A Possible Relation between Elevated FSH Levels and Leydig Cell Dysfunction in Azoospermic and Oligospermic Men

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Plasma testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels were measured in the male partners of 69 infertile couples and in 260 allegedly fertile men requesting vasectomy. All hormone levels were within normal range in men with total sperm counts (TSCs) above 25 million/ejaculate, while FSH levels were abnormally elevated in azoospermic subjects and some (not all) men with TSCs below 25 million/ejaculate. The mean TSC of oligospermic men with elevated FSH levels was not statistically different from the mean TSC of men with normal FSH levels and sperm outputs below 25 million/ejaculate. Thus, the elevation of FSH levels observed in some oligospermic men was not related solely to decreased sperm counts. LH levels were higher in patients with TSCs below 25 million/ejaculate and high FSH levels than in men with TSCs below 25 million/ejaculate and normal FSH levels. FSH levels were directly correlated with LH levels and negatively correlated with testosterone levels. These results suggest a relation between Leydig cell dysfunction and elevation of FSH levels in oligospermic men.

Key words: follicle-stimulating hormone, luteinizing hormone, testosterone, oligospermia, human testis, Leydig cell dysfunction.

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Except for patients with hypothalamic–pituitary disorders, severe spermatogenic damage is frequently associated with elevated plasma and urinary levels of follicle-stimulating hormone (FSH) (Paulsen, 1968; Franchimont, 1971; De-Kretser et al, 1972 and 1974; Hunter et al, 1974; Christiansen, 1975; Smith and Steinberger, 1977; Hopkinson et al, 1977; Nankin et al, 1977; Rodriguez-Rigau et al, 1980). This observation has been cited in support of the inhibin hypothesis. The production of an FSH-inhibiting substance by the seminiferous epithelium was first postulated by McCullagh in 1932, who named this hypothetical substance "inhibin." In the rat, the Sertoli cell has been demonstrated to be the source of an FSH-inhibiting factor (A. Steinberger and E. Steinberger, 1976 and 1977; Chowdhury et al, 1978). In man, although inhibin activity has been demonstrated in seminal plasma (Franchimont, 1972), no direct information is available regarding the cellular origin of inhibin.

Although, as a group, azoospermic and severely oligospermic men exhibit abnormally elevated FSH levels, many severely oligospermic men have FSH levels within normal range (Hunter et al, 1974; Hopkinson et al, 1977; Nankin et al, 1977). This suggests that in some oligospermic men the production of inhibin is preserved despite disturbance in spermatogenesis. The hormonal regulation of inhibin production is largely unknown. In the rat, other Sertoli cell-specific proteins (e.g., androgen binding protein (ABP)) are regulated by

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FSH and testosterone (Elkington et al, 1975; Hansson et al, 1975 and 1978; Louis and Fritz, 1977; E. Steinberger et al, 1978). It seems possible that inhibin production may also be regulated by these hormones. Thus, deficiency in testicular testosterone production (Leydig cell dysfunction) could lead to decreased production of inhibin and a rise in FSH levels, as well as to spermatogenic disturbance. Recent studies have suggested a relatively high incidence of Leydig cell dysfunction in azoospermic and oligospermic men (DeKretser et al, 1972; Franchimont et al, 1973; Mecklenburg and Sherins, 1974; Nankin et al, 1977; Oshima et al, 1977; Weiss et al, 1978; Rodriguez-Rigau et al, 1978a and 1978b; E. Steinberger et al, 1980). The study reported here was designed to investigate the question of whether elevation of circulating levels of FSH in men with decreased sperm output is related to Leydig cell dysfunction.

Materials and Methods

Subjects

Infertile Group. The male partners of 86 infertile couples consecutively seen in our office were evaluated. This evaluation included complete history and physical examination, a minimum of four semen analyses (spaced at least one week apart), measurement of circulating levels of FSH, luteinizing hormone (LH), and testosterone, and when indicated, chromosomal analyses, scrotal exploration, and bilateral testicular biopsy. Seventeen men were excluded: four men with Klinefelter syndrome; three with bilateral testicular atrophy secondary to torsion, orchitis, or radiation; two with hypogonadotropic hypogonadism; and eight with bilateral epididymal obstruction.

Prevasectomy Group. Semen analyses (one sample) and measurements of circulating FSH, LH, testosterone, and estradiol levels were performed in 260 allegedly fertile men requesting vasectomy. Some of these data have been published previously (Smith and Steinberger, 1977).

Semen Analysis

Sperm counts were performed in duplicate using a hemocytometer. Semen volumes were measured in a graduated test tube. The total sperm counts (TSCs) were calculated as the product of the sperm count and the ejaculate volume.

