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Long-term Subcutaneous Pulsatile Low Dose LH-RH Administration for Treatment of Infertile Men with Secondary Hypogonadotrophic Hypogonadism

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ABSTRACT

Chronic pulsatile subcutaneous low dose LH-RH treatment was given to three infertile men with longstanding (2-4 years) secondary hypothalamic pituitary failure. Before the therapy they had very low serum concentrations of gonadotrophins and testosterone. They were impotent and could not produce any ejaculate for sperm analysis. The pulsatile LH-RH treatment, which was continued up to 250 days, was given by means of a small portable automatically-timed infusion pump. Fifty μl of the LH-RH solution was infused during one min every 90 min. The LH-RH doses were 1, 5 and 20 μg.

The serum concentrations of the gonadotrophins and testosterone were normalized in the three patients within 10 days of pulsatile low dose LH-RH therapy. Libido and potency returned. The first ejaculates contained no sperms. With continued LH-RH treatment spermatogenesis was induced and normalized. Two of the men fertilized their wifes. The pregnancy tests were positive after 181 and 230 days of treatment, respectively. Two healthy girls have been born. Paternity tests were positive. The third man is still receiving pulsatile LH-RH therapy. He has up till now been treated for four months.

Chronic pulsatile s.c. low dose LH-RH administration is a very promising new therapy for those hypogonadal men who previously have required human gonadotrophin treatment to restore fertility.

INTRODUCTION

Male infertility caused by hypogonadotrophic hypogonadism has so far required treatment with human gonadotrophins (HMG/HCG) to restore spermatogenesis and testosterone production (6,10,11,18). This therapy is expensive as it has to be continued for long periods of time. Furthermore, development of HCG induced antibodies has caused failure of prolonged human gonadotrophin therapy (3,17). In the mid-seventies high dose LH-RH therapy was

reported to induce spermatogenesis in four of twelve hypogonadal men (12). However, less successful results have been obtained in later studies with similar therapy regimens in male hypogonadotrophic hypogonadism (1,7,9,14).

Here we report on successful treatment of three infertile men with secondary hypothalamic hypogonadotrophic hypogonadism by long-term pulsatile subcutaneous (s.c.) low dose LH-RH therapy.

CASE REPORTS

Three infertile men with secondary hypogonadotrophic hypogonadism volunteered for the pulsatile LH-RH therapy. They had passed a normal puberty and were living in stable relations with normal sexual life before they fell ill.

Patient 1, a 23-year-old man, had received radiotherapy (53 Gy) of a hypothalamic intracerebral tumour at the age of 21. After the treatment, he developed diabetes insipidus and hypogonadism due to pronounced gonadotrophin insufficiency. He was successfully substituted with DDAVP (Minirin®, Ferring GmBH, Kiel, FRG) and testosterone (Testoviron - Depot®, Schering AG, Berlin, FRG). Eighteen months after the radiotherapy, the patient and his wife were referred to our department because of infertility. His ejaculate then contained no sperms. Neuroradiological examination showed regress of the intracerebral tumour and the patient was offered LH-RH treatment. The testosterone substitution therapy was discontinued and the result was loss of ejaculation and later impotence. The patient had increased in weight from 80 kg to 105 kg during the last three years. He was 193 cm tall.

The pretreatment levels of gonadotrophins were very low: follicle stimulating hormone (FSH) 0.28 μg/l and luteinizing hormone (LH) 0.17 μg/l. The acute gonadotrophin secretory response to LH-RH (100 μg intravenously, i.v.) was very low. He had a moderate hyperprolactinaemia with a serum prolactin (PRL) level of 35 μg /l. The serum testosterone (T) level was low, 4.0 nmol/l. He had normal thyroid and adrenal function.

Patient 2, a 26-year-old man, had experienced sudden onset of diabetes insipidus followed by progressive decrease of pituitary gonadotrophic and gonadal function. Modern neuroradiological techniques did not reveal any organic desease. This patient has previously been described in detail (15). Before the LH-RH treatment, he was impotent and could not produce any ejaculate for sperm count. His weight was 75 kg and he was 179 cm tall.

The pretreatment serum levels of FSH (<0.20 μ/l) and LH (<0.16 μg/l) were below the detection limit of the assay. There was no acute gonadotrophin response to LH-RH (100 μg i.v.). The serum level of prolactin was slightly elevated, 28 μg/l.

