CME

Inhibin B is a better marker of spermatogenesis than other hormones in the evaluation of male factor infertility

Philip Kumanov, M.D., Ph.D.,[a] *Kalyana Nandipati, M.D.,*[b] *Analia Tomova, M.D., Ph.D.,*[a] *and Ashok Agarwal, Ph.D*[b]

[a] Clinical Centre of Endocrinology and Gerontology, Medical University, Sofia, Bulgaria; and [b] Center for Advanced Research in Human Reproduction, Infertility, and Sexual Function, Glickman Urological Institute and Department of Obstetrics-Gynecology, The Cleveland Clinic Foundation, Cleveland, Ohio

Objective: To assess the role of inhibin B in the evaluation of male factor infertility.
Design: Prospective study.
Setting: Reproductive endocrinology clinic.
Patient(s): Seventy-five patients with infertility problems (mean age 31.2 ± 7.5 years) and 12 controls (32.1 ± 8.8 years) with proven fertility.
Intervention(s): None.
Main Outcome Measure(s): Semen analysis was performed according to World Health Organization guidelines. Testicular volume was assessed with the Prader's orchidometer. Serum levels of inhibin B (pg/mL), LH (mIU/mL), FSH (mIU/mL), prolactin (micro IU/mL), and testosterone (nmol/L) were assessed.
Result(s): The mean ± SEM inhibin B and testosterone levels were significantly lower in the patients than in the controls (inhibin B: 116.4 ± 11.7 vs. 181.2 ± 20.9, $P=.008$; testosterone: 13.6 ± 0.9 vs. 25.1 ± 2.9, $P=.008$). In general, sperm count and testicular volume in the patients were significantly and positively correlated with inhibin B (sperm count: $r = 0.476$, $P<.0001$; testicular volume, right: $r = 0.57$, $P=.0001$; left: $r = 0.53$, $P=.0001$); the inhibin B-FSH index was negatively correlated with FSH. Inhibin B was more strongly correlated with testicular volume and semen parameters than FSH. Inhibin B in the patients was negatively correlated with FSH ($r = -0.723$, $P=.0001$) and LH ($r = -0.52$, $P=.0001$) and was positively correlated with testosterone ($r = 0.4$, $P=.0013$).
Conclusion(s): Inhibin B measurement is a better marker of fertility status than FSH and LH. Concentration of inhibin B in patients with infertility may provide useful information on spermatogenesis and possibly serve as a more direct marker of spermatogenesis than FSH. (Fertil Steril® 2006;86:332–8. ©2006 by American Society for Reproductive Medicine.)

Key Word(s): Inhibin B, FSH, LH, male infertility, spermatogenesis

Subfertility affects 15% of all couples in the world (1). Assessment of spermatogenesis plays a central role in the evaluation of the subfertile couple. Semen analysis, endocrine evaluation, and testicular biopsy constitute the most important investigations for the evaluation of male factor infertility. After the initial semen analysis, levels of endocrine markers, such as FSH and LH, can be measured to determine whether the subfertility is being caused by testicular impairment or an obstructive disorder (2).

Follicle-stimulating hormone plays a major role in the induction and maintenance of spermatogenesis. Serum FSH measurement can be a useful marker of the histological condition of the testis. However, the diagnostic accuracy of FSH was questioned due to a wide overlap of FSH levels in regular and reduced spermatogenesis states (3). This observation led researchers to search for more specific and direct markers of spermatogenesis.

There is a growing interest regarding the role of inhibin in the evaluation of infertility. The existence of inhibin as a glycoprotein substance was proposed in early 1920s (4). However, it was only in the mid-1980s when this substance was isolated from bovine follicular fluid (5). Inhibin B is a dimeric hormone that is composed of α and β_B subunits. The free α-subunits usually do not have any physiological effects. Therefore, the bioactivity of the inhibin depends on the formation of a dimeric α-β structure, and only dimeric forms of inhibin are biologically active (6). In the mid-1990s, a specific immunoassay technique (7) was developed to determine bioactive forms of inhibin (A and B). The technique further established that inhibin B is the most relevant physiological form and that it directly reflects the function of

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Reprint requests: Ashok Agarwal, Ph.D., Cleveland Clinic's Lerner College of Medicine of Case Western Reserve University, Center for Advanced Research in Human, Reproduction, Infertility, and Sexual Function, Glickman Urological Institute and Department of Obstetrics-Gynecology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Desk A19.1, Cleveland, Ohio 44195 (FAX: 216-445-6049; E-mail: agarwaa@ccf.org).

