

IMPROVED SEMEN QUALITY IN SUBFERTILE MALES WITH VARICOCELE-ASSOCIATED OLIGOSPERMIA FOLLOWING TREATMENT WITH CLOMIPHENE CITRATE

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Varicocelectomy has been found to improve the spermogram in many subfertile men. However, there still remains a sizable group of subfertile men whose counts fail to improve sufficiently following surgery. Clomiphene citrate, which has been shown to improve fertility in idiopathic oligospermia, was similarly tried in men with varicoceles. The counts of 71% were raised to the low-normal range, and 36% achieved pregnancies. Medical therapy with clomiphene citrate may prove not only to be a useful adjunct to varicocelectomy but may prove to be first-line therapy for counts under 10 million/ml (8 of 13 improved to over 20 million/ml) when surgical therapy has not been successful. Fertil Steril 33:423, 1980

The association of varicocele and subfertility has been known for 25 years.¹ The incidence of varicocele in the male population is estimated to range between 8% and 23%.^{2, 3} Despite extensive studies, the mechanism of reduced fertility associated with varicoceles is unknown.

Varicocele is considered the most common cause of male infertility.⁴ Varicocelectomy has been reported by some centers to improve the semen quality in about 65% of cases and to produce fertility rates above 50%.⁵⁻⁷ It is not known why the spermograms of some men fail to improve despite successful varicocele ligation. In a large number of cases no etiologic factor for the oligospermia is found (idiopathic). Since 50% of men with varicoceles have normal spermograms,⁸ in those not responding to surgery it is possible that the varicocele is incidental and the same factors as in idiopathic oligospermia may be present.

Clomiphene citrate has been shown to improve significantly the fertility rates in men with idiopathic oligospermia.⁹⁻¹¹ The present study was initiated to determine the effectiveness of clo-

miphene citrate in helping subfertile men with varicoceles or those whose spermograms did not improve following varicocelectomy to achieve fertile sperm counts.

MATERIALS AND METHODS

Twenty-eight men with easily palpable varicoceles or a history of a previous varicocele ligation were included in the study. A complete history was obtained from each man and a physical examination was performed to help rule out any endocrine disturbance. Furthermore, blood samples were obtained for measurement of serum levels of luteinizing hormone, follicle-stimulating hormone, thyroxine, triiodothyronine uptake, prolactin, and testosterone. Each man also produced a 24-hour urine collection for measurement of 17-ketosteroid, hydroxycorticosteroid, and pregnanetriol concentrations. The results of all endocrine tests on each patient had to be normal as a condition for his inclusion in the study. Each man was treated with 25 mg of clomiphene citrate daily for 25 days, stopping for 5 days and resuming each month. Baseline semen evaluations represent the average of three specimens taken a minimum of 2 weeks apart. The first portions of split ejaculates were used for 25 of the 28 men. In no one individual

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TABLE 1. Effect of Clomiphene Citrate on Sperm Counts in Oligospermic Men with Varicocele-Associated Infertility

| Patient | Sperm counts after months of therapy | | | | | | | | | | | | | | | | | |
|-----------------|--------------------------------------|-----|-----|----|-----|-----|------------------|-----|-----|-----|----|-----|----|-----|----|-----|-----|-----|
| | 0 ^a | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | |
| 1 | 18 | 5 | 30 | | | | 92P ^b | | | | | | | | | | | |
| 2 | 16 | | | | 36 | | | 53 | | P | | | | | | | | |
| 3 | 17 | 30 | P | | | | | | | | | | | | | | | |
| 4 ^c | 8 | | | | 24P | | | | | | | | | | | | | |
| 5 ^c | 18 | | | | 17 | | | | | 24 | 28 | 33 | | P | 23 | | | |
| 6 | 2 | | | 4 | | 3 | | | 3 | | 6 | | | | | | | |
| 7 | 7 | | 16 | | | 25 | 34 | | | | | | | | | | | |
| 8 ^c | 8 | | 22 | | | 80 | 33 | | 32 | 100 | 32 | 64 | | 58 | 85 | 64 | 75P | |
| 9 ^c | 4 | | 8 | 13 | 25 | 15 | 10 | | | | | 16 | | | | | | |
| 10 | 12 | | | 25 | | 64 | | | | 140 | | | | | | | | |
| 11 | 17 | | | 65 | 50 | 48 | | | | | 85 | 112 | 90 | 32 | 65 | 106 | 100 | |
| 12 ^c | 16 | 24 | 37 | 32 | 64 | | 72 | | | 18 | 22 | 23 | 28 | 27 | 24 | 48 | 90 | 106 |
| 13 | 6 | | 11 | | 4 | | | | | | | | | | | | | |
| 14 | 23 | 45 | | | 18 | 18 | | 8 | | | 17 | 60P | | | | | | |
| 15 | 60 | 100 | 148 | | | 110 | P | | | | | | | | | | | |
| 16 ^c | 15 | 52 | 110 | 60 | | 105 | | 107 | | | | 110 | 85 | 120 | | | | 108 |
| 17 ^c | 1 | | 1 | | | | 2 | | | | | 2 | | | | | | |
| 18 | 7 | 22 | | P | | | | | | | | | | | | | | |
| 19 | 13 | | 24 | 15 | | 85 | | 22 | | | | | | | | | | |
| 20 | 2 | | 2 | 2 | | | | | | 26 | | | 11 | | | | | |
| 21 | 21 | | | 6 | | | | | | | | | | | | | | |
| 22 ^c | 22 | | 96 | | 46 | 72 | | 110 | 150 | | | | | | | | | |
| 23 | 17 | | | | | 37 | | | | 28 | 22 | | | | | | | |
| 24 | 1 | | 15 | 68 | | | | | | 25 | | | | | | | | |
| 25 | 9 | | 8 | 22 | | | | | | | | | | | | | | |
| 26 ^c | 4 | | | 13 | 44P | | | | | | | | | | | | | |
| 27 | 2 | 18 | 19 | | 23 | | | | | | | | | | | | | |
| 28 | 34 | | 17 | | 93 | | | | | | | | | | | | | |