Patient 3, a 29-year-old hypogonadal man, had noticed decreasing libido,

potency and loss of ejaculation since four years. The coitus frequency was once a month. Sexual activity was initiated by his wife. The patient had increased in weight during the last years, from 95 kg to 102 kg. His height was 186 cm. He complained of no other symptoms. The clinical examination, which included computerized axial tomography of the hypothalamic-pituitary region showed no demonstrable organic lesion.

The endocrinological examination showed low serum levels of gonadotrophins and testosterone (FSH: 0.71 µg/l, LH: 0.57 µg/l, T: 1.15 nmol/l). The gonadotrophin response was low at the pre-treatment LH-RH test (100 µg i.v.). The serum PRL concentration was normal. The thyroid and adrenal function was normal.

The reference ranges for the hormones at the time of the study were the following for men: FSH: 0.5 - 3.0 µg/l; LH: 0.4 - 3.0 µg/l (20); PRL: <15 µg/l; T: 10 - 45 nmol/l.

HORMONE ASSAY METHODS

Immunoreactive FSH and LH in serum were assayed by a radio-immunotechnique using indirectly coupled antibodies (21). PRL and T in serum were also measured with radioimmunological techniques (4,15).

LH-RH THERAPY

LH-RH was administered intermittently by means of a small automatically-timed infusion pump (Zyklomat®, Ferring GmbH, Kiel, FRG). The small pump, which the patients carried in a girdle around the waist, was connected to a chronic induelling catheter, inserted in the subcutaneous fat tissue of the lower abdominal wall. The catheter was changed approximately once every month or when local irritation occurred at the catheter site.

The pump infused 50 µl of the LH-RH solution/min every 90 min. The 26-year-old man received 1 µg LH-RH/50 µl during the first 90 days of therapy and 5 µg LH-RH/50 µl during the rest of the treatment period. The LH-RH solution contained 62.5 IU Heparin/ ml during the first 112 days of his therapy. The two other patients were treated with an LH-RH solution which contained 20 µg LH-RH/50 µl. Heparin was not used during their therapy.

The men were treated as out-patients and were seen every 10th day for supply of LH-RH solution. The LH-RH therapy was monitored by clinical examinations, sperm analyses and frequently taken peripheral venous blood samples for determinations of gonadotrophins, prolactin and testosterone. The patients kept a diary of their sexual activities during the treatment.

RESULTS

Serum concentrations of gonadotrophins, PRL and testosterone during the 250 days of consecutive pulsatile LH-RH treatment LH-RH of patient 1 are shown in Figs. 1 and 2. The serum levels of FSH and LH increased to the normal range after four days of treatment with 20 μg LH-RH s.c. every 90 min. (Fig. 1). This was accompanied by an increase of the serum T level, which reached the normal range for men after eight days of therapy. The serum concentration of T then remained within the normal range during the whole treatment period except during treatment day 95 to 120 (Fig.2). The decrease of the serum T level occurred when the LH-RH dose was reduced to 5 μg LH-RH s.c. every 90 min. The T level rapidly normalized when treatment with the higher dose of 20 μg LH-RH s.c. was resumed. The serum level of PRL varied between 30 and 50 μg/l during the whole treatment period. The serum concentration of T rapidly decreased to the very low pretreatment level when the pulsatile LH-RH therapy was discontinued.

Libido and potency returned and normalized within one month of pulsatile LH-RH treatment. The capacity of ejaculation also returned. The first ejaculate for sperm count was analysed after 21 days. It contained no sperms. With continued LH-RH treatment spermatogenesis was induced. After 65 days of therapy the ejaculate contained 90×10^6 sperms of which 50 % were mobile 2 h after ejaculation. The sperm count improved and contained 200×10^6 sperms with 60 % mobility 2 h after ejaculation on LH-RH treatment day 207. The patient's wife conceived. The pregnancy test was positive after 230 days of pulsatile LH-RH therapy. A healthy girl was born after a normal term pregnancy. Paternity tests were positive.

The patient decreased 10 kg in weight during the treatment period despite the fact that he did not start any physical training. He also noticed a marked increase in the growth of beard and body hair.

