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Original Research Article

Role of Aromatase Inhibitor to Improve Semen Quality in Case of Eugonadotropic Hypogonadism

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Abstract

Background: Excess aromatase activity is common in males with severely impaired sperm production, as shown by low Semen testosterone and somewhat increased estradiol levels. Elevated estrogen levels cause inhibitory effects of the hypothalamic-pituitary-gonadal axis, resulting in a reduction in LH required for testosterone production and FSH to maximize sperm motility. The main objective of this study was to see how an aromatase inhibitor to Improve Semen Quality in Case of Eugonadotropic Hypogonadism. ***Methods:*** This Prospective study was conducted in the Department of obstetrics and gynecology, Dhaka Medical College Hospital, Dhaka, Bangladesh during the period from June 2020 to May 2021. The sample size was 40 subfertile men with oligospermia. (≤ 10 million/ml), low semen testosterone level (<300 ng/dl) and low testosterone to estradiol ratio (<10). All patients were treated with Aromatase Inhibitor 2.5 mg daily for 4 months. At the end of the 4 months the semen analysis was performed. Statistical analysis was carried out by using IBM Statistical Package for Social Sciences version 25 for windows (SPSS version 25.0). ***Results:*** The sperm concentration, sperm motility and total motile sperm count significantly increased after Aromatase Inhibitor treatment. The side effects were mild and well tolerated. ***Conclusions:*** According to the findings of this study, some men with oligospermia, low Semen testosterone levels, and normal gonadotropin levels may have curable endocrinopathy. In infertile males with a low Semen testosterone to estradiol ratio, Aromatase Inhibitor may be administered to enhance sperm parameters.

Keywords: Aromatase Inhibitor, Eugonadotropic, Hypogonadism, Semen.

INTRODUCTION

Worldwide, 48.5 million (45.0 million, 52.6 million) couples are unable to have a child, with 19.2 million (17.0 million, 21.5 million) couples unable to have their first child and 29.3 million (26.3 million, 32.6 million) couples unable to have another child [1]. Approximately 8% of males of reproductive age seek medical help for infertility issues. Up to 10% of these guys have a reversible reason impacting their reproductive potential [2]. Testicular function includes both testosterone production and spermatogenesis, and it is heavily controlled by the hypothalamic-pituitary-gonadal axis. Spermatogenesis is dependent on maintaining high levels of intra-testicular testosterone and activation of the sertoli cells by follicle stimulating hormone [3]. Infertility affects an estimated 15% of couple's worldwide, totaling 48.5 million couples, with male factors accounting for around 50% of the reason [4]. Recent research has shown a possible unique endocrine abnormality in individuals with severe male factor infertility [5]. Some men with substantially reduced sperm production have a relative excess of estrogen to testosterone, which is quantified as a higher testosterone/estradiol (T/E2) ratio. Because there are no effective medications to improve fertility in males with idiopathic infertility, medical therapy is empirical and aimed at optimizing fertility. Increased sperm production or motility, on the other hand, has been linked to empiric medical treatment with estrogen

receptor modulators such as clomiphene citrate or tamoxifen citrate. Unfortunately, the usage of estrogen receptor modulators increases both estrogen levels and testosterone production [6]. It inhibits aromatase, an enzyme that transforms androgen precursors in adipose tissue to estrogen, in a reversible manner [7]. By suppressing aromatization, you can prevent the conversion of androstenedione and testosterone to estrogen. In the last two decades, research has found that aromatase inhibitors increased sperm quality in males with normal gonadotropin levels and idiopathic oligospermia [5, 8]. Aromatase inhibitors have been used clinically in the treatment of idiopathic infertility with the goal of lowering estrogenic effects on the male reproductive system, ie by decreasing feedback inhibition of the hypothalamic-pituitary-gonadal axis.

The main objective of this study was to see how an aromatase inhibitor to improve semen quality in case of Eugonadotropic hypogonadism.