Circulating Hormone Levels

FSH, LH, and testosterone levels were measured by radioimmunoassay, as previously described (Smith et al, 1974; Rao et al, 1978). The normal ranges for men in our laboratory are 200–1200 ng/dl for testosterone and 0–5 mIU/ml for FSH and LH (Smith and Steinberger, 1977). Plasma estradiol levels in prevasectomy subjects were measured by radioimmunoassay, as previously reported (Smith et al, 1976).

Statistical Analyses

When indicated, results were grouped and the groups were compared by one-way analysis of variance and Duncan's multiple range test. Correlations between variables were investigated by linear regression analysis. Coefficients of correlation and t values were calculated by standard techniques.

Results

Infertile Group

The mean (± SE) semen volume, sperm count, and total sperm count of the 69 subjects were 3.0 ± 0.1 ml, 16.6 ± 2.5 million/ml, and 42.5 ± 8.3 million/ejaculate, respectively. These 69 men were divided into three groups on the basis of their TSCs: group 1, azoospermic men (n = 12); group 2, men with TSCs below 25 million/ejaculate (n = 30); group 3, subjects with TSCs above 25 million/ejaculate (n = 27). Mean semen volume of azoospermic men was 3.1 ± 0.6 ml. Mean semen volume, sperm count, and TSC in subjects of group 2 (TSCs < 25 million/ejaculate) were 3.0 ± 0.3 ml, 2.8 ± 0.6 million/ml, and 7.0 ± 1.2 million/ejaculate, respectively. In group 3 (subjects with TSCs above 25 million/ejaculate) mean semen volume was 2.9 ± 0.3 ml, mean sperm count 39.2 ± 6.5 million/ml, and mean TSC 100.8 ± 17.6 million/ejaculate.

The mean levels of FSH, LH, and testosterone in groups 1, 2, and 3 are presented and compared in Table 1. The levels of both gonadotropins were significantly higher in group 1 (azoospermic men) than in groups 2 and 3 ($P < 0.001$). FSH and LH levels were significantly higher in group 2 than in group 3 ($P < 0.001$). Testosterone levels were significantly lower in group 1 than in groups 2 or 3 ($P < 0.01$); testosterone levels in groups 2 and 3 were not statistically different. All azoospermic patients (group 1) had abnormally elevated FSH levels, and eight of the 12 subjects had LH levels above the normal range. In group 2, (TSCs below 25 million/ejaculate) FSH levels were abnormally elevated in 14 subjects and within normal range in 16 men; LH levels were high in five and normal in 25. FSH and LH levels were within normal range in all subjects in group 3 (TSCs above 25 million/ejaculate). Plasma testosterone levels were within normal range in all 69 subjects.

Linear regression analyses of data from groups 2

TABLE 1. Follicle-stimulating Hormone (FSH), Luteinizing Hormone (LH), and Testosterone (T) Levels (Mean ± SE) in Relation to Total Sperm Count (TSC) in 69 Male Partners of Infertile Couples*

Group (TSC)	No. of Subjects	FSH (mIU/ml)	LH (mIU/ml)	T (ng/dl)
I (azoospermia)	12	15.3 ± 2.0[a]	8.3 ± 1.7[a]	383 ± 27[d]
II (<25 million/ejaculate)	30	5.8 ± 0.6[b]	3.8 ± 0.3[b]	532 ± 33[e]
III (>25 million/ejaculate)	27	2.2 ± 0.2[c]	2.2 ± 0.2[c]	556 ± 39[e]
Normal range		<5	<5	200–1200

* Statistical analysis (one-way analysis of variance and Duncan's multiple range test): a > b, $P < 0.001$; b > c, $P < 0.001$; a > c, $P < 0.001$; d < e, $P < 0.01$.

and 3 demonstrated a significant negative correlation between FSH levels and TSCs ($r = -0.41$, $P < 0.01$), as well as between LH levels and TSCs ($r = -0.3$, $P < 0.025$). Analysis of data on subjects from all three groups revealed a statistically significant direct correlation between FSH and LH levels ($r = 0.72$, $P < 0.001$), and a significant negative correlation between FSH and testosterone levels ($r = 0.3$, $P < 0.025$). Elimination of group 1 (azoospermic men) did not alter these correlations significantly (FSH vs. LH: $r = 0.78$, $P < 0.001$; FSH vs. testosterone: $r = 0.3$, $P < 0.05$).

