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The Effect of Aromatase Inhibitors on Infertile Men and its Relation to Sexual Desire

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Abstract--Background: Aromatase inhibitors (AI) can boost endogenous testosterone production without increasing circulating estrogen levels, as shown with estrogen receptor modulators, Aim and Objectives: The study's goal was to determine the efficacy of aromatase inhibitor medication in improving spermatogenesis in oligozoospermic and azoospermic males, as well as its relationship to sexuality. Subjects and methods: This study was done on eighty man subjects joining the outpatient clinic of Andrology, Kasr El Aini Hospital, Cairo University during the peroid from April 2018 – April 2020, and they were divided into (2) groups, 40 subjects in each group. Results: There was a statistically significant difference in serum total testosterone measured before and after treatment in normal FSH patients with a p value ≤ 0.05 . There was a notably not important change in sexual desire questionnaire measured before and after treatment in normal FSH patients with a p value > 0.05 , Conclusion: ERs and aromatase share topographic sites in the brain with pheromones, indicating that estrogen influences both early sexual maturation and sexual behavior in adults. Estrogen can maintain libido while also influencing the number of serotonin

receptors in the brain, which modulates mood, mental state, cognition, and emotion. Aromatase inhibitors as letrozole can be used in treatment of severe male factor (oligozoospermic, cryptozoospermic and NOA azoospermic) have disturbed T/E2 ratio as it increase sperm count and motility.

Keywords---azoospermic, oligozoospermic, aromatase inhibitors, testosterone, sexual desire, infertility.

Introduction

Spermatogenesis is controlled by the combination of endocrine and paracrine signals, and it is based on the maintenance of raised rates of intratesticular testosterone as well (1) as FSH stimulation of Sertoli cells. Furthermore, LH secreted by the anterior pituitary gland attaches to receptors on the surface of Leydig cells, stimulating T synthesis, a steroid hormone that diffuses in the seminiferous tubules. There are no perfect treatments for men suffering from idiopathic infertility. Improved sperm generation or motility, clomiphene citrate or tamoxifen citrate on the other hand, has been connected to empiric therapeutic intervention with estrogen receptor modulators like clomiphene citrate or tamoxifen citrate. Increased intratesticular testosterone concentration and stimulation of FSH release have been the mainstays of spermatogenesis-improving medical therapy. Unfortunately, using estrogen receptor modulators raises levels of estrogen and decreases testosterone secretion. (2).

Aromatase inhibitors (AI) can boost endogenous testosterone production without increasing circulating estrogen levels, as shown with estrogen receptor modulators (3). Some males with substantially reduced sperm production have a relative overflow of estrogen to testosterone, which is quantified as a higher testosterone/estradiol (T/E) ratio.

According to Pavlovich et al. (3), individuals with significant male infertility have a T/E ratio of 6.9, while those with normal sperm production have a T/E ratio of 14.5. They established a cutoff value of ten as the lower threshold of regular T/E ratios in males (measured in ng/dL for T and pg/mL for estradiol) based on the results. Aromatase inhibitors have been tested in males with abnormal T/E ratios, defective sperm production, and low blood testosterone concentrations (2). Control with an aromatase inhibitor to boost spermatogenesis would be more reasonable for men with low blood testosterone and a low T/E ratio than treatment with a selective estrogen receptor modulator. As a result, the goal of our study was to conduct a review of the efficacy and safety of aromatase inhibitors in infertile men's spermatogenesis.

Patients and Methods

This study was done on eighty male subjects attending the outpatient clinic of Andrology, Kasr El Aini Hospital, Cairo University during the period from April 2018 – April 2020, and they were divided into (2) groups, 40 subjects in each group; 80 oligozoospermic or azoospermic patients with disturbed T/E2 ratio

confirmed by semen analysis, hormonal profile. We divide patients into 2 groups: Infertile men with high serum FSH. Infertile men with normal serum FSH. And each group will administrate aromatase inhibitors (letrozole 2.5mg) daily for 3 months. Semen analysis is according to WHO recommendations twice: before to confirm oligozoospermia or azoospermia and after 3 months of aromatase inhibitors administration. Hormonal profile before and after 3 months of aromatase inhibitors administration and including: FSH, estradiol, total testosterone. Sexual desire questionnaire before and after 3 months of aromatase inhibitors administration.