METHODS

This Prospective study was conducted in the Department of obstetrics and gynecology, Dhaka Medical College Hospital, Dhaka, Bangladesh during the period from June 2020 to May 2021. The sample size was 40 sub fertile men with oligospermia. (≤ 10 million/ml), low semen testosterone level (<300 ng/dl) and low testosterone to estradiol ratio (<10). All patients were treated with Aromatase Inhibitor 2.5 mg daily for 4 months. At the end of the 4 months the semen analysis was performed. Inclusion criteria were age 25 to 45 years, Patients with oligospermia (presence of sperm concentration ≤10 million per ml in both semen samples collected 30 days apart), semen testosterone concentration <300 ng/dl, Testosterone to estradiol ratio <10. Patients who have additional causal factors of infertility such as varicocele or ejaculatory duct obstruction. Patients who have undergone surgery for male factor infertility such as varicocele and ejaculatory duct obstruction. Personal history of regular intake of alcohol, smoking, use of drugs like antipsychotics, antihypertensive, antiepileptic, dopamine antagonists or recreational drugs. Suffering from infections like sexually transmitted disease and tuberculosis known case of systemic and chronic disease like diabetes mellitus, hypothyroidism, renal or liver disease. Patients taking fertility treatment or under oral or intravenous fertility medication in the recent 2 months were excluded. Statistical analysis was carried out by using IBM Statistical Package for Social Sciences version 25 for windows (SPSS version 25.0).

Table 1: Distribution of the study patients by demographic variables (n=40)

Demographic parameter		n (%)
Age (in years)	≤ 30	13(32.5)
	31 – 35	19(47.5)
	36 – 40	6(15.0)
	41- 45	2(5.0)
	Mean ± SD	33.37±3.864
	Range (min - max)	27- 41
Occupation	Service	6(15.0)
	Business	9(22.5)
	Private job	11(27.5)
	Others	12(30.0)
Monthly income (Taka)	<10000	7(17.5)
	10000 - <25000	15(37.5)
	25000 - <50000	24(60.0)
	>50000	4(10.0)
	Mean ± SD	24000 ±7700
	Range (min-max)	5500 – 50000
Habitat	Urban	31
	Rural	9

Table 2: Distribution of the study patients (n=30) by duration of infertility, BMI and type of semen parameters

Characteristics		n(%)
Duration of infertility (in years	<5	5(12.5)
	5-10	32(80.0)
	>10	3(7.5)
	Mean ± SD	1.97 ± 0.414
	Range (min - max)	15-Dec
BMI (Kg/m2)	18-24.9	14
	25-29.9	26
	Mean ± SD	25.41±1.52

Characteristics		n(%)
	Range (min-max)	23-28
Semen parameter	Oligospermia.	20(50.0)
	Oligoasthenozoospermia	9(22.5)
	Oligoasthenoteratozoospermia	11(27.5)

Table 3: Distribution of the study patients by endocrine evaluation (n=30)

Endocrine evaluation	n (30)	
	Mean ± SD	Range (min-max)
S.FSH (IU/L)	05.14±01.14	03.49-07.97
S.LH (mIU/ml)	05.19±01.34	03.40-08.70
S. Testosterone (ng/dl)	217.96±15.70	194.23-260.0
S. Estradiol (pg/ml)	40.69±05.92	29.13-49.51
Testosterone: Estradiol ratio	05.48±01.01	04.03-07.83

Table 4: Mean pretreatment and post treatment sperm parameters (n=30)

Sperm parameter	Pre-treatment	Post treatment	P Value
	Mean±SD	Mean±SD	
Ejaculate volume	01.93±0.28	1.900±0.203	0.326
Sperm count(million/ml)	05.93±2.49	15.83±10.43	0
Motility (%)	37.03±19.10	52.50±17.92	0
Total motile sperm count (million)	04.68±3.64	17.17±15.03	0

Table 5: Association of the type of oligospermia with response defined by rise of TMC to more than 10 million

