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*Andrology Unit of the Department of Dermatology*[1]
*2nd Department of Internal Medicine Großhadern*[2] *and*
*Institute for Clinical Chemistry Großhadern*[3],
*Ludwig- Maximilians University of Munich, Munich, FRG*

# Combined hMG/hCG treatment in subfertile men with idiopathic normogonadotrophic oligozoospermia

By

W.-B. Schill[1], D. Jüngst[2], P. Unterburger[2] and S. Braun[3]

Forty-eight patients with idiopathic normogonadotrophic oligozoospermia were treated with hMG plus hCG over a period of 3 months. Total sperm output increased by an average of 15.3 million spermatozoa per ejaculate and a similar significant increase was seen in the percentage of motile spermatozoa. Sixteen of the 48 men increased their sperm output by 25 million or more. Follow-up information was available in 33 patients. Ten pregnancies were reported within one year after initiation of treatment. Six of 12 responders impregnated their wives, whereas only 4 pregnancies were reported in a group of 21 non-responders. Endocrinological investigations showed no differencies in mean basal levels of LH and FSH, or in the gonadotrophin response to a 100 µg GnRH stimulation between responders and non-responders. However, mean basal plasma testosterone concentration was significantly lower in the responder group than in the non-responders. Responsiveness to gonadotrophin treatment tended to be better in patients with basal plasma testosterone concentration lower than 4.5 ng/ml. Combined hMG/hCG treatment in subfertile men with idiopathic oligozoospermia seems to be efficient in only a small proportion of cases.

*Key words:* gonadotrophins – hMG – hCG – therapy – oligozoospermia.

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Gonadotrophin replacement in males with hypogonadotrophic hypogonadism is effective in restoring fertility (Schill 1979). The use of gonadotrophins in treating subfertile men with either azoospermia or oligozoospermia and increased FSH levels is generally regarded as of no value. Controversy exists as to whether or not gonadotrophin treatment may be of benefit in normogonadotrophic oligozoospermic patients. Furthermore, no suitable selection criteria are available to predict the possible outcome of gonadotrophin treatment.

Lunenfeld et al. (1979) suggested that the gonadotrophin releasing hormone (GnRH) test was useful in selecting those patients with relative FSH deficiency who would have a better chance to respond to gonadotrophin treatment. Patients with normal basal FSH levels but exhibiting exaggerated response upon GnRH stimulation were considered inappropriate for this form of treatment.

The aim of this study was to re-evaluate the efficacy of gonadotrophin treatment in men with normogonadotrophic idiopathic oligozoospermia (sperm count less that 20 mill/ml) and to investigate whether hormonal selection criteria are available to predict gonadotrophin treatment to be successful.

## Material and Methods

Forty-eight subfertile men, mean age 34.4 ± 5 years, with more than 2 years of involuntary infertility and suffering from idiopathic oligozoospermia with sperm counts consistently below 20 million per ml were selected for this study. Oligozoospermia was demonstrated in at least 3 semen analyses performed within a period of 6 months. Two of these semen analyses were performed 1 month and immediately before initiation of treatment, respectively. At least one additional semen analysis was available dating from 3 to 6 months before initiation of the trial. All patients had a negative medical history, and any medical disease possibly impairing their fertility status was excluded. Patients had testes of normal volume and consistency, no obvious epididymal abnormality was found, and they had no varicocele or signs of genital tract infection. Patients had received no treatment during the 6 months before enrolment in the study.

The female partners were checked by different gynaecologists who had performed either hysterosalpingography or pertubation or laparoscopy without detecting any significant abnormalities. A cervical, tubal or ovarian factor was not found. The females did not receive any kind of treatment during the study period of one year.

Endocrinological investigations included determination of basal concentrations of testosterone, LH and FSH, as well as the response of LH and FSH 30 min after an intravenous bolus injection of 100 μg GnRH (Serono).

Blood samples were collected between 9 and 11 a.m. A group of 19 men with normal semen characteristics (normozoospermia) served as controls for the

hormonal investigations. Normal ranges for LH were 0.9–3.5 ng/ml, for FSH 0.9–3.5 ng/ml and for testosterone 3.0–10.0 ng/ml.