A rapid increase of both the gonadotrophins and T in serum also occurred in the 26-year-old man, who received initial treatment with 1 μg LH-RH s.c. once every 90 min. (Fig. 3). The serum level of T reached the normal range for men after one week of therapy. The testosterone level then decreased and remained low during the rest of the 1 μg LH-RH treatment period. The fall in testosterone occurred at the same time as s.c. haematomas appeared at the catheter site. The serum T concentration did not normalize until the LH-RH dose was increased to 5 μg s.c. once every 90 min and heparin was excluded from the LH-RH solution (Fig. 4). During the remainder of the pulsatile LH-RH treatment the serum T level remained well within the normal range for men. The slightly elevated PRL level was unchanged during the first 90 days of treatment and then increased somewhat.

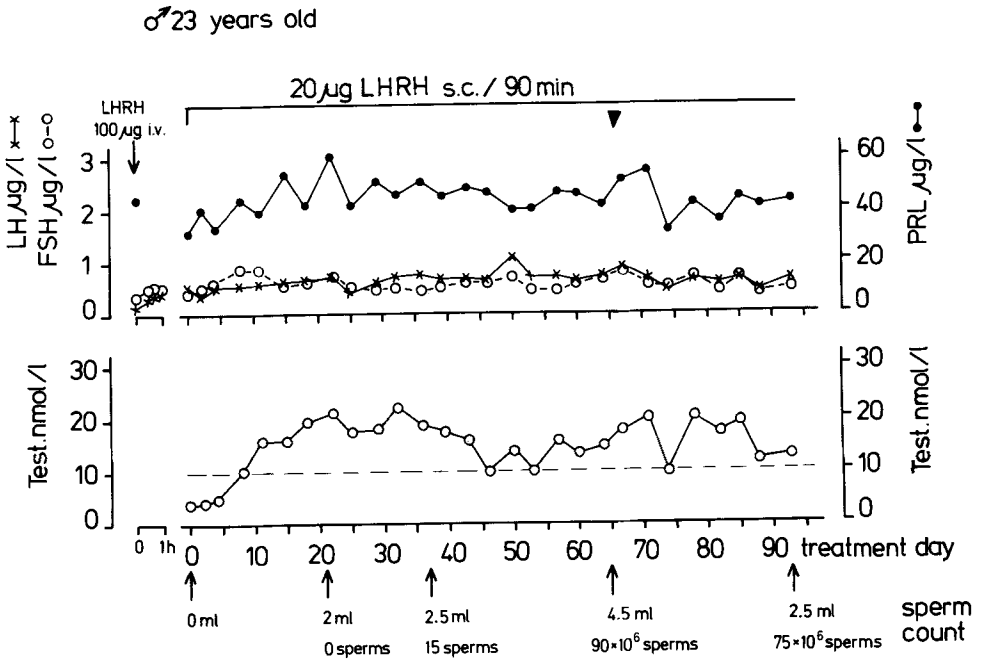

Fig. 1. Serum concentrations of FSH, LH, PRL, testosterone (test.) and sperm counts in a 23-year-old man with secondary hypogonadotrophic hypogonadism before and during 93 days of pulsatile low dose LH-RH treatment.
---- = lower limit of normal range of serum testosterone in men.

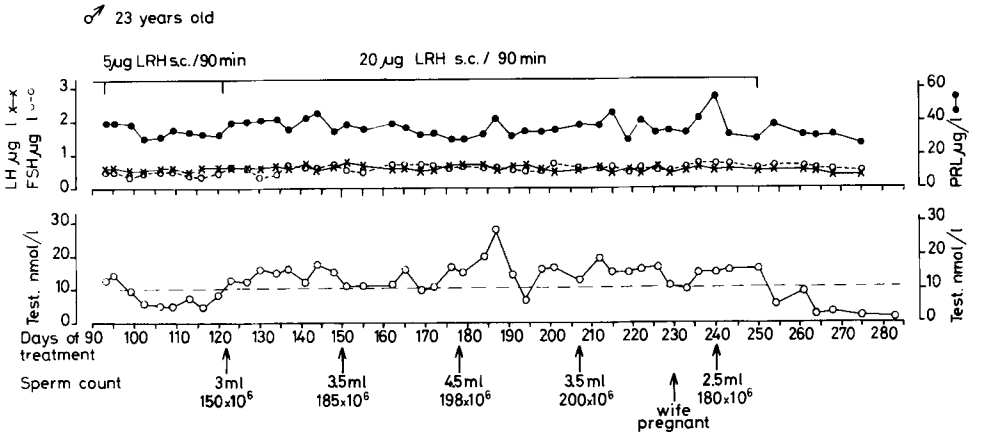

Fig. 2. Serum concentrations of FSH, LH, PRL, testostrone (test.) and sperm counts in a 23-year-old man with secondary hypogonadotrophic hypogonadism during 157 days of pulsatile low dose LH-RH treatment.
---- = lower limit of normal range of serum testosterone in men.

