Effect of growth hormone therapy in men with severe idiopathic oligozoospermia

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Some studies have suggested that growth hormone (GH) may enhance folliculogenesis in women, and similarly may enhance spermatogenesis in men with hypogonadotrophic hypogonadism. In this prospective open-controlled pilot study, we investigated the effect of daily subcutaneous GH for 5 months in 12 endocrinologically normal men with severe idiopathic oligozoospermia (< 10 million/ml). All the men had normal karyotype and endocrine tests, including a GH response of > 20 000 mU/l to insulin hypoglycaemia. Nine men with similar sperm counts acted as controls. During treatment, each patient was examined monthly, asked for side effects and had glycosylated haemoglobin, glucose and blood counts monitored. Five semen samples were obtained in the 4 months before treatment, two samples per month during treatment and three samples after stopping treatment. The mean insulin-like growth factor I (IGF-I) was normal before treatment and 1 month after ending treatment, at 206 and 182 µg/l, respectively, but increased significantly during treatment to 444 µg/l (p < 0.0001, ANOVA). The mean (sd) sperm counts were 2.6 (2.5), 2.5 (3.7) and 2.3 (2.1) million/ml before, during and after GH treatment, respectively, and did not show any statistically significant differences (ANOVA). We conclude that GH does not increase or decrease sperm counts in men with severe idiopathic oligozoospermia.

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Although there have been some significant recent advances in sperm processing techniques and the use of microinjection devices, the prognosis for achieving fertility in men with severe idiopathic oligozoospermia is still quite poor (1, 2). Studies have shown that growth hormone (GH) and insulin-like growth factors (IGFs) may augment gonadotrophin action on the ovary in vitro and in experimental animals (3, 4). These actions of GH are thought to be mediated mainly by IGF-I, which is produced primarily in the liver (5) but is produced also in the ovary (4), although a recent report suggests that there might be a direct stimulatory effect of GH on oestrogen production by human ovarian granulosa cells in vitro (6).

The recent availability of recombinant GH has made possible clinical studies in humans. These have suggested that GH may decrease the gonadotrophin requirement in subfertile women undergoing ovulation induction with exogenous gonadotrophins (7, 8). In addition, GH has been used with some success in the treatment of subfertile women without GH deficiency (9), although not all placebo-controlled studies concur (10). In the male reproductive system, a similar role for GH and IGFs may be likely (11, 12) and in a recent study in men with hypogonadotrophic hypogonadism, the addition of GH to exogenous gonadotrophins seemed effective in stimulating spermatogenesis in two men who had remained azoospermic after 12 weeks of conventional gonadotrophin stimulation (13). Furthermore, a preliminary report suggested that GH-releasing hormone might be useful in the treatment of infertile men with idiopathic oligospermia (14). We therefore conducted a prospective open pilot study to see whether GH might improve sperm counts in men with severe idiopathic oligozoospermia.

Patients and methods

Patients

Sixteen men with idiopathic oligozoospermia (sperm count < 10 million/ml) and infertility of more than 1-years duration were recruited from the infertility clinic at our hospital. None of the men were on any medication and all were otherwise normal and healthy on a full physical examination. Their mean (± sd) age was 34.0 (± 4.9) years. None of the patients had any infection of the genitourinary tract. All procedures were in accordance with the Helsinki Declaration of 1975, as revised in 1983, and the study was approved by the Clinical Trials Committee of the Ministry of Health and the Ethics Committee of the National University.
Hospital. Written informed consent was obtained from both husband and wife before entry into the study.

A group of nine untreated men with similar sperm counts attending the infertility clinic at the same time were studied as controls. Their mean age was 34.5 (±4.5) years.

**Evaluation of endocrine function**

On entry into the study, baseline investigations were carried out and each patient had normal serum testosterone, LH, FSH, prolactin, thyroxine and TSH levels. Karyotyping was performed on peripheral leucocytes and was normal male 46,XY for each patient. Patients then were admitted to hospital and had dynamic anterior pituitary function tests carried out after an overnight fast. A combined intravenous insulin hypoglycaemia (0.15 U/kg body wt), TRH (200 µg) and LHRH (100 µg) test was carried out. Each patient had normal responses in LH, FSH, TSH, prolactin and cortisol levels; and the GH response to induced hypoglycaemia was > 20 000 mU/l for each patient. An oral glucose tolerance test (75 g) was performed on another day and each patient had a normal response according to WHO criteria.