Type of Oligospermia	Not improved to TMC>10million	Improved to TMC >10 million	P value
Moderate oligospermia. (sperm concentration 5-10 million/ml)	47.40%	52.60%	
Severe oligospermia. (sperm concentration < 5 million/ml)	37.44%	62.56%	0.039

DISCUSSION

This prospective observational study was carried out with an aim to evaluate the effect of Aromatase Inhibitor, administered at a dose of 2.5 mg daily for 4 months, upon semen parameters of infertile men. The increase in sperm concentration, sperm motility and total motile sperm count at the completion of treatment were statistically significant (p<0.001). There was pregnancy in four cases during study period and they were excluded from analysis. BMI had an extensive range, with a mean of about 25.41±1.52 kg/m2 in the present study. In Peivandi *et al.,* [9] after treatment with Aromatase Inhibitor, oligozoospermic men showed significant improvement in sperm count (p=0.03), total motile sperm count (p= 0.016) and ejaculate volume (p=0.031). Additionally, 2 of 10 oligozoospermic men achieved spontaneous pregnancy. The findings of this study corresponded to the present study except the ejaculate volume. They concluded that the use of Aromatase Inhibitor in infertile men with low testosterone to estradiol ratio could be effective in improving in hormonal and sperm parameters. Peivandi *et al.,* conducted a quasi-experimental clinical trial on 41 oligozoospermic infertile men with Aromatase Inhibitor 2.5 mg daily for 4 months to see the effect of Aromatase Inhibitor on semen parameters and hormonal profile [10]. After Aromatase Inhibitor treatment the sperm concentration, sperm motility and sperm forward motion significantly increased. The findings corresponded to the present study. Gregoriou *et al.,* conducted a prospective nonrandomized comparative study between Aromatase Inhibitor and anastrazole to see the hormonal changes and seminal parameters following treatment with aromatase inhibitors in 29 infertile men with low testosterone estradiol ratio (<10) [13]. The patients were treated with either Aromatase Inhibitor 2.5mg or anastrazole 1 mg daily for 6 months. Both treatment groups showed statistically significant increase in hormonal and semen parameters including ejaculate volume (p<0.001), sperm count (P<0.001) and sperm motility (p<0.001). The findings of semen parameters were similar to the present study except the ejaculate volume. They concluded that some men with severe oligospermia, low testosterone levels and normal gonadotropin concentration may have a treatable endocrinopathy. Raman and Schlegel treated 140 subfertile men with abnormal testosterone to estradiol ratios using either testolactone 100-200 mg or anastrazole 1 mg daily [8]. A comparison of the efficacy of these two therapies on both hormonal and semen parameters showed similar effects. There was significant increase in sperm concentration (from 5.5 million/ml to 15.6 million /ml) and sperm motility (14.7 % to 21%) but no pregnancies were reported during treatment. The findings agreed with the results of the present study in sperm concentration and motility, but disagreed with the pregnancy data. However, those authors included patients with Klinefelter syndrome and varicocele. Patry *et al.,* reported that after the treatment of

