Hyperprolactinemia And Hypergonadotropins In Infertile Males With Sever Oligospermia And Azoospermia

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Citation

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Abstract

Serum prolactin (PRL), luteinizing hormone (LH), and follicle stimulating hormone (FSH) were analyzed in 120 infertile male including: 78(65%) asthenozoospermic, 24(20%) sever oligospermic, 10(8.3%), oligospermic, and 8(6.7%) azoospermic using immunometric assay. Hormonal seric values were correlated with sperm count, motility, and antisperm antibody as detected by Latex Agglutination Test . No clinical importance of autoantibody was appeared in all groups of subjects investigated. A significant week correlation was found between serum LH and sperm count in all infertile males (p=0.002) but not motility, whereas PRL and FSH showed an inverse relationship with motility (r = -0.469 p<0.005, r = -0.316 p< 0.005) respectively. The mean PRL level (reference range 2.5-17 ng/ml) was found to be higher in sever oligospermia and azoospermia (mean 17.9 ±12.7 and 18.6 ±11.7 respectively). On the other hand, the mean LH levels (reference range 0.8-7.6 mIU/ml) and FSH (reference range 0.7-11.1 mIU/ml) was found to be higher in azoospermia (19.9±14.9 and 24.8±32.4 respectively). Increasing profile of FSH and PRL is useful in routine investigation of azoospermic male (p=0.001). These data demonstrate that when using lower semen parameters, the most common serum hormone abnormality is increased in PRL and gonadotrophins. The study gives an impression concerning serum PRL, FSH, and LH in infertile males in Jordan.

INTRODUCTION

Male fertility depends on the proper function of a complex system of organs and local balance between androgen and estrogen which is important for spermatogenesis ([1]). Abnormalities in hormone production may be a factor in male infertility that can be recovered by hormone replacement therapy ([2], [3]). Hypogonadotropic hypogonadism which is the failure of the pituitary gland to produce adequate amounts of FSH and LH can lead to decreased sperm counts and a state of infertility ([4]).

Studies relating serum LH, FSH, and prolactine (PRL) with sperm concentration and motility are conflictive. Serum hormonal concentrations have been reported to be lower or higher in oligozoospermics in comparison with normozoospermic men. In all of these studies, the series of normozoospermics and oligozoospermics include indistinctly, subjects with both normal and diminished sperm motility. Moreover, studies relating sperm motility with serum PRL reported decreased or higher levels of the hormone in asthenospermics with respect to subjects with normal sperm motility ([5], [6], [7], [8], [9]). However, normal serum concentrations of PRL have been shown to exert permissive roles in the male reproductive tract ([5]), but excessive serum PRL concentration was correlated with infertility, hypogonadism, impotence, and galactorrhea ([10]).

Tests for hormonal levels are indicated if semen analysis is abnormal or there are other indications of hormonal disorders. Very high FSH levels, for example, with normal levels of other hormones indicate abnormalities in initial sperm production. However, when the sperm producing capacity of the testis is diminished, the pituitary makes more FSH in an attempt to make the testes do its job. Therefore, if a man's FSH is significantly elevated there is a strong indication that his testicles are not producing sperm optimally ([1]). The changes in LH and FSH may be one of the reasons that cause the dysfunction of spermatogesis and sperm maturation in patients with idiopathic azoospermia and oligospermia ([4]). Local balance between androgen and estrogen is important for spermatogenesis. This fact appeared in infertile males which have an elevated seminal plasma estradiol, with a reduction in testosterone and testosterone/oestradiol ratio ([1]).

There is extensive literature on the interaction between the immune system and the pituitary, particularly with reference to prolactin. It exerts its effect on immune function by

facilitating T- cell immunocompetence ([11]). Several studies demonstrate the relationship between sperms autoimmunity with antisperm antibody production (ASA) and hyperprolactinemia ([12]).

