

Assessment of mesterolone therapy in oligospermic males

Keerti Singh¹, Asha Singh¹, Dr. A.K. Sarada²

Departments of Anatomy¹, and Surgery², Maulana Azad Medical College and associated
LN Hospital, New Delhi, India.

* Presently at Department of Basic Medical Science¹, Anatomy section, Faculty of Medical Sciences,
The University of West Indies, Mona Campus, Kingston 7, Jamaica, West Indies

BRIEF SYNOPSIS: Infertility is known to us since ages. There is an alarming rate of increase of infertility especially in the young urban males in India. Keeping this in mind the present study was undertaken we took up this study to evaluate the role of Mesterolone in oligospermic males. We also compared the effects of Mesterolone with the effects of a combined therapy of mesterolone and clomiphene citrate on semen parameters, effect on pituitary axis and liver function.

Thirty males with idiopathic oligospermia were included in this study. Out of the thirty subjects, 10 were given only tab mesterolone 50 mg b.d. Ten were given 50 mg of tab mesterolone 1 b.d and 25 mg of clomiphene citrate 1 o.d. The remaining 10 were used as controls and given tab vitamin C 75 mg b.d for 4 months. A follow-up study was conducted at the end of 100, 150 and 200 days for group A, B and C respectively. A complete semen analysis including the differential count was done. The results showed that the combination of mesterolone and clomiphene citrate showed a 40 percent increase in sperm count compared with -31.62 percentage for mesterolone alone.

ABSTRACT:

Objective: To study the effects of Mesterolone alone and combination of Mesterolone and Clomiphene Citrate on semen parameters, pituitary axis and liver function in Idiopathic Oligospermic males.

Materials and Methods: 30 males with Idiopathic Oligospermia (sperm count < 20-million/ml) between 20-45 years of age were included in the study. Of the 30 subjects, 10 were given tab Mesterolone 50 mg b.d (Group A), 10 males were given 50 mg of tab Mesterolone 1 b.d and 25 mg of Clomiphene Citrate 1 o.d. (Group B), 10 were used as controls and were administered placebo (Group C) for 4 months. A follow up study was conducted at the end of 100 days, 150 days and 200 days, in groups A, B and C respectively. The patients from each group were evaluated for semen parameters, serum hormonal levels, liver function tests and percentage of conception following therapy.

The following semen parameters were determined: semen volume (ml), viscosity, sperm count in million/ml, percentage of grade III motility, percentage of sperms with normal morphology, percentage of living sperms, percentage of immature sperms and differential sperm count.

Results: It was shown that the combination of Mesterolone with Clomiphene was more effective in increasing sperm count (40%) than Mesterolone alone (-31.62%) ($p=0.118$).

Conclusion: The combination of Mesterolone with clomiphene was more effective than mesterolone. It produced an increase in sperm count (40%) compared with Mesterolone alone (-31.62%). We have tried to formulate this new regimen of both Mesterolone and Clomiphene, which has proven to yield better results.

Keywords: Oligospermia, Mesterolone, Male Infertility.

I. INTRODUCTION

Infertility is known to us as far as the recorded history of mankind. The definition of infertility proposed by the American Fertility Society and the one that is widely accepted states that, "A marriage is considered barren or infertile when pregnancy has not occurred after a year of coitus without contraception." ^{1,2} Recognition of the male factor as a cause of infertility has been steadily growing. There is no single accepted mode of classification of infertility. However, anatomically one can classify it in males as pretesticular, testicular and post testicular.

Functionally it can be classified as primary or secondary testicular failure. Furthermore, from an endocrinological point of view it is possible to differentiate between hypogonadotropic, normogonadotropic and hypergonadotropic patients. It is also caused either by faulty sperm production or faulty sperm transit. Androgens are necessary for normal sperm formations and defective androgen binding noted in genital skin fibroblasts, may be a cause of infertility.

Semen analysis and analysis of the stages of maturation are the first and simple procedures to determine the defect in spermatogenesis. A patient may be suspected of developing autoantibodies which can be detected if spontaneous agglutination occurs on semen analysis. Final confirmation of autoimmunity is provided by anti sperm antibodies.

Different medications including hormonal and non-hormonal have been tried for the treatment of male infertility. Unfortunately, many patients are still treated empirically by non specific therapy.