Inclusion criteria: Males who were participants in infertile relationships with a 1 - year failure to conceive, Oligozoospermic males with a lower T/E2 percentage (<10) and Non-obstructive azoospermic (NOA) individuals who produced no spermatozoa with fine needle and cryptozoospermic men with T/E2 percentage <10.

Exclusion criteria: Major uncontrolled medical disorders (eg: hepatic or renal dysfunction), chronic heavy smokers, congenital absent vas deferens, history of repeated UTI, low semen volume < (1.5 ml), pyospermia, leucocytozoospermia more than 10/HPF or 1 million/ml, patients who received hormonal treatment within the last 3 months of investigations, men with known contact to testicular toxins, containing chemotherapeutic agents, radiation, industrial chemicals, pesticides and heavy alcohol consumption, history of cryptorchidism or mumps orchitis, evidence of hypogonadotropic Hypogonadism and demonstrable chromosomal abnormality.

Group 1: (Infertile males with normal serum FSH): Patients presenting with 1ry or 2ry Infertility for more than 1 year with repeatedly normal semen volume and azoospermia or low sperm count (less than 5 million per ml) and have normal FSH level.

Group 2: (Infertile males with high serum FSH): Patients presenting with 1ry or 2ry Infertility for more than 1 year with repeatedly normal semen volume and azoospermia or low sperm count (less than 5 million per ml) and have high FSH level.

All patients were subjected to:

- 1 *Personal History:* Name, age, residence, occupation, marital status and special habits of medical importance particularly smoking
- 2 *Sexual History:* The existence, frequency, and strength of morning erectile. Visual or manual excitation, as well as extramarital affairs, can cause erectile dysfunction. Frequency of intercourse and last Sexual coitus. The relation of the couple and the partner's attitude toward sex and if there is any marital trouble. Sexual desire questionnaire according to IIEF which was taken twice: before initiation of letrozole treatment and 3 months after treatment (discussed later).
- 3 *Wife History:* Including age of wife, menstrual history, Co-operation during intercourse and Investigations done to her concerning fertility.
- 4 *Past History:* History of medical diseases particularly diabetes mellitus, hypertension, coronary heart disease, liver or kidney and neurological disorders, Tuberculosis or Bilharziasis. History of drug intake especially those

affecting sexual function or fertility. History of previous operations, accidents or genital trauma.

5 *Physical examination:*

General examination: General examination including general condition, weight, waist circumference, height, body mass index, 2ry sexual characters, fat distribution, gynecomastia and presence of scar of previous operations.

Genital examination: - Penoscrotal investigation: the penis was examined for tenderness and plaques, as well as the size and location of the urethral meatus. To identify clinical varicocele and rule out cases of congenital missing vas, a genital investigation includes measuring testicular size, consistency (whether the testes are rubbery, stiff, hard, or soft), and inspection of the spermatic cord.

Investigations: All patients were studied between 8 and 11 am, Venous blood was sampled for measurements of serum testosterone (total), estradiol and FSH. Both Serum testosterone (Total), estradiol (E2), were measured using the electro-chemiluminescence immunoassay (ECLIA). All assays were performed on Cobas E411 immunoassay analyzer, Roche Diagnostics GmbH (Mannheim, Germany), according to the manufacturer's instruction.

6 *Semen analysis:* The patients were instructed to abstain for (2-7 days), and bring the sample by masturbation using no lubricants or detergents in a clean wide glass container, making sure that the whole specimen is collected. The sample is then labeled with the patient name and the time of collection. The semen analysis was done twice one before letrozole 2.5mg daily treatment and one after 3 monthes of treatment.

7 *Sexual desire questionnaire:* The 15-question International Index of Erectile Function (IIEF) Questionnaire is a self-administered, verified, multi-dimensional assessment. Each of the 15 questions, which test the four key domains of male sexual function: erectile function, orgasmic function, sexual desire, and intercourse satisfaction, is given a score ranging from 0 to 5.