FSH, LH, and prolactin serum levels estimations are one part of the most diagnostic procedures in andrology but their prediction value was under discussion all the time.

Experimental data support a role for gonadotropic releasing hormone and prolactin in the reproductive process in humans, but the effect of excess levels on sperm concentration and motility in men showed conflicted results.

MATERIALS AND METHODS

SUBJECTS

Our study group consists of 120 infertile men, aged 22 to 34 years. Patients were attending infertility department at Medical Hussein Center in Jordan, during the period of six months. All subjects did not take any medications for at least six months before the study. All of them were non smokers, non alcohol drinker, and showed no sign of genital tract infection. Seminal fluid was collected by masturbation. Blood samples were obtained from each subject after overnight fasting.

SEMINAL FLUID ANALYSIS

Seminal fluid was collected by masturbation after 3 to 5 days of sexual abstinence. Sperm concentration and motility was performed within two hours after collection of semen. All seminal analysis was done by the same person. Sperm concentration and the degree of motility were estimated according to WHO guide line for seminal fluid analysis ([13]). Motility is graded from a to d. Grade a (fast progressive) sperm are those which swim forward fast in a straight line. Grade b (slow progressive) sperm swim forward, but either in a curved or crooked line, or slowly (slow linear or non linear motility). Grade c (non progressive or sluggish) sperm move their tails, but do not move forward (local motility only). Grade d (immotile) sperm do not move at all. Sperm of grade c and d are considered poor.

ANTISPERM ANTIBODIES

Antibodies to sperm in the seminal plasma are detected by Latex Agglutination Test (LAT) (Bioserv, Germany). Ten microletter of specimen with 490 microleter of dilution buffer was thoroughly mixed and centrifuged at 1000g for ten minutes. A serial dilution of supernatant using log 2 was made (1:100, 1:200, and 1:400). Diluted specimen (20 ul) was added to 10ul of antigen suspension on a slide and mixed for 2 minute. Agglutination was considered to be positive with regard to the presence of sperm antibodies only in the specimen dilutions of 1:100 and higher.

HORMONAL ASSAY

Blood samples were obtained from each subject after overnight fasting. Determinations of hormonal levels (LH, FSH and PRL) were achieved using Immunometric assay ([14], [15], [16]). The reference values that used were: LH, 0.8-7.6 mIU; FSH, 0.7-11.1 mIU/ml; and prolactin 2.5-17 ng/ml. Blood tests for testosterone and follicle-stimulating hormone (FSH) levels are usually taken first. If testosterone levels are low, then luteinizing hormone (LH) and prolactin levels are measured.

STATISTICAL ANALYSIS

Analysis of the data was done using the chi-square, one way analysis of variance (ANOVA), person correlation coefficient(r).

RESULTS

Subjects were classified depending on the results of semen analysis. Seventy eight (65%) of the infertile male have asthenozoospermia (less than 60 % motile or less than 30% with excellent activity), twenty four (20%) have sever oligospermia ($\leq 10 \times 10^6$ sperm/ml), and ten (8.3%) have oligospermia ($< 20 \times 10^6$ sperm/ml). Azoospermia (no sperm) was found in eight (6.7%) of the examined patients. No significant association between poor semen analysis and the presence of sperm antibodies (the only detected titer was below 1:100 which is non significant).

The mean prolactin levels (reference range, 2.5-17 ng/ml) was 18.6 in azoospermia, 18.0 in sever oligospermia, 7.8 in oligospermia, and 11.0 in asthenozoospermia cases. In addition, the mean LH and FSH levels (reference range,0.8-7.6 mIU/mL, and 0.7-11.1 mIU/mL, respectively) was detected to be19.85, 24.8 in azoospermia, 4.4, 6.1 in sever oligospermia, 3.5, 4.16 in oligospermia, and 4.4, 4.3 in asthenozoospermia cases respectively.

