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Correlation between Post-Tamoxifen Hormonal Changes and Seminal Fluid Analysis Parameters Improvement.

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ABSTRACT

Oligoasthenoteratozoospermia is a prevalent cause of male infertility. (iOAT). It is generally acknowledged that, due to the fact that spermatogenesis is a sex-hormone-dependent process, specific endocrine treatments might enhance or recover male fertility. The typical negative feedback of sex steroids is disrupted by anti-estrogen medication, leading to a rise in endogenous gonadotropin-releasing hormone secretion (FSH and LH) straight from the pituitary. The stimulation of Leydig cells in the testes by FSH and LH is thought to promote local testosterone synthesis, which in turn may improve spermatogenesis. The study sample consisted of 42 iOAT patients. Baseline seminal fluid analysis (SFA) and hormonal assessment (FSH, LH, prolactin, and testosterone) were taken. Each patient was given medical treatment with tamoxifen (20 mg/day) for three months. SFA, FSH, and testosterone were taken after three months. There was a significant increase in FSH, testosterone, sperm concentration, and progressive motility after treatment (p value <0.001), furthermore, there was no significant correlation between hormonal changes and changes in SFA study markers (p value > 0,05). Improvements in hormone levels following tamoxifen treatment for patients with idiopathic oligoasthenoteratospermia do not correlate with alterations in SFA markers.

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KEYWORD

Tamoxifen, Oligoasthenoteratospermia, FSH, Testosterone

1. Introduction

About 15% of individuals of reproductive age in industrialized nations are thought to experience infertility, which is known as the inability to conceive after one year of unprotected sexual intercourse. (Guo L, et al.,2015 [1]). Male infertility is caused by abnormalities in the standard sperm indices (concentration, motility, and morphology) and manifests as oligozoospermia, asthenozoospermia, and/or teratozoospermia. DNA damage, chromatin compaction, and mitochondrial function are just a few of the bio-functional sperm parameters that may be compromised. In addition, a wide range of environmental, inflammatory, infectious, and genetic factors, such as obesity (which can impact both male and female fertility), varicocele, radiation, and immunologic, and genetic factors, such as Y chromosome microdeletion and other genetic abnormalities, contribute to male infertility (Choy JT,2018 [2]; Jensen CFS et al.,2017[3]; Katib A, 2015; Krausz C and Riera-Escamilla, 2015[4]). There are hormonal and non-hormonal approaches to medical therapy. (Duca Y, et al.,2019 [5]). Follicular-stimulating hormone (FSH) is administered to oligozoospermic males with normal FSH levels because of its stimulating influence on spermatogenesis and is one of the hormonal treatment alternatives. Tamoxifen, clomiphene citrate, raloxifene, and toremifene are all examples of selective estrogen receptor modulators (SERMs) that can either work as estrogen agonists or antagonists depending on the tissue, they're in (Plouffe LEO and Siddhanti S,2001 [6]). They inhibit oestrogen receptors in the brain and pituitary, promoting GnRH secretion and, consequently, pituitary LH and FSH secretion increased. (Kumar R et al., 2006 [7]; Cocuzza M and Agarwal A,2007 [8]). The rationale for giving SERMs to patients with low sperm counts is that they raise gonadotropin

levels, which in turn enhance sperm formation .

In humans, normal male reproductive growth and function depend on a suitable equilibrium between androgen and estrogen. Aromatase cytochrome P450 is responsible for maintaining this equilibrium, and its expression is also regulated spatially and temporally. The effects of oestrogen are mediated in the testis through ERa and/or ERb oestrogen receptors and the membrane-associated G-protein-coupled functional ER (GPER). The effects of oestrogen on fertility in men are more sophisticated than initially assumed. When it comes to the male reproductive system, the androgen/oestrogen balance and its control in the masculinization programming window (MPW) throughout foetal life are of the utmost importance. Inadequate maintenance of this equilibrium during MPW may have deleterious effects on the male reproductive system. Oestrogens may cause male infertility, according to recent research from genetically modified mice and male infertile patients. This occurs because oestrogens encourage the engulfment of living Leydig cells by macrophages. (Skorupskaite K,2014 [9]). Thus, SERMs are employed to counteract the deleterious effects of elevated oestrogen on a man's ability to reproduce. This investigation evaluates the relationship between hormonal fluctuations and shifts in SFA parameters before and after a course of tamoxifene treatment lasting three months

2. Materials and Methods

This is a prospective clinical study that was conducted in the infertility centre of Al-Nahrain High Institute for Infertility Diagnosis and Assisted Reproductive Technologies from April 2019 to November 2020. Patients referred to a male fertility clinic who have iOAT were selected for our study. Individuals with clinical varicocele, azoospermia, abnormal hormonal analysis, and taking medical treatment

(gonadotropins, anabolic steroids, and chemotherapy) were excluded from this study. Forty-two males were included in this study.