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Sertoli cells of the testis. Inhibin is primarily produced by the gonads and appears to negatively regulate pituitary FSH secretion and synthesis (8, 9).

Various studies reported that Inhibin B levels could be a potential marker for spermatogenesis and testicular function (9, 10). Its levels are either undetectable or reduced in subfertile men except in those with obstructive azoospermia or spermatogenic arrest at some stages (11, 12). However, the precise relation between inhibin B and sperm disturbances—and its role in the evaluation of male factor infertility—is not clearly understood. It is possible that complex interaction among the hormones and diurnal, postural, and periodic variations in the hormonal concentrations might explain why inhibin B has not been established as a marker of male factor infertility.

In this study, we evaluated the significance of various hormones (inhibin B, FSH, LH, and testosterone) and their indices (inhibin B-FSH and inhibin B-testosterone) in the evaluation of male factor infertility and their correlation with sperm parameters and testicular volume. We also evaluated the correlation between the sperm parameters and hormones in various etiologies of male factor infertility.

MATERIALS AND METHODS

In this prospective study, we included 75 men (mean age 31.2 ± 7.5 years) who presented with infertility problems to our clinic between 2003 and 2005. Infertility was defined as history of ≥1 year of unexplained childlessness, after obvious problems in the female partner had been excluded. Twelve healthy, fertile men (mean age 32.1 ± 8.8 years) with proven fertility served as controls. The study population underwent complete clinical evaluation by the principal investigator (P.K.). A history of any previous surgeries for undescended testicles, varicocelectomy, and orchiectomy was noted. After the initial clinical evaluation, testicular volume was measured and semen and hormonal analyses were performed. Testicular measurements were taken with Prader's orchidometer. Of a total of 75 patients, 20 had left varicocele, 10 had history of cryptorchidism, and 2 underwent orchidectomy followed by chemotherapy for testicular malignancy. Two were diagnosed to have Klinefelter's syndrome, 1 with Kallmann's syndrome, 2 with idiopathic hypogonadotrophic hypogonadism (IHH), and 2 with Sertoli-cell-only syndrome (confirmed on testicular biopsy). Eight patients had a history of previous genital tract infections. In 7 patients, infertility was associated with diabetes (n = 2), obesity (n = 3, body mass index >30), history of testicular hematoma (n = 1), history of testicular torsion (n = 1), and inguinal hernia (n = 1). Vasovasostomy was performed in one patient. Twelve patients were diagnosed with idiopathic infertility (no known cause of infertility in the past and in the present with normal FSH levels). Patients with azoospermia and normal gonadotropin levels were excluded from this group.

Sperm Analysis

Semen specimens were collected by masturbation after a period of 2–3 days of sexual abstinence. After liquefaction, manual semen analysis was performed using a MicroCell counting chamber (Conception Technologies, San Diego, CA) to determine sperm concentration and motility. Smears of the raw semen were stained using the Diff-Quik kit (Baxter Healthcare Corporation, Inc., McGraw Park, IL) to assess sperm morphology using World Health Organization criteria. Normal values for sperm parameters were as follows: sperm concentration $\geq 20 \times 10^6$/mL; forward progressive motility ≥50%; and normal sperm forms ≥30%, with leukocytes <1 in 10^6/mL (13).

Hormonal Analysis

Blood hormone analysis (FSH, LH, testosterone, prolactin, and inhibin B levels) was performed in all patients and controls. The blood samples that were taken to determine hormone levels were always collected in the mornings after the patients had observed an overnight fast and were placed in the supine position. The FSH serum levels were determined with electrochemiluminescence immunoassay (ECLIA) (Hoffman-LaRoche Inc., Nutley, NJ) kits. Normal FSH levels are 1.5–12.4 mIU/mL (5–95 percentiles, mean 4.6 mIU/mL). Serum inhibin B was measured in a double-antibody immunoenzyme-metric assay, a solid-phase sandwich ELISA (Oxford Bio-innovation, Oxfordshire, United Kingdom) using a monoclonal antibody raised against the inhibin β_B-subunit in combination with a labeled antibody raised against the inhibin α-subunit (7). The inhibin B assay has intraassay and interassay coefficients of variation <12% and <17%, respectively. The other hormones in serum were also assayed with commercially available kits (normal levels: LH 1.7–8.6 mIU/mL and prolactin 86–390 micro IU/mL). Testosterone levels were measured with ECLIA with 5–95 percentiles at 9.9–27.8 nmol/L and 50% at 17.5 nmol/L. The measuring range according to the producer was 0.069–52.0 nmol/L (minimum-maximum), and the functional sensitivity was 0.42 nmol/L (12, 14).

