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Serum Levels of Follicle-Stimulating Hormone and Luteinizing Hormone After Subcutaneous Administration of Human Menopausal Gonadotropin During Pituitary Suppression

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ABSTRACT: Objective—The present study investigated the pharmacokinetics of a single subcutaneous dose of human menopausal gonadotropin (hMG) on serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations. **Subjects and Methods**—Six healthy female volunteers, aged 20–40 years, with regular menstrual cycles and normal endocrine profiles, who were not receiving any hormonal medication, were treated with the gonadotropin-releasing-hormone agonist buserelin to suppress endogenous gonadotropin release. One volunteer dropped out during treatment. When the serum estradiol concentration had fallen to below 500 pmol/L, an injection of 150 IU hMG (Humegon[®]) was given subcutaneously. Immediately before injection and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15, 20, 24, 48 and 96 hours after, blood samples were drawn for determination of FSH and LH concentrations. **Results**—The baseline FSH level was 2.8 IU/L, and peak concentration (6.8 IU/L) was reached 12 hours after hMG injection (median values). Exogenous LH could not be measured because of the presence of endogenous LH. **Discussion**—The pattern of serum FSH concentrations after a single injection of hMG was found to resemble that seen after intramuscular hMG administration, although the peak FSH value was reached somewhat later. *Int J Fertil* 40(6):307-310, 1995

KEY WORDS: human menopausal gonadotropins (hMG), subcutaneous administration, pharmacokinetics, FSH, LH, ovarian stimulation, recombinant hMG

INTRODUCTION

GONADOTROPIN PREPARATIONS, SUCH as human menopausal gonadotropin (hMG), are usually administered via the intramuscular (i.m.) route. The recent development of gonadotropin preparations of high purity, especially recombinant human follicle-stimulating hormone (FSH), makes possible subcutaneous (s.c.) adminis-

tration. Compared with i.m. administration, s.c. injections are less painful, and self-administration by the patient is more feasible.

The most appropriate dosage interval for s.c. administration is not known, since information is sparse regarding the pharmacokinetics of exogenous FSH and luteinizing hormone (LH) after s.c. gonadotropin injection. We therefore decided to study the effect of a single s.c. hMG injection on

