Menstrual Phase Key in Tracking Hs-CRP Levels

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SEATTLE — Careful timing in measuring high-sensitivity C-reactive protein during the menstrual cycle can make all the difference in classifying young women's risk of cardiovascular disease, new data show.

In a study of 259 healthy premenopausal women, high-sensitivity C-reactive protein (hs-CRP) levels fluctuated over the course of the menstrual cycle, with the highest (and most variable) levels seen during menses and the lowest seen at ovulation, researchers noted.

The proportion of women classified as having a high or moderate risk for cardiovascular (CV) disease based on their levels of hs-CRP was significantly greater when levels measured during menses were used (41%) than when levels at ovulation were used (29%).

"The measurement of CRP in clinical settings and in future research studies should be standardized to the menstrual cycle phase," said lead investigator Audrey J. Gaskins, a postbaccalaureate fellow at the National Institute of Child Health and Human Development in Rockville, Md.

Since ovulation can be difficult to time, "Any time other than menses, would be ideal," she said.

Evidence suggests that estrogen may modulate inflammation to a clinically relevant extent when it comes to CV outcomes, Ms. Gaskins noted.

"The risk of coronary events rises in women after menopause, and this corresponds to when endogenous estrogen levels decrease," she said. "Studies have shown that in regularly menstruating women, there are more acute coronary events in the early follicular phase, when estrogen levels are lowest."

Ms. Gaskins and colleagues analyzed data from normally menstruating women, average age 27 years, who were followed for up to two menstrual cycles in the BioCycle Study. Serum samples collected at eight distinct times during the menstrual cycle were assayed for levels of hormones and hs-CRP. Any hs-CRP values exceeding 10 mg/L were excluded.

Ms. Gaskins noted that the population was more diverse than those in previous studies. Some 59% of the women were white, 20% were black, and 21% were of other races. Although 61% had a body mass index in the normal range, 25% were overweight, 10% obese, and 3% underweight (percentages rounded). Seventy four percent were nulliparous, and 4% were smokers.

Hs-CRP levels varied widely over the menstrual cycle. They were highest and also showed the greatest inter-individual variability during menses, and lowest at ovulation, with a 1.6-fold difference in values between these two times.

In adjusted models, hs-CRP was significantly associated both with estradiol across the menstrual cycle and with progesterone during the luteal phase. Specifically, hs-CRP levels fell by 24% with each tenfold increase in estradiol level and increased by 19% with each tenfold increase in luteal progesterone level.

In a final analysis, the investigators used the American Heart Association risk classification system, whereby CV disease risk is considered high if hs-CRP level is greater than 3 mg/L and moderate if it is 1-3 mg/L.

Although 32% of women had hs-CRP levels in the high-risk category at at least one time point during the menstrual cycle, only 2% consistently had levels in this category at all eight time points.

Some 41% of the women had hs-CRP levels that placed them in the high- or moderate-risk category during menses; only 29% had high levels at ovulation. The percentages at all other times, except for the midluteal time point, were also significantly lower than those at menses.

"This is the largest study by far to look at hs-CRP and reproductive hormones in healthy premenopausal women," noted Ms. Gaskins. "Our results support the hypothesis that estrogen might have anti-inflammatory effects. In regard to progesterone, our results support an inflammatory role."

Ms. Gaskins reported that she had no relevant conflicts of interest. ■