Patients of group 2 were further divided into two subgroups: 14 men with abnormally elevated FSH levels (>5 mIU/ml) and 16 men with FSH levels within normal range (<5 mIU/ml). No significant difference in TSCs between these two subgroups was observed (Table 2). However, LH levels were significantly higher in patients with abnormally elevated FSH levels ($P < 0.01$). Testosterone levels were higher in subjects with normal FSH levels, but the difference was not statistically significant.

Prevasectomy Group

A statistically significant negative correlation between FSH levels and TSCs was observed ($r = 0.13$, $P < 0.025$). FSH levels were significantly higher in men with TSCs below 25 million/ejaculate than in those with TSCs above 25 million/ejaculate ($P < 0.001$, Table 3). No significant differences in FSH levels were noted in men with TSCs ranging from 25 to over 500 million/ejaculate.

The group of 32 men with TSCs below 25 million/ejaculate was further subdivided into those men with TSCs above and below 12.5 million/ejaculate, and no significant differences in FSH levels were observed (4.5 ± 1.2 and 5.9 ± 2.1 mIU/ml, respectively). Eight of the 32 subjects with TSCs below 25 million/ejaculate had abnormally elevated FSH levels, while the remaining 24 men had FSH levels within normal range. No significant differences in TSCs, testosterone, or estradiol levels between these two groups were observed (Table 4). On the other hand, LH levels were significantly higher in men with elevated FSH levels than in subjects with FSH levels within normal range ($P < 0.01$). A significant direct correlation between FSH and LH levels was observed for the entire group of 260 subjects ($r = 0.33$, $P < 0.001$).

Discussion

The significant negative correlation between TSCs and FSH levels demonstrated in this study

TABLE 2. Total Sperm Count (TSC), Follicle-stimulating Hormone (FSH), Luteinizing Hormone (LH), and Testosterone (T) Levels in Patients with TSC below 25 million/ejaculate and Normal or Elevated FSH Levels*

Subjects	No. of Subjects	TSC (million/ejaculate)	FSH (mIU/ml)	LH (mIU/ml)	T (ng/dl)
High FSH (>5 mIU/ml)	14	4.9 ± 0.9‡	8.2 ± 1.0†	4.8 ± 0.6†	491 ± 45‡
Normal FSH (<5 mIU/ml)	16	8.8 ± 2.0	3.7 ± 0.2	2.9 ± 0.2	571 ± 51
Total	30	7.0 ± 1.2	5.8 ± 0.6	3.8 ± 0.3	532 ± 33

* Statistical analysis (Student *t* test): † = $P < 0.01$; ‡ = not significant).

TABLE 3. Relation of Total Sperm Count (TSC) to Follicle-stimulating Hormone (FSH) Levels in 260 Prevasectomy Subjects

TSC (million/ejaculate)	No. of Subjects	FSH (mIU/ml)
<25.1	32	5.1 ± 1.1*
25.1–50.0	29	2.3 ± 0.2
50.1–100.0	52	2.4 ± 0.2
100.1–200.0	67	2.8 ± 0.2
200.1–300.0	42	2.5 ± 0.2
30.1–400.0	15	2.2 ± 0.3
400.1–500.0	12	2.5 ± 0.4
>500.0	11	2.1 ± 0.2
Total	260	2.8 ± 0.2

*$P < 0.001$.

for 69 male partners of infertile couples and 260 prevasectomy subjects is in agreement with reports by other investigators (Franchimont, 1971; DeKretser et al, 1972 and 1974; Hunter et al, 1974; Hopkinson et al, 1977; Nankin et al, 1977). In the present study it was observed that FSH levels were within normal range in all men with TSCs above 25 million/ejaculate, while they were elevated in azoospermic patients and in some of the subjects with TSCs below 25 million/ejaculate. We recognize that the dividing point between male fertility and subfertility is difficult to determine, since the sperm output in fertile and infertile men probably is a continuum. Thus, the division of the populations into groups of men with total sperm counts above and below 25 million/ejaculate was somewhat arbitrary. We selected this figure as a dividing point on the basis of two previous reports. In the first study we compared the frequency distributions of TSCs in 1,000 male partners of infertile couples and over 4,000 prevasectomy subjects (Zukerman et al, 1977). Significant differences were noted only in the groups of men with TSCs below 25 million/ejaculate. In the second study the pregnancy rates in a large group of infertile couples were related to the male partners' TSCs; significantly lower pregnancy rates were observed when TSCs were below 25 million/ejaculate, and there were no differences when TSCs were above 25 million/ejaculate (Smith et al, 1977). FSH levels were normal in all subjects of this study with TSCs above 25 million/ejaculate. They were elevated in men with TSCs below 12.5 million/ejaculate, but were also elevated in men with TSCs between 12.5 and 25 million/ejaculate. Thus, 25 million/ejaculate appeared to be a reasonable dividing point for comparison of circulating hormone levels.