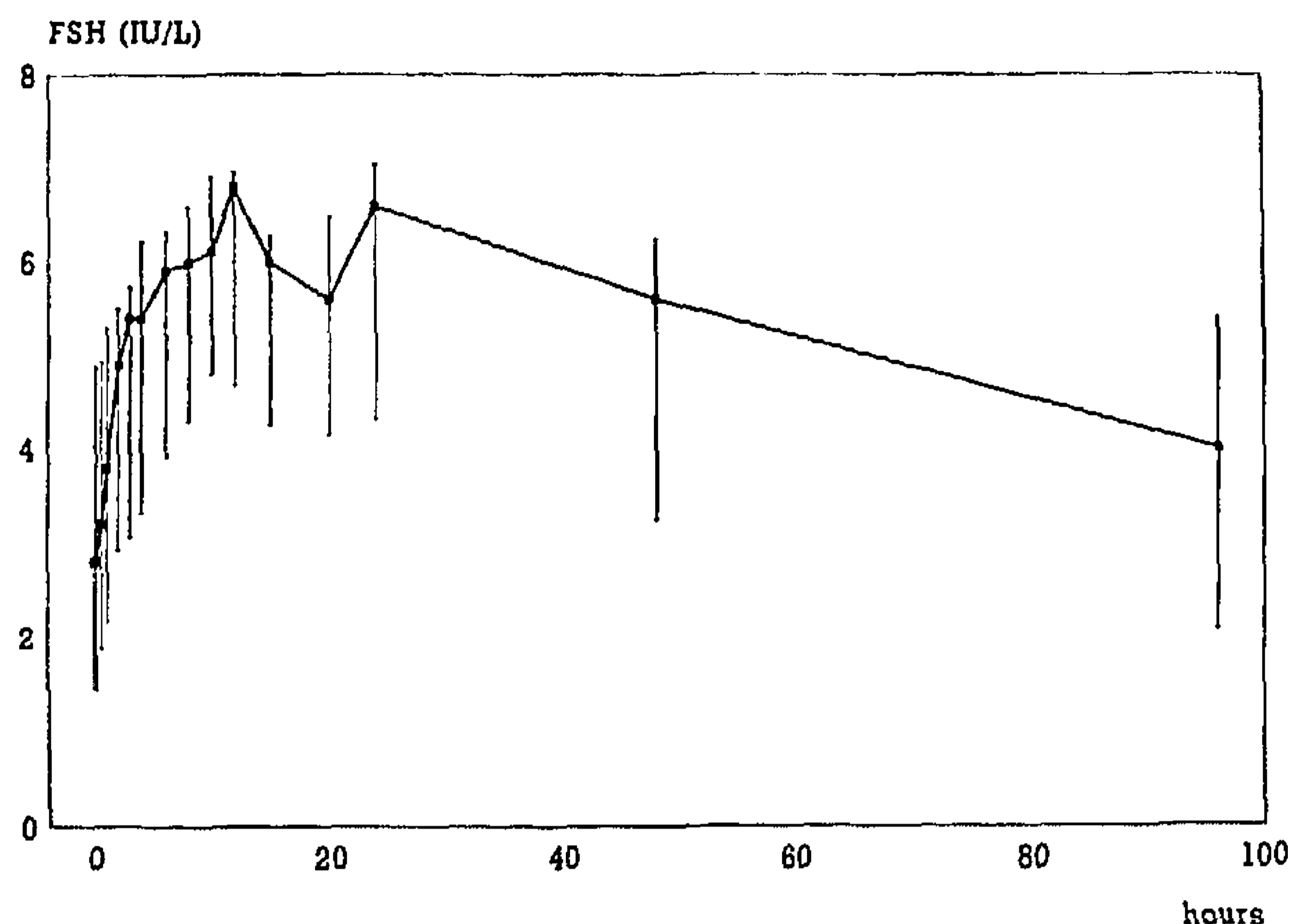


FIG. 1. Median serum follicle-stimulating hormone (FSH) concentrations and 10th and 90th percentiles after a single subcutaneous injection of 150 IU human menopausal gonadotropin during pituitary suppression by buserelin, in five female volunteers.