All patients undergo a full medical history, physical examination, and baseline SFA and hormonal assessment, including FSH, LH, prolactin, and testosterone, by Vidas: BIOMÉREUX, France. Patients were treated with tamoxifen (20 mg/day) per day for three months. SFA, FSH, and testosterone are measured after three months. Samples of sperm were obtained through masturbation after the subject had abstained from sexual activity for three to five days before to and following the administration of tamoxifen for three months. The World Health Organisation guidelines were considered guidelines for sperm analysis (Cooper T et al. 2015 [10]).

3. Results

In this study, a total of 42 males with varying spermograms and hormonal levels were tested both before and after receiving therapy with tamoxifen. Patients ranged in age from 19 to 51 years old during the study (mean ± standard deviation was 30.80 ± 6.91). The mean differences of testosterone (ng/ml) and FSH (mIU/ml) before treatment and after three months of treatment among patients who used Tamoxifen was assessed. There were significant differences between means of testosterone (ng/ml) and FSH (mIU/ml) before treatment and three months after treatment (P-value <0.001) (table 1). Furthermore, the mean differences of progressive sperm (%) and sperm count (million/ml) before treatment and after three months of treatment among patients who used tamoxifen was assessed. There were significant differences between means of progressive sperm (%) and sperm count (million/ml) before treatment

and three months after treatment (P-value ≤0.001) (Table 2). Furthermore, there were no significant differences between means of Normal sperm (%) before treatment and after treatment. Finally, no significant correlation was found between the change in testosterone (ng/ml) and FSH (mIU/ml) and the change in study markers, including (Normal sperm (%), progressive sperm (%), and sperm count (million/ml) between baseline reading and reading after three months of treatment with Tamoxifen (Table 4)

Table (1): The mean differences of testosterone (ng/ml) and FSH (mIU/ml) before treatment and after three months of treatment among patients who used Tamoxifen.

Study variable	Periods of assessment	Mean ± SD	Paired t-test	P-value
Testosterone (ng/ml)	Before treatment	4.33 ± 2.36	-6.945	**<0.001***
	Three months after treatment	7.48 ± 3.10		
FSH (mIU/ml)	Before treatment	3.78 ± 1.86	-8.295	**<0.001***
	Three months after treatment	6.83 ± 2.95		

Table (2): The mean differences of Progressive sperm (%) and Sperm count (million/ml) before treatment and three months after treatment among patients who used Tamoxifen.

Study variable	Periods of assessment	Mean ± SD	Paired t-test	P-value
Progressive sperm (%)	Before treatment	16.81 ± 14.31	-3.435	**0.001***
	Three months after treatment	22.88 ± 14.55		
	Before treatment	6.13 ± 4.38	-3.809	**<0.001***

Sperm count (million/ml)	Three months after treatment	9.75 ± 7.31		

Table (3): The mean differences of Normal sperm (%) before treatment and after three of treatment.

Study variable	Periods of assessment	Mean ± SD	Paired t-test	P-value
Normal sperm (%)	Before treatment	25.19 ± 16.97	-0.515	**0.609**
	Three months after treatment	26.55 ± 16.84		

Table (4): SPSS output for the area under the curve (ROC curve analysis)

Change between baseline and after three months of treatment	Normal sperm (%)		Progressive sperm (%)		Sperm count (million/ml)	
	r	P-value	r	P-value	r	P-value
Testosterone (ng/ml)	0.051	0.748	0.004	0.98	0.086	**0.588**
FSH (mIU/ml)	0.159	0.315	0.088	0.578	-0.042	**0.792**

4-Discussion

It is well-known that spermatogenesis is a complicated and well-coordinated process that results in an ongoing generation of spermatozoa. This process depends on the hypothalamic–pituitary–gonadal (HPG) axis (Jarow JP and Zirkin BR,2005 [11]; Neto FTL, 2016,2016 [12]). The hypothalamus is responsible for producing GnRH, which is then sent into the bloodstream to stimulate the pituitary gland into producing LH and FSH (Skorupskaite K et al.,2014[9]). In

males, the production of testosterone (T), which is required for the process of spermatogenesis (Taylor P et al., 2015 [13]). Is stimulated by the hormone luteinizing hormone (LH). Under the catalytic action of the enzyme aromatase (Walker WH and Cheng J,2005 [14]). a portion of the hormone T is transformed into the oestrogen estradiol

(E2). It is absolutely necessary to have FSH in order to keep the regular functioning of Sertoli cells, which are an essential part of the testicular microenvironment or niche that is responsible for spermatogenesis (Zhao N et al., 2019 [15])

The empiric treatment for idiopathic oligozoospermia includes (a) Anti-estrogens. (b) Gonadotropin-releasing hormone (GnRH) (c) follicle-stimulating hormone (FSH) (Lunenfeld, B et al.,1979 [16]). In the current study. There were significant differences between means of progressive sperm (%) sperm concentration before treatment and after treatment in three periods of assessment. Moreover, there were significant differences between means of FSH (mIU/ml) and testosterone