aromatase inhibitor, Aromatase Inhibitor, orally once daily for 4 months, final testicular biopsy showed normal spermatogenesis in one man with primary infertility, normal semen FSH level and pattern of non-obstructive azoospermia on a testicular biopsy [10]. In a retrospective study by Shoshany *et al.,* showed that 21 sub fertile hypo androgenic oligospermic men were treated with anastrazole 1 mg daily for 6 months and sperm concentration and total motile sperm count were significantly improved in 18 out of 21 oligospermic male. The results were similar to the present study [11]. As early as 1981, in an oligospermic men [12]. These authors reported that 80% of men treated demonstrated an increase in sperm count, and there was no change observed in sperm motility. In Pavlovich *et al.,* study, 63 sub fertile patients with testosterone to estradiol ratio of 6.9 compared with 14.5 in fertile controls [5]. In a subset of 25 patients with oligospermia an increase in semen parameters after anastrazole therapy was observed. These authors proposed a threshold testosterone to estradiol ratio of 10, representing the lowest 20th percentile of fertile subjects in the control group. In the present study the T/E2 ratios were < 10 and the mean was 5.48±1.01 and semen parameters significantly improved after Aromatase Inhibitor treatment. So, the results of this study are in agreement with that of the present study. In a randomized, controlled trial conducted by Clark and Sherins in Georgia, the effect of treatment with aromatase inhibitors on idiopathic oligospermia has been studied. In that study, 25 patients with idiopathic oligospermia were treated with testolactone 2 g/day or placebo for 8 months, followed by cross over for 8 months. Sperm parameters remained unchanged during treatment with testolactone and placebo and no pregnancy occurred during the 16 months follow up [16]. These data have shown that long term administration of testolactone was not effective in the treatment of infertility due to idiopathic oligospermia [13]. The findings of the Clark and Sherins study differed from the present study [13]. The subjects in their study had normal testosterone concentrations and likely testosterone to estradiol ratios above the threshold of 10, because the mean testosterone and mean estradiol in the placebo and testolactone inhibition arms were 479±50 ng/dl and 27.2±2.3 pg/ml, and 521±6.0 ng/dl and 23.2±1.8 pg/ml respectively. The estradiol and testosterone concentrations did not change with treatment during the trial. The reason for the different results of seminal parameters from the present study was most likely to be related to the use of testolactone, a first generation aromatase inhibitor with less potency. In this present study, Aromatase Inhibitor was used which is 20 times more potent in inhibiting the aromatase enzyme than other aromatase inhibitors. The third generation aromatase inhibitors have a greater estrogen inhibition than the first generation and second generations, which is one thousand times more potent. Aromatase Inhibitor in contrast to the previous two generations acts selectively and does not interfere with the secretions of glucocorticoids, mineralocorticoids and/or thyroxin secretion [14]. So, a reasonable conclusion from Helo *et al.,* and Clark and Sherins study is that men who are not hypo androgenic or who have abundant sperm concentration, may not benefit from treatment with aromatase inhibitors [15, 13]. In a prospective study Shuling *et al.,* treated fifteen men with idiopathic severe oligospermia (sperm concentration <5million/ml) with normal testosterone to estradiol ratio (>10) by Aromatase Inhibitor, 2.5 mg daily for 4 months [16]. After treatment there was 5.5-fold increase in sperm concentration (p=<0.0001). This finding agreed with the finding of present study and heralds a possibility that Aromatase Inhibitor may be effective in oligospermic males with normal testosterone to estradiol ratio. No study described so far defined an outcome of improvement to TMSC to more than 10 million, a threshold for reasonable success in intrauterine insemination, In the present study, 90% of men with oligospermia demonstrated significant increase in sperm concentrations and the total motile sperm count (>10 million) was improved in 74%patients. So more than 70% of the oligozoospermic patients became eligible for IUI considering a total motile sperm count threshold >10 million, and these patients could consequently choose an alternative to IVF. As a rule, in the present study, Aromatase Inhibitor was safe and well tolerated. In most of the patients, no severe side effects were observed with the treatment. Mild headache was present in two men, decreased libido in two men, but not severe enough to discontinue treatment. This finding may suggest that estrogen could play a role in supporting libido. The significance of estrogen in the male physiology is gradually unfolding. The optimal estradiol concentrations may be associated with increased bone resorption and a reduction in bone mass density [17]. As a result, long-term skeletal safety remains a concern, and it is critical to consider doing bone density scans in patients who have been using aromatase inhibitors for an extended period of time.

Limitation of the Study

Semen testosterone and estradiol levels were assessed just once, using enzyme immunoassays, which may reduce the efficiency of assessing low testosterone and testosterone to estradiol ratios.

CONCLUSION

Aromatase Inhibitor treatment, motility and total motile sperm count improve significantly in oligozoospermic infertile guys with a low blood testosterone to estradiol ratio. An Aromatase Inhibitor may be effective in improving sperm parameters and reproductive potential in this subset of infertile men with eugonadotropic hypogonadism.