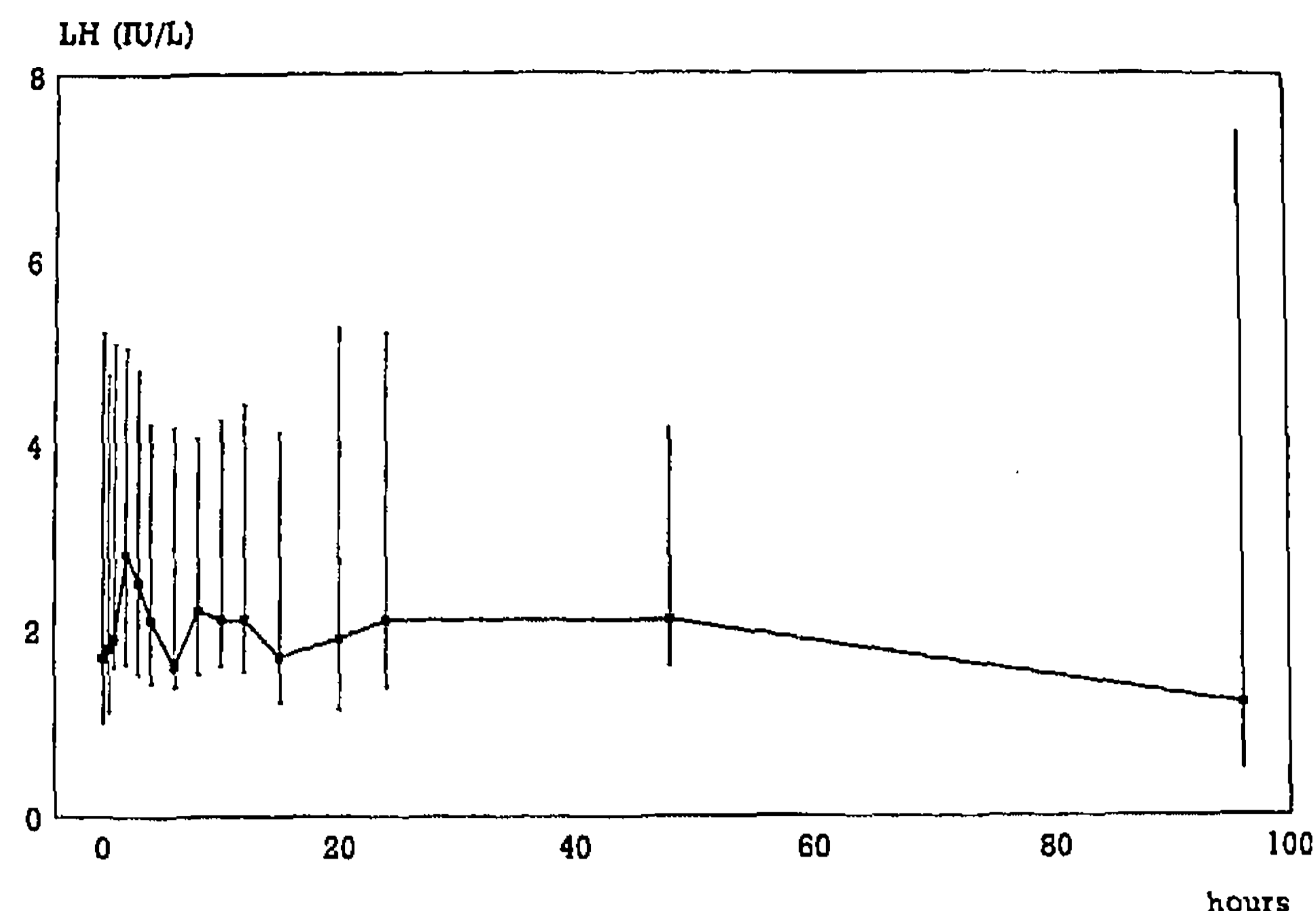


FIG. 2. Median serum luteinizing hormone (LH) concentrations and 10th and 90th percentiles after a single subcutaneous injection of 150 IU human menopausal gonadotropin during pituitary suppression by buserelin, in five female volunteers.

serum FSH and LH concentrations in female volunteers. Since the presence of high levels of endogenous FSH and LH complicates interpretation of the results, pituitary function was suppressed by administering the gonadotropin-releasing-hormone (GnRH) agonist buserelin.

MATERIALS AND METHODS

Six female volunteers participated in the study. The inclusion criteria were as follows: age 20–40 years, a regular menstrual cycle (between 24 and 35 days), a normal endocrine serum profile in the early follicular phase of the cycle (FSH concentration below 8 IU/L, LH/FSH ratio less than 3, testosterone concentration below 2.5 nmol/L, prolactin concentration below 750 mIU/L, and thyroxine concentration between 58 and 148 nmol/L) and no intake of hormonal medication, including oral contraceptives, for at least 3 months prior to the study. The median age of the five volunteers who completed the study was 29 years (range 29–38 years) and the median body mass index was 20.4 kg/m² (18.4–27.3 kg/m²).

All the women were treated with the GnRH-agonist buserelin (Suprefact[®] nasal spray, Hoechst A.G., Frankfurt, Germany) at a dose of 300 µg three times a day, from day 21 of the previous menstrual cycle

onwards. On day 10 of the buserelin treatment, the serum 17β-estradiol concentration was determined and then measured every three or four days until it was below 500 pmol/L. One volunteer dropped out during the buserelin treatment because of sinusitis and nasal bleeding. As soon as the estradiol concentration was found to be below 500 pmol/L, a single subcutaneous injection of 150 IU Humegon[®] (NV Organon, Oss, The Netherlands) was given the next day at 8 a.m. and the buserelin treatment was continued. Two ampules of Humegon were diluted in 0.5 mL solvent and injected subcutaneously in the abdomen using a syringe injector (Monoject[®], Sherwood Medical, St. Louis, USA). Each ampule contains 75 IU FSH and 75 IU LH activity, as determined by *in vivo* bioassays. Due to inherent inaccuracy of bioassays, results of determinations are within 80–125% of stated activity. One batch of Humegon was used for the study.

Blood samples were collected, either by venipuncture or via an intravenous cannula, immediately before injection and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15, 20, 24, 48 and 96 hours after. Buserelin administration was stopped after the last blood samples were taken. The samples were centrifuged within three hours after collection and serum was frozen at -20°C until assayed.

The serum estradiol concentration on the tenth

day of buserelin treatment was determined by a time-resolved fluoroimmunoassay (Delfia[®], Wallac Oy, Turku, Finland). The limit of 500 pmol/L was chosen because of the low sensitivity of the assay in the range from 150 to 500 pmol/L. The estradiol concentration immediately before the hMG injection was measured retrospectively by a more sensitive radioimmunoassay [1]. FSH and LH concentrations were determined in all serum samples by immunoradiometric assays (IRMAs), as previously described [2].