**Treatment and monitoring**

**Treatment.** Recombinant human GH (Norditrophin), kindly provided by Novo-Nordisk, Gentofte, Denmark, at 0.6 U·kg⁻¹·week⁻¹, was self-injected subcutaneously every night before sleep for 5 months. Each patient was examined monthly, asked about symptoms and examined for side effects and had glycosylated haemoglobin A1c, fasting glucose and full blood counts monitored. The GH dose was reduced to 0.4 U·kg⁻¹·week⁻¹ if side effects were significant and reduced further to 0.3 U·kg⁻¹·week⁻¹ if necessary.

**Semen analysis.** On entry into the study, before starting GH treatment, five semen samples were obtained over a 4-month period. During GH treatment, two samples were obtained every month, and after completion, three samples were obtained between 1 and 3 months after stopping treatment. Patients were instructed to abstain for 5 days before providing semen samples and there was a minimum interval of five days between consecutive samples during the treatment period. Semen analyses were performed according to the WHO Laboratory Manual for the Examination of Human Semen and sperm–cervical mucus interaction (15). In addition, aliquots of semen were analysed as described previously (16) by computer-automated analysis using the Celsoft (Version 3.1; 25 Hz system) machine (CRYO Resources, New York, NY) for curvilinear velocity, mean amplitude of lateral head displacement (ALH), linearity and beat/cross frequency, except when the sperm count was too low (< 0.01 million/ml) for such measurements. Patients in the control group had semen analyses before and after an interval of 4–5 months.

**Compliance.** Compliance was assessed during the treatment period by questioning the patient and by counting the vials of GH and the syringes/needles. Serum IGF-I measurements made after completion of the study were further confirmation of patient compliance.

**Other assays**

Fasting glucose, glycosylated haemoglobin A1c and haemogram were monitored monthly at the hospital routine laboratory. The protocol for the study required a discontinuation of GH administration if there was an abnormality in any of these parameters; however, all the values remained within the normal limits throughout the study and no patient required discontinuation of treatment.

In addition to the above, serum samples were taken monthly and stored at −70°C for IGF-I measurement using a commercial kit (Nichols, CA, USA) after C₁₄ Sep-Pak column (Waters, USA) extraction of acidified serum. Growth Hormone assay was carried out with a commercial kit (Nichols, CA, USA) calibrated with National Pituitary Agency (Bethesda, MD, USA) standards. All the samples were assayed at the same time and the intra-assay coefficients of variation were < 10%.

**Statistics**

All the individual values of sperm counts before, during and after treatment were entered and compared by univariate analysis of variance (ANOVA) for repeated measurements, using the general linear models (GLM) procedure in the SAS package (version 5.1, SAS Institute, USA). Data on the other sperm parameters were analysed in a similar way, except where indicated otherwise.

**Results**

Twelve out of the 16 patients recruited completed the 4-month pretreatment observation period, the full 5 months of GH treatment and 3 months after completing treatment, and provided semen samples before, during and after completion of treatment. Of the four men who withdrew, two stopped GH self-injections after 3 weeks of treatment because of "feeling awful", one was excluded for non-compliance and one refused to provide semen samples after completing 5 months of GH treatment. Eight of the 12 who completed treatment spontaneously reported adverse effects consisting of arthralgia, joint swelling and tingling of the fingers after 1 month. Treatment dose was reduced to 0.4 U·kg⁻¹·week⁻¹ of GH in these patients. In two
of these eight patients, symptoms persisted for another 2 weeks and the treatment dose of GH was further reduced to 0.3 U · kg⁻¹ · week⁻¹. The severity of the symptoms decreased after these decreases in GH dose and the symptoms disappeared completely within 1 month of stopping GH at the end of the study. There were no significant changes in glycosylated haemoglobin, fasting glucose nor in full blood count.

No adverse events were reported in the control patients during the period of observation and semen analyses.