Semen analysis showed no active or weak progressive motility among samples examined, while the most dominant type of motility was weak sluggish with low percentage of active sluggish type motility (table 1). Mean concentration of hormones was studied for its correlation with the four categories of infertility as shown in figure 1.

Figure 1

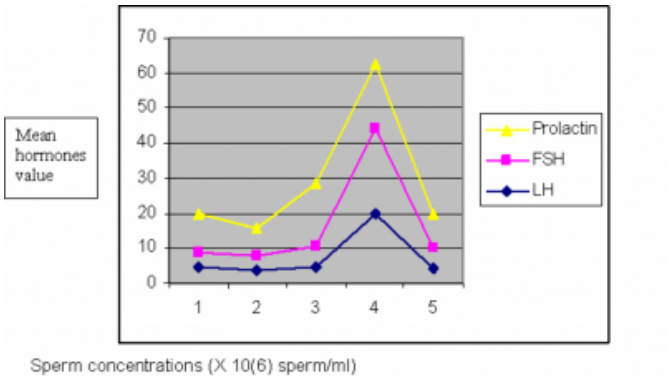
Table 1: Relationship between hormones concentration in infertile groups and mode of sperm motility

Sperm motility	LH r (p value)	Prolactin r(p value)	FSH r (p value)
Active sluggish	-	-	-
Week sluggish	-0.231(O.O5)	-0.283(O.OO1)	-0.281(0.001)
Active progressive	-	-	-
Week progressive	-	-	0.255(O.OO1)

P ≤ 0.05 significant

Figure 2

Figure 1: Variation in the levels of LH, FSH, and prolactin hormone in the serum of infertile groups.



1=Asthenozoospermia, 2=Oligospermia, 3=Sever oligospermia, 4= Azoospermia, 5= Normal level of the hormones

A significant negative correlation was found between sperm motility in all cases with serum prolactin and FSH level (r = -0.469 p<0.005, r = -0.316 p< 0.005) respectively. In addition, no significant correlation was found between serum LH and sperm motility. The overall, PRL, and FSH was increased in 18(15%), 16(13.3%) of the cases respectively. In contrast, only 8(6.6%) of the patients had elevated serum LH level.

Patients with azoospermia, however, showed higher level of serum prolactin, FSH, and LH. Sever Oligospermic patients also revealed an elevated level of prolactin in their serum. The level of serum PRL was correlated significantly with the level of FSH (r=0.303, P=0.001) among the study group.

DISCUSSION

Tests for hormonal levels are indicated if semen analysis is abnormal (especially if sperm concentration is less than 10 million per milliliter) or there are other indications of hormonal disorders. In this study, the high concentration of FSH, LH, and prolactin associated with a statistically significant decrease in the seminal fluid parameters may characterized a group of patients who may have a better prognostic outcome regarding the tubular gonadal function and thus the fertility potential.

The endocrine milieu on which spermatogenesis and sperm maturation mainly depends was evaluated quantitatively with simultaneous measurement of FSH, LH, and PRL concentrations in the serum. Sperm concentration and motility was determined in a group of patients categorized according to sperm count and motility. Their mean PRL level was found to be higher in azoospermia and sever oligospermia, whereas the mean LH and FSH were found to be higher in azoospermia. This might indicates some disturbance in the spermatogenesis process, since LH is essential in promoting spermatogenesis, while FSH has a role in development of the immature testis ($_{17}$) and has a direct role in the maintenance of spermatogenesis ($_{19}$). Controversy persist as to whether FSH is essential for the maintenance of adult spermatogenesis. The changes of LH, FSH may be one of reasons that cause the dysfunction of spermatogenesis and sperm maturation in patients with azoospermia and oligospermia ($_{4}$).