(ng/ml) and three months after treatment. As far as our search, there is no previous study highlight on the correlation between the degree of changes of FSH testosterone before and after treatment and the change of sperm parameters. Furthermore, there is no significant correlation between the change in testosterone (ng/ml) and FSH (mIU/ml) and the change in study markers, including (Normal sperm (%), progressive sperm (%), and sperm count (million/ml)) between baseline reading and reading after three months of treatment with Tamoxifen. We discovered that a large rise in SFA variables occurs whenever there is an increase in the hormonal level in patients who respond favorably to tamoxifen treatment, regardless of the level of hormonal change. This is consistent with the widely held belief that administering gonadotropins to

male patients suffering from azospermia or oligozoospermia while their FSH levels are elevated is often ineffective (Knuth UA et al.,1987[17]). In another study, 39 males with severe oligospermia were selected from a placebo-controlled, double-blind trial. In this trial, the sperm counts and the proportion of normal-morphology spermatozoa were comparable in the hCG/hMG treated group and the placebo-controlled group (Schill WB et al.,1982 [18]). On the other hand, Schill et al., 1982 showed that a combination of hCH/hMG therapy in 48 infertile males with idiopathic oligozoospermia was successful in some of the instances (Schill WB et al.,1982 [18]). Therefore, other factors should be evaluated to predict the response rate.

The pharmacogenetics of FSH is an additional component that plays an essential role in the process of determining the rate of treatment response. It has been demonstrated that the presence of the single nucleotide polymorphism known as p.N680S in exon 10 of the FSH receptor gene (FSHR) in females can alter the ovarian response to ovarian stimulation (Behre HM et al., 2005 [19]). Thus, it was only reasonable to investigate the impact of p.N680S on the FSH therapy of people who had normogonadotropic idiopathic infertility (Simoni M et al., 2016 [20]). In addition, total DFI decreased greatly from the start of the investigation until the completion of the study in patients who possessed the p.N680S homozygous N polymorphism of the FSH receptor. However, this was not the case in patients with the p.N680S homozygous S polymorphism of the FSH receptor. According to these data, it appears that it may be feasible to choose suitable normogonadotropic individuals for FSH medication, and it also appears that various patients may benefit from varied treatment regimens. (Nordhoff V et al.,2011[21])

The current study noticed no significant variations in sperm morphology before and after treatment. This contradicts the findings of other research, which

noticed substantial variations in the levels of normal sperm percentage before and after treatment. Other investigations claim that the enhancement in sperm parameters is caused by the hormonal balance created by letrozole via the blocking of estradiol and the increase of FSH and testosterone levels as markers of spermatogenesis and Sertoli cells. (Lu DİMTUĞ , 2009 [22]; Bibancos M et al. (2015 [23]; Cavallini G et al., 2011[24]; Cavallini G et al., 2013 [25] ; Saylam B et al., 2011 [26] ; Kooshesh L et al. , 2020 [27]).

This contradiction is probably related to excluding criteria of patient selection as many factors affect sperm morphology like environmental, occupational, smoking, diet habits, genetics, infections, etc. (Males I et al., 2024 [28], Jawed HM, et al. 2022 [29]). These factors affect sperm formation, DNA integrity, and morphology through its effect of ROS level. In addition, prior studies have indicated that the levels of ROS in infertile males are considerably greater than those found in normal males (Jayasena CN et al., 2019 [30]). The HPA is negatively impacted by reactive oxygen species (ROS), which results in less LH and FSH being secreted, consequently leading to a lower intratesticular testosterone level. On the contrary, ROS has been shown to increase aromatase activity, which in turn leads to an increase in the generation of E2 and a suppression of the synthesis of testosterone. It would appear that a high ROS level is likely to be connected with raised E2 in iOAT patients as long as the T: E2 ratio is less

than 10. However, in order to test this idea, additional studies are essential. In addition, it is essential to keep in mind that testosterone possesses antioxidant activity (Darbandi M et al., 2018 [31]), but a high amount of oestrogen can, on the other hand, inhibit the expression of an antioxidant enzyme (Aitken RJ et al. 2008 [32]). Therefore, they assert that the reduction in ROS levels seen in their study might be linked to the

hormonal equilibrium that was achieved in patients (Kooshesh L et al., 2020 [27]).

6- Conclusion

Idiopathic oligoasthenospermia treated empirically with tamoxifen. This led to an increase in hormonal levels, which caused improvements in SFA parameters. Furthermore, there is no significant correlation between incremental increases in hormonal levels and changes in SFA parameters. Therefore, we cannot predict response rate from changes in hormonal levels; furthermore, extending the treatment period for a non-responding patient for more than three months is ineffective, even with an incremental increase in hormonal levels. Further study of other factors that correlate with the response of those patients to Anti-estrogen therapy is recommended.

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Author Contribution

Ali Abdulkhaleq performed the study, and Ula AL-kawaz supervised the work .

Conflict of Interest

The authors declare no conflict of interest .

Ethical Clearance

The Ethical Approval Committee approved the study.

Financial Disclosure

There is no financial disclosure.

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