CLOMIPHENE TREATMENT OF OLIGOSPERMIA

by

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The favourable results of ovulation induction following the use of clomiphene citrate in anovulatory women served as a prelude to its use in oligospermic subfertile men. Clomiphene citrate stimulates pituitary gonadotropin synthesis and secretion, which in turn stimulates hormone secretion in men. Numerous reports in the literuature have doccumented the therapeutic efficacy of clomiphene in oligospermic men. (Paulson, 1975; Epstein, 1977; Check and Rakoff, 1977; Ross *et al*, 1980; and Rajan, 1981). Nonetheless, treatment of oligospermia with clomipthene is still very controversial since discrepancies exist in proper patient selection, the need for pretherapeutic investigations and the optimal dose schedule (Paulson, 1977; Charny, 1979; and Newton, 1980).

The present study reports our experience with clomiphene citrate (Fertyl) in oligospermic and asthenospermic subfertile males. One group of patients had pretreatment testes biopsy done, and in them the predictive value of biopsy in selecting the clomiphene responders has been evaluated. The dose of clomiphene employed and the duration of therapy advocated was identical for all the patients studied.

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Material and Methods

The patients were selected from couples consulting the senior author at his Infertility Unit or at his private office. The men had undergone extensive evaluation prior to their inclusion in the study. The state of oligospermia, sperm count below 20 million per ml of semen, and the degree of asthenospermia were confirmed by studying several samples of semen collected at proper intervals. Varicocele, one of the common causes for oligospermia, was carefully excluded, and the possibility of any hormone dysfunction was also ruled out in these men. Thus a group of 69 subfertile men with 'Idiopathic Oligospermia' was registered for the present clinical trial with clomiphene (Fertyl) between January, 1979 and May, 1981. Bilateral testes biopsy was performed as a part of the pretreatment investigation in 24 men. Irrespective of the testicular morphology treatment was initiated for all subjects.

The treatment regime followed was that advocated by Paulson and Wacksman in 1976: Clomiphene citrate (Fertyl, Biddle Sawyer) was administered in a dose of 25 mgm daily for 25 days, with five days'

rest, for a period of 6 to 9 months or till pregnancy resulted in the wife. Semen studies were repeated at 2 months interval, and frequently a post-coital test was performed to ensure sperm survival in the female genital tract. A thorough preliminary evaluation of the female partner was completed before initiating clomiphene treatment for the male.

In a few patients registered recently the treatment was started after determining their serum luteinising hormone (LH), follicle stimulating hormone (FSH), testosterone, estrogen and prolactin levels. However, this study does not permit any analysis of the results based on the hormone profile of these patients.

Results

Age of the oligospermic men registered ranged from 20 to 47 years, with a mean of 31.84 years. Duration of barren union ranged from 1 to 17 years with a mean of 5.08 years. Among the 69 subjects registered 7 are still under treatment, and 12 subjects had to be eliminated for other reasons such as poor follow-up, and thus the analysis relates to the details of only 50 patients.

A patient was considered to be a responder to clomiphene if he achieved a pregnancy during therapy with improvement in at least one parameter of the semen analysis or had a substantial increase in the sperm count and improvement of sperm motility over the pretreatment levels. By these criteria, 25 of the 50 patients were considered responders, for a total response rate of 50 per cent.

Among the 50 subjects treated with clomiphene and carefully followed, 13 had successfully impregnated their wives to date. This is 26 per cent of the total treatment group or 52 per cent of the total responders. Atleast one of the seminal parameters had improved in all these 13

