Elevated Serum Follicle-Stimulating Hormone Levels in Men with Normal Seminal Fluid Analyses

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Elevated serum follicle-stimulating hormone levels in men with normal seminal fluid analyses*

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Three men who volunteered as normal subjects were found to have abnormally high levels of serum follicle-stimulating hormone (FSH) despite having normal seminal fluid analyses and fertility. Two of the men had a history of previous orchitis, and one had an atrophic testis. Serum luteinizing hormone and testosterone levels were normal. These cases appear to represent compensated primary testicular disease, with normal sperm counts and fertility maintained at the expense of chronically elevated FSH levels. These results imply that in certain situations, the measurement of serum FSH levels may be a more sensitive index of testicular disease than the performance of seminal fluid analyses. Fertil Steril 39:333, 1983

Men with primary testicular failure and severe oligospermia or azoospermia frequently exhibit serum follicle-stimulating hormone (FSH) levels that are elevated when compared with levels found in normal men.[1] This increase in FSH levels is due to a deficiency in testicular factor(s) that normally exert negative feedback on FSH secretion. Because of the severity of the testicular disease often associated with increased FSH levels, an elevated FSH has been used as an adverse prognostic factor for fertility in men with spermatogenic disorders.[2]

In recruiting normal men for contraceptive development studies, we have encountered three men who exhibited normal seminal fluid analyses and fertility but who showed chronic elevations of serum FSH levels. Endocrine studies in these three subjects were compared with control groups of normal men. In addition, a hemicastrated man was studied to assess the effect of a 50% loss of testicular tissue on serum FSH levels.

MATERIALS AND METHODS

SUBJECTS

Seventy-five men responded to advertisements recruiting normal men for studies of male contraceptive development. The men were characterized by normal seminal fluid analyses (three successive sperm counts > 20 million/ml with semen volume between 1 and 5 ml, > 60% oval forms, and > 50% motility) and no clinical history of

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infertility. Blood samples were obtained from each man for measurement of serum luteinizing hormone (LH), FSH, and testosterone (T) by radioimmunoassay (RIA). Three subjects were found to have serum FSH levels that greatly exceeded the normal range despite having normal levels of LH and T and normal seminal fluid analyses. These three subjects are described in more detail.

Subject A. This subject, who was 36 years of age, had a history of mumps orchitis at age 33. He had never attempted to father children. His physical examination was normal, including testicular measurements of 4.6 × 2.8 cm on the right and 3.5 × 2.3 cm on the left.

Subject B. This subject, was was 44 years of age, had a history of orchitis at age 16. However, he had fathered four children, the youngest of whom was 1 year old. Physical examination was normal, with the exception of an atrophic left testis, measuring less than 0.5 cm in length. The right testis was normal, measuring 4.4 × 2.5 cm.

Subject C. This subject, who was 37 years of age, had a normal medical history. He had fathered one child 8 years prior to this study. His physical examination was normal, including testicular measurements of 4.0 and 2.5 cm bilaterally.

HEMICASTRATED PATIENT

A male patient who was 39 years of age had been evaluated for infertility, oligospermia, and a small right testis 10 years previously. He underwent bilateral testicular biopsies and was found to have carcinoma in situ of the right testis.[3] This testis was surgically removed 8 years prior to this study. This man fathered two normal children who were 3 years of age and 1 year of age at the time of this study. His remaining testis measured 4.3 × 2.3 cm. Three successive seminal fluid specimens obtained within 3 months of these hormonal studies (8 years after hemicastration) revealed sperm counts of 37, 24, and 43 million/ml with normal morphologic features and motility.

SEMINAL FLUID ANALYSIS

The men provided semen collected by masturbation following 48 hours of abstinence from ejaculation. Sperm counts, motility studies, and morphologic studies were performed as described previously.[4] Normality was defined as having three successive sperm counts between 20 and 200 million/ml with semen volume between 1 and 5 ml, > 60% oval forms, and > 50% motility.