Radioimmunological measurements of LH, FSH and testosterone were performed using well established methods. Semen analysis included measurements of sperm concentration, total sperm output, total and progressive motility, sperm morphology, ejaculate volume and seminal plasma fructose (Eliasson 1971; Schirren 1982).

Semen analyses were performed one month (−1) and immediately prior to initiation of treatment (0) as well as 1, 3, and 5 (+1, +3, +5) months later.

Human gonadotrophin treatment consisted of intramuscular injection 3 times per week (Monday, Wednesday, Friday) of each 2 ampules of hMG (Pergonal 500, Serono) and twice weekly (Monday and Friday) 2500 IU hCG (Pregnesin 2500, Serono). Treatment was continued for 3 months.

Statistical analysis was performed by means of the Student's *t*-test for paired observations and the $\chi^2$-test. The mean of the semen analyses performed at minus 1 and 0 months before initiation of treatment served as baseline to calculate the influence of gonadotrophin treatment. Furthermore, the effect of treatment was studied in 4 subgroups according to the pre-treatment sperm count: Group A: 1 to 5 million/ml (n = 9), Group B: 5.1 to 10 million/ml (n = 12), Group C: 10.1 to 15 million/ml (n = 18) and Group D: 15.1 to 20 million/ml (n = 9).

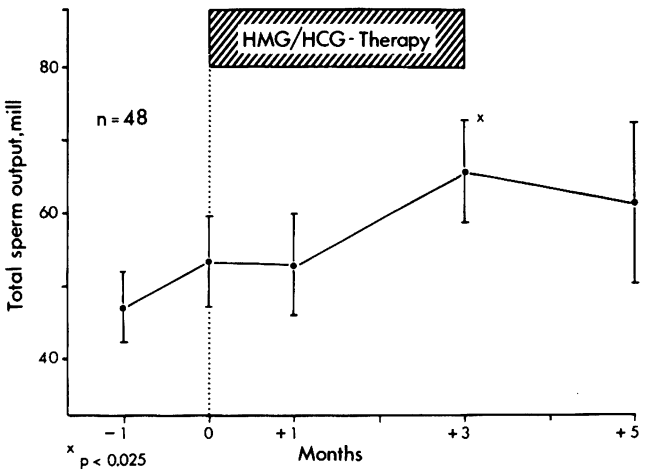


*Fig. 1*

Combined hMG/hCG treatment in 48 men with normogonadotrophic oligozoospermia treated over a period of 3 months with weekly 3 times 2 ampules hMG (1 ampule ≙ 75 IU FSH + 75 IU LH) and weekly 2 times 1 ampule hCG (1 ampule ≙ 2500 IU LH). Mean values (±SEM) of the total sperm output (spermatozoa/ejaculate) are plotted. Statistical calculation was done on the basis of the mean value of the 2 semen analyses performed before initiation of therapy.

## Results

### A. *Semen parameters*

1. *Sperm concentration and total sperm output*

Sperm counts before treatment varied between 1 and 20 million per ml with a mean of 10.9 million per ml. Mean total sperm output was 50.6 million per ejaculate. Three months after initiation of gonadotrophin treatment a significant increase ($P < 0.025$) in the mean number of spermatozoa per ejaculate was noticed. The increase averaged 15.3 million per ejaculate (Fig. 1). Two months after withdrawal of treatment the output of spermatozoa decreased without reaching the initial values.

Mean sperm concentration correspondingly increased from 10.9 million per ml to 14.9 million per ml following the treatment ($P < 0.025$). The individual resonse of the patients towards the treatment is shown in Fig. 2.