Results

There are 16 azoospermic patients of total 80 patients 12.8% (11 of patients have normal FSH, 5 of patients have high FSH) before treatment. After treatment there are 10 azoospermic patients of total 80 patients 8% (6 of patients have normal FSH, 4 of patients have high FSH). 6 azoospermic patients have count after treatment for 3 monthes 4.8% (5 of normal FSH patients, 1 of high FSH patients). Table (1).

There was a statistically significant difference in sperm count measured before and after treatment in normal FSH patients with a p value ≤ 0.05 . Table (2). There was a statistically significant difference in sperm total and rapid progressive motility measured before and after treatment in normal FSH patients with a p value ≤ 0.05 . Table (3)

There was a considerable variation difference in serum total testosterone measured before and after treatment in normal FSH patients with a p value less than or equal 0.05. There was a statistically not important change in sexual desire questionnaire measured before and after treatment in normal FSH patients with a p value > 0.05 . Table (4)

There was a statistically significant difference in sperm count measured before and after treatment in high FSH patients with a p value less than or equal 0.05. There was a statistically significant difference in serum total testosterone measured before and after treatment in high FSH patients with a p value less than or equal 0.05. Table (5)

There was a significant variation in sexual desire questionnaire measured before and after treatment in normal FSH patients with a p value ≤ 0.05 . Table (6) There was a statistically not important change in sperm count measured before and after treatment between the two FSH groups p value > 0.05 . There was a statistically not significant difference in sperm total and rapid progressive motility measured before and after treatment between the two FSH groups a p value > 0.05 . There was a statistically not important change in serum total testosterone measured before and after treatment between the two FSH groups a p value > 0.05 . There was a statistically not significant difference in serum estradiol measured before and after treatment between the two FSH groups a p value > 0.05 . There was a statistically not important change in total testosterone\estradiol ratio measured before and after treatment between the two FSH groups a p value > 0.05 . There was a statistically important change in sexual desire questionnaire measured before and after treatment between the two FSH groups a p value less than or equal 0.05. Table (7)

Table 1
Descriptive analysis of azoospermic patients

	Azoospermic normal FSH	Azoospermic High FSH	Total azoospermic
Before	11	5	16 (12.8%)
After	6	4	10 8%)

Table 2
Comparison between mean values of sperm count measured before and after treatment in normal FSH patients

	Before	After	t value	P value
Count	1.87 $\pm$ 1.56	3.53 $\pm$ 2.61	-8.634	0.001*

The information is presented as mean $\pm$ SD.

t value= paired t test.

p more than 0.05= not important

**p $\leq$ 0.05= important*

Table 3
Comparison between mean values of sperm total and rapid progressive motility measured before and after treatment in normal FSH patients

	Before	After	t value	P value
Total motility	17.50 $\pm$ 14.98	26.75 $\pm$ 20.99	-5.286	0.001*
Rapid progressive motility	7.25 $\pm$ 9.45	12.72 $\pm$ 13.82	-3.727	0.001*

The information is presented as mean $\pm$ SD.

t value= paired t test.

p > 0.05= not important

**p less than or equal 0.05= important*

Table 4
Comparison between mean values of total testosterone, sexual desire questionnaire measured before and after treatment in normal FSH patients

	Before	after	t value	P value
Total testosterone	305.78±3.81	399.18±2.25	-139.872	0.001*
Sexual desire questionnaire	8.90 ± 0.78	8.10 ± 2.34	Z= -1.406	0.160

Table 5
Comparison between mean values of sperm count and total testosterone measured before and after treatment in high FSH patients

	Before	After	t value	P value
Count	1.31 ± 1.20	2.62 ± 2.24	-7.033	0.001*
Total testosterone	305.75 ± 4.54	397.98 ± 1.78	-117.139	0.001*

The information is presented as mean ± SD.

t value= paired t test.

p more than 0.05= not important

**p less than and equal 0.05= important*

Table 6
Comparison between mean values of sexual desire questionnaire measured before and after treatment in high FSH patients

	Before	After	t value	P value
Sexual desire questionnaire	9.10 ± 0.71	3.88 ± 2.09	Z= -5.346	0.001*

The information is presented as mean ± SD.

t value equal paired t test.

Z value= Wilcoxon Signed Ranks test.