HORMONE MEASUREMENT

RIAs for LH, FSH, and T were performed as described previously.[4] Human pituitary extract (LER-907) was used as the standard for both gonadotropin assays. Normal ranges for each hormone were defined as the 5th through 95th percentiles of the values found in normal men 21 to 45 years of age.[5]

LUTEINIZING HORMONE-RELEASING HORMONE (LH-RH) ADMINISTRATION

LH-RH (Ayerst Pharmaceuticals, Inc., New York, NY) was administered to each of the 3 subjects, to the hemicastrated man, and to 11 normal adult male controls by constant intravenous infusion (0.2 μg/minute for 4 hours). Blood samples were obtained through an antecubital venous cannula 30 minutes, 15 minutes, and 1 minute before the start of the infusion. Further blood sampling was at 15-minute intervals for the first

Table 1. *Sperm Counts and Hormonal Data*[a]

	Sperm counts	Semen volume	FSH	LH	T
	× 10^6/ml	ml	ng/ml	ng/ml	ng/ml
Subjects					
A	42 ± 8	2.9 ± 0.3	279 ± 6	53 ± 0.6	5.3 ± 0.5
B	56 ± 5	1.1 ± 0.2	322 ± 7	66 ± 5	6.7 ± 0.4
C	52 ± 6	2.3 ± 0.3	287 ± 3	50 ± 5	7.1
Hemicastrated man	35 ± 6	4.7 ± 0.6	109 ± 2	25 ± 2	4.2
Normal range	20–200	1.0–5.0	30–230	15–80	2.7–8.8
Mean	84	2.6	107	37	6.0

[a]Hormonal and seminal fluid data for each man are presented as the mean ± standard error of the mean (SEM) (n = 4 to 6 determinations of each variable in each man except for T levels in subject C and the hemicastrated man, for which there was one measurement in each case).

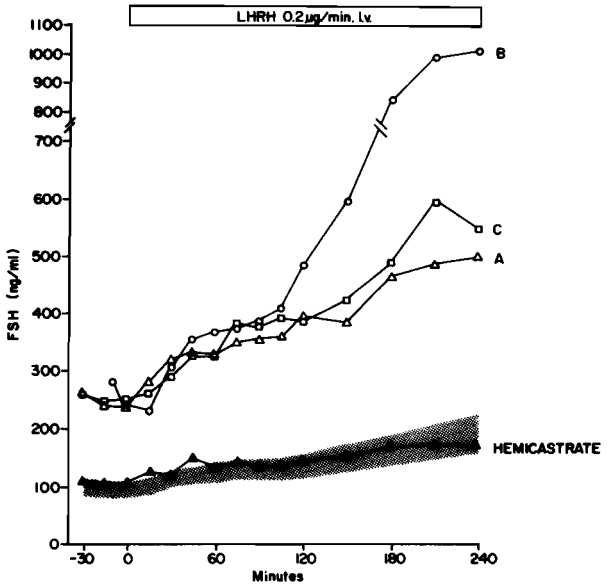

Figure 1
Serum FSH levels before and during LH-RH administration (0.2 μg/minute intravenously for 4 hours) in normal men (mean ± SEM, *shaded area*, $n = 11$) and in the three subjects and one hemicastrated man.

2 hours of the infusion and at 30-minute intervals for the second 2 hours. LH and FSH were measured in each blood sample; all samples from each man were included in a single assay.

TESTOSTERONE SUPPRESSION

T enanthate, 200 mg intramuscularly was administered weekly for 4 months to each of the three subjects with elevated basal FSH levels. During this time, serum LH and FSH levels were measured once a month, and seminal fluid analyses were performed twice a month.

RESULTS

Subjects A, B, and C were characterized by normal sperm counts (Table 1) and by normal sperm motility (always > 50%) and morphologic features (always > 60%). These men also had normal serum levels of LH and T (Table 1). However, serum FSH levels were clearly elevated. Repeated measurements of serum FSH in these three men at monthly intervals for 3 months demonstrated values that were always well above the upper limit of normal (Table 1). The hemicastrated man demonstrated sperm counts and basal hormone levels within the normal range.

All three subjects exhibited markedly greater increases in serum FSH levels during LH-RH infusion than were found in normal men (Fig. 1). The response of the hemicastrated man was indistinguishable from the normal response (Fig. 1). One of the subjects also demonstrated an LH response to LH-RH that was clearly greater than normal (Fig. 2). The LH responses of the other two subjects and of the hemicastrated man were not clearly distinguishable from those found in normal men (Fig. 2).