Subgroup Analysis

Patients were further classified according to FSH levels: group 1 (elevated FSH, n = 34) and group 2 (normal FSH levels, n = 20). Mean FSH levels in the control group were considered an index for classification (4.6 ± 0.5). This was based on a study by Andersson et al. (15), who proposed that men with proven fertility constitute the most appropriate reference group in the evaluation. We further excluded the patients with Kallman's syndrome, idiopathic hypogonadotrophic hypogonadism, and low FSH levels from this subgroup analysis. Sperm parameters and hormones were compared between both groups and with the controls.

Subgroup analysis was also performed after classifying patients according to the possible cause of infertility. Three major subgroups in our study included for this analysis were:

TABLE 1

Characteristics of the study population.

Variable	Cases (n = 75) Mean ± SEM	Cases (n = 75) Median	Controls (n = 12) Mean ± SEM	Controls (n = 12) Median	*P* value
Right testis volume (mL)	15.6 ± 0.9	15.0	23.8 ± 0.9	25.0	.001
Left testis volume (mL)	14.5 ± 0.9	15.0	23.3 ± 0.9	25.0	.001
Count (millions/mL)	13.3 ± 2.7	1.0	61.6 ± 8.9	53.5	.0001
FSH (mIU/mL)	12.4 ± 1.6	7.3	4.6 ± 0.5	4.7	.133
LH (mIU/mL)	6.8 ± 0.8	4.1	4.9 ± 0.3	5.0	.67
Testosterone (nmol/L)	13.6 ± 0.9	12.4	25.1 ± 2.9	24.7	.008
Prolactin (mIU/mL)	255 ± 17.4	249.0	238.1 ± 56.9	244.0	.8
Inhibin B (pg/mL)	116.4 ± 11.7	90.0	181.2 ± 20.9	162.5	.008
Inhibin indices					
Inhibin B-FSH	41.5 ± 7.1	12.6	11.3 ± 3.3	8.2	.4
Inhibin B-testosterone	17.3 ± 5.8	6.8	7.9 ± 0.9	7.6	.7

Note: $P<.05$ considered statistically significant by Mann-Whitney *U* test.

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idiopathic infertility group (n = 12), varicocele group (n = 20), and cryptorchidism (n = 10).

Statistical Analysis

Individual parameters were expressed as mean ± SEM. Inhibin indices (inhibin B-FSH and inhibin B-testosterone) were calculated with simple division. The Mann-Whitney U test was used to calculate the difference in the hormone levels between the cases and controls and various groups and subgroups. Correlations between serum hormone levels (inhibin B, FSH, and LH), testicular volume, inhibin indices, and sperm parameters were tested by Spearman's rank correlation coefficient. For each subject, an inhibin B-FSH ratio was calculated as inhibin B (pg/mL)/FSH (IU/L), and the inhibin B-testosterone ratio was calculated as inhibin B (pg/mL)/testosterone (nmol/L). The Statistical Package for the Social Sciences (SPSS) for Windows, version 10.0.7 (SPSS Inc., Chicago, IL) was used for all calculations and statistical analysis.

RESULTS

The inhibin B and testosterone concentrations were significantly lower in the patients than in the controls ($P<.05$). However, no significant difference was observed in FSH, LH, prolactin concentrations, and inhibin indices ($P>.05$) (Table 1). In the total study population, inhibin B demon-

TABLE 2

Correlation between hormones and parameters of study population.

Variables	Inhibin B	FSH	Testosterone	LH	Inhibin indices: Inhibin B/FSH	Inhibin indices: Inhibin B/testosterone
Right testicular volume	0.57, .0001	−0.33, .004	0.44, .0001	−0.25, .04	0.36, .0001	0.31, .001
Left testicular volume	0.53, .0001	−0.35, .002	0.48, .0001	−0.24, .048	0.35, .002	0.21, .07
Sperm motility	0.36, .003	−0.27, .024	0.15, .22	−0.27, .032	0.34, .005	0.28, .02
Sperm count	0.48, <.0001	−0.41, .0007	0.10, .4	−0.34, .002	0.48, <.0001	0.37, .002
Morphology	0.34, .004	−0.29, .01	0.08, .52	−0.28, .03	0.35, .003	0.31, .009

Note: Values are r (correlation coefficient), *P* value. $P<.05$ was considered significant by Spearman's rank correlation.