The first erection occurred after 8 days of LH-RH treatment and coital activity was resumed after 14 days. Spermatogenesis was induced. The first mobile sperms were found in the ejaculate after 90 days. The sperm count improved and his wife's pregnancy test became positive after 181 days of LH-RH therapy. The pregnancy was normal and a healthy girl was born at term. Paternity tests were positive.

The prolonged pulsatile LH-RH treatment was well accepted by the patient. He could maintain his daily life activities and resumed his physical training including soccer playing and jogging.

The 29-year-old man has until now received four months of pulsatile s.c. LH-RH therapy with 20 µg LH-RH once every 90 min. During the first days of therapy there was a marked increase of the serum gonadotrophin levels. The FSH secretion increased to a maximal level of 2.5 µg/l on treatment day 7. On the same day the increasing serum T level reached the normal range for men. The serum concentration of T has stabilized around 30 nmol/l. The PRL level is still within the normal range.

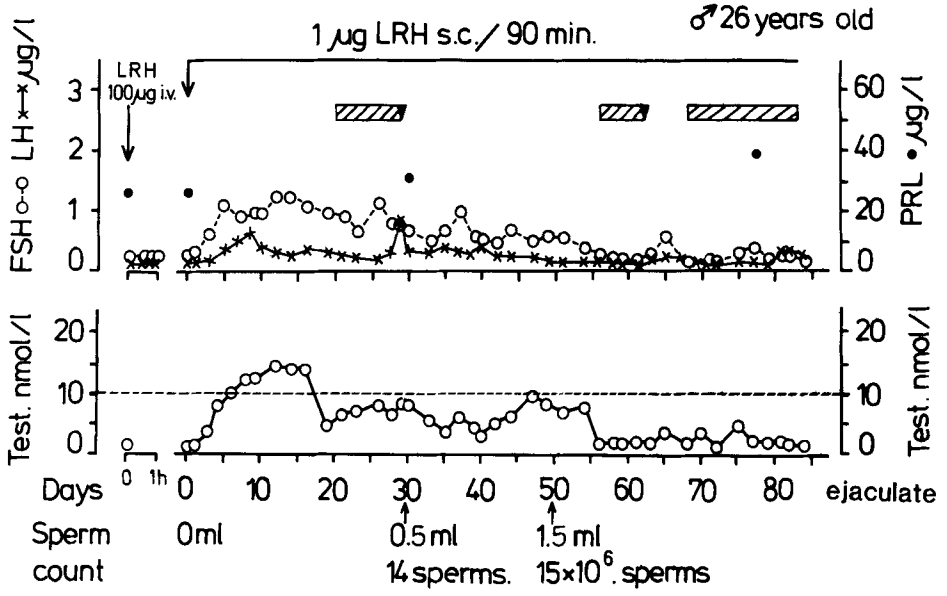

Fig. 3. Serum concentrations of FSH, LH, PRL, testosterone (test.) and sperm counts in a 26-year-old man with secondary hypogonadotrophic hypogonadism before and during 85 days of pulsatile low dose LH-RH treatment. ▨ = subcutaneous haematoma at catheter site; ▼ = change of s.c. catheter; ---- = lower limit of normal range of testosterone in men. Reproduced from Skarin et al. (15), with permission.

