Comparison of the effectiveness of placebo, clomiphene citrate, mesterolone, pentoxifylline, and testosterone rebound therapy for the treatment of idiopathic oligospermia

Christina Wang, M.D.*
Chi-Wing Chan, M.B. †
Kwok-Kee Wong, M.B.‡
Kwok-Keung Yeung, M.B.§
University of Hong Kong, Queen Mary Hospital, Hong Kong

Forty-six subfertile men with idiopathic oligospermia were randomly assigned to 6 months of treatment with a placebo, clomiphene citrate (25 or 50 mg/day), mesterolone (100 mg/day), or pentoxifylline (1200 mg/day) or 4 months of testosterone enanthate treatment (100 or 250 mg on alternate weeks). Treatment with the placebo, mesterolone, pentoxifylline, and testosterone rebound therapy did not result in a significant increase in the mean sperm concentration or pregnancy in the partners. Clomiphene citrate at both dosages significantly increased the mean sperm concentration without improving sperm motility or morphology during the 6-month treatment period. Pregnancy rates of 36.4% and 22% were observed in partners of men receiving clomiphene citrate 25 mg/day and 50 mg/day, respectively. This study also illustrates the difficulties in identifying suitable patients for and assessing the efficacy of different treatment regimens. Fertil Steril 40:358, 1983

Numerous pharmacologic agents have been used to treat idiopathic male subfertility.1,2 The etiologic basis of subfertility in most of these patients is unknown.3 Specific therapy can be directed to only a few with hypogonadotropic hypogonadism4,5 or hyperprolactinemia.6 The effects of drug therapy are also difficult to assess, because these men are only subfertile, and the occurrence of pregnancy in the partners during treatment may not prove that the drug is effective.7,8 We have studied a group of men with idiopathic oligospermia and compared the effects of a placebo, clomiphene citrate (CC; Clomid, Merrell-Dow Pharmaceuticals, Cincinnati, OH), mesterolone (Proviron, 1α-methyl-17β-ethynolandrost-4-en-3-one, Schering AG, Berlin, West Germany), pentoxifylline (Trental, a methylxanthine derivative, Hoechst AG, Frankfurt, West Germany), and testosterone enanthate (TE; Testoviron Depot, Schering AG, Berlin) rebound therapy in these subjects. These forms of empiric treatment had previously been reported to be useful in the treatment of idiopathic oligospermia.9-15

MATERIALS AND METHODS

SUBJECTS

We studied 46 men with idiopathic oligospermia, between 28 and 45 years of age (33.7 ± 4.4
years, mean ± standard deviation). They were all new patients attending the male infertility clinic at Queen Mary Hospital. All subjects except one had at least six consecutive sperm concentrations < 20 million/ml. Their basal follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), and prolactin levels were within the normal adult male range of our laboratory. They had not received treatment with pharmacologic agents for 1 year prior to entry into the trial. Their female partners were assessed simultaneously at gynecologic clinics. None of them had irreversible causes of female infertility. If the partners had ovulatory problems, these were corrected with medication prior to the subject’s entry into the trial. All couples were advised on frequent intercourse around the days of the expected time of ovulation, assessed usually by basal body temperature charts.

Testicular biopsies were performed, and testicular histologic features were assessed in all but three subjects at least 6 months prior to the initiation of treatment. Semen analyses were performed at 2-week intervals, clinical examination and hormone analyses were done at monthly intervals for 3 to 6 months before treatment and throughout the treatment period. Semen analyses included assessment of volume, motility, concentration, and morphology according to the World Health Organization (WHO) Laboratory Manual for the Examination of Human Semen and Semen-Cervical Mucus Interaction. Serum FSH, LH, and T were measured by radioimmunoassays previously described, using reagents provided by the WHO matched assay reagents program. The normal adult male ranges in our laboratory were as follows: FSH, 0.5 to 0.8 IU/I; LH, 0.5 to 5 IU/I; and T, 10 to 40 nmol/l.

After an interval of 3 months with at least six basal semen analyses, the subjects were randomly assigned to one of the therapy groups as shown in Table 1. They were given oral medication for 6 to 9 months. TE was given intramuscularly for a period of 4 months. After the treatment period, if there was no clinical response (e.g., an increase in sperm concentration/motility or pregnancy in the partner), the subjects were reassigned to another treatment schedule after at least 5 months of observation without any drug therapy.