RECOMMENDATION

The study limited data on post-treatment semen testosterone, estradiol, and testosterone to estradiol ratios, which might have provided further information to better characterize Aromatase Inhibitor's efficacy.

REFERENCES

1. Mascarenhas, M. N., Flaxman, S. R., Boerma, T., Vanderpoel, S., & Stevens, G. A. (2012). National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS medicine*, 9(12), e1001356.
2. Esteves, S. C., Miyaoka, R., & Agarwal, A. (201). An update on the clinical assessment of the infertile male. *Clinics*, 66(4), 691-700.
3. Jarow, J. P., & Zirkin, B. R. (2005). The androgen microenvironment of the human testis and hormonal control of spermatogenesis. *Ann N Y Acad Sci*, 1061, 208-20.
4. Agarwal, A., Mulgund, A., Hamada, A., & Chytte, M. R. (20150. A unique view on male infertility around the globe. *Reproductive Biology and Endocrinol*, 13, 37.
5. Pavlovich, C. P., King, P., Goldstein, M., & Schlegel, P. N. (2001). Evidence of a treatable endocrinopathy in infertile men. *J Urol*, 165, 837-41.
6. Bharti, S., Misro, M. M., & Rai, U. (2013). Clomiphene citrate potentiates the adverse effects of estrogens on rat testis and down-regulates the expression of steroidogenic enzyme genes. *Fertil Steril*, 99, 140-8.
7. McArthur, H. L., & Morris, P. G. (2010). Aromatase inhibitor strategies in metastatic breast cancer. *Int J Women's Health,* 1, 67-72.
8. Raman, J. D., & Schlegel, P. N. (2002). Aromatase inhibitors for male infertility. *J Urol*, 167, 624-9.
9. Peivandi, S., Hamed, J., Mina, A., & Ebadi, A. (2019). Effect of letrozole on spermogram parameters and hormonal profile in infertile men: A clinical trial study. *Endocrine Regulations*, 53, 231-6.
10. Patry, G., Jarvi, K., Grober, E. D., & Lo, K. C. (2009). Use of the aromatase inhibitor letrozole to treat male Infertility. *Fertil Steril*, 92, 892.
11. Shoshany, O., Abhyankar, N., Mufarreh, N., Daniel, G., & Niederberger, C. (2017). Outcomes of anastrazole in oligozoospermic hypoandrogenic subfertile men. *Fertil Steril*, 107(3), 589-94.
12. Vigersky, R. A., & Glass, A. R. (1981). Effects of testolactone on the pituitary-testicular axis in oligozoospermic men. *J Clin Endocrinol Metab*, 52, 897-902.
13. Clark, R. V., & Sherins, R. J. (1989). Treatment of men with idiopathic oligozoospermic infertility using the aromatase inhibitor, testolactone. Results of a double-blinded, randomized, placebo-controlled trial with crossover. *J Androl*, 10, 240-7.
14. Smith, I. E., & Norton, A. (1998). Fadrozole and letrozole in advanced breast cancer: clinical and biochemical effects. *Breast cancer Res Treat*, 49, 67-77.
15. Helo, S., Ellen, J., Mechlin, C., Feustel, P., Grossman, M., Ditkoff, E., & McCullough, A. (2015). A randomized prospective double-blind comparison trial of clomiphene citrate and anastrozole in raising testosterone in hypogonadal infertile men. *The Journal of Sexual Medicine*, *12*(8), 1761-1769.
16. Shuling, L., Kuei, M. L. S., Saffari, S. E., Jiayun, Z., Yeun, T. T., Leng, J. P. W., ... & Hao, T. H. (2019). Do men with normal testosterone–oestradiol ratios benefit from letrozole for the treatment of male infertility?. *Reproductive biomedicine online*, *38*(1), 39-45.
17. De Ronde, W., & de Jong, F. H. (2011). Aromatase inhibitors in men: effects and therapeutic options. *Reprod Biol Endocrinol*, 9, 93.