^aRepresents the baseline count which is an average of three counts taken a minimum of 2 weeks apart before clomiphene citrate therapy was started.

^bP, Pregnancy.

^cPatients with previous varicocelectomy.

was a split ejaculate compared with a whole specimen as treatment progressed. In all instances there was a minimum of 1 year of infertility and subnormal spermograms had been demonstrated for at least 1 year. The recommended period of abstinence before collection of semen samples was 48 hours; this instruction was followed by most patients with just a few exceptions, when the abstinence period was 72 to 96 hours.

RESULTS.

Seventy-five per cent of the men showed a persistent increase in their sperm counts of more than 10 million/ml, and 57% showed improvements of more than 20 million/ml (Table 1). The semen of 68% of the men demonstrated at least an additional 25% motile sperm, and 86% showed some improvement in quality of motility (Table 2). The quality of motility was graded from 0 to 10. Neither the ejaculate volume nor the sperm morphology showed any significant change with therapy. The most common morphologic abnormality was the

presence of tapered sperm heads, but this persisted in about the same percentage despite clomiphene therapy.

A spermogram revealing 20 million/ml, 50% motility, grade 7, was considered borderline normal. All 28 men had baseline subnormal specimens. According to these criteria, 71% of the men produced borderline normal specimens after therapy. Thirty-nine per cent achieved a good-quality spermogram of 40 million/ml, 70% motility, grade 8. Thirty-six per cent achieved a pregnancy.

Thirteen patients had baseline counts under 10 million/ml. In eight of these patients the sperm counts rose to over 20 million/ml, and five achieved pregnancies.

Nine patients in the group had previously undergone varicocelectomy. In two-thirds of these patients the semen specimens improved to at least a borderline level, and in one-third they improved to above 40 million/ml, 70% motility, grade 8. Two men impregnated their wives.

Only eight wives did not have any concurrent fertility problems. Twelve women had ovulation

TABLE 2. Effect of Clomiphene Citrate on Sperm Motility in Subfertile Men with Varicocele and Asthenospermia

