CLOMIPHENE CITRATE: A TREATMENT OF IDIOPATHIC OLIGOSPERMIA IN MALE INFERTILITY

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ABSTRACT

Objective: To determine the efficacy of clomiphene citrate therapy in improving seminal parameters of idiopathic oligospermic male partners.

Study design: Quasi-experimental study.

Place and duration: Department of Urology, Combined Military Hospital, Lahore from June 2008 to June 2010.

Materials and methods: This study was conducted in a sample of 50 idiopathic oligospermic men from local population. Clomiphene citrate was administered at a dose of 50 mg per day for 25 days followed by a 5 day rest. The cycle was continued for 03 months. Strict inclusion and exclusion criteria were followed.

Results: Repeat semen analysis was done at the end of 03 months and all the routine seminal parameters were re-evaluated. Clomiphene citrate administration resulted in statistically highly significant increase in semen volume (p<0.001), sperm density (p<0.001) and total sperm motility (p<0.001).

Conclusion: As clomiphene citrate leads to endogenous gonadotrophin increase, when there is no end organ pathology, this increase results in improving semen volume, sperm count, sperm motility and to a certain extent sperm morphology.

Key Words: Clomiphene citrate, Infertility, Oligospermia, Seminal parameters.

INTRODUCTION

Infertility remains a serious socio-medical problem worldwide. A subnormal sperm count is encountered frequently in male partner[1]. Clomiphene citrate is a synthetic, non-steroidal drug that binds to oestrogen receptors in hypothalamus and pituitary,[2,3,4] blocking the action of normally low levels of oestrogen on the male hormone axis and resulting in increased secretion of GnRH, FSH and LH[5]. The testosterone is produced by the leydig cells in response to LH secretion, which maintains gametogenic function of the testis.

The most commonly accepted definition of the term infertility is the lack of pregnancy (regardless of cause), after one year of unprotected intercourse[6,7]. Infertility affects approximately 15% of couples of reproductive age.[7,8] In Pakistan there are roughly 10-15% newly married couples who require some kind of medical help before they can become parents. Even if the wife is fertile and husband is normal, there is roughly one in three chances of wife to conceive. Evaluation of infertile couples, has revealed that male factor infertility contributes to the problem up to 50% of cases[6,8,9,10]. In our society where there is male dominance, illiteracy and poverty, men hardly agree to get investigated for infertility.

A subnormal sperm count is frequently encountered in an infertile male. One of the difficult aspects of treating infertile males with idiopathic oligospermia is the non-availability of recommended medical therapies for men[11]. Clomiphene neutralizes the normal negative feedback control of oestrogen and results in increased secretion of GnRH, FSH and LH. The enhanced output of these hormones increases the testosterone production and gametogenesis[12]. The empiric therapy is continued for three months to incorporate full 74 days spermatogenic cycle.

The objective of the study was to evaluate the effects of clomiphene citrate on seminal parameters like semen volume, sperm density and total sperm motility in a sample of local population suffering from idiopathic

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oligospermia and determine its role in male infertility.

PATIENTS AND METHODS

This quasi-experimental study was conducted at the Department of Urology, Combined Military Hospital Lahore from June 2008 to June 2010. The subjects included were primarily from Lahore, but other patients referred from different peripheral hospitals were also included. A total of 50 patients were included in this study. A detailed history was taken regarding age, occupation, previous illness, personal habits and smoking. A thorough physical examination was conducted.

The inclusion and exclusion criteria were as follows.

Inclusion Criteria:

1 Infertile men having oligospermia (Sperm count <20 million/ml).

2 Healthy men aged 18-35 living in stable relationship and desiring fertility.

3 Male having normal levels of serum FSH, LH, and testosterone.

4 Patient willing to provide written consent.

5 Normal female partner.

Exclusion criteria:

1 Patient suffering from autoimmune disease

2 Patients on cytotoxic drugs, antituberculosis treatment or alpha blockers.

3 Previous history of mumps orchitis, trauma to testis, cryptorchidism or varicocele.

4 Previous treatment of infertility.

Every patient was given tablet clomiphene citrate 50 mg (orally) daily for 25 days followed by a five days rest. The cycle was continued for 03 months. Semen samples were collected from subjects by masturbation following five days of abstinence of intercourse. The patients were instructed not to use saliva or any lubricant because of suspected spermicidal properties. Only liquid paraffin was allowed if needed. A clean sterile wide mouthed jar was provided to each patient for semen collection. First semen sample was collected before treatment and repeat semen analysis was done at the end of three months of treatment. Pre and post-treatment, three seminal parameters were evaluated. Semen amount was noted and sperm count was done using Neubauer chamber[10,13]. Sperm motility and grade of motility were noted[14].

Statistical Analysis:

Data was analyzed using SPSS version 15. Descriptive statistics were used to describe the data. Mean levels of different variables were compared by paired t-test. p <0.05 was considered as significant.

RESULTS

Fifty patients included in this study were males with a mean age of 26.07 + 5.89 years. All had normal hormone profile (serum FSH, LH and testosterone).

The semen analysis performed after three months showed an increase in the semen volume (Fig. 1), sperm density (Fig. 2) as well as the total sperm motility (Fig. 3). The statistical analysis revealed a p-value of <0.001 in all the three parameters which was highly significant statistically (Table).

DISCUSSION

If a couple is unable to conceive at the start of its married life, it gets socially and psychologically disturbed. Every sphere of couple's life becomes affected. In many regions of Pakistan, various social taboos are observed, which are quite evident from the fact that in

Table: Comparison of seminal parameters before and after clomiphene citrate treatment (n=50)

No	Seminal Parameter	Before Treatment		After Treatment		p-Value
		Mean	SD	Mean	SD	
1.	Volume (ml)	2.04	0.38	3.44	0.54	<0.001
2.	Sperm Concentration (million /ml)	11.72	3.61	22.62	4.34	<0.001
3.	Sperm motility in percentage	48.60	4.17	57.82	4.08	<0.001

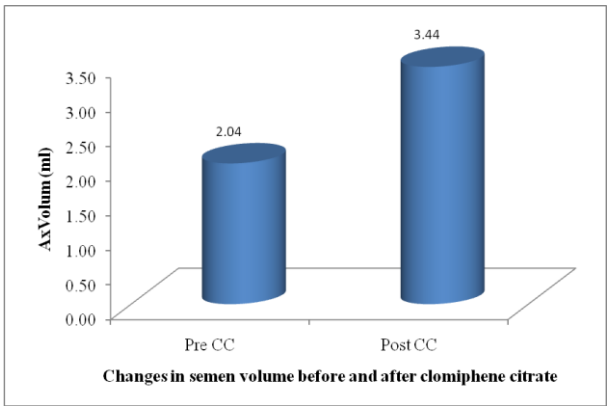

Fig. 1: Changes in semen volume before and after clomiphene citrate treatment (n=50)

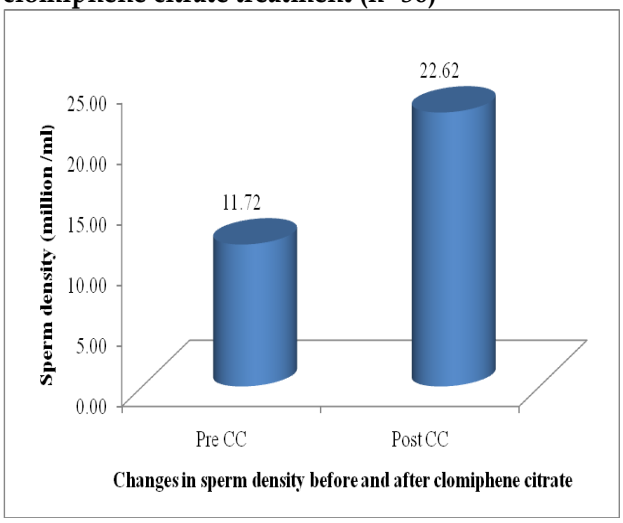

Fig. 2: Changes in sperm density before and after clomiphene citrate treatment (n=50)