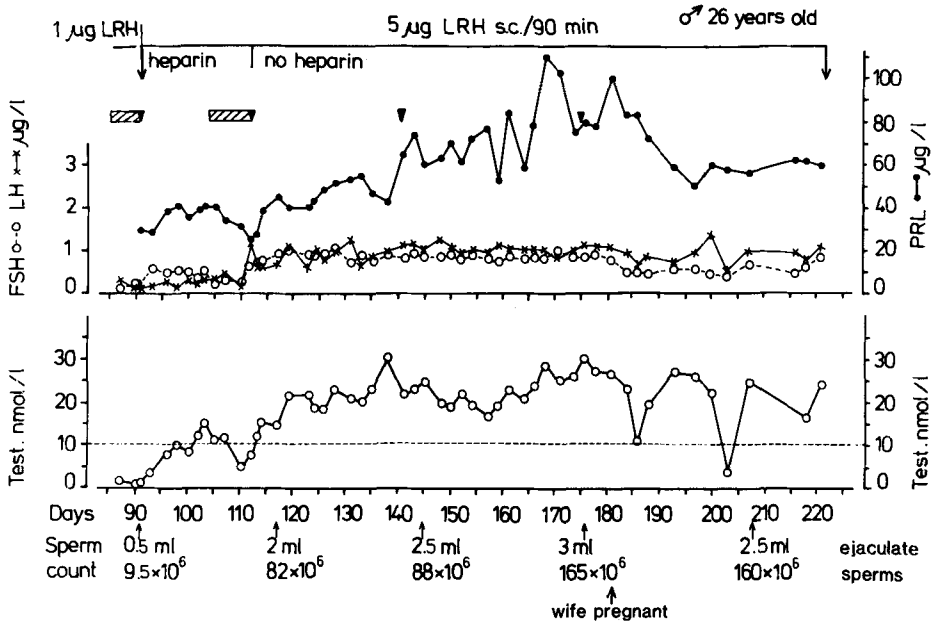

Fig. 4. Serum concentrations of FSH, LH, PRL testosterone (test.) and sperm counts during 135 days of pulsatile low dose LH-RH treatment of a 26-year-old man with secondary hypogonadotrophic hypogonadism.
▨ = subcutaneous haematoma at catheter site; ▼ = change of s.c. catheter; ---- = lower limit of normal range of serum testosterone in men. Reproduced from Skarin et al. (15), with permission.

The pulsatile LHRH treatment resulted in a marked increase in libido. After three weeks of therapy the patient and his wife had reestabliched their normal coital frequency (2 - 3 coitus weekly). Ejaculations returned and spermatogenesis was induced. No sperms were found in the first ejaculates. After 60 days of LH-RH treatment the ejaculate contained 50 x 10^6 sperms with 60 % mobility 4.5 h after ejaculation.

The patient's physical and his mental well-being improved. His general physical activity increased and he decreased 8 kg in weight.

DISCUSSION

Chronic pulsatile s.c. administration of low doses of LH-RH proved to be a very effective therapy for the three infertile men with secondary hypogonadotrophic hypogonadism. Their gonadal function rapidly normalized with testosterone production and spermatogenesis. Two of the men fertilized their wives after 6 and 7.5 months of pulsatile LH-RH treatment, respectively. The third man has until now been treated for only 4 months. The subcutaneous route of

LH-RH administration was safe and well accepted by the patients during the prolonged treatment periods. The only adverse effect was s.c. haematomas which appeared in one patient. This complication ceased to occur when heparin was excluded from the LH-RH solution. The men continued their daily life activities and even resumed physical training during the pulsatile s.c. LH-RH treatment.

The low s.c. dose of 1 μg LH-RH every 90 min, which was used initially in one of our patients, was similar to that used i.v. in hypogonadotrophic men by Valk et al. (19). Because of low serum T level after 90 days of treatment the LH-RH dose was increased to 5 μg s.c. every 90 min. In this patient the 5 μg dose resulted in normal serum T concentrations during the remainder of the therapy. The other two men received an LH-RH dose of 20 μg s.c. every 90 min. In one of them reduction of the dose to 5 μg LH-RH resulted in decreasing serum levels of T. Thus, there seems to be an individual variation in the optimal LH-RH dose.

It is interesting to notice that the gonadal function normalized in the two men with moderate hyperprolactinaemia. This gives indirect evidence that the sexual difficulty in hyperprolactinaemic males is mediated through deranged LH-RH secretion and not through direct gonadal effects. Similar conclusions were drawn from studies of hypogonadal men with prolactin-secreting pituitary tumours (2,13).

We have previously shown that chronic pulsatile s.c. low dose LH-RH treatment can restore fertility in a hypogonadal man with secondary hypogonadotrophic hypogonadism (15). Furthermore, reports of successful induction of male puberty with similar treatment regimens have recently appeared (5,8,16). This study confirms that s.c. long-term pulsatile administration of low doses of LH-RH is a very promising new treatment to restore normal gonadal function with testosterone production and spermatogenesis in most of those infertile men who have previously required human gonadotrophin therapy.

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