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EFFECT OF PROLACTIN AND TESTOSTERONE LEVELS ON SEMEN PARAMETERS OF MEN WITH PRIMARY AND SECONDARY INFERTILITY

Othman Hashem Mohammed*
PhD 1- Al-kut Hospital, Infertility center, Wasit, Iraq.

Rania Sabri Hasan
PhD Microbiology, Alkut hospital, Ministry of Health, Wasit, Iraq
*Corresponding author's email: Othmanh78@gmail.com

Abstract
The regular interactions and balance of the relationship of prolactin, gonads and testicular hormones and their suitability ensure that the sperm is normal in males. So this study is an attempt to classify male infertility depending on WHO criteria of seminal changes and to evaluate serum Prolactin, Testosterone FSH and LH levels in the participants, also determine the association between serum Prolactin, Testosterone levels and subtypes of male infertility. This study involved three hundred infertile males having infertility more than one year (cases group) and three hundred age-matched fertile males with definite paternity in past two years (control group) were included to the study from Jan 2020 -Dec 2021 at Al-Kut Hospital, Infertility Center in the Alkut city. Serum levels of hormones were measured by electrochemiluminescense immunoassay technique. Approximately half of patient's age ranged between 30- 39 years. Sixty eight percentage of cases complained from primary infertility. About 71.3% of patients had infertility duration between 1 - 5 years. This percentage decreased with increasing the infertility years. Most common infertile group was Asthenospermia (34.3%). A higher significant levels of serum Prolactin, FSH and LH found in cases than controls ($p<0.001$). However, the serum Testosterone levels was significantly lower in cases than controls ($p<0.05$). Moreover, serum Prolactin levels were found significantly elevated in all infertile subgroups (except Normospermic subgroup) compared to control group, while serum Testosterone levels were significantly decreased in all infertile subgroups (except Normospermic subgroup) compared to control group ($p<0.05$). So we conclude that; Poor spermatogenesis is associated with high serum Prolactin, FSH,LH levels and low serum Testosterone levels in patients with male infertility. Moreover, elevated serum Prolactin levels and decreased serum Testosterone levels were significantly associated with A, AT, OAT, Azoo and OA infertile males.

Keywords: Male infertility, primary and secondary infertility, Prolactin, Testosterone, spermatogenesis

INTRODUCTION

Infertility is typically defined as the inability to conceive after at least one year of regular, unprotected sex. This affects 15–20% of couples [1]. Male infertility represents around half of the general problem of infertility with male factor as a sole cause in about 20%, and is today a great health and social problem in term of both prevention and therapy [2].

Male infertility can result from genetic abnormalities, neurological diseases, infections, trauma, endocrine (hormonal disturbance), gonadotoxins and development of sperm antibodies [3].

The Hypothalamus releases gonadotropin-releasing hormone (GnRH), stimulates the pituitary gland for the secretion of lutenizing hormone (LH) and follicle-stimulating hormone (FSH). FSH stimulates spermatogenesis directly by acting on seminiferous tubules in Sertoli cells whereas LH induces sperm production indirectly via testosterone synthesis in Leydig cells. Prolactin hormone secreted by the pituitary, controls the production of LH and FSH via the regulation of GnRH through feedback mechanism on the hypothalamus. Prolactin has no known target organ or defined role in male reproduction. Yet, expression of Prolactin receptors on choroid plexuses and hypothalamus presupposes a latent role for this hormone in the regulation of male fertility [4,5].

Acute hyperprolactinemia can suppress testosterone synthesis and male fertility through Prolactin-induced hypersecretion of adrenal corticoids or by inhibiting the secretion of GnRH through Prolactin receptors on hypothalamic dopaminergic neurons [6].

Semen analysis comprises a set of descriptive measurements of spermatozoa and seminal fluid parameters that help to estimate semi quality [7].

AIM OF THE STUDY

The present study was aimed to: classify male infertility depending on WHO criteria of seminal changes, find the level of serum Prolactin, FSH, LH and Testosterone in participants, moreover to find any relationship between serum Prolactin, Testosterone levels with male infertility subgroups and types of infertility.

METHODS

This study is a case control study conducted between January 2020 until December 2021, three hundred infertile men with age ranged from 20 to 60 years and age-matched three hundred fertile males after confirmed paternity in the last two to three years enrolled as control group, attended Al-Kut Hospital, Infertility Center in the Al-kut city. After taking the consent from all participants, specific data were collected; age, fertility status, type and duration of infertility.