Statistical analyses were done by two-way analysis of variance.

RESULTS

TESTICULAR BIOPSY HISTOLOGY

Testicular biopsies were performed in all but three subjects. Testicular histologic examination showed marked hypospermatogenesis in 1, moderate hypospermatogenesis in 11, mild hypospermatogenesis in 19, and focal sclerosis/atrophy in 12 subjects. As shown in Table 2, more than 50% of the subjects with moderate hypospermatogenesis had mean sperm concentrations < 5 million/ml, whereas only 26% of the subjects with mild hypospermatogenesis had the same degree of severe oligospermia. The mean sperm concentration was higher and the serum FSH lower in

Table 1. Pharmacologic Agents Used for the Treatment of Idiopathic Oligospermia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>No. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3 tablets per day</td>
<td>7</td>
</tr>
<tr>
<td>Clomiphene</td>
<td>25 mg/day orally</td>
<td>10</td>
</tr>
<tr>
<td>clomit</td>
<td>50 mg/day orally</td>
<td>15</td>
</tr>
<tr>
<td>metoclopramide</td>
<td>50 mg twice daily orally</td>
<td>12</td>
</tr>
<tr>
<td>fenoldipine</td>
<td>450 mg three times daily orally</td>
<td>13</td>
</tr>
<tr>
<td>testosterone</td>
<td>100 mg intramuscular injection once every 2 weeks</td>
<td>6</td>
</tr>
<tr>
<td>200 mg intramuscular injection once every 3 weeks</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Relationship Between the Histologic Features of the Testis, the Severity of Oligospermia, and Serum FSH Levels in 40 Patients with Oligospermia

<table>
<thead>
<tr>
<th>Histologic features</th>
<th>No. of subjects</th>
<th>No. of subjects with sperm concentration &lt; 1</th>
<th>1-6</th>
<th>7-10</th>
<th>&gt; 10</th>
<th>Mean sperm concentration</th>
<th>Mean serum FSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypospermatogenesis</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.8 ± 0.6</td>
<td>6.9</td>
</tr>
<tr>
<td>Moderate hypospermatogenesis</td>
<td>11</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>6.3 ± 5.0</td>
<td>5.6 ± 2.4</td>
</tr>
<tr>
<td>Mild hypospermatogenesis</td>
<td>19</td>
<td>1</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>9.6 ± 5.4</td>
<td>3.8 ± 1.6</td>
</tr>
<tr>
<td>Focal sclerosis/atrophy</td>
<td>15</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>9.9 ± 4.8</td>
<td>6.1 ± 2.7</td>
</tr>
</tbody>
</table>

*Mean ± standard deviation.
the group with mild hypospermatogenesis when compared with the group with moderate hypospermatogenesis. The group of subjects classified as focal sclerosis/atrophy were very variable. Their mean sperm concentration and mean serum FSH levels were between those of the groups with mild and moderate hypospermatogenesis.

PLACEBO

As shown in Figure 1 and Table 3, placebo treatment did not increase mean sperm concentration. Sperm motility and morphology did not show any improvement. No pregnancy was reported by the subjects’ partners.

CLOMIPHENE CITRATE

Figures 2 and 3 and Table 3 show the effect of CC on the mean sperm concentration of 11 subjects treated with 25 mg/day and 18 subjects treated with 50 mg/day. The response to CC was extremely variable among subjects. As a group the mean sperm concentration during 4 to 6 months of treatment with 25 mg CC daily (15.3 ± 14.8 million/ml) was significantly higher than in the pretreatment period (8.8 ± 7.2 million/ml, \(P < 0.05\)). Four pregnancies were reported by the partners (36.4%), three of these occurred within 3 months of treatment and the other in the fifth treatment month. Three of these four subjects had basal sperm counts > 10 million/ml. In the group receiving 50 mg/day, the mean sperm concentration in the third month (10.3 ± 11.5 million/ml, \(P < 0.05\)) and in the sixth month of treatment (10.9 ± 11.5 million/ml, \(P < 0.05\)) were both significantly higher than in the pretreatment period (7.1 ± 7.2 million/ml). The increase in mean sperm count was evident in six subjects. Four of the 18 subjects’ wives became pregnant (22.2%), 1 during the first 3 months of treatment, 2 during 4 to 6 months, and 1 after 3 months of drug withdrawal. In three of these four subjects, the mean basal sperm count was > 10 million/ml. In both groups of subjects, the increase in sperm concentration was not accompanied by parallel increases in sperm motility or the percentage of oval sperm. Table 4 shows the mean serum FSH, LH, and T levels in the subjects receiving CC. Mean serum FSH increased two- and fivefold after 25 mg/day and 50 mg/day CC therapy, respectively. Mean serum LH and T levels rose six- and twofold, respectively, in both treatment groups.