Mesterolone alone is an orally active anabolic steroid with little direct anabolic properties. It has good binding qualities with the androgen receptor, but most of the mesterolone never reaches the androgen receptor in muscle tissue, as it is enzymatically converted to diol. It is, however, effective as an anti-aromatase and is believed to also act in an anti-oestrogenic manner due to certain oestrogen receptor down-regulation. This makes it a very effective compound for preventing feminization.⁽⁴⁾ Mesterolone also helps to restore sexual dysfunctions caused by steroid cycling, increasing sexual desire as a result of the increased androgen levels. However one disadvantage of this effect can be permanent erections in some males⁽⁵⁾.

Although Mesterolone is commonly used, its effect is inconclusive^(6,7,8). The present study was therefore undertaken to investigate the effects of Mesterolone in idiopathic oligospermic males and to study/compare the effects of combined therapy of Mesterolone and Clomiphene Citrate on selected semen parameters, liver and pituitary function.

II. SUBJECTS AND METHODS

Thirty male patients of Indian origin, with Idiopathic Oligospermia (sperm count <20 million/ml), attending the surgical Out Patient Department and family Welfare Clinic at Lok Nayak Jai Prakash Narayan (LNJP) Hospital, New Delhi, India were selected for this study.

Details of the history related to infertility were elicited by interviewing the couples, who were all married. The male partners were subsequently interviewed separately because it was observed that more detail information could be obtained. Patients were subjected to general and local examinations. Hernia, hydrocele, varicocele, spermatocoele, reduced testicular size and penile abnormalities, if any, were ruled out. All patients who were referred from the family welfare clinic at LNJP hospital, New Delhi were recruited for the study. The patients were selected with the following selection criteria: Males with sperm count < 20-million/ml between 20 – 45 years of age, persistent oligospermia even after being operated for varicocele, Normal basal hormonal levels of LH, FSH, T and Prolactin, Normal liver function tests, Female factor for infertility were ruled out. The research protocol was approved by the Local Ethics Committee. The nature of study was explained to the patients and all the selected patients gave their voluntary informed oral and written consent to participate in the study. Investigations of hormone assays (Serum Leutinizing Hormone, Follicle Stimulating Hormone and Testosterone) and LFTs were done two weeks before starting the treatment. 5ml of venous blood was taken from each subject to perform hormonal assays and liver function tests on the serum by IFCC (International Federation of Clinical Chemistry and laboratory medicine.)

For semen analysis the patients were advised to provide a sample after two days of abstinence. Semen was obtained by masturbation and ejaculation in a clean, wide mouthed sterile plastic container provided by the investigators.

The following parameters were studied, according to WHO manual for examination of Human Semen and Semen Cervical mucus Interaction (9). Volume, Viscosity, Sperm conc. (million/ml), percentage Grade III motility, percentage spermatozoa with normal morphology, percentage live sperms, percentage immature sperms, percentage mature sperms, percentage exfoliated immature seminiferous cells, Differential count. Cytological parameters were studied after staining the air dried smears with Giemsa.

Treatment and Evaluation Schedule :

The study was double-blind and the patients were divided into three treatment groups:

Group A: 10 males received tab. Mesterolone bd x 16 weeks

Group B: 10 males received tab. Mesterolone 50 mg bd + tab. Clomiphene Citrate 25 mg OD X 16 weeks

Group C: 10 males received placebo (Tab Vit C 75 mg bd) x 16 weeks

The tablets were self administered each morning by the patients. Apart from one diabetic patient none of the patients were on any other medication.

Treatment was done over a period of 16 weeks. A follow-up study of all the above parameters was conducted at the end of 100 days, 150 days and 200 days for groups A, B and C, respectively. During the last follow up one patient from the placebo group dropped out.

Pre-treatment and post-treatment values of various parameters studied were recorded and their mean values calculated. Statistical analysis was done by “ Wilcoxon’s signed Rank Test” (Non-parametric) and “Students Paired t Test” (Parametric) to assess significant changes ($P<0.05$) between groups.

III. RESULTS

Tables 1, 2, 3 show the statistical analysis done on the various parameters.