P more than 0.05= not significant.

**p less than and equal 0.05= significant.*

Table 7
Comparison between mean values of difference of studied parameters in the two FSH subgroups

	Normal FSH (n= 40)	High FSH (n= 40)	Z value	P value
Count	1.67 ± 1.22	1.31 ± 1.18	-1.418	0.156
T. motility	9.25 ± 11.07	7.75 ± 11.54	-0.841	0.400
RP motility	5.48 ± 9.29	4.20 ± 10.49	-1.051	0.293

T.T	93.40 ± 4.22	92.22 ± 4.98	-0.150	0.881
E2	-30.60 ± 2.37	-31.75 ± 2.84	-1.682	0.093
T/E2	7.92 ± 0.47	7.72 ± 0.45	-1.734	0.083
Sexual desire Questionnaire	-0.80 ± 2.46	-5.22 ± 2.25	-5.953	0.001*

Data are expressed as mean ± SD.

Z value equal Mann Whitney test.

**p less than and equal 0.05= significant.*

P more than 0.05= not significant.

Discussion

Aromatase inhibitors can boost endogenous testosterone synthesis without the enhancement in circulating estrogens that estrogen receptor modulators cause (3). E2's role in male fertility is complicated. Aromatase is expressed in Leydig cells, Sertoli cells, and all stages of germ cells in humans.(4) The spermatogenesis of men with aromatase insufficiency or estrogen resistance is aberrant. (5).

The current study was carried out at the outpatient clinic of Andrology and STDs, KasrAl_Ainy Hospital, Cairo University This study was carried on on 80 oligozoospermic or azoospermic male patients with disturbed T/E2 ratio during the period from April 2018 – April 2020, and they were divided into (2) Groups, 40 subjects in each group as follows: Group 1 (Infertile men with high serum FSH) and Group 2 (Infertile men with normal serum FSH).

The study shows that there was a statistically significant difference in sperm total and rapid progressive motility measured before and after treatment (increased significantly) in both normal and high FSH patients with a p value ≤ 0.05. Sperm total and rapid progressive motility in both patients with normal FSH and those with high FSH:

Total motility increased from 17.50±14.98 to 26.75±20.99 after treatment in normal FSH patients Total motility increased from 20.75±14.39 to 28.50±21.67 after treatment in high FSH patients. Rapid progressive motility increased from 7.25±9.45 to 12.72±13.82 after treatment in normal FSH patients. Rapid progressive motility increased from 8.48±9.62 to 12.68±14.94 after treatment in high FSH patients. The study demonstrated no significant variation in sperm concentration, total motility, or rapid progressive motility between the two FSH groups with and without therapy with a p value > 0.05.

The difference from our study is the type of aromatase inhibitors letrozole in our study, testolactone and anastrozole in Raman and Schlegel, (6) study and duration of treatment 3 months in our study, 4-6 months in Raman and Schlegel, (6) study and the study did not divide the patients into groups according to FSH level if high or normal as in our study.

Gregoriou et al., (7) treated 29 men with low T/E2 ratios less than (10) and 14 patients were managed with anastrozole or letrozole in a poorly controlled clinical research, which agreed with our findings (alternate allocation of enrolled patients). As in the other investigations, fifteen subjects were given six months of letrozole 2.5 mg/d. Improvements in sperm count, motility, and morphologically

normal sperm and ejaculate were seen in individuals given either letrozole or anastrozole. Patients who received anastrozole had a numerically larger rise in sperm concentration, but the advantage did not show to be statically important.

The difference from our study is the type of aromatase inhibitors (letrozole in our study, letrozole and anastrozole in Gregoriou et al., (7) study and duration of treatment 3 months in our study 6 months in Gregoriou et al., (7) study and the study did not divide the patients into groups according to FSH level if high or normal as in our study.

Another study by Shoshany, Abhyankar et al., (8) was in agreement with our study done on 50 oligospermic, 28 azospermic and 8 cryptozoospermic all with decreased T/E2 ratios treated by Anastrozole 1 mg daily for 4 months showed increase in sperm count and motility significantly. The difference from our study is the type of aromatase inhibitors letrozole in our study, anastrozole in by Shoshany, Abhyankar et al., (8) study and duration of treatment 3 months in our study, 4 months in by Shoshany Abhyankar et al., (8) and the study did not divide the patients into groups according to FSH level if high or normal as in our study.