Figure 4 shows the response to CC (50 mg/day) in a subject with mild hypospermatogenesis. He was observed for 9 months before CC therapy was instituted. After the commencement of treatment, a gradual increase in sperm concentration was noted, which peaked to 70 million/ml, with
sperm motility of 40%; his wife became pregnant. Serum levels of FSH, LH, and T rose within the first month of treatment.

The response to CC was illustrated by another subject with moderate hypospermatogenesis (Fig. 5). His basal sperm counts were very low, often < 1 million/ml. His sperm motility showed wide fluctuations. His basal serum FSH was in the upper normal range. He was given mesterolone for 5 months, with no improvement. After observation for another 5 months, he was treated with CC 50 mg/day. A marked increase in sperm count was noted, which peaked to 50 million/ml after 3 months. During his first treatment course, his wife did not become pregnant. Six months after the first course, he was given a second course of CC. This resulted in a sperm count of 11 million/ml. During the third month of treatment, his wife conceived. Sperm motility still showed wide excursions during treatment. Parallel increases in FSH, LH, and T were demonstrated during both treatment periods.

MESTEROLONE

Mesterolone caused no significant change in mean sperm count (Fig. 6, Table 3), sperm motility, or sperm morphology in the 12 subjects. However, in two subjects with mild hypospermatogenesis, the mean sperm concentration doubled and peaked during 4 to 6 months of mesterolone treatment. None of the partners reported pregnancy during or after drug treatment.

PENTOXIFYLLINE

Similar to placebo or mesterolone, pentoxifylline did not significantly increase sperm concentration (Fig. 7, Table 3) or sperm motility in the 11 subjects. Hormone levels did not alter during the treatment period. None of the partners became pregnant.

TESTOSTERONE REBOUND THERAPY

As shown in Figure 8 and Table 5, injections of 100 mg TE given every 2 weeks were inadequate to suppress spermatogenesis. Suppression in sperm concentration was observed in two of six subjects and azoospermia in one of these subjects. As a group, the mean sperm concentrations were significantly increased 6 months after drug withdrawal. This was caused by a more than twofold increase in mean sperm concentration in two subjects. None of the partners became pregnant. Sperm motility and morphology showed no improvement after drug withdrawal.

With 250 mg TE every 2 weeks, suppression of spermatogenesis was noted during treatment and 3 months after drug withdrawal (Fig. 9, Table 5). In all subjects, azoospermia was maintained for a period of at least 1 month. The mean sperm concentration 6 and 12 months after drug withdrawal was not significantly different from that of the pretreatment period. Similarly, sperm motility or morphology were not improved by rebound treatment.
therapy. Only one of nine subjects showed a four-fold rebound in mean sperm concentration 6 and 12 months after drug withdrawal. No pregnancy was reported by the partners of the subjects.

SIDE EFFECTS

For the dose and the schedule used, none of the subjects experienced untoward side effects. No subject developed gynecomastia during drug treatment.

DISCUSSION

We have shown in this study that of the five methods of medical treatment (placebo, CC, mesterolone, pentoxifylline, and T rebound therapy) for idiopathic oligospermia, CC was the most effective in increasing sperm concentration and pregnancy rates. Patients with moderate hypospermatogenesis and marked oligospermia (e.g., < 5 million/ml) in general do not respond to any form of treatment.

As expected, placebo treatment did not alter sperm concentration. The weak androgen, mesterolone, which does not suppress gonadotropins, had been reported to stimulate spermatogenesis. Like Keogh et al.,11,12 we found that mesterolone had no effect on sperm concentration in our patients. Neither did it improve sperm motility.

Methylxanthine derivatives including pentoxifylline increased the duration of activity of ejaculated human spermatozoa.22 Previous clinical studies with pentoxifylline for 4 to 12 months did not significantly change the mean sperm concentration, although the sperm motility was slightly improved.13 When we treated our oligospermic patients with pentoxifylline, there was no improvement in sperm concentration or in progressive motility.