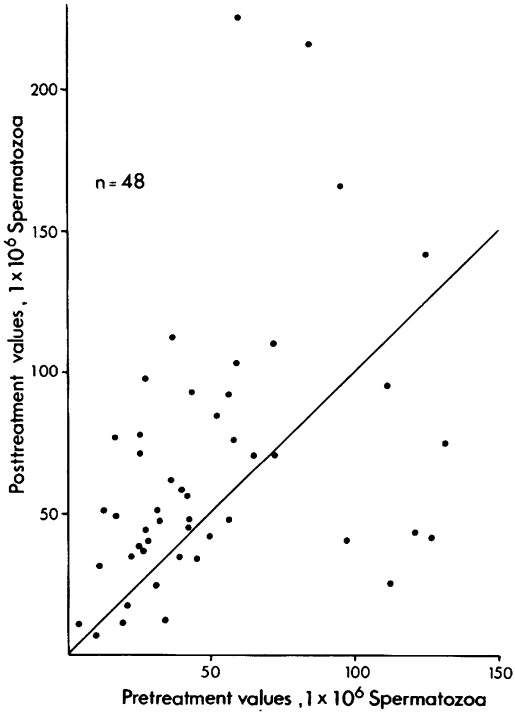


*Fig. 2.*
Diagram comparing the number of spermatozoa per ejaculate (total sperm output) of the same individuals immediately before treatment with those obtained 3 months after human gonadotrophin application. Points below this slope indicate a decrease, points above the slope an increase of the total sperm output.

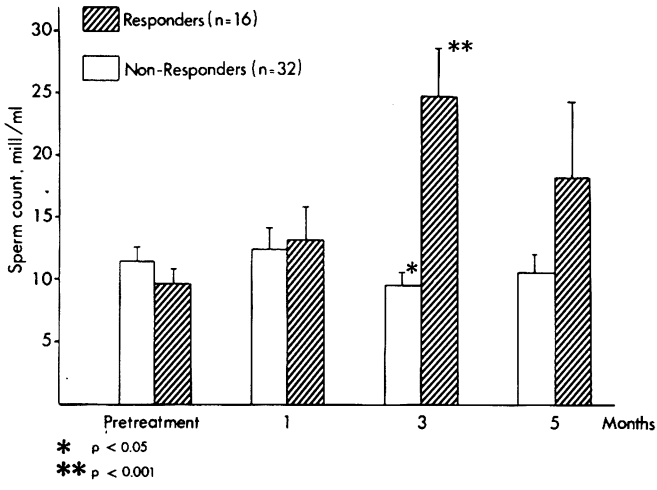


*Fig. 3.*
Mean sperm count (mill/ml, ± SEM) of the responder group (n = 16) and the non-responder group (n = 32) before, during and after treatment with human gonadotrophins.

In 29 out of 48 cases (60.4%) total sperm output increased by more than 10 million spermatozoa, of these 17 cases (35.4%) showed an increase of more than 20 million spermatozoa per ejaculate, 11 men (22.9%) displayed an increase of more than 40 million spermatozoa per ejaculate, and in 6 men (12.5%) the increase exceeded 60 million spermatozoa per ejaculate. Sixteen patients in whom total output of spermatozoa was increased by at least 25 million per ejaculate were classified as responders. A comparison of the mean sperm count between responders and non-responders is shown in Fig. 3.

Patients of Groups A and C presented a significant increase in sperm count and output, whereas patients of groups B and D did not present any improvement.

2. *Other semen parameters*

Before treatment mean total motility equalled 31.5% and mean progressive motility 12.5%. One month after initiation of the gonadotrophin treatment a significant increase ($P < 0.01$) of the percentage of motile spermatozoa was observed. Maximum improvement was noted at the end of the treatment period (average increase 29.3%). Thereafter motility decreased without returning to the initial values.

Twenty-two patients (45.8%) displayed improvement of total motility by 50% or more. Again improvement occurred in subgroups A and C but was absent in patients of subgroups B and D. Thus most patients responding with improvement

*Table 1.*

Mean basal hormone levels (± SD) of responders, non-responders, total oligozoospermic group and a normozoospermic control group.

| | FSH (ng/ml) | Δ FSH (ng/ml) | LH (ng/ml) | Δ LH (ng/ml) | Testosterone (ng/ml) |
|---|---|---|---|---|---|
| Responders (n=16) | 1.77 ± 0.66 | 1.48 ± 1.21 | 1.91 ± 1.01 | 8.53 ± 5.13 | 4.13 ± 1.57* |
| Non-responders (n=32) | 1.73 ± 0.56 | 1.31 ± 0.98 | 1.94 ± 1.13 | 7.28 ± 4.17 | 5.20 ± 2.38* |
| Total group (n=48) | 1.74 ± 0.59 | 1.36 ± 1.05 | 1.93 ± 1.04 | 7.70 ± 4.50 | 4.84 ± 1.71 |
| Control group (n=19) | 2.00 ± 0.69 | 1.09 ± 0.68 | 1.97 ± 0.69 | 6.31 ± 2.76 | 4.32 ± 1.37 |

*Difference between both groups is statistically significant ($p < 0.025$).