Any subject with testicular varicocele, hormonal medications or steroid preparations, previous scrotal surgery, genital infections or known HIV positive men, heavy smoking, chronic alcohol intake excluded from this study.

Semen samples were collected from each patient after 3- 5 days of sexual abstinence, after semen quality assay, the patients were categorized in different subtypes according to the WHO criteria (World Health Organisation, 2000): Azoospermia,

Asthenospermia, Asthenoteratospermia, Oligoasthenospermia, Oligoasthenoteratospermia and Normospermia.

About 10 ml of venous blood was collected from each subject of both groups for prolactin, testosterone, LH and FSH hormone assays were carried out using Roche e411 analyzer (Roche Diagnostics, USA) using electrochemiluminescense immunoassay technique. Normal reference ranges of serum Prolactin, Testosterone, LH and FSH for men were 4.04-15.2 ng/ml, 4.59-31.0 ng/ml, 1.7-8.6 mIU/ml and 1.5-12.4 mIU/ml, respectively.

Statistic

Statistical analysis was completed by using the SPSS software tool (version 24). Frequency distribution, percentage and continuous data in mean ± standard deviation (SD). Unpaired t-test was used to test difference in the mean, and Pearson's correlation coefficient (r) showed the correlation between two parameters. A statistically significant level was set at $P \leq 0.05$.

RESULTS

The findings in Table (1) indicates that both groups were comparable in age (p=0.43). Over half (52%) of 300 infertile men were of age ranged between 30 and 39 years, followed by (22.6%) of age 20- 29 years, followed by (20.7%) of age ranged between 40-49 while, older age (≥50years) were only 4.7% of total infertile men.

Table 1 : Distribution of age in the study participants

Age /years	Infertile group No. (%)	Control group No. (%)	P value
20-29	68 (22.6)	78 (26)	20-29
30-39	156 (52)	130 (43.3)	
40-49	62 (20.7)	72 (24)	
≥50	14 (4.7)	20 (6.7)	
Total	300	300	
Mean of age	33,98 ± 6.72	35.02 ± 8.18	0.43

Table (2), represent that Sixty eight percentage of total infertile men complained from primary infertility and the rest (32%) complained from secondary infertility. About 71.3% of patients had infertility duration between 1 and 5 years. This percentage decreased with increasing the infertility years, so that, patients who had infertility duration between 6 and 10 years, were found in 17.7% and those with infertility duration more than 10 years were found in percentage equal to 11% of total infertile men. Most common infertile group was Asthenospermia (A)which includes 103 patients (34.3%) of the total. Followed by 28% of Asthenoteratospermia (AT), 20.3% of Oligoasthenoteratospermia (OAT), while Azoospermia (Azoo), Oligoasthenospermia (OA) and Normospermia were found in 6.7% , 4% and 6.7% respectively.

Table 2: Data about Type and Duration of Infertility

Parameters		Number	Percentage
Type of Infertility	Primary	204	68
	Secondary	96	32
Duration of Infertility/ Years	1-5	214	71.3
	6-10	53	17.7
	≥10	33	11
Type of infertility based on seminal changes	A	103	34.3
	AT	84	28
	OAT	61	20.3
	Azoo	20	6.7
	OA	12	4
	Normospermia	20	6.7

Table (3), Highly significant differences ($p<0.001$) were observed in the mean of serum Prolactin, FSH, LH levels in infertile group compared to control group (26.5±9.43 vs13.4± 7.51, 13.66±7.43 vs 3.97±1.57, 9.46±5.12 vs 4.35±2.08) respectively. These hormones levels were significantly higher in infertile group compared to controls. Moreover, the mean serum Testosterone levels were lower in infertile group than the control group. (3.8± 4.56 vs 7.4± 6.85) respectively, $p<0.01$, Table (3).

Table 3: Serum Prolactin, Testosterone, FSH and LH levels in the study participants

Parameters	Infertile group (n=300)	Control (n=300)	P value
Prolactin (ng/ml)	26.5±9.43	13.4± 7.51	<0.001
Testosterone(ng/ml)	3.8± 4.56	7.4± 6.85	<0.05
FSH(mIU/ml)	13.66±7.43	3.97±1.57	<0.001
LH(mIU/ml)	9.46±5.12	4.35±2.08	<0.00

Table (4) ,The mean levels of serum Prolactin elevated significantly in A, AT, OAT , Azoo and OA infertile males were 24.7±8.73, 21.5± 9.45, 30.5± 9.83, 25.55±8.09, 31.5± 9.21 (ng/ml) respectively compared to controls (13.4±7 ng/ml).
So, serum Prolactin levels were found significantly elevated in all infertile subgroups (except Normospermic subgroup) compared to control group. Interestingly, serum Testosterone levels were significantly decreased in all infertile subgroups (except Normospermic subgroup) compared to control group ($p<0.05$) (Table 4).

