual activity status (currently sexually active vs. abstinent). As a secondary analysis, we also considered the potential effect of frequency of sexual activity (within sexually active women only), as this may reflect how the immune system interprets sexual activity as a reflection of reproductive state and, by extension, the need for flexibility in how it interprets the "self." One of the most puzzling questions in immunology is how the immune system adapts its responsiveness over time, maintaining vigilance while also learning tolerance of elements that are different from the original self but not harmful (e.g., commensurate microbes, the body's own cells as it grows and changes over time). One recent theory addresses this problem by introducing the concept of the "liquid self," a flexible state that adapts the distinction between self and nonself over time. The individuals' life history and reproductive state are particularly important in how the immune system considers the self, increasing the dynamicity of potential responses (40). For example, a fetus is nonself and thus could potentially trigger an inflammatory response; however, these cells are tolerated by the maternal immune system owing to the flexible immune response associated with the reproductive state of pregnancy. Similarly, there may be different responses during the fertile window of the menstrual cycle versus nonfertile times. Finally, immune responsivity includes regulatory processes;