ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Characterization of follicle stimulating hormone profiles in normal ovulating women

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Objective: To describe FSH profile variants.
Design: Observational study.
Setting: Multicenter collaborative study.
Patient(s): A total of 107 women.
Intervention(s): Women collected daily first morning urine and underwent serial ovarian ultrasound.
Main Outcome Measure(s): FSH.
Result(s): The individual FSH cyclic profiles demonstrated a significant departure from the currently accepted model. A decline in FSH levels at the end of the follicular phase was observed in only 42% of cycles. The absence of this decline was significantly associated with a shorter luteal phase and higher pregnanediol-3α-glucuronide, FSH, and LH levels at the time of ovulation. In 34% of the cycles, significant FSH variability was observed throughout the follicular phase; this variability was associated with higher body mass index and lower overall FSH and LH levels throughout the cycle. The FSH peak occurs on average 2 hours before ovulation. The FSH peak duration was shorter than the LH peak.
Conclusion(s): These results suggest that average FSH profiles may not reflect the more complex dynamics of daily hormonal variations in the menstrual cycle. It is possible that discrepancies between the average normal FSH profile and the individual day-to-day variants can be used to detect abnormalities. (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)
Key Words: Follicle-stimulating hormone, ovulation, menstrual cycle

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Several recent publications have renewed interest in the assessment of individual hormonal profiles during the menstrual cycle (1–3). Although simplifications of the menstrual cycle are necessary for a basic understanding of physiology, there may be a place in clinical practice and research to take into account the departure of individual hormonal profiles from that the average population, particularly for LH and FSH.

For example, it was recently shown that most individual LH profiles differed from the classic mean curves: Long or double LH surges are frequent and extremely variable in configuration, amplitude, and duration (3). Differences in hormonal profiles were associated with differences in the luteinization process (3). In another study, it was shown that a deficiency in corpus luteum function was associated with implantation failure, which may relate to individual hormonal profiles (4).

Individual FSH patterns also are of particular interest because this hormone is known to assist in the recruitment and growth of ovarian follicles as well as the selection of the dominant follicle. During the normal menstrual cycle, FSH rises in the late luteal or early follicular phase (5, 6). FSH levels are typically

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assessed on days 2–4 of the cycle. Nevertheless, FSH has been shown to be rather unstable during this early follicular phase, with day-to-day variations (7, 8). During the late follicular phase, FSH falls to a relatively low level, a decline which is thought to interact with the follicular selection process (9). An FSH midcycle peak has been described as occurring the day of the LH peak, but many authors have questioned the temporal relationship between these two events (10–12).

In the present study, individual FSH profiles are analyzed to describe variations in the overall trend from early to late follicular phase, the day-to-day variability in the follicular phase, the change in FSH during the transition between two successive cycles, and the temporal relationship between the FSH midcycle peak and ovulation.

MATERIALS AND METHODS

Patients

Patients were recruited from 1996 to 1997 from eight natural family planning clinics in France, Italy, Germany, Belgium, and Spain. The inclusion criteria consisted of women aged 19–45 years with previous menstrual cycle lengths of 24–34 days. Exclusion criteria included women with a consistent history of anovulatory cycles, infertility or active hormonal treatment of infertility in the past 3 months, use of hormonal contraception or hormonal replacement in the past 3 months, abnormal cycles (polycystic ovary syndrome or luteal defect), hysterectomy, tubal ligation(s), or pelvic inflammatory disease. In addition, runners and breastfeeding or postpartum mothers (<3 months) were excluded.

A total of 107 women were finally recruited, contributing an average of three cycles. The study examined 326 cycles which have been analyzed in other studies (3).

The study was approved by the local Ethics Committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Lyon). Each of the participants gave her written informed consent, and the study procedures were carried out in accordance with the Ethical Standards for Human Experimentation established by the Declaration of Helsinki. Owing to legal-commercial disclosure agreements, the results regarding hormonal details were not published until now; this paper presents those results.

Investigations

Data collected from patients included information on age, age at menarche, parity, past oral contraceptives use, lifestyle habits, such as smoking, diet, and physical activity (h/wk), sleep duration (h/d), and stress levels (subjective assessment). Height and weight were measured and body mass index (BMI) calculated.

Hormonal investigations. The women collected first morning urine samples daily, which were stored frozen until assayed in the laboratory for quantitative hormone detection of estrone-3-glucuronide (E1G), 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 were adjusted for creatinine (Cr). Interassay variations were negligible.

Ultrasound investigations. Serial transvaginal ovarian ultrasounds with follicle measurement were performed by a single physician per center. Ovarian scanning started on the first day women observed cervical mucus or when an LH surge was detected by LH home tests (Quidel Corp.), whichever came first. Scanning was performed every other day until a follicle reached 16 mm and then daily until evidence of ovulation. Details regarding ultrasound investigations were previously published (13).

Other Characteristics of the Menstrual Cycle

Phases of the cycle. The first day of the menstrual cycle was self-reported by the women. This was defined as the first day of the menstrual period where the woman observed bright red blood. Brown spotting was not considered to be a menstrual period.

For the purposes of this study, the menstrual cycle was divided into three phases: the latent phase, the fertile window, and the luteal phase. The latent phase is from the first day of the cycle to the day before the fertile window. The fertile window based on pregnancy probabilities has been shown to be a 6-day period ending on the day of ovulation (14). In the present study, the fertile window was defined as the first day of mucus observed at the vulva to the end of the ultrasound-determined day of ovulation (US-DO; the presence of mucus, felt or seen at the vulva by the woman, has been shown to be the main observable sign of fertility [15]). The luteal phase is from the day after US-DO until the day before the first day of next menses. Cycles with a luteal phase of >17 days were considered to be possible pregnancies. Proven pregnancies were defined by a positive urine β-hCG test.

Hormonal levels. To characterize hormonal levels during the three phases of the cycle, the average level of each hormone was calculated on days 2, 3, and 4 after the first day of menses (latent phase), on US-DO $\pm$1 day (fertile window), and on US-DO +5, +7, and +9 days (luteal phase).

To assess the evolution of FSH approaching ovulation quantitatively, we calculated the average FSH level on US-DO −12, −11, and −10 days (early follicular phase), and on US-DO −3, −2, −1 days (late follicular phase). The trend was estimated with the use of the difference between these two values (without logarithm transformation). The variance of logarithm-transformed FSH levels from day −11 to day −2 was estimated to reflect the stability or fluctuation of FSH.

The day of peak concentration for FSH and LH was identified within a 10-day window beginning 5 days before and ending 5 days after US-DO, which was designated as day 0. The days of maximum concentration of FSH, i.e., the midcycle peak, was identified, and the number of days from US-DO to the day of that peak was recorded.

Statistical Analysis

The geometric means of all 283 FSH and LH profiles were calculated and displayed graphically. US-DO was used as a reference day.