Group A- showed a decline in semen parameters by (-31.62) percent. However, Group B- showed a 40% increase in sperm count . There was a significant increase in the sperm concentration ($P=0.004$), Necrospermia ($P=0.135$) and the number of mature sperms ($P=0.08$) (table 1) . In Group C- All the parameters remained unchanged .

The mean age of the patients under study was 32.7 years. **The pre-treatment mean semen volume was 2.5 and post treatment mean volume was 3.1 ml. Thus, there was no significant change in the mean volumes of any of the three treatment groups. Two patients in group A were chronic smokers and alcoholics. One of them had Grade 0 motility with sperm count 0.5 million/ml. The other had grade I motility and sperm count of 13 million/ml, both their parameters remained the same as they did not give up smoking as advised.** Grade III motility in Group A decreased from 30% to 20%, in Group B the motility increased from 20% to 60% and no change was observed in Group C. There was no significant change in percentage teratospermia except a 10% improvement in group B, which was not significant.

There was no significant effect of any of the drugs on either liver function or the pituitary axis (tables 2 and 3). No pregnancies occurred in any of the treatment groups.

IV. DISCUSSION

In this study, the combined use of Mesterolone with clomiphene citrate in the males with idiopathic oligospermia showed significant results. However the use of Mesterolone alone showed marked decrease on the semen parameters which were not significant . The present finding concords with the findings of other authors(^{10,11}) who had suggested a potential benefit by the use of Mesterolone, especially when given in a high dose.

Paulson reported that majority of the male patients experienced marked improvement in spermatozoal motility after Mesterolone therapy(¹³).Whereas Damania and Bhatena concluded that no statistically significant change was noticed in sperm motility both pre and post treatment, in patients with Mesterolone therapy(¹²). According to our study the percentage of Grade III motility in Group A decreased from 30 to 20 % after treatment with Mesterolone. Whereas in Group B, Grade III motility increased from 20 to 60% and Group C showed no change.

Smoking cigarettes is associated with reduced linearity of sperm motion , and fewer motile sperms . Therefore, it is advisable for men to quit smoking, should they have marginal semen quality(¹⁴).

In our study two patients were chronic cigarette smokers and alcoholics. One had Grade O motility with sperm count of 13 million/ml, both these parameters remained unchanged as they did not give up smoking as advised. In Group B, one patient gave a history of chronic alcoholism and smoking 20 *beedis* (Indian cigar). His motility was Grade O and sperm count was 0.05 million/ml.We cannot make a comment due to the small number of patients.

A study on the role of Mesterolone in Oligospermia done in Mumbai, India⁽¹²⁾ showed that 100 mg Mesterolone/ day produced a significant improvement in the sperm count. At the completion of 16 weeks of therapy 16 of 28 patients had marked increase in sperm concentration.Christina Wang(¹⁵) in her comparative study concluded that Clomiphene Citrate at a dose of 25 mg/ day for 6 months and 12 months was the most effective drug in increasing the sperm counts and pregnancy rates. Mesterolone and Placebo treatment had no effect on sperm counts. This was supported by Gerris(¹⁶) who reported that, sperm count, total motility and morphology were similar in Mesterolone treated and Placebo controls. The two groups did not show any statistical significance.

The results of our present study indicated that there was a significant increase in sperm count in the patients who were administered combined therapy (Clomiphene citrate + Mesterolone). But there was no significant change with Mesterolone treatment.

A high incidence of Necrospermia was found in Group A which did not decrease after Mesterolone treatment.Results were similar for Placebo Group C. But Group B receiving both drugs combined showed a decrease in Necrospermia after completion of therapy which was not significant($p=0.135$)

Gerris(¹⁶) reported a transient increase of serum T concentration in Placebo treated controls after three months whereas the Mesterolone treated cases showed a sustained significant decrease. Decreasing serum LH values was observed in Mesterolone treated cases and the placebo controls, whereas serum FSH concentration remained unchanged. This was supported by The Scottish Infertility Group trial(⁷) who state that the patients receiving mesterolone had significantly lower serum testosterone at 3 and 6 months. The Serum LH,FSH,T and Prolactin levels remained unchanged post-treatment in all the three groups of our study (table 2).

Rapid development has taken place in the management of male infertility. Investigations of male infertility have renewed in semen analysis by CASA (Computer Assisted Semen Analysis). But the basic semen

analysis done by light microscopy, which includes subjective estimation of sperm concentration, motility and morphology still largely remains accepted as the first line of investigation(¹⁷).

