Relationships between the luteinizing hormone surge and other characteristics of the menstrual cycle in normally ovulating women

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Objective: To describe the LH surge variants in ovulating women and analyze their relationship with the day of ovulation and other hormone levels.
Design: Secondary analysis of a prospective cohort observational study.
Setting: Eight natural family planning clinics.
Subjects: Normally fertile women (n = 107) over 283 cycles.
Intervention(s): Women collected daily first morning urine, charted basal body temperature and cervical mucus discharge, and underwent serial ovarian ultrasound.
Main Outcome Measure(s): Urinary LH, FSH, estrone-3-glucuronide (E3G), pregnanediol-3α-glucuronide (PDG), and day of ovulation by ultrasound (US-DO).
Result(s): Individual LH surges were extremely variable in configuration, amplitude, and duration. The study also showed that LH surges marked by several peaks were associated with statistically significant smaller follicle sizes before rupture and lower LH level on the day of ovulation. LH surges lasting >3 days after ovulation were associated with a lower E3G before ovulation, a smaller corpus luteum 2 days after ovulation, and a lower PDG value during the first 4 days after ovulation.
Conclusion(s): In clinical practice, LH profiles should be compared with the range of profiles observed in normally fertile cycles, not with the mean profile. (Fertil Steril® 2013;99:279–85. ©2013 by American Society for Reproductive Medicine.)
Key Words: LH surge, ovulation, menstrual cycle, luteinizing hormone

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In clinical practice, as in research on menstrual cycles, the gonadotropin and ovarian hormone secretion profiles considered to be normal are averages of individual hormonal profiles, with a "normal range." This range of normal variability is used in everyday practice to diagnose cycle abnormalities. However, the variability of menstrual cycles, both between and within women, is a well known phenomenon (1–3). In the past, studying cycles that they supposed to be normal, many researchers discarded a significant number of these cycles before calculating the normal variability. For example, Renaud et al. (4), Queenan et al. (5), and Polan et al. (6) classified as abnormal 44%, 22%, and 36% of spontaneous cycles, respectively. These proportions are too high to be accepted without further consideration.

In the past decade, several authors have proposed to go beyond a simple description of a range of normal values and classify hormone trajectories. Alliende (7) showed that most individual hormone trajectories in women of proven fertility differed considerably from the mean hormone curves. That author recommended giving more attention to this diversity in future research.

Park et al. (8) emphasized the extreme variability of the LH surge and showed that ovulatory LH surges

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are not of a single type but are rather extremely variable in configuration, amplitude, and duration. The LH surge configuration is classically described as a single peak, but it may also be a double-peak or a plateau (7, 8). Park et al. described a large range of LH amplitudes: 2.5–14.8 times the baseline level. The duration of the LH surge, classically 3 days, was found to range from 5 to 11 days. However, those authors did not study the relationships between LH surge variants (8) (configuration, amplitude, and duration) and the profiles of other hormones, nor did they identify the timing of the LH surge relative to the day of ovulation.

In the middle 1990s, a database collected daily urinary hormone measures, recordings of basal body temperature, cervical mucus observations, and serial ovarian ultrasound in normally ovulating women. A previous analysis (9) has examined the mean hormone levels and their correlation with ovulation but did not analyze the variants of ovarian and gonadotropin secretions. The present article is a secondary analysis addressing the question of the relationships between the LH surge variants, the profiles of other hormones, and the process of ovulation and luteinization.

MATERIALS AND METHODS

Subjects

The subjects of this prospective cohort study were approached in the middle 1990s in eight natural family planning centers across five European countries: Aix-en-Provence, Dijon, and Lyon, France; Milano and Verona, Italy; Düsseldorf, Germany; Liège, Belgium; and Madrid, Spain.

The inclusion criteria were ostensibly healthy menstruating women aged 18–45 years, with a history of previous menstrual cycle lengths of 24–34 days and an experience in natural family planning methods, i.e., recording of basal body temperature and observation of cervical mucus. Women with frequent anovulatory cycles, taking any hormonal treatment, with known disturbances of follicular development, or with a history of infertility were excluded. Women with a history of gynecologic surgery, such as hysterectomy, tubal ligation(s), or pelvic inflammatory disease, as well as runners, breastfeeding women, and those $\leq$3 months postpartum were also excluded. Each of the 107 women meeting all of the inclusion criteria contributed with an average of 3 cycles. The study examined 326 cycles.

At study initiation, each woman completed a standard questionnaire and underwent a physical examination. The data collected were current age, age at menarche, current body mass index (BMI), gynecologic history, parity, past oral contraceptive use, lifestyle habits, such as smoking, special diets, and physical activity (hours per week), and current stress (general subjective feeling).

The initial study for which the data were collected was a multicentered collaborative study coordinated by Claude Bernard University (Lyon, France) (9). The study obtained Institutional Review Board approval from the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Lyon. The women were informed of the purpose of the investigation and told that they were free to withdraw at any time, and each of the participants gave her written informed consent. The study procedures were carried out in accordance with the Ethical Standards for Human Experimentation established by the Declaration of Helsinki.

Investigations

During the studied cycles, each woman recorded daily, in a specific individual chart, her basal body temperature (BBT) before bed rise, as well as the date, the day of the cycle, and any event or condition that might affect BBT (late rise, stress, illness, insomnia, etc.) (10, 11).

Two or three times daily, each woman checked the opening of the vagina for changes in cervical mucus and recorded in her chart the sensation (dry, moist, wet, or lubricative) and the consistency (tacky, creamy, or stretchy) (12–14).

The women collected daily first morning urine samples, which were immediately divided into aliquots of 10–12 mL and frozen at -20°C in tubes containing gentamicin sulphate. They were later unthawed and assayed in the same laboratory in a single session for quantitative hormone detection of estrone-3-glucuronide (E3G), pregnanediol-3α-glucuronide (PDG), FSH, and LH with the use of time-resolved fluorometric immunosorbent assays (Delfia). All samples from each woman were tested in duplicate in the same assay and the results adjusted for creatinine (Cr). Interassay variations were negligible; intra-assay variations were 5.7%, 6.8%, 7.9%, and 8.0% for PDG, E3G, LH, and FSH, respectively (9).

Serial transvaginal ovarian ultrasounds with follicle measurement were performed by a single physician per center. Scanning was performed every other day until a follicle reached 16 mm and then daily until evidence of ovulation.

The maximum follicle size was the maximum diameter of the largest follicle observed by ultrasonography during the cycle. The ultrasound-determined day of ovulation (US-DO) was defined as the 24-hour interval between the visualization of a mature follicle in one scan and evidence that ovulation had occurred in the subsequent scan.

Further details concerning investigations were previously published (9).

LH Surge Variants

The LH surge was the series of high LH values close to the US-DO.

Amplitude. In agreement with Park et al. (8), we computed the baseline LH as the mean of five daily LH values immediately before the onset of the LH surge. The LH peak was the maximum LH value during the surge. The amplitude of the LH surge was the difference between the peak and the baseline LH values. The LH surge fold increase was the peak LH value divided by the baseline LH value.

Duration. To define the onset and the end of the LH surge, we drew a horizontal line at 30% of the amplitude of the LH peak. The onset and the end of the surge were respectively the first and last days when the LH surge was above the 30% line. The duration of the LH surge was the number of days above that line.

Configuration. The LH surge was classified as single spiked if the LH peak was maintained over the horizontal line at 30% of the amplitude of the LH peak for $\leq$5 days. It was classified as