Table 1 gives the mean (±sd) serum IGF-I and GH values before, during and after treatment. Serum IGF-I was similar before starting treatment, i.e. 206 (±47) µg/l, and 1 month after ending treatment, i.e. 182 (±51) µg/l, but increased significantly during GH treatment to 444 (±188) µg/l (p < 0.0001, ANOVA, Duncan). Fasting serum GH levels were 1500 (±3100), 2600 (±2900) and 400 (±1100) mU/l before, during and after treatment, respectively (p = 0.06, ANOVA). There was no statistically significant correlation between the serum levels of IGF-I and the presence or absence of side effects of GH administration.

Sperm parameters before, during and after GH treatment are shown in Table 1. The differences in the sperm count or semen volume were not statistically significant (see Fig. 1). Semen analysis by microscopy (WHO criteria) did not show any significant change with treatment. Computer-automated sperm analysis showed a small but statistically significant increase in the mean (±sd) sperm velocity from 33.2 (±6.2) to 36.2 (±7.6) µm/s with GH treatment, which decreased after treatment stopped to 33.9 (±7.2) µm/s (p < 0.05, ANOVA, Duncan). The differences in mean ALH, linearity and beat/cross frequency were not statistically significant (ANOVA). Untreated patients in the control group showed no statistically significant change in any of the parameters (Table 1).

There were no pregnancies in the 16 couples (nor in the nine control couples) during the study period or in a 1-year follow-up period after completion of treatment.

Discussion

In the present study, we have given recombinant hGH for 5 months to 12 normal healthy men with longstanding idiopathic oligozoospermia. The men were otherwise “normal” in that there were no abnormalities detectable on a complete physical examination, biochemically, nor by standard dynamic tests of pituitary function. In particular, the men had normal serum IGF-I levels and normal GH responses (> 20 000 mU/l) to insulin-induced hypoglycaemia. Four of the men did not complain of any side effects when given 0.6 U · kg⁻¹ · week⁻¹ of GH, but 11 men had side effects that resulted in their withdrawal from the study or in reduction in the dose of GH administered. This variability in the occurrence of side effects of GH has been seen in previous studies of GH given in physiolo-
gical doses to adult GH-deficient men (17). All symptoms and side effects disappeared completely 1 month after ending GH treatment and there have been no detectable side effects of GH treatment on deliberate questioning during follow-up of these men for more than 1 year. This is reassuring, although caution and careful long-term follow-up still would be necessary to confirm the complete safety and total reversibility of side effects of prolonged supraphysiological GH administration.

Our study showed that GH (sufficient to double the mean serum IGF-I levels) for 5 months did not increase or decrease the sperm count significantly, although there was a small increase in sperm curvilinear velocity, the physiological significance of which is unknown. The magnitude of this decrease in velocity, ∼3 μm/s, was quite minimal and was smaller than the difference in the control group, which was not statistically significant (Table 1).

The lack of any change in sperm parameters despite a sustained change in serum IGF-I was disappointing. Spermatogenesis in these patients with idiopathic oligozoospermia may be abnormal and/or the duration of GH administration may have been inadequate. A previous study of 12 GH-deficient men had similar findings in that there was no significant increase in the low sperm counts after 4 months of physiological GH replacement (18). However, in that study, six of the patients had multiple hormonal deficiencies and were receiving testosterone replacement rather than gonadotrophins. Growth hormone effects would have been difficult to detect in such patients and thus it was possible that a positive effect of GH on sperm count could have been masked. Studies in transgenic mice with excess GH have shown no change but they had normal sperm counts and were not oligozoospermic at any time (19). The study by Shoham et al. (13) suggested that GH may augment gonadotrophin action in the testes, just as it does in the ovary in some reports. Our present study, however, does not support a beneficial effect of GH in men with idiopathic oligozoospermia and with normal serum GH and IGF-I.

Oligozoospermia is poorly understood and is likely to be multifactorial in its causation, in a manner similar to the subgroup of infertile women known as “poor responders” who respond with very few follicles despite the huge doses of gonadotrophin given to them in ovulation induction regimes. Supraphysiological GH as a co-factor in gonadotrophin treatment in these women has produced encouraging results in some studies (9) and less so in others (10). Our results, therefore, do not negate the possibility of a role of GH as a co-factor in spermatogenesis and further studies may be required to investigate if different treatment regimes may help this group of infertile men.

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References

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