OVARIAN RESPONSE TO EXCESSIVE DOSES OF HUMAN MENOPAUSAL GONADOTROPHIN IN TWO PATIENTS WITH PRIMARY PITUITARY INSUFFICIENCY

By
Vagn Sele and Jørgen Starup

ABSTRACT

Two patients with primary pituitary insufficiency were treated with excessive doses of HMG only for 10 and 14 days. The total dose was 3360 IU and 6320 IU FSH, respectively. The excretion of total oestrogens and pregnanediol was determined daily before, during and after the treatment. Furthermore, the excretion of total gonadotrophins was determined on a few occasions after the treatment with HMG was discontinued.

It was confirmed that patients with primary pituitary insufficiency need a high dose of HMG (800 IU and 2560 IU FSH) before any oestrogen is excreted.

In spite of the extreme stimulation and the resulting high oestrogen excretion, the ovaries were not enlarged at any time during the observation period. It is concluded that the administration of both HMG and HCG is necessary for the development of a hyperstimulation syndrome.

Furthermore, it was shown that the excretion of oestrogens continued to increase for a couple of days after the treatment with HMG was stopped. At the same time it was found that the excretion of total gonadotrophins remained elevated for about 8–10 days after the last dose of HMG had been given. These findings indicate that HMG has a prolonged effect.

Therefore, it has been proposed to change the commonly used scheme of treatment with HMG-HCG in such a manner that HGG is given 2–3 days after the last dose of HMG in order to reduce the risk of hyperstimulation.

The observation of Johannisson et al. (1961) that the excretion of oestrogens in women with amenorrhea is increased significantly and reaches a peak 10–13 days after the administration of a single dose of HPG (human pituitary...
gonadotrophin), may be explained in one of the three following ways: 1) that the follicle, once sufficiently stimulated, continues to grow independently, 2) that the exogenous FSH (follicle stimulating hormone) is taken up by the ovarian tissue and persists there during the growth of the follicle, or 3) that the endogenous secretion of FSH is capable further to stimulate the growth of the follicle, once it has been stimulated, since the exogenous FSH is rapidly eliminated from the circulation and no longer present in the urine in two to six days (Johannisson et al. 1961; Apostolakis et al. 1962).

The clinical experience that patients with amenorrhoea without any detectable endogenous secretion of gonadotrophins need a higher dose of HPG in order to be stimulated (Gemzell & Roos 1966), indicates a synergism between the exogenous and the endogenous FSH.

The finding of Rabau et al. (1967) that the hyperstimulation syndrome is never seen following treatment with HMG (human menopausal gonadotrophin) only, even if the oestrogen excretion exceeds 300 µg/day, indicates that HCG (human chorionic gonadotrophin) is an essential factor for the development of a hyperstimulation syndrome during HMG-HCG treatment. Crooke et al. (1966) believe that the dose of FSH is the principal factor in the production of the hyperstimulation syndrome, and that the dose of HCG is fairly unimportant in this respect. However, Shearman (1969) may be right in saying that HMG may load the gun, but it takes HCG to pull the trigger.

The purpose of the present investigation is further to elucidate some of the above mentioned problems.

MATERIAL AND METHODS

The material consists of two patients with primary hypogonadism, i.e. at the age of 18 years they had primary amenorrhoea, undeveloped secondary sex-characteristics, and retardation of the bone-age. Furthermore, both patients had a urinary excretion of total gonadotrophins of less than 3 MUU/day as determined by the method of Johnsen (1958), while the oestrogen excretion was 0 µg/day (Brown et al. 1968).

Case no. 1 (MSP)

26 years old. Seen in the department for the first time when 18 years old because of primary amenorrhoea and infantilism. Two years earlier treated with HCG 1500 IU X 10 without any effect. Height: 157 cm. Weight: 53 kg. Karyotype: 46/XX. Severe hypogonadism with undeveloped breasts, scanty secondary growth of hair, and infantile external and internal genitalia.

The excretion of both total gonadotrophins and total oestrogens, determined biologically, was on several occasions undetectable. The function of the adrenals and the thyroid was normal. Bone-age (Greulich & Pyle 1959): 13–14 years.

Exploratory laparotomy showed a small uterus (3 X 3 X 3 cm) and small ovaries (1/2 X 1 X 4 cm). Ovarian biopsies revealed many unstimulated primordial follicles, no follicles in development and no corpora lutea.
At the age of 20 substitution therapy with cyclically administered oestrogen-gestagen was initiated, and during this treatment vaginal bleeding occurred, and a fair development of the secondary sex-characteristics occurred. The treatment with oestrogen-gestagen was stopped 8 months before the treatment with HMG was started, and it was confirmed that the excretion of total gonadotrophins was still less than 3 MUU/day.

Case no. 2 (LP)
23 years old. Seen in the department for the first time when 22 years old because of primary amenorrhoea and undeveloped secondary sex-characteristics. Two years before admittance she had been treated cyclically with oestrogen-gestagen for nearly one year. During this substitution therapy vaginal bleeding occurred, and some development of the secondary sex-characteristics took place. Furthermore, this patient had been treated elsewhere with PMG (pregnant mares’ gonadotrophin) and HCG on two occasions without any effect.

Height: 168 cm. Weight: 61 kg. Karyotype: 46/XX. Slightly developed secondary sex-characteristics and slightly infantile genitalia.

The excretion of both total gonadotrophins and total oestrogens was undetectable at repeated determinations. The function of the adrenals and the thyroid was normal. Bone-age (Greulich & Pyle 1959): 18 years.

For a short period sequential therapy with oestrogen-gestagen. During this treatment vaginal bleeding occurred. The oestrogen-gestagen treatment was discontinued one month before the treatment with HMG was initiated, and it was confirmed that the excretion of total gonadotrophins was still less than 3 MUU/day.