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TABLE 3

Characteristics of the cases classified by the potential cause of infertility.

Variable	Idiopathic infertility (n = 12)		Varicocele (n = 20)		Cryptorchidism (n = 10)	
	Mean ± SEM	Median	Mean ± SEM	Median	Mean ± SEM	Median
Right testicular volume (mL)	20.2 ± 2.0	15.0	16.6 ± 1.9	20.0	11.1 ± 2.73	10.0
Left testicular volume (mL)	19.3 ± 1.8	13.5	16.1 ± 1.5	20.0	12.3 ± 2.95	9.0
Count (millions)	28.5 ± 6.5	1.6	18.7 ± 6.8	5.0	4.5 ± 2.5	0.5
Motility	21.5 ± 3.5	2.5	13.4 ± 3.9	5.0	12.5 ± 7.2	2.0
Morphology (%)	25.6 ± 4.4	30.0	23.3 ± 5.1	20.0	6.8 ± 4.18	8.0
FSH (mIU/mL)	4.4 ± 0.8	4.7	12.5 ± 2.5	9.4	19.34 ± 6.31	13.2
LH (mIU/mL)	4.3 ± 0.6	4.1	6.2 ± 1.2	4.3	8.1 ± 2.5	7.7
Inhibin B (pg/mL)	190.7 ± 30.5	102.0	116.3 ± 24	82.0	63.7 ± 13.96	88.5
Testosterone (nmol/L)	16.9 ± 1.7	13.4	13.9 ± 1.3	12.2	11.8 ± 2.87	10.5

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strated a significant positive correlation with sperm parameters and testicular volume. The FSH and LH concentrations demonstrated a significant negative correlation with sperm parameters and testicular volume. Inhibin B showed a strong correlation with testicular volume and semen parameters compared with FSH (Table 2).

A significant negative correlation was observed between inhibin B and FSH levels (r = −0.723, P=.0001) and LH levels (r = −0.52, P=.0001). A significant positive correlation was observed between inhibin B and testosterone levels (r = 0.4, P=.0013). The inhibin B-FSH index also indicated a significant correlation with sperm parameters and testicular volume similar to inhibin B. However, inhibin B-testosterone index correlations were not consistent (Table 2).

Subgroup Analysis According to the Etiology

Inhibin B levels were significantly lower in the varicocele group compared with the controls (116.3 ± 24 vs.181.2 ± 20.9, P=.02) (Table 3). Inhibin B had significantly stronger correlations with sperm parameters and testicular volume than FSH in the varicocele group, which was similar to a trend observed in the whole study population (Table 4). The FSH levels were not significant compared with the controls in the varicocele (P=.08) group.

Inhibin B levels were significantly lower in the cryptorchidism patients compared with the controls (63.7 ± 13.96 vs. 181.2 ± 20.9, P=.0002) and the idiopathic infertility group (63.7 ± 13.96 vs. 190.7 ± 30.5, P=.002) (Table 3). The FSH levels in the cryptorchidism group appeared to be significantly elevated compared with those

TABLE 4

Correlation among inhibin B, FSH, and sperm parameters in different subgroups.

Variable	Idiopathic infertility (n = 12)		Varicocele (n = 20)		Cryptorchidism (n = 10)	
	Inhibin B	FSH	Inhibin B	FSH	Inhibin B	FSH
Right testicular volume	0.6, .06	−0.3, .3	0.4, .04	0.3, .3	0.39, .26	−0.35, .3
Left testicular volume	0.6, .06	−0.3, .3	0.6, .03	0.3, .2	0.01, .8	−0.38, .3
Sperm motility	0.2, .5	−0.02, .9	0.5, .02	−0.6, .005	0.49, .15	−0.28, .43
Sperm count	0.32, <.32	−0.2, .5	0.5, .02	−0.6, .005	0.49, .16	−0.26, .47
Morphology	0.2, .5	−0.2, .5	0.4, .6	−0.4, .22	0.4, .3	−0.2, .58
LH	−0.42, .006	0.8, .001	−0.6, .005	0.9, .0001	−0.83, .02	0.9, .05
Testosterone	0.3, .4	−0.5, .09	0.4, .07	0.1, .53	0.02, .9	−0.12, .8

Note: Values are r (correlation coefficient), P value. P<.05 was considered significant by Spearman's rank correlation.