T rebound therapy was shown by Heller et al.14 to improve sperm counts in oligospermic men. Subsequently, this was confirmed by others.15,16 with an improvement in sperm concentration in ~50% of the patients after drug withdrawal. In contrast, in our study of subfertile patients with basal sperm concentrations persistently < 20 million/ml, T rebound therapy did not significantly increase sperm concentration even when the duration of observation was extended to 12 months after drug withdrawal. In previous studies,14 rebound to fertile levels was usually seen 3 to 4 months following cessation of therapy. The strict criteria of selecting our subjects with persistent oligospermia caused by hypospermatogenesis or focal sclerosis/atrophy as confirmed by testicular histologic examination probably contributed to the absence of beneficial effects of T rebound therapy.

The antiestrogen, CC, had been used for male subfertility since the report of Mellinger and Thompson.10 In various studies,10,11,12 improvement in sperm counts has been demon
strated with CC at both 25 and 50 mg/day. Others have reported no beneficial effect.\textsuperscript{24, 25} Our study showed significant but modest increases in the mean sperm concentration during 6 months of CC therapy in both groups of subjects (25 or 50 mg/day). The higher dosage of 50 mg/day had no advantage over the lower dosage. Similar to other reports,\textsuperscript{22, 23} no increase in sperm motility was observed. The degree of stimulation of the serum gonadotropins and T was also similar to that in previous reports.\textsuperscript{22, 23}

The pregnancy rates in the partners of the subjects treated with CC were 22.2% in the 50 mg/day group and 36.4% in the 25 mg/day group, similar to the overall pregnancy rate of \textasciitilde 20.7% in other CC-treated patients.\textsuperscript{4} The pregnancy rates of the placebo, mesterolone, pentoxifylline, and T rebound groups were all zero. This was in distinct contrast to the other reports of a 20% to 40% "pregnancy rate" in the partners of men with subfertility problems.\textsuperscript{7, 8} The differences could be partially accounted for by the strict criteria of selection of subjects into the trial. All our subjects (except one) had multiple sperm concentrations < 20 million/ml before treatment. Testicular biopsies done in the majority of patients confirmed seminiferous tubule dysfunction, either as hypospermatogenesis of varying degree or as focal sclerosis/atrophy. Although these patients had
serum FSH levels within the normal adult range, they all had definite testicular damage. The low "background" pregnancy rates in the placebo and other treatment groups could also be accounted for by the long period of observation (~ 6 to 9 months) before treatment was instituted in our group of subjects. The increased pregnancy rates observed in the CC-treated groups of patients in this report were therefore probably the result of drug therapy.

Although our study showed that in comparison to the placebo, mesterolone, pentoxifylline, and T rebound therapy, CC was apparently the most effective in increasing mean sperm concentration and achieving pregnancy. However, not all the patients responded to CC, and the increase in mean sperm concentration was modest. In the four patients whose wives became pregnant after CC (25 mg/day) treatment, the mean basal sperm concentration was > 10 million/ml in three. In the group receiving 50 mg/day, pregnancy occurred in the wives of three subjects with mean basal sperm concentrations > 10 million/ml.

Thus, pregnancy occurred in the partners of six of eight subjects after CC therapy when their pretreatment sperm concentration was > 10 million/ml. The prognosis was less favorable in subjects with lower basal sperm counts. This observation was similar to that of Ronnberg.

The subfertile oligospermic men consisted of a heterogeneous group of subjects. Most of the underlying causes of the testicular damage are at present unknown. The problem for the clinician remained the difficulty in selecting the right patient for the suitable type of empirical medical treatment and in assessing the efficacy of different regimens. In this study, we attempted to demonstrate several factors that might be useful in selecting patients for medical treatment.

Acknowledgments. We thank Professor Ho-Kei Ma for her interest; the World Health Organization for the provision of reagents for hormone radioimmunoassay; Hoechst Aktiengesellschaft for the supply of pentoxifylline; Schering AG for the supply of mesterolone; Andy Shea, Andrew Leung, and Daniel Leung for their expert technical assistance; and Susie Yim for typing the manuscript.

REFERENCES

2. Schill WB: Recent progress in pharmacological therapy of male subfertility—a review. Andrologia 11:77, 1979

Wang et al. Treatment of idiopathic oligospermia 365