Table 4: Serum Prolactin and Testosterone levels in control group and infertile subgroups.

Groups	Hormones	
	Prolactin ng/ml (mean± SD)	Testosterone ng/ml (mean± SD)
Controls	13.4±7.51	7.3± 6.85
A	24.7±8.73*	4.30±4.47 *
AT	21.5± 9.45*	4.39±4.86 *
OAT	30.5±9.83 *	3.02±4.61*
Azoo	25.55±8.09*	2.85 ±4.23 *
OA	31.5± 9.21*	2.96 ±4.17 *
Normospermia	16.6± 8.27	7.81± 6.44

Significant difference($p<0.05$).

Table (5), A significant negative correlation of FSH and LH levels with sperm count ($r= -0.26$; p0.05). Also there were no significant correlation between Prolactin, Testosterone, FSH, LH and semen volume ($p>0.05$) (Table 5).

Table 5: Correlation of serum hormones with semen profile of infertile men.

Semen profile	Hormones			
	Prolactin	Testosterone	FSH	LH
Semen volume r (p value)	0.02(0.91)	0.05(0.61)	-0.002(0.76)	-0.02(0.56)
Sperm count (10^6/ml) r (p value)	0.08(0.42)	0.12(0.13)	-0.26(<0.001)	-0.21(0.002)
Sperm motility r (p value)	-0.05(0.45	0.08(0.18)	-0.21 (0.002)	-0.22(0.001)
Sperm morphology r (p value)	0.06(0.62)	0.05(0.6)	-0.34(<0.001)	-0.33(<0.001)

Table (6),Mean of age in the primary infertile group were significantly younger than the mean of age in secondary infertility group (31.86± 5.11 versus 35.95± 7.02 years; p= 0.02). The duration of infertility as well as volume, sperm motility, sperm count and abnormal forms of the semen were not significantly different between the primary and secondary groups $p>0.05$. Also, there were no statistical differences in the hormonal parameters (serum Prolactin and Testosterone levels) between the two groups $p>0.05$ (Table 6).

Table 6: Demographics, semen profile, serum Prolactin and Testosterone levels of the primary and secondary infertility groups.

Parameters	Primary infertility	Secondary infertility	P value
Age (year) (Mean ±SD)	31.86± 5.11	35.95± 7.02	0.02
Duration (year) (Mean ±SD)	7.02± 5.76	6.34 ± 5.12	0.62
Volume (ml) (Mean ±SD)	2.62± 2.3	3.12 ± 3.45	0.67
Count (10^6/ml) (Mean ±SD)	30.1± 45.33	28.98 ± 38.56	0.55
Motility (%) (Mean ±SD)	32.75 ± 25.89	24.77±20.56	0.45
Abnormal form (%) (Mean ±SD)	26.51± 33.58	39.923± 35.56	0.07
Prolactin (ng/ml) (Mean ±SD)	24.9±8.72	26.9±9.31	0.65
Testosterone (ng/ml)(Mean ±SD)	3.2± 5.21	4.5± 5.62	0.46

DISCUSSION

The spermatogenesis depends on the appropriate functioning of a compound work of reproductive hormones but alterations in the level of these hormones lead to abnormal spermatogenesis and cause infertility. Therefore, endocrinological assessment is important in infertile males for correct diagnosis and treatment.

In the present study, over half (52 %) of total infertile men were of age ranged between 30 and 39 years, followed by (22.6%) of age 20- 29 years, these findings could be related to the relatively delayed marriage age of Iraqi men to around thirties, because of economic situation. Also Bhale et al. found most infertile patients in the age group of 25-40 years, which is in concert to our findings [8], but our findings not in line with [5] et al. who found the majority of the infertile male (40%) were in the age group of 26-30 years [5].

The primary infertility prevalence was high in our region (68%), which stand with similar findings in previous study [9],but differed from study conducted in South East Nigeria [10]. This high frequency of primary infertility could be due to hidden genetic defects, many of idiopathic azoospermia, or oligospermia have a genetic basis. [11] et al., found that infertile men have an approximately 10-folds increase in the incidence of chromosomal anomalies compared with normal controls [11]. Another explanation for the predominance of primary infertility in this study could be attributed to the high cost of infertility treatment programs, the prolonged follow up periods, and the discouraging success pregnancy rate. These make patients with primary infertility seek medical help more promptly than those who have already conceived particularly when the male factor is the cause of infertility problem in the couple.