TABLE I

Effect of Colomiphene (Fertyl) on Oligospermic Men Who Achieved Pregnancy

Age	Duration Infertility	Pre-treatment semen values			Duration Treatment	Post-treatment semen values			Remarks
		Count	Motility	Grade		Count	Motility	Grade	
28 yrs	2 yrs	18^6	80%	I	2 months	46^6	90%	II	Pregnancy after 2 mths
32 yrs	1 yr	12^6	20%	I+	2 months	22^6	35%	II	Pregnancy after 6 mths
30 yrs	2 yrs	5^6	50%	I	6 months	60^6	30%	II	Pregnancy after 2 mths
21 yrs	2 yrs	5^6	50%	I	2 months	30^6	90%	III	Pregnancy after 3 mths
35 yrs	3 yrs	18^6	80%	I	4 months	35^6	30%	II	Pregnancy after 4 mths
31 yrs	2 yrs	15^6	30%	II	4 months	96^6	90%	II+	Pregnancy after 4 mths
29 yrs	3 yrs	3^6	50%	II+	2 months	28^6	90%	II+	Pregnancy after 2 mths
39 yrs	6 yrs	12^6	10%	I	2 months	40^6	10%	III	Pregnancy after 2 mths
33 yrs	10 yrs	3^6	0	0	3 months	8^6	50%	II+	Pregnancy after 3 mths
26 yrs	2 yrs	15^0	30%	I+	4 months	30^6	60%	II+	Pregnancy after 4 mths
23 yrs	3 yrs	12^6	80%	I	4 months	12^6	90%	II+	Pregnancy after 4 mths
30 yrs	4 yrs	5^6	50%	I+	2 months	30^6	30%	II	Pregnancy after 2 mths
41 yrs	6 yrs	18^6	60%	II	2 months	60^6	90%	II	Pregnancy after 2 mths

subjects. The details of the successful group are summarized in Table I.

While the treatment regimen was continued for 6 to 9 months in some patients, all the responders had shown improvement in seminal parameters as early as after 2 months of treatment. Those who failed to respond in 2 months period did not show any improvement after that period eventhough the treatment was continued for 9 months. The group which achieved conception had a treatment period ranging from 2 to 6 months in 12 subjects and 9 months in 1 subject. Thus it appears that the results of treatment with clomiphene becomes obvious in majority of patients within a period of 6 months.

As a part of the pre-treatment evaluation, testicular morphology was studied in 24 subjects of whom the results could be analysed in 17 subjects. Normal spermatogenesis was evidenced in 4 patients and in this group 2 improved the semen parameters. Of the 5 subjects with mixed tubular morphology, 3 showed improvement and of the 6 subjects with tubular hypofunction, 2 showed improvement. None of the 2 subjects with spermatogenic maturation arrest evidenced any improvement in semen quality. Results of this limited group reveal that testicular morphology does not identify the specific group who could respond favourably to clomiphene therapy.

Discussion

Our results confirm that significant improvements in oligospermia and asthenospermia may be achieved in men with 'Idiopathic Oligospermia', by treatment with repeated cycles of clomiphene citrate, 25 mg daily for 25 days. with 5 days' rest.

While there is controversy over the appropriate dosage schedule and the method of pre-treatment evaluation for identifying the clomiphene responders, we are of opinion that a careful clinical evaluation combined with the meticulous seminal study will result in improvement in semen quality in 50 per cent and conception rate in 26 per cent of the patients treated with clomiphene in this low dose cyclical pattern. We are not convinced about the role of testes biopsy in predicting the clomiphene responders. Nonetheless, eventhough our study is not complete on hormone study, the hormone profile of the patients should enable the selection of 'pregerminal hypofertility' group with the best chance for response to clomiphene treatment (Paulson, 1977).

Our experience is that the clomiphene responders could be identified just after 2 months of treatment, because either they show improvment at that period or never. Those who show improvement, when maintained on therapy, at least 50 per cent of them, achieve a pregnancy within 2 to 6 months, and at the most 9 months. Hence we would not advocate continued clomiphene treatment if no response is obtained just after 2 months of starting the treatment.

We are aware of the possibility of spontaneous conception resulting with poor quality semen, having a sperm count of less than 20 million and poor sperm motility (Rajan and Usha *et al*, 1980). However, conception rate in such a group over the period of 6 to 9 months cannot be as high as 26 per cent, and hence we believe that clomiphene has a definite therapeutic role in improving the fertility of oligospermic men.

Compared to our earlier report on the same subject (Rajan *et al*, 1980) there have been not much difference in the pregnancy rate in the present series. The pregnancy rate was 25.80 per cent and 26

per cent respectively. The dosage regimen followed in either group was identical, repeated cycles of clomiphene 25 mg daily for 25 days with 5 days' rest. As suggested by Ross *et al* (1980) an altered dose schedule may possibly improve the success rate of clomiphene treatment.

Conclusion

This study convincingly proves the effectiveness of clomiphene citrate in the treatment of oligospermic subfertile male. Pretherapeutic evaluation of the hormone profile of the patient as well a different dose schedule appear to promise further improvement in the results.

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