| Patient | Percentage and quality ^a of motility after months of therapy | | | | | | | | | | | | | | | | |
|---------|---|------|-------|------|-------|------|--------------------|------|------|------|-------|------|------|------|------|-------|------|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| 1 | 50-5 | 50-5 | 60-7 | | | | 85-8P ^b | | | | | | | | | | |
| 2 | 20-5 | | | | 50-6 | | | 50-7 | | P | | | | | | | |
| 3 | 50-6 | 80-8 | P | | | | | | | | | | | | | | |
| 4 | 30-5 | | | | 60-8P | | | | | | | | | | | | |
| 5 | 50-6 | | | | 55-7 | | | | | 75-8 | 75-8 | 75-8 | | 75-8 | | | |
| 6 | 30-6 | | | 50-8 | | 50-7 | | | 40-8 | | 50-8 | | P | | | | |
| 7 | 20-2 | | 60-7 | | | 60-7 | 40-6 | | | | | | | | | | |
| 8 | 20-5 | | 45-7 | | | 75-8 | 70-7 | 70-8 | 80-8 | 50-7 | 65-8 | | 70-7 | 80-8 | 75-8 | 70-8P | |
| 9 | 30-5 | | 30-5 | 40-5 | 80-6 | 50-7 | 50-6 | | | | 80-8 | | | | | | |
| 10 | 60-7 | | | 35-8 | | 70-7 | | | 80-9 | | | | | | | | |
| 11 | 10-3 | | | 35-8 | 40-8 | 40-7 | | | | | | | | | | | |
| 12 | 45-5 | 70-8 | 85-9 | 75-8 | 75-8 | | 85-7 | | 60-8 | 50-7 | 75-8 | 70-8 | 60-7 | 80-8 | 80-9 | 80-8 | 70-8 |
| 13 | 10-4 | | 35-5 | | 65-6 | | | | | | | | | | | | |
| 14 | 30-8 | 75-8 | | | 70-8 | 70-8 | | 60-7 | | 70-7 | 70-8P | | | | | | |
| 15 | 10-3 | 70-7 | 85-9 | | | 80-8 | P | | | | | | | | | | |
| 16 | 20-7 | 85-9 | 85-9 | 80-8 | | 80-8 | | 85-9 | | | 75-8 | 80-8 | 80-8 | | | | 85-8 |
| 17 | 30-4 | | 30-4 | | | | | 20-5 | | | 40-4 | | | | | | |
| 18 | 70-8 | 80-8 | | P | | | | | | | | | | | | | |
| 19 | 15-3 | | 45-6 | 55-7 | | 35-8 | | 30-7 | | | | | | | | | |
| 20 | 30-5 | | 60-7 | | 40-6 | | | | | 35-6 | | 75-8 | | | | | |
| 21 | 25-4 | | | 40-7 | | | | | | | | | | | | | |
| 22 | 65-7 | | 85-10 | | 70-8 | 65-8 | | 80-9 | 80-9 | | | | | | | | |
| 23 | 10-2 | | | | | 70-8 | | | | 70-8 | 65-7 | | | | | | |
| 24 | 20-2 | | 85-8 | 80-8 | | 85-8 | | | 75-8 | | | | | | | | |
| 25 | 50-5 | | 50-5 | 70-8 | | | | | | | | | | | | | |
| 26 | 60-3 | | | 70-7 | 50-9P | | | | | | | | | | | | |
| 27 | 50-5 | 60-7 | 60-8 | | | 75-7 | | | | | | | | | | | |
| 28 | 30-3 | | 60-7 | | 80-8 | | | | | | | | | | | | |

^aThe number to the left of the hyphen in each column represents the percentage of motile sperm. The number to the right of the hyphen in each column represents the quality of motility, with 1 indicating the lowest grade (motile only in place) and 10 indicating excellent, rapid, linear progressive motion.

^bP, Pregnancy.

defects, three had ovulation defects and endometriosis, one had an ovulation defect and a tubal factor, and four had cervical problems.

DISCUSSION

This study demonstrates that medical therapy with clomiphene citrate may be effective in improving fertility in men with a varicocele or in those men who fail to improve following varicocelectomy. There is still some debate as to what constitutes a fertile sperm count. The data were thus analyzed according to both the value estimated at 40 million/ml by The American Fertility Society¹² and the value of 20 million/ml established over 25 years ago by MacLeod and Gold¹³; 71% of the men surpassed the latter value, and in 39% the counts rose to more than 40 million/ml.

Evaluation of the effect of any therapy on subsequent semen analysis is complicated in general by occasional wide variations in count and sensitivity to noxious influences, such that a fever can depress the count for several months. In every case in this report the low counts had been present for at least 1 year. Furthermore, once improved, the counts

remained persistently elevated while the patient was taking clomiphene citrate; this makes the likelihood of chance transient elevation seem very unlikely. In fact, in one-fourth of the patients the sperm counts increased at least 60 million/ml over baseline.

Although it is possible that clomiphene citrate is effective only in those subfertile men whose varicoceles are incidental, it is possible that varicocele ligation and medical therapy may actually be treating the same problem, analogous to wedge resection and clomiphene citrate for anovulation in the polycystic ovary syndrome.

Varicocele ligation has been an effective therapy for subfertile men for over 20 years. The results with clomiphene citrate thus far are sufficiently encouraging that this agent may prove to be the main medical adjunctive therapy for those men failing to improve following surgery. Since results with varicocelectomy show only a 33% improvement when the baseline count is under 10 million/ml,⁷ medical therapy may prove to be the first-line therapy in this group since in this preliminary study the sperm counts of 61% improved to over 20 million/ml.

Clomiphene citrate is generally well-tolerated by most men taking it, a mild weight gain being the most common side effect. However, some complications have been described,¹⁴ and therefore clomiphene citrate should be used mainly by fertility centers until its efficacy and risk factors in a larger series of patients can be determined. The drug has not yet been approved for this use by the Food and Drug Administration, and all patients must be made clearly aware of this before taking it.

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