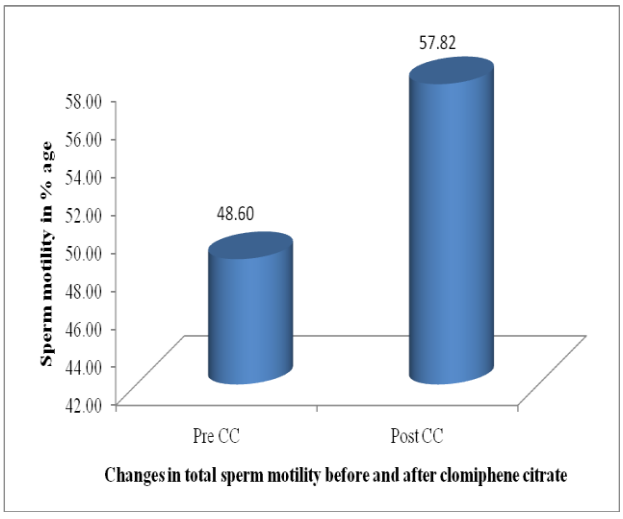

Fig. 3: Changes in total sperm motility before and after clomiphene citrate treatment (n=50)

case of infertility, the male partner does not report to a doctor for investigations but prefers marrying twice, thrice or even more for being issueless. We believe that as a general rule, it is preferable to treat the male in order to improve the fertility status rather than ignoring the male factor and focusing entirely on the female partner, using high cost advanced technologies which places the burden of treatment and risk on the female for a male problem.

Clomiphene citrate, 1-[p-(beta-diethyl aminoethoxy) phenyl]-1,2 diphenyl chloroethylene, is an orally active non-steroidal agent distantly related to diethylstilbestrol. It is thought to stimulate pituitary gonadotropin release by excluding oestradiol from hypothalamic receptor sites. This interaction neutralizes the normal negative feedback control of oestrogen and results in enhanced secretion of gonadotropin releasing hormones/GnRH (LH-RH, FSH-RH) and gonadotropins (FSH, LH). Testosterone is produced by the Leydig cells in response to LH secretion. The concentration of testosterone in the tubular environment (intra-testicular) is believed to maintain the gametogenic function of the testis[2,3,4,15,16]. Impaired spermatogenesis could be a result of subnormal testosterone level. The rationale behind the use of clomiphene citrate in male infertility, is the final increase in the testosterone level in the tubular environment. In the literature different doses and protocols for clomiphene citrate are reported with the most common being 50mg daily, 50mg every other day, 25mg every other day, 25mg daily for 25 days followed by a drug free interval of 05 days. Clomiphene citrate also stimulates adrenal androgen biosynthesis selectivel[17]. These steroids are converted into testosterone thereby enhancing its intra-testicular level. Clomiphene citrate also stimulates sertoli cells which help in the better supply of iron to developing germ cells resulting in better production of spermatocytes[18]. Increased endogenous testosterone is related to seminal vesicle functions[19,20].

Patankar et al[21] evaluated the role of clomiphene citrate regarding the seminal parameters including sperm count and motile sperm count in cases of oligospermia. Like our study they also reported significant improvement in these parameters. Similarly

Moradi et al[22] also documented increase in the sperm count, motility and semen volume with the use of clomiphene citrate alone or in combination with L-carnitine. Fuse et al[17] also noted improvement in sperm concentration after clomiphene citrate. Contrary to these findings, Shanis et al[23] had different observations. They noted that treatment for greater than three months caused a highly significant decrease in percentage of normal sperm forms. Three months of clomiphene citrate caused no change in the absolute number of morphologically normal sperm, but longer periods (greater than 6 months) were associated with a significant decrease.

CONCLUSION

Clomiphene citrate effectively increases the semen volume, sperm density and total sperm motility, which are essential seminal parameters directly effecting the male fertility potential. The awareness of the physicians is essential especially when a patient has to be labeled as infertile or not. Treating infertility does not necessarily mean pregnancy, but all efforts should be made for the conception. It is recommended that further prospective randomized studies should be done to asses the role of clomiphene citrate in the treatment of idiopathic oligospermia.

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