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TABLE 5

Correlations between patients with normal FSH levels and those with elevated FSH levels.

	Normal FSH group (n = 20)		Elevated FSH group (n = 34)	
Variables	**Inhibin B**	**FSH**	**Inhibin B**	**FSH**
Right testicular	0.2, .4	0.22, .35	0.6, .0001	−0.65, .001
Left testicular	0.12, .4	0.22, .22	0.33, .01	−0.67, .01
Motility	0.2, .6	−0.03, .9	0.39, .03	−0.23, .2
Count	0.2, .33	−0.25, .32	0.52, .004	−0.35, .05
Morphology	0.2, .6	−0.55, .9	0.3, .01	−0.3, .1
Testosterone	0.11, .65	0.4, .032	0.34, .05	−0.12, .5
LH	−0.14, .59	0.7, .0001	−0.52, .003	0.8, .0001

Note: Values are r (correlation coefficient), *P* value. $P<.05$ was considered significant by Spearman's rank correlation.

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in the control group (19.34 ± 6.3 vs. 4.6 ± 0.5, $P=.02$) and the idiopathic infertility group (19.34 ± 6.3 vs. 4.4 ± 0.8, $P=.02$). Inhibin B did not have a significant correlation with sperm parameters and testicular volume in the idiopathic infertility group and the cryptorchidism group.

Testosterone levels were significantly lower in all three groups compared with the controls (idiopathic infertility: 16.9 ± 1.7 vs. 25.1 ± 2.9, $P=.03$; varicocele: 13.9 ± 1.3 vs. 25.1 ± 2.9, $P=.001$; and cryptorchidism – 11.8 ± 2.87 vs. 25.1 ± 2.9, $P=.005$).

Normal FSH Group (n = 20) vs. Raised FSH Group (n = 34)

Further subgroup analysis by FSH levels indicated that the group with elevated FSH levels had significantly lower inhibin B levels than the normal FSH group (46.8 ± 6.3 vs. 172.6 ± 17.7, $P<.05$) and controls (46.8 ± 6.3 vs. 181.2 ± 20.9, $P<.001$). However, no significant difference was noted in the inhibin B levels between the normal FSH group and controls (172.6 ± 17.7 vs. 181.2 ± 20.9, $P>.05$). Inhibin B correlations in the elevated FSH group were significantly higher than correlations in the normal FSH group (Table 5).

We further analyzed the inhibin B levels in obstructive (n = 15) vs. secretory azoospermia (n = 12) in our study population. Inhibin levels in the population with obstructive azoospermia were significantly higher than the population with secretory azoospermia (141 vs. 32.3, $P=.003$).

DISCUSSION

The role of inhibin B in male factor infertility was uncertain until the development of a highly sensitive and specific dimeric assay in the mid-1990s. With this assay, Illingworth and coworkers demonstrated an inverse relationship between inhibin B and FSH in men with normal and abnormal spermatogenesis (6). Similarly, we noticed a significant negative correlation between serum FSH and inhibin B levels in our patients. These results support the fact that inhibin B is the testicular feedback signal for FSH (6, 16, 17).

Several authors reported that men who underwent castration and those with Klinefelter's syndrome had undetectable inhibin B levels, confirming the fact that serum inhibin B levels reflect testicular function and, more precisely, Sertoli cell function (9, 10). Our results also revealed that inhibin B levels are significantly reduced in men with infertility problems, irrespective of etiology, compared with fertile men. However, no such significant difference was observed in the levels of other hormones between the fertile and infertile men. Our results indicate that inhibin B levels are a more sensitive marker of male factor infertility than other available hormones, irrespective of the etiology.

In our study, sperm parameters and testicular volume in infertile men appear to be significantly and positively correlated with inhibin B, and significantly and negatively correlated with FSH. However, we noticed that correlations between inhibin B levels and sperm parameters were more significant than the correlations of FSH levels with the sperm parameters. These results probably can be explained by the fact that inhibin B is more directly related to the changes in the testicular function than FSH, which is an indirect marker for spermatogenesis (18). Similar results were observed in subgroup analysis, where inhibin B levels had more significant correlations than FSH levels.