*Table 2.*
Basal testosterone levels and responsiveness to gonadotrophin therapy.

| Basal testosterone | < 4.5 ng/ml | > 4.5 ng/ml |
|---|---|---|
| No. of patients | 24 | 24 |
| Responsive to therapy | 12 (50%)* | 4 (17%) |
| Non-responsive to therapy | 12(50%) | 20 (83%) |

* $P < 0.025$.

of sperm motility also showed increased sperm concentrations. Progressive sperm motility, however, remained unchanged.

Morphology of the spermatozoa remained unchanged during treatment; the percentage of normally shaped spermatozoa, however, decreased two months after withdrawal of the medication ($P < 0.025$).

Ejaculate volume was not affected, the concentration of fructose in seminal plasma displayed a small, but significant decrease after one month of gonadotrophin treatment ($P < 0.025$), but was restored to normal after 3 and 5 months.

3. *Conception rates*

Follow-up information is available from 33 out of 48 patients. Ten pregnancies were reported within one year after initiation of treatment. Of these 2 ended in abortion. The overall conception rate thus equals 30%; 80% of the pregnancies occurred within the first 6 months after initiation of treatment with maximal incidence around the 4th and 5th month. Six out of 12 responders impregnated their wives whereas only 4 out of 21 non-responders reported pregnancy. The difference between both groups, however, does not reach statistical significance.

Distribution of conceptions within the different subgroups was as follows: conception occurred in 4 out of 7 wives of Group A patients, 1 out of 7 wives of Group B patients, 5 out of 12 wives of Group C patients and none in group D patients.

There seems to be a tendency towards more conceptions in those subgroups who showed an improvement of the semen parameters following gonadotrophin treatment, however, the number of pregnancies was too small to draw any conclusions.

## B. *Hormone parameters and responsiveness to gonadotrophin therapy*

In order to solve the question whether any hormonal selection criteria would be available to predict the success of gonadotrophin therapy, endocrinological para-

*Table 3.*
Gonadotrophin levels (basal and after GnRH) and responsiveness to gonadotrophin therapy.

| | Basal levels of | | | | | |
|---|---|---|---|---|---|---|
| | FSH | | LH | | LH/FSH ratio | |
| | ≤ 2 ng/ml | > 2 ng/ml | ≤ 2 ng/ml | > 2 ng/ml | ≤ 1 ng/ml | > 1 ng/ml |
| No. of patients | 31 | 17 | 28 | 20 | 21 | 27 |
| Responsive to therapy | 9 (29%) | 7 (41%) | 9 (32%) | 7 (35%) | 7 (33%) | 9 (33%) |
| Non-responsive to therapy | 22 (71%) | 10 (59%) | 19 (68%) | 13 (65%) | 14 (67%) | 18 (67%) |

| Gonatrophin increase after GnRH | FSH | | LH | |
|---|---|---|---|---|
| | ≤ 50% | > 50% | ≤ 500% | > 500% |
| No. of patients | 19 | 29 | 35 | 13 |
| Responsive to therapy | 7 (37%) | 9 (31%) | 12 (34%) | 4 (31%) |
| Non-responsive to therapy | 12 (63%) | 20 (69%) | 23 (66%) | 9 (69%) |

meters were compared in patients and normal controls (Table 1). No differencies were found on basal levels of FSH and LH and testosterone between the 48 oligozoospermic men and the control group of 19 normozoospermic patients. Furthermore, no difference occurred in basal FSH and LH levels as well as in GnRH response between responders and non-responders. Mean basal levels of testosterone, however, were significantly lower in the responder group ($P < 0.025$). Patients having a basal testosterone level below 4.5 ng/ml tended to respond better to gonadotrophin treatment than those with higher basal testosterone levels (Table 2). In contrast, patients with basal FSH and LH levels below 2.0 ng/ml showed no