In our results, about 71.3% of patients had infertility duration between 1 and 5 years. This percentage decreased with increasing the infertility years, so that, The decrease in the percentage of infertile men with the increasing in the duration of infertility could be due to the increase in awareness of the man as a cause of infertility and the earlier interest in seeking advice. [12]et al. found that the time to pregnancy increased with the male age and association between increased male age and increased time to pregnancy and the frequency of subfecundity[12].

Most common infertile group was A followed by AT,OAT , while Azoo, Normospermia and OA were found in low percentage in the current study, These results are partially similar to that reported by Öztekin et al. who found that A was the leading cause of male infertility in 77 patients (19%), mixed pathology (OAT) was seen in 68 cases (16.7%). forty-two patients (10.3%) had Azoo, and 22 (5.4%) had Oligozoospermia[9], In contrary, [5] et al gave different results and found that most of the infertile patients were with Azoo (46.2%) followed by A (34.5%), O (12.7%) and Normozoospermia (6.4%) [5]. [13] et al. evaluated the patients admitted to three infertility clinics in Turkey, and the Azoospermia rate was 5.85% among the 9,733 patients in that study [13].

The discrepancy between the incidence in our results and in others may be due to geographic, environmental, socioeconomic, racial differences, smoking, radiation exposure stress, and ethnicity, season of sample collection, varicocele, infection and genital abnormalities.

er in infertile group than the control group, while the mean serum Testosterone levels were lower in infertile group than the control group, this result is supported by findings of [5] et al.2020 In contrary, no significant difference in the mean of serum testosterone levels between infertile cases and fertile controls was found by other authors [14].

Significant elevation of serum Prolactin levels may result from Prolactin secreting pituitary macroadenoma that produces galactorrhoea. The mechanism by which high serum Prolactin causes poor spermatogenesis in healthy men is not so certain [15]. Also elevated levels of serum Prolactin have a detrimental effect on male reproduction through inhibition of the pulsatile release of gonadotrophins from the anterior pituitary gland, and a direct effect on spermatogenesis. Treatment of confirmed hyperprolactinaemia with dopamine agonists leads to significant improvements in both semen parameters and hormone levels [6].

In the current study, elevated of Prolactin levels and decreased Testosterone levels were significantly associated with A, AT, OAT, Azoo and OA patients in comparing with controls. These outcomes indicate abnormal spermatogenesis of infertile males, this study is strengthen by some previous studies [16] .

[17] et al., illustrated that hyperprolactinemia causes infertility in around 11% of oligospermic males [17] Hyperprolactinemia inhibits the pulsatile secretion of the gonadotrophin releasing hormone, which causes decreased pulsatile release of FSH, LH, and testosterone, which in turn causes spermatogenic arrest, impaired sperm motility, and altered sperm quality. It later produces secondary hypogonadism and infertility [15].

In our study, FSH and LH hormones were inversely correlated with sperm count, motility and morphology. while prolactin and testosterone was positively correlated with all semen parameters except a poor negative correlation was found between serum Prolactin and sperm motility . Since, FSH is known to have a direct role in immature testis development as well as in maintaining spermatogenesis, while LH is required to promote spermatogenesis indirectly via testosterone. Though, elevated LH and FSH levels stimulate Leydig and Sertoli cells for balanced production and secretion of testosterone thus enhancing spermatogenesis. At definite plasma threshold of gonadotropins, high LH and FSH levels generate a negative feedback

effect on hypo thalamopituitary-gonadal axis. Therefore, the serum testosterone level becomes low or normal. [18].

In the present study, except for the age of infertile male in the primary infertility group which was significantly less than in infertile male with secondary infertility, the other parameters were not significantly different between 2 types of infertility, these findings were in consistence with [19]et al

CONCLUSIONS

In this study; over half of total infertile men were of age ranged between 30 and 39 years. The primary infertility prevalence was higher in ourregion than secondary infertility. More than two thirds of the patients had infertility duration between 1 and 5 years and most common infertile group was Asthenospermia. Poor spermatogenesis is associated with high serum Prolactin, FSH, LH levels and low serum Testosterone levels in patients with male infertility. Moreover, elevated serum Prolactin levels and decreased serum Testosterone levels were significantly associated with A, AT, OAT, Azoo and OA infertile males. These findings are interesting for further confirmation using more patients of multiple cohorts.

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