Unlike estrogen receptor modulators, aromatase inhibitors have the power to enhance endogenous testosterone synthesis without causing the raise in circulating estrogens that is shown with estrogen receptor modulators. (3). The study shows that there was a statistically significant difference in sexual desire questionnaire measured before and after treatment between the two FSH groups with a p value ≤ 0.05 .

Sexual desire was affected much more in infertile patients with high FSH after treatment by aromatase inhibitors for 3 monthes (decreased IIEF questionnaire for high FSH patients from 9.10 ± 0.71 to 3.88 ± 2.09 while those with normal FSH decreased IIEF from 8.90 ± 0.78 to 8.10 ± 2.34 , patient ≤ 6.3 has decreased sexual desire).

Our study is in agreement with Shoshany et al., (8) done on 50 oligospermic, 28 azospermic and 8 cryptozoospermic all with decreased T/E2 ratios treated by Anastrozole 1 mg daily for 4 months showed some side effect of anastrozole as Decreased libido, irritability, depression, bilateral breast tenderness, ocular pruritus/pain, and dry mouth but differ from our study in type of aromatase inhibitors and duration of treatment and the study did not divide the patients into groups according to FSH level if high or normal as in our study.

Cavallini et al., study (9) was in agreement with our study, which done on only 4 non-obstructive azoospermia proven by FNAP were treated by letrozole 2.5mg daily for 3 months, All four males who were treated reported a decrease in libido, with one reporting anxiousness and two reporting rash. It differs from our study in small numbers of patients and they all azospermic and the study did not divide the patients into groups according to FSH level if high or normal as in our study .

Our study is in disagreement with Saylam et al., study (10), treated a total of twenty seven infertile patients who had low serum testosterone ranks and T/E

percentages by letrozole 2.5mg for 6 months two of twenty seven male described mild headaches, not needing cessation of therapy with no other side impact recognized.

Gregoriou et al., (7) study was also in contradiction with our study, which treated 29 males with low T/E2 percentages (less than 10) in a poorly controlled clinical study, Fourteen of whom were given anastrozole or letrozole (alternate allocation of enrolled patients). In a study of 15 subjects managed with six months of letrozole 2.5mg/day, the researchers found only minimal side effects in all of the twenty nine males given letrozole or anastrozole, with transient liver enzyme irregularities in fewer than 10percent of males throughout therapy and no other side effects found.

But our study differ from it at duration of treatment (6 monthes) in Gregoriou et al., (7) study, type of aromatase inhibitors used (anastrozole or letrozole in Gregoriou et al. 2012 study while we used only letrozole in our study) and that study did not divide the patients into groups according to FSH level if high or normal as in our study.

Despite having supra-physiological concentration of testosterone, FSH, and LH, all of the patients suffered a decrease in libido, though in a study on the sexual activity of males who have an aromatase congenital abnormality, a decrease of libido was observed even when testosterone levels were above the physiological range. This shows that estrogens may play a role in enhancing libido in some people (11).

Unlike estrogen receptor modulators, aromatase inhibitors have the ability to stimulate endogenous testosterone synthesis without causing the raise in circulating estrogens that is seen with estrogen receptor modulators (3). Men who have aromatase deficit or estrogen resistance have defective spermatogenesis, which can be fatal (5). However, an excessive amount of E2 is deleterious to spermatogenesis. Aromatase inhibitors dramatically increase the number and quality of spermatozoa in infertile men who have a low blood T/E2 percentage (12).

Conclusion

ERs and aromatase share topographic locations in the brain with pheromones, indicating that estrogen has a role in both early sexual development and mature sexual behavior. Estrogen can increase libido and modify the number of serotonin receptors in the brain, which influences mood, mental condition, cognition, and feeling. Aromatase inhibitors as letrozole can be used in treatment of severe male factor (oligozoospermic, cryptozoospermic and NOA azoospermic) have disturbed T/E2 ratio as it increase sperm concentration and activity.

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