The results revealed no significant correlation between serum LH and sperm motility in all infertile groups. However, it was observed that in patients with normozoospermic and asthenozoospermic, sperm morphologies were inversely correlated with luteinizing hormone ($_{18}$). The balance of the three hormones can help determine specific problems are present. Very high FSH levels, for example, with normal levels of other hormones indicate abnormalities in initial sperm production. Usually this occurs only if the testicles are severely defective, causing sertoli cell –only syndrome in which sperm-manufacturing cells are absent. Some references reported that hyperprolactinemia was relatively uncommon cause of male infertility ($_{20}$). However, there is strong evidence suggesting that serum prolactin has a direct effect on sperm motility ($_{5}$). Our data ascertain the role of prolactin on sperm concentration and showed that the mean serum PRL level in sever oligospermic and azoospermic cases was different from their values in those subjects having normal sperm concentration and grouped according to abnormal sperm motility (asthenozoospermia). However, ANOVA analysis in the overall groups of subjects with abnormal sperm motility demonstrated a significant inverse correlation with their serum levels of PRL and FSH hormone (-0.469, and

-0.316 respectively). Based on the present data, it is difficult to determine the role of serum PRL in sever oligospermic and azoospermic patients. Experimental studies revealed the presence of specific receptors for prolactin in the prostate , the major source of citric acid, and that higher concentration of serum prolactin resulted in an inhibition on the growth of the prostate([21], [22]).

A detectable increase in the level of prolactin was observed in azoospermia and severs oligospermia cases as shown in fig.1. Similarly, some reports found higher levels of serum PRL in oligospermic and azoospermic men ([7]). The fact that many subjects with hyperprolactinemia have normal sperm concentration makes it difficult to find a relevant role for serum PRL on sperm concentration. Merino et al ([7]) recorded that two-thirds of the patients with oligospermia, asthenozoospermia, and azoospermia have normal prolactin levels.

Very high FSH levels was found in seven (11.6%) of the examined patients. The rise in FSH is in accordance with the theory of inhibin release during the maturation of states of spermatogenesis. The rise in LH might indicate a separate feedback mechanism mediated by the early stages of spermatogenesis and not by testosterone alone ([22]). However, it was suggested that spermatogenesis-related feed back factors may inhibit LH as well as FSH secretion ([23]). The occurrence of depressed spermatogenesis and elevated FSH levels seems to be relatively good indicator for the presence of certain disorders in the testis.

Although it was found that Sperm concentration and motility decrease and FSH level increase with age ([9]), our data showed no ageing effect observed considering the levels of hormones and seminal fluid analysis. Obesity is another factor that showed to be associated with hormonal level and sperm concentration in cases with oligospermia ([24]). So far, this fact wasn't valued in our study. However, group of patients were roughly quite similar in their weight (mean=75kg).

Our finding in relation to ASA was not consistent with the finding by Sullivan and Quinlivan ([25]) that reported an elevated level of IgA, IgG in cases with azoospermia and oligospermia or self agglutination of spermatozoa. Our result showed no detectable significant level of ASA observed in the seminal fluid of the study groups which might explain the role of other factors including the hormones in the abnormality of sperm count and subsequent reduction in the motility. In a study done by Fuller et al ([12]), a relationship between sperm autoantibody and hyperprolactinemia was present in a secondary infertile male with a possible interaction between the two diseases.

Varicoceles was detected in 34(28%) of the infertile men, in which elevated FSH, LH, and PRL was found in 4(28%), 1(25%), and 4(40%) of the cases with abnormal high concentration of the three hormones respectively. This consist with the results of Pasqualotto et al ([9]) who mentioned that infertile patients with varicocele have higher levels of FSH and lower sperm concentration and motility as compared to controls with out varicocele. This might explain the abnormalities in sperm motility in asthenozoospermic cases, since (28%) of the patients showed varicocele.

The results showed that the cases of infertility somehow, are reasonably correlated with hyper production of these hormones in addition to other factors.

Infertility in males due to moderate hypergonadotrophin, and hyperprolactinemia are associated with the decrease in sperm number and motility.

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