In spite of the significant negative correlations between TSCs and FSH levels, 16 of 30 male partners of infertile couples with TSCs below 25 million/ejaculate had FSH levels within normal range. Similarly, 24 of 32 prevasectomy subjects with TSCs below 25 million/ejaculate had normal FSH levels. When oligospermic men with normal FSH levels were compared to those with abnormally elevated FSH levels, no significant differences in sperm output were observed, suggesting that the rise in FSH was not related solely to decreased sperm output.

The demonstration of high LH and low testosterone levels in the group of azoospermic men is suggestive of Leydig cell dysfunction. A relation between elevation of FSH levels and Leydig cell dysfunction is suggested in this study by the demonstration of a significant direct correlation between FSH and LH levels, of higher LH levels in oligospermic men with abnormally elevated FSH levels than in oligospermic men with normal FSH levels, and of a significant negative correlation between FSH and testosterone levels. It seems possible that Leydig cell dysfunction could result in decreased production of inhibin and subsequent elevation of FSH levels. An alternative hypothesis has been proposed by other investigators to explain the correlation between FSH and LH levels. This hypothesis suggests that inhibin plays a role, not only in the feedback regula-

TABLE 4. Total Sperm Count (TSC), Follicle-stimulating Hormone (FSH), Luteinizing Hormone (LH), Testosterone (T), and Estradiol (E) Levels in Prevasectomy Subjects with TSC below 25 million/ejaculate and Normal or Elevated FSH Levels*

Subjects	No. of Subjects	TSC (million/ejaculate)	FSH (mIU/ml)	LH (mIU/ml)	T (ng/dl)	E (ng/dl)
High FSH (>5 mIU/ml)	8	11.8 ± 2.9§	12.9 ± 3.4‡	3.4 ± 0.5†	511 ± 124§	3.5 ± 0.6§
Normal FSH (<5 mIU/ml)	24	12.4 ± 1.8	2.6 ± 0.2	2.4 ± 0.1	446 ± 44	3.2 ± 0.2

*Statistical analysis (Student t test): † = $P < 0.01$; ‡ = $P < 0.001$; § = not significant.

tion of FSH, but also of LH; a decrease in inhibin production would cause a rise in both FSH and LH levels (Hopkinson et al, 1977; Rosenfield et al, 1977). Although this hypothesis would explain the finding of higher LH levels in patients with elevated FSH levels when compared to subjects with normal FSH levels, it does not explain the negative correlation between FSH and testosterone levels observed in this study. In the presence of normal Leydig cell function, the rise in LH levels should result in increased testosterone production, and therefore one would expect a positive rather than a negative correlation between FSH and testosterone levels.

Recently, Sherins et al (1979) reported a monotropic increase in FSH levels in the rat resulting from decreased testosterone levels in association with high–normal estradiol levels. If this observation applies to man, the negative correlation between FSH and testosterone levels observed in this study could be explained by a similar mechanism. Unfortunately, estradiol levels were not measured in subjects of the infertile group. However, no differences in estradiol or testosterone levels were observed in the prevasectomy group when men with normal and elevated FSH levels were compared. Therefore, it seems unlikely that the elevation of FSH levels in these men was caused by decreased testosterone levels in the presence of high estradiol levels.

Since all hormone determinations were performed in single rather than multiple blood samples in this study, the results should be interpreted with some caution. Rapid oscillations in circulating testosterone levels have been demonstrated (Naftolin et al, 1973; Smith et al, 1974). However, Rosenfield et al (1977) demonstrated that a single plasma testosterone level is very closely correlated with the mean testosterone level obtained from multiple sampling over 3 hours ($r = 0.91$). Furthermore, oscillation of levels in individuals does not invalidate the finding of statistically significant differences between levels in groups of subjects. Such oscillations would only raise questions regarding the validity of conclusions based on negative results (e.g., lack of statistically significant differences).

In summary, this study confirms previous reports of association between decreased sperm output and elevation of circulating FSH levels. However, the results also suggest a relation between Leydig cell dysfunction and rise of FSH levels in oligospermic men. This observation calls into question the generally accepted theory that elevation of FSH levels, in the presence of LH and testosterone levels within normal range, indicates isolated disturbance of the seminiferous epithelium. Further studies will be necessary to ascertain the mechanisms involved in the control of FSH in man.

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