Statistical analysis was performed using the Wilcoxon signed-rank test.

RESULTS

The median estradiol concentration immediately before the hMG injection, as measured by radioimmunoassay, was 88 pmol/L (range <75–390 pmol/L). The median values of the FSH and LH concentrations and the 10th and 90th percentiles, before and after Humegon[®] injection, are shown in Figures 1 and 2, respectively. The median FSH concentration before injection was 2.8 (10th percentile (p₁₀) 1.4 IU/L; 90th percentile (p₉₀) 4.9 IU/L). Median FSH concentrations started to increase within the first half-hour after injection and reached a maximum value of 6.8 IU/L (p₁₀ 4.7 IU/L; p₉₀ 7.0 IU/L) after 12 hours (p₁₀ 10 hours; p₉₀ 12 hours), the increase being statistically significant ($P < .05$). Serum LH concentrations remained at a low level throughout the study. A small increase in median LH concentrations was seen in the first two hours after the Humegon injection, but there was great interindividual variation and the increase was not statistically significant.

The subcutaneous injections were well tolerated. Two patients experienced transient pain at the injection site, starting 7 and 10 hours after injection, respectively, and lasting for a few hours. In one of these two patients the injection site showed redness without swelling (diameter of red area 1 to 2 cm). The symptoms were not severe in either case.

DISCUSSION

Subcutaneous administration of 150 IU hMG leads to an increase in serum FSH concentrations, reaching a peak approximately 12 hours after injection

and gradually decreasing thereafter. In a previous study of similar design, the effect of a single i.m. or i.v. injection of 150 IU hMG on serum FSH and LH levels was described [3]. The increase in serum FSH levels after i.m. injection of hMG showed a substantially similar pattern to that following s.c. injection, although the peak concentration seemed to occur somewhat earlier (8 hours after i.m. injection as against 12 hours after s.c. injection).

In a study by Le Cottonnec et al [4], serum FSH concentrations were determined in male subjects after single i.m. and s.c. injections of 150 IU highly purified urinary FSH (Metrodin HP[®]). These investigators found similar patterns of FSH concentrations after s.c. and i.m. administration, with maximum concentrations occurring 13 and 18 hours after i.m. and s.c. injection, respectively. In a study by Saal et al [5], pharmacokinetic parameters were described after single s.c. and i.m. injections of human chorionic gonadotropin (hCG) in male subjects. Serum hCG concentrations reached a peak value 6 and 16 hours after i.m. and s.c. injection, respectively, the half-lives being 31 ± 3 and 38 ± 3 hours. The authors concluded that diffusion of hCG into the circulation was slower after s.c. administration. These investigations differed from ours as regards the groups studied (male instead of female subjects) and the preparations administered (highly purified FSH and hCG instead of hMG). Nevertheless, serum concentrations showed a slightly slower and more prolonged increase after s.c. administration than after i.m. administration in all studies.

Serum LH concentrations were insufficiently suppressed to enable measurement of exogenous LH. There was great interindividual variation in the serum LH profiles and no clear pattern could be seen.

In the present study, a single s.c. hMG injection was well tolerated by all subjects. Repeated s.c. injections with hMG might induce local skin reactions, such as swelling, redness or induration, since the urine-derived hMG preparations are of low purity and contain a large number of non-gonadotropin proteins [6]. However, a recombinant human FSH preparation of very high purity has been developed recently [7]. In contrast to hMG, recombinant human FSH should be very suitable for daily s.c. administration.

Since the FSH profile after s.c. injection showed that serum concentrations remained adequate over a period of 24 hours, subcutaneous gonadotropin

injections can presumably be given once daily. This assumption is supported by the findings of Howles et al [8], who treated in vitro fertilization patients with a highly purified urinary FSH preparation which was administered once daily subcutaneously. This treatment schedule was found to be effective in stimulating multiple follicular development. The injections were also well tolerated. A pharmacokinetic study now needs to be carried out to measure serum FSH concentrations after repeated s.c. gonadotropin injections.

It may be concluded from the results of the present study that once-daily subcutaneous administration of gonadotropins induces adequate serum concentrations of FSH and LH.

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