Luteinizing Hormone Pulse Characteristics in Depressed Women

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Objective: Luteinizing hormone (LH) pulse characteristics in depressed and normal women were compared to determine whether hypothalamic dysregulation in depression extends to the hypothalamic-pituitary-gonadal axis. Method: The subjects were 10 depressed and 13 normal comparison women admitted to a clinical research center. For each woman, an intravenous line was started and blood was withdrawn every 10 minutes for 8 hours. Blood samples were assayed for LH and LH pulse characteristics determined by using the computerized cluster algorithm of Veldhuis and Johnson. Results: The depressed women differed significantly from the comparison women in LH pulse amplitude, rhythmicity, and area under the curve. Conclusions: Major depressive disorder is associated with abnormal regulation of luteinizing hormone. Gonadotropin regulation may provide a hormonal link between major depressive disorder and impaired fertility.

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Major depression is a common disorder that will affect at least 10% of women (DSM-III-R, p. 229). It is associated with abnormal hypothalamic regulation of a variety of neuroendocrine systems. If this dysregulation affects the hypothalamic-pituitary-gonadal (HPG) axis, potential physiologic manifestations could include impaired fertility, a condition of increasing clinical and social relevance for which an estimated 3 million couples sought treatment in 1995 (1).

Regulation of the HPG axis depends on hypothalamic control of gonadotropin-releasing hormone. The frequency, amplitude, and perhaps other characteristics of the pulsatile release of gonadotropin-releasing hormone must fall within certain limits for maintenance of normal HPG axis functioning (2). Peripheral plasma concentrations of gonadotropin-releasing hormone are too small to be accurately assayed. However, because of its high correlation with luteinizing hormone (LH) release, gonadotropin-releasing hormone can be indirectly assessed by characterization of LH secretory patterns (3, 4). In the current study, 8-hour LH pulse characteristics of depressed women and normal subjects were compared in order to determine whether depression alters HPG axis function.

METHOD

Twenty-three women between the ages of 18 and 40 years were recruited. Ten were psychiatric outpatients who met the DSM-III-R criteria for current major depressive episode (eight had major depression, recurrent; two had bipolar disorder not otherwise specified and were currently depressed), and 13 were normal subjects without any current axis I diagnoses. The mean age of the depressed women was 30.7 years (SD=3.8, range=26–37). The mean age of the comparison women was 30.1 years (SD=6.3, range=20–39). The depressed patients were initially diagnosed in a clinical interview using DSM-III-R criteria. They also met the Research Diagnostic Criteria (eight had recurrent unipolar depression; two had bipolar disorder and were currently depressed) according to the Schedule for Affective Disorders and Schizophrenia (SADS) (5). The comparison subjects were screened with the nonpatient version of the SADS. A subject was excluded if she had a history of other axis I diagnoses, current major medical illness, current use of birth control pills, a history of endocrinopathy, oophorectomy, current hormone replacement, or current amenorrhea. Each subject was free of psychotropic medications and was tested during the first week of her menstrual cycle. After complete description of the study to the subjects, written informed consent was obtained.

The subjects were admitted to the University of Minnesota General Clinical Research Center at 10:30 a.m. An accurate weight was obtained, and an intravenous line with 5% dextrose in water (to keep it open) was started. Beginning at 11:00 a.m., a 5-ml blood sample was collected every 10 minutes for 8 hours, the "intensive sampling method" (6). Blood was drawn into heparinized tubes, immediately placed on ice, and centrifuged within 1 hour. The plasma was then stored at –70°C until assayed.

The plasma samples were assayed for LH by means of a commercially available enzymatic-immune assay. The intra-assay coefficients of variation were 5.5%, 3.1%, and 3.6% at 5.4, 43.2, and 82.5 mIU/ml, respectively. The interassay coefficients of variation were 8.7%, 6.4%, and 6.2% at these concentrations.

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TABLE 1. Eight-Hour Luteinizing Hormone Pulse Characteristics of 10 Depressed Women and 13 Normal Comparison Women

	Depressed Women		Comparison Women		ANOVA		
Pulse Characteristic	Mean	SD	Mean	SD	F	df	p
Number of peaks over 8 hours	3.7	1.2	4.3	1.1	1.63	1, 21	0.20
Maximum change in amplitude (IU/liter)	1.9	0.9	1.3	0.5	1.84	1, 21	0.05
Net area under the curve (IU/min·liter)	95.8	66.9	49.7	19.3	5.63	1, 21	0.03
Log-transformed standard deviation of interpeak intervals (log min)	1.65	0.39	1.29	0.33	4.95	1, 18	0.04

The LH pulse characteristics for each subject were analyzed by means of the computerized algorithm cluster analysis of Veldhuis and Johnson (7). Pulse characteristics such as amplitude, interpeak interval, mean peak duration, area under the curve, and peak and valley frequencies were determined (8). Rhythm was defined as the standard deviation of the interpeak intervals. Because standard deviation is typically not normally distributed, this value was log transformed.

The pulse characteristics of the depressed and comparison groups were then compared by using one-way analysis of variance (ANOVA). Possible interference from the potentially confounding variables weight, age, and day of cycle was examined by using multiple regression analysis for each characteristic.

RESULTS

When the two groups were compared statistically, significant differences emerged in the mean values for amplitude (maximum change), peak area (net area under the curve), and rhythmicity (standard deviation of interpeak intervals) (table 1). Although the difference in mean peak frequency did not reach statistical significance (table 1), it is interesting that 90% of the depressed women (N=9) had fewer than five peaks in 8 hours, compared to 46% of the comparison women (N=6) (Yates-corrected χ^2= 3.05, df=1, p<0.08). Five peaks per 8 hours was the modal frequency for the comparison group and is considered "normal" in the literature (9).

As a group, the depressed women displayed high amplitude pulses in a nonrhythmic fashion and had a somewhat lower frequency. A multiple regression analysis of weight, day of period (day 2 to day 7), and age yielded no significant findings, implying that these potentially important variables were not confounding the results.

DISCUSSION

Before discussion of the potential implications of these results, it is appropriate to comment on certain aspects of the methods. Because the subjects were not age matched at the outset, age could be an important confounding variable. Fortunately, the mean ages and age ranges were similar, and age did not emerge as a confounder in the multiple regression. It therefore seems unlikely that any group differences are accounted for by age.

The 8-hour sampling period was chosen since Berga et al. (8) demonstrated significant differences in LH area under the curve between normal women and women with hypothalamic amenorrhea during an 8-hour period in the afternoon and evening.

It is striking that in this small study group there were significant differences, with depressed women displaying abnormal pulse characteristics. These were similar to abnormalities noted in women with "functional hypothalamic amenorrhea," who frequently display low frequency and variable amplitude (10) and have impaired fertility.

None of these subjects was attempting to become pregnant, and we cannot say which, if any, was infertile. However, as a group, the depressed women displayed abnormal LH pulse characteristics, which is consistent with epidemiological data suggesting impaired fertility in women with severe affective disturbance (11, 12). Gonadotropin dysregulation may provide an important hormonal link between major depressive disorder and impaired fertility.

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