*Table 4.*
Hormone values of men who impregnated their wives after gonadotrophin therapy.

| ng/ml (X ± SD) | FSH | Δ FSH | LH | Δ LH | Testosterone |
|---|---|---|---|---|---|
| Fathers (n=10) | 1.76 ± 0.64 | 1.75 ± 1.41 | 1.85 ± 1.02 | 9.46 ± 4.89 | 4.75 ± 1.42 |
| Non-Fathers (n=38) | 1.73 ± 0.58 | 1.26 ± 0.93 | 1.82 ± 1.13 | 7.23 ± 4.33 | 4.63 ± 2.08 |

better response to gonadotrophin treatment than those with higher FSH or LH levels (Table 3). The LH/FSH ratio was equal in the group of the responders (1.2) and the non-responders (1.19).

Finally no differences were found in the hormonal assessment of men who impregnated their wives as compared to those who did not (Table 4).

## Discussion

Our data confirmed the reports of others (Paulsen et al. 1970; Da Rugna et al. 1074; Glezerman & Lunenfeld 1976; Rosemberg 1976; Schreiber 1977; Lunenfeld et al. 1979; Schellen & Bruine 1980) in demonstrating some effect of the combined gonadotrophin treatment in patients with normogonadotrophic idiopathic oligozoospermia. However, to prove the efficacy of this treatment, a controlled trial would be necessary. Whereas increased sperm concentration generally occurred at the end of the 3 months' treatment period, some patients, however, only increased their sperm count at 5 months after initiation of treatment. In other cases the sperm count already dropped 2 months after interruption of treatment. Considering the effects of treatment depending on the pre-treatment sperm count, subgroup A, B, C and D responded at random indicating that the initial sperm count did not influence the gonadotrophin response and did not allow prediction of response.

Improvement of total sperm motility occurred already one month after initiation of treatment and tended to persist 2 months after withdrawal of medication. Improvement of sperm motility generally occurred in the same patients also presenting increase in sperm concentration. Improvement of sperm motility seems to be more closely related to the fertility status of the patient than an increase of the number of spermatozoa (Ulstein 1973; David et al. 1980). This finding could be of importance. The significance of the temporary decrease in semen fructose and post-treatment decrease in the percentage of normally shaped spermatozoa remains questionable.

In comparisons with other authors (Lunenfeld & Insler 1978) the conception rate found in our study (30%) is rather high, it is, however, comparable to other forms of treatment evaluated in our patient material (Schill 1979, 1982b).

The conception rate in the non-responder group (19%) is similar to the spontaneous conception rate in our patient material, being 16% (Schill 1977).

The higher conception rate in responders (50%) tends to support the idea that treatment has favourably influenced the fertility status of these cases.

Our search for selection criteria to predict the effectiveness of gonadotrophin treatment was unsuccessful. The only prognostic hint concerns the basal testosterone level being significantly lower in the responder than in the non-resonder group. This finding agrees with the observations of Lunenfeld et al. (1979).

Individual prediction of treatment outcome, however, reveals impossible.

In conclusion combined hMG/hCG treatment in men with normogonadotrophic idiopathic oligozoospermia should be considered an empirical form of therapy. The results obtained are poor in terms of improved semen parameters compared to those reported for other treatments e.g. anti-oestrogens or kallikrein (Schill 1982a). Nevertheless, conception rate was found above that observed during placebo treatment, which in our patient material is between 10 and 20% (Schill 1977, 1982b).

However, considering the relative small number of responders and the high cost of human gonadotrophins, this mode of treatment should not be considered a significant progress in the management of idiopathic oligozoospermia.

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*Authors' addresses:*

W.-B. Schill, Andrology Unit of the Department of Dermatology,
University of Munich, Frauenlobstr. 9–11, D-8000 München 2, FRG.

D. Jüngst und P. Unterburger, Second Department of Internal Medicine Großhadern,
University of Munich, Marchioninistr. 15, D-8000 München 70, FRG.

S. Braun, Institute for Clinical Chemistry, Großhadern,
University of Munich, Marchioninistr. 15, D-8000 München 70, FRG.