Krause performed semen analysis employing a CASA system in comparison with visual estimation with microscope. He concluded that the determination of elaborate motility characteristics obtained by CASA was of limited value to optimise the evaluation of male infertility status(¹⁸).The above statements support and justify the use of light microscopy for all semen analysis done in our study.

V. SUMMARY

The combination of Mesterolone and clomiphene has shown a significant improvement in the semen parameters of males with idiopathic oligospermia. The improvement was 40% that is 5 million above the baseline, due to a possible agonistic action between the two drugs. However the use of Mesterolone alone showed marked decrease (-31.62 %) which were not statistically significant. Though it has proven to be a safe drug with no adverse effects on the liver and pituitary gonadal axis. Due to time constraints and small number of the study group we could not include a fourth group that could have received only Clomiphene Citrate.

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LEGENDS

Table 1: Comparison of effects of Mesterolone, Placebo and Mesterolone + Clomiphene on various semen parameters

- N.S: Not significant
- S: significant

Table 2: Assessment of effects of Mesterolone, Mesterolone + Clomiphene and Placebo on hormonal profile

Table 3: Assessment of effects Mesterolone, Mesterolone + Clomiphene and Placebo on liver function tests

G P	Volum e in ml.	Viscosity	Sperm conc. Million/ml	% Grade III motilit y	% spermatozo a with n. morphology	% live spermatozo a	% immatur e sperms	% mature sperms	% exfoliated immature seminiferou s cells
A	N.S P=0.4	N.S	N.S P=0.23	N.S	N.S P=0.9	N.S P=0.18	N.S P=0.42	N.S P=0.88	N.S
B	N.S P=0.3	N.S	S P=0.006	N.S	N.S P=0.11	S P=0.04	N.S P=0.68	S P=0.04	N.S
C	N.S P=0.6	N.S	S P=0.02	N.S	N.S P=0.18	N.S P=0.4	N.S P=0.48	N.S P=0.41	

Table 2: Assessment of effects of Mesterolone, Mesterolone + Clomiphene and Placebo on hormonal profile

Group	L.H	F.S.H	T	PROLACTIN
A	N.S P=1	N.S P=0.16	N.S P=0.34	N.S P=0.13
B	N.S P=1	N.S P=0.26	N.S P=0.62	N.S P=0.67
C	N.S P=0.8	N.S P=0.24	N.S P=0.17	N.S P=0.74

Table 3: Assessment of effects of Mesterolone, Mesterolone + Clomiphene and Placebo on Liver Function Tests

Group	S.BIL	S.G.O.T	S.G.P.T
A	N.S P=0.4	N.S P=0.4	N.S P=0.14
B	N.S P=0.6	N.S P=0.28	N.S P=0.15
C	N.S P=0.72	N.S P=0.34	N.S P=0.7

Means and Standard Deviations

	N	Sperm Count Mean (SD)		Teratospermia Mean (SD)		Necrospermia Mean (SD)	
		Before	After	Before	After	Before	After
Group A	10	4.59 (4.23)	3.14 (3.56)	2.90 (4.51)	3.9 (4.7)	36.10 (41.55)	37.30 (42.62)
Group B	10	2.43 (2.89)	6.65 (5.76)	4.00 (4.78)	2.60 (2.99)	35.20 (29.45)	27.20 (20.27)
Group C	10	6.59 (4.46)	6.55 (4.51)	1.80 (1.99)	1.00 (1.89)	40.5 (32.26)	41.80 (31.83)

Table of significance of before and after comparisons by Study Group (Paired t-test)

	N	Sperm Count	Teratospermia	Necrospermia
Group A	10	NS p=0.118	NS P=0.568	NS 0.14
Group B	10	S P=0.004	NS P=0.094	NS 0.135
Group C	10	NS 0.674	NS 0.168	NS 0.217

NS= Not Significant

S=Significant

Table of Significance of differences between study groups (ANOVA and Kruskal-Wallis test)

Comparison between the Groups	Significance (p-values)
Difference in Sperm Count	S P=0.000
Difference in Teratospermia	NS P=0.297
*Difference on Necrospermia	S P=0.013

* Kruskal-Wallis test done for Necrospermia only