Both patients received excessive doses of HMG* starting with 160 IU of FSH daily, and then with gradually increasing doses as shown in Figs. 1 and 2. In case no. 1 the total dose of FSH was 3360 IU and in case no. 2 it was 6320 IU. The treatment with HMG was not followed by treatment with HCG.

The urinary excretion of total oestrogens (Brown et al. 1968) and pregnanediol (Klopper et al. 1955) was determined daily before, during and after the treatment with HMG. Moreover, the excretion of total gonadotrophins (Johnsen 1958) was determined on a few occasions in both patients after cessation of treatment. Finally, both patients had a pelvic examination every day during the whole observation period in order to determine the size of the ovaries and the amount of cervical mucus.

**R E S U L T S**

Figs. 1 and 2 show the daily urinary excretion of total oestrogens and pregnanediol in the two patients before, during and after treatment with HMG.

In case no. 1 (Fig. 1) the pre-treatment value of total oestrogens was 0 µg/day. HMG was then administered daily in increasing doses for a period of 10 days. On day 4, after a total dose of 800 IU FSH, the excretion of oestrogens began to increase. At the end of the treatment period the oestrogen excretion was 167 µg/day, but the increase in the oestrogen output continued,

* The FSH/LH ratio of this HMG-preparation is nearly 1.
and an excretion of 460 μg/day was found on day 15, i.e. five days after the last dose of HMG was given. From day 15 the oestrogen excretion decreased until a value of 0 μg/day was found again on day 26. The excretion of pregnanediol was almost unchanged during the observation period with a maximum value of 1.1 mg/day on day 12. Finally, the excretion of total gonadotrophins was 7 MUU/day on day 19 and less than 3 MUU/day on day 24. In spite of the excessive dose of HMG and the high oestrogen level, the ovaries were not found to be enlarged at any time during the observation period.

In case no. 2 (Fig. 2) the pre-treatment value of total oestrogens was also
Urinary excretion of total oestrogens, pregnanediol and total gonadotrophins in a 23 years old patient with primary pituitary insufficiency before, during and after treatment with HMG.

0 µg/day. This patient received HMG daily in increasing doses for a period of 14 days. On day 9, after a total dose of 2560 IU FSH, the excretion of oestrogens began to increase. At the end of the treatment period the oestrogen excretion was 462 µg/day, but the increase in the oestrogen output continued, and an excretion of 933 µg/day was found on day 16, i.e. two days after treatment with HMG was discontinued. From day 16 the oestrogen excretion decreased until a value of 0.3 µg/day was found on day 26. In this patient too the excretion of pregnanediol showed only small changes during the observation period with a maximum value of 1.4 mg/day on day 16. Unfor-
fortunately, in this patient the excretion of total gonadotrophins was only determined on day 19, when a value of 29 MUU/day was found. No enlargement of the ovaries was found at any time during the observation period in spite of the very high oestrogen levels attained in this patient.

**DISCUSSION**

The effect of exogenous human gonadotrophins on the ovaries is most clearly demonstrated in patients with primary pituitary insufficiency, since these patients do not have any detectable endogenous secretion of gonadotrophins, which may interfere with the action of the administered gonadotrophins. The site of the lesion in the so-called primary pituitary insufficiency is not known, but many facts indicate that it is probably a defect in the hypothalamo-pituitary system. Thus for instance, it is known that ovarian biopsies from these patients show numerous, but unstimulated follicles, and it is also well documented that treatment with gonadotrophic hormones in these patients will very often result in ovulation, and that pregnancy may occur.

In the present study two patients with primary pituitary insufficiency were treated with increasing doses of HMG only for a period of 10 and 14 days. The total dose was 3360 IU and 6320 IU FSH, respectively. In spite of this extreme stimulation and the resulting high excretion of oestrogens in the urine with a maximum of 460 μg/day and 933 μg/day, the patients did not show any enlargement of the ovaries during the observation period. This is in good agreement with the statement of Rabau et al. (1967) that the hyperstimulation syndrome is never seen following treatment with HMG only, even when the oestrogen excretion is very high. On the other hand, we have never seen development of a hyperstimulation syndrome, when patients with anovulation were treated with HCG only. It is therefore reasonable to conclude, that administration of both HMG and HCG is necessary for the development of this syndrome, even if HMG is probably the principal factor (Crooke et al. 1966).

Our investigation confirmed the finding of Gemzell & Roos (1966) that patients with primary pituitary insufficiency need high doses of exogenous gonadotrophins to be stimulated, but also that in these patients there seems to be a great individual variation in the response, probably due to differences in the sensitivity of the ovaries.

Another interesting finding in the present study was that the excretion of total oestrogens continued to increase for 5 and 2 days respectively after the administration of HMG was discontinued, and then the excretion gradually decreased for the next 10–11 days, until the pre-treatment level was reached again. Furthermore, we were able to demonstrate the excretion of total
gonadotrophins in the urine for about 8–10 days after the last dose of HMG had been given. These findings indicate that the further increase in the oestrogen excretion after treatment with HMG is discontinued is due to and can fully be explained by a prolonged effect of the exogenous administered FSH. Because of this prolonged effect of HMG it should be considered whether it is desirable to change the commonly used scheme for treatment with HMG-HCG, where HCG is given immediately after the last dose of HMG. Probably, it would be a better idea after the last dose of HMG, to wait for 2 or 3 days and then follow the course of the oestrogen excretion curve before HCG is given. If HCG is then only administered in those cases in which the oestrogen excretion does not exceed 150 μg/day, we believe that the number of cases with severe hyperstimulation could be considerably reduced.

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REFERENCES


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