

ADVERSE EFFECT OF CLOMIPHENE CITRATE ON SPERM MORPHOLOGY

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The beneficial effect of clomiphene citrate (CC) in treating male infertility is controversial. To evaluate the effects of CC on sperm morphology using strict criteria, the semen analyses of 74 men were evaluated at intervals ranging from 1 to 18 months of treatment. Seventy patients receiving no medication were used as control. The patients in each category were divided into three subgroups: A (1-3 months), B (4-6 months), and C (>6 months). In the control group, there were no significant differences in percentages or total normal forms between baseline and repeat semen analysis at any interval. Treatment with CC for 1-3 months did not adversely affect percentages of normal forms. Treatment for greater than 3 months caused a highly significant decrease in percentage of normal forms. Three months of CC caused no change in the absolute number of morphologically normal sperm, but longer periods (>6 months) were associated with a significant decrease. There was significant deterioration of sperm function as measured by percentage of normal forms in patients treated with CC for 4-18 months. The physiological clinical significance remains to be investigated.

Key Words: Clomiphene citrate; Sperm; Ovulation induction; Infertility.

INTRODUCTION

Clomiphene citrate (CC) has been used to treat men with subnormal sperm parameters. There is disagreement regarding the beneficial effects of CC. Several reports showed increased sperm counts following therapy [9, 10]. Sperm motility improved in the majority of patients in one study [7]. Another study showed no improvement on a traditional dosage of CC, 25 mg per day, but motility did improve on a lower dosage, 25 mg every other day [4]. Other studies showed no significant change in sperm count or motility with medication [2, 11]. Sperm morphology evaluated by the World Health Organization (WHO) criteria showed no change on CC therapy [4]. Using newer strict criteria proposed by Kruger et al. [6], sperm morphology has been demonstrated to be predictive of outcome of IVF [5].

In the present study the effect of CC on sperm morphology was evaluated after various periods of medications.

MATERIALS/METHODS

The experimental group consisted of 74 men with a subnormal motile density ($> 10 \times 10^6/\text{mL}$) on routine computerized semen analysis performed after 48-72 h abstinence. They were treated with CC at

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a dosage of 25 mg daily for 25 days/month or 25 mg every other day. The control group (70 men) included patients tested during the same time period who had repeat testing at a later date but were not given the medication. Normal sperm morphology was evaluated using strict criteria as described by Kruger et al. [6]. Both percentage of normal forms and total normal forms per ejaculate (volume multiplied by the count times the percent normal forms divided by 100) were recorded at baseline and at various intervals between 1 and 15 months. The patients were divided into three subgroups: A (1-3 months of therapy), B (4-6 months), and C (>6 months).

Differences among the treatment and control groups were compared using analysis of variance for repeated measures. A p value < .05 was required for statistical significance. Data are reported as means \pm SD.

RESULTS

The effect of clomiphene citrate (CC) on sperm morphology is shown in Tables 1 and 2. In the control group there were no significant differences in percentage of total normal sperm forms between baseline and repeat analysis at any interval. Administration of CC for 1-3 months did not adversely effect percentage of total normal sperm forms. Treatment for 4-6 months (B) caused a significant decrease in percentage of normal sperm forms. Although there was a trend toward decreasing total number of normal forms at 4-6 months, this was not significant. Group C showed a highly significant drop in percentage of normal forms and total normal sperm forms.

Baseline percent normal forms and total normal forms were different in the control and 3 treatment groups. Group C patients had higher values than the other 2 treatment groups. There was no significant difference between groups A and B.

DISCUSSION

Conflicting reports make it unclear whether CC therapy for men results in any improvement in sperm quality. This study deals with a specific negative effect of the medication. Morphology has been suggested to be the most predictive of sperm parameters by a study that reported decreased sperm count/motility to be less well correlated [8]. Aitkens et al. [1] showed no significant differences in other parameters of the conventional semen analysis; only the percentage of normal morphology was significantly lower in the infertile group.

Newer strict criteria for morphology [6] have good predictive value for fertilization in IVF

TABLE 1 Effect of Clomiphene Citrate (CC) on Percentage of Normal Sperm Forms

Group		<i>n</i>	Baseline	Repeat
A (1-3 mos)	CC-treated	37	7.4 \pm 4.3	7.1 \pm 4.4
	control	37	10.4 \pm 7.3	9.7 \pm 6.6
B (4-6 mos)	CC-treated	22	8.7 \pm 5.3	4.9 \pm 3.5 ^a
	control	17	9.1 \pm 5.2	8.4 \pm 4.8
C (>6 mos)	CC-treated	15	12.5 \pm 6.9	6.7 \pm 3.6 ^b
	control	16	9.7 \pm 7.3	10.0 \pm 6.8

^a p < 0.05 vs baseline.

^b p < 0.01 vs baseline.

TABLE 2 Effect of Clomiphene Citrate (CC) on Total Normal Sperm Forms

Group		n	Baseline	Repeat
A (1-3 mos)	CC-treated	37	8.0 ± 7.8	8.7 ± 9.5
	control	37	10.6 ± 9.6	13.1 ± 17.2
B (4-6 mos)	CC-treated	22	10.1 ± 13.2	5.6 ± 6.0
	control	17	13.8 ± 22.2	16.0 ± 18.1
C (>6 mos)	CC-treated	15	16.9 ± 19.7	7.4 ± 6.5 ^a
	control	16	5.3 ± 4.2	6.1 ± 6.5

^ap < 0.05 vs baseline.

in patients with "acceptable" sperm counts and motility [5]. We were unable to demonstrate that same correlation with IVF [3].

The implications of this study, which shows a decrease in sperm morphology with prolonged CC treatment, rests on resolving the differences between various reports. Only if normal morphology is a significant factor of fertilizing ability will this detrimental effect of CC be of importance.

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