Inhibin B and testosterone originate from different types of cells in the testis. Even so, studies reported that both have a positive correlation with testicular function (19, 20). Several authors proposed that some unidentified factors produced by Leydig cells may modulate the inhibin B production in the tubular compartment of the human testis (19). However, a study by Kolb et al. indicated no significant correlation between inhibin B and testosterone levels (21). In

our study, we also found that inhibin B levels were positively correlated with testosterone levels, supporting the hypothesis that Leydig cells might influence inhibin B secretion. However, testosterone was not significantly correlated with sperm parameters in our study. This is probably because spermatogenesis occurs in a different cell population in the testis.

Andersson et al. (15) reported that the inhibin B-FSH ratio (index) is a more sensitive marker than inhibin B or FSH alone. In our study, we found that inhibin B-FSH and inhibin B alone had significantly higher correlations with testicular volume and sperm parameters than FSH or LH alone. These results indicate that the inhibin B-FSH ratio can also serve as a direct marker for spermatogenesis. However, our results indicated that inhibin B alone has stronger correlations than the index, suggesting the probability that inhibin B alone is a more sensitive indicator of infertility than the index.

We also assessed whether the inhibin B-testosterone ratio can be a useful marker for spermatogenic potential. Although both are produced directly from the testis, the correlations with the inhibin B-testosterone index and sperm parameters were not consistent. This variation may be because of diverse etiological groups in our study population and may be due to the lack of correlation between sperm parameters and testosterone.

Varicocele has been associated with infertility and disturbed spermatogenesis. Mormandi et al. (22) and Fujisawa et al. (23) reported that inhibin B has a significant positive correlation with sperm parameters in varicocele patients. Similarly, in our study, inhibin B had a significant positive correlation with sperm parameters and testicular volume in the varicocele group. However, no such correlations were observed with FSH levels, indicating that inhibin B can serve as a potential marker for testicular damage in varicocele patients. Whether inhibin B levels in varicocelectomy patients can predict improvement in sperm parameters and spontaneous pregnancy rates needs to be confirmed in future prospective randomized trials.

Infertility has been one of the common complications in patients with cryptorchidism. Studies reported that infertile men with a previous history of cryptorchidism have low inhibin B levels compared with normal controls (24). de Gouveia Brazao et al. (25) reported that inhibin B levels are low in infertile men with cryptorchidism compared with men with idiopathic subfertility and normal controls. Similarly, in our study, inhibin B levels were significantly lower in patients with cryptorchidism than in the patients with idiopathic infertility and the normal fertile controls. This decrease in inhibin B levels was mostly due to irreversible damage that had occurred in these patients. The low inhibin B levels were associated with a significant rise in FSH levels. These results indicate that men with cryptorchidism who have low inhibin B levels may have problems with fertility. Inhibin B levels in men with cryptorchidism can serve as a marker of spermatogenesis.

The FSH level is a useful initial marker for the evaluation of spermatogenesis. Elevated FSH levels are commonly seen in men with testicular diseases, and low levels are observed in those with central disorders (10). In our study, we evaluated the role of inhibin B in patients with elevated FSH levels and normal FSH levels. We found that inhibin B levels in the elevated FSH group were significantly correlated with testicular volume and sperm parameters. However, this was not observed in the normal FSH group. Elevated FSH levels are commonly associated with primary testicular disorders. The fact that inhibin B levels were significantly correlated with sperm parameters in the elevated FSH group indicates that the condition more commonly represents primary testicular disorders. These results further confirm the fact that inhibin B is more useful in patients with primary testicular disorders and that it can serve as a direct marker of testicular function.

For years, FSH has been the most useful marker for assessing a man's fertility status and differentiating between peripheral and central disorders. However, inhibin B may be a more useful and direct marker of testicular function. It may also be a better marker of spermatogenesis and may be useful for formulating new therapeutic methods in the evaluation and treatment of male factor infertility.

Inhibin B levels may be a better marker for evaluating male factor fertility than FSH and LH. In patients with infertility, measuring inhibin B levels may provide useful information on spermatogenesis and possibly serve as a more direct marker of the spermatogenesis than FSH. The inhibin B-FSH index may also be a potentially useful marker of male factor infertility along with inhibin B. However, further prospective studies are essential to define the significance of these indices in male factor infertility evaluation.

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