During the administration of T enanthate, all three subjects demonstrated undetectable serum levels of LH and FSH, and sperm counts were suppressed to less than 5 million/ml.

DISCUSSION

The three subjects reported here demonstrated seminal fluid analyses that were well within the normal ranges of sperm count, motility, and morphologic characteristics. Two of the three men had demonstrated fertility (1 and 8 years earlier), while the third had not attempted to induce pregnancy.

Despite these normal characteristics of their ejaculates, all three men exhibited clearly ele-

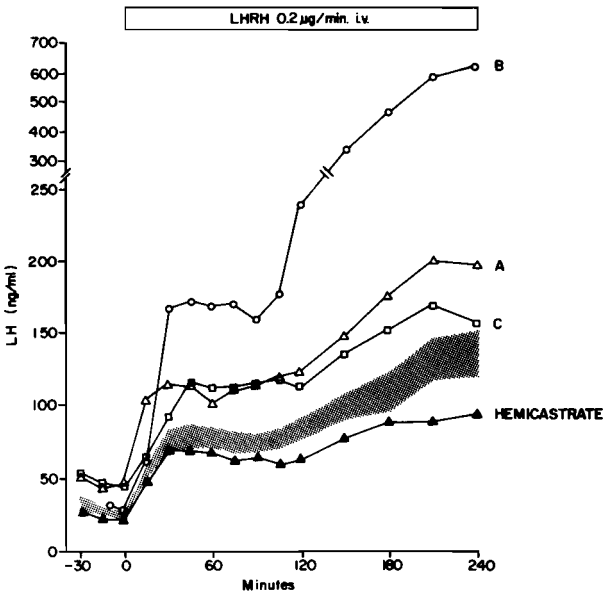

Figure 2
Serum LH levels before and during LH-RH administration (0.2 μg/minute intravenously for 4 hours) in normal men (mean ± standard error of the mean [SEM], *shaded area*, $n = 11$) and in the three subjects and one hemicastrated man.

vated serum levels of FSH. The degree of elevation in FSH levels was similar to that found in many men with idiopathic oligospermia.[1] In addition to the elevations in basal levels, FSH responses to LH-RH infusions were much greater than those found in normal men. That the increased basal FSH values were not due to autonomous pituitary function was demonstrated by the ability of T administration to suppress FSH to undetectable levels.

Two of the three men recounted a history of orchitis, and one was found to have an atrophic testis. The third man had no known history of testicular disease or trauma. A possible explanation for the increases found in FSH levels is that all three men had had significant testicular damage at some point in the past. The rise in FSH could have been a response to this testicular damage. The presumably damaged testes, under the stimulatory effect of high gonadotropin levels, were able to maintain sufficient sperm production to result in normal seminal fluid analyses and fertility.

It is not presently possible to measure the bioactivity of circulating FSH, nor to determine its molecular structure. When such techniques become available, it will be of interest to assess the bioactivity and structure of FSH in men such as the three subjects in this study.

It is likely that the testicular disease in these three men affected both testes. This assumption is supported by our studies of one man after unilateral orchiectomy. Despite losing one testis as an adult, this man maintained normal basal FSH levels and FSH responsiveness to LH-RH. The implication of these findings is that there must be a loss of more than 50% of normally functioning testicular tissue to cause increased FSH secretion.

This presumed situation of compensated testicular failure is analogous to previously described syndromes involving other endocrine tissues. For example, partial thyroid failure, as in Hashimoto's disease or in treated Graves' disease, can result in normal serum thyroxine levels maintained at the expense of elevated thyroid-stimulating hormone values.[6]

Our results in these three men imply that in certain situations the measurement of serum FSH levels may be a more sensitive index of testicular disease than the performance of seminal fluid analyses. This implication is of particular relevance in screening programs for environmental hazards to male reproductive capacity.[7] Our results also suggest that the finding of an elevated FSH level may not necessarily imply irreversibility in men with infertility due to spermatogenic disorders.

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