Menogon®

Menotropin (HMG)

What the Papers Say

Hypogonadotropic hypogonadism

"In treating this group of patients, the superior efficacy of hMG compared with purified FSH preparation is beyond question"[4].

IVF after pituitary desensitization

"The fertilization rate on hMG was 60% and on pure-FSH was 55%"[5].

Oocyte donation

"The fertilization rate (2PN/cell) was significantly higher in the HMG group (48%, 170/355) than the FSH-HP group (36%, 109/304) (P<0.01)"[6].

IVF in down regulated normogonadotrophic women

"The mean fertilization rate was significantly (P<0.05) higher in the HMG group (56%) than the HP-FSH group (50%)..."[3]

"In conclusion, no detrimental effect of the LH activity of HMG on the clinical outcome of IVF in GnRHa down-regulated normogonadatrophic women was found"[3].

ABBREVIATED PRESCRIBING INFORMATION

MENOGON

Menotropin (human menopausal gonadotropin) for intramuscular administration. Presentation: Menogon is presented as a sterile freeze-dried powder in an ampoule, containing 75 i.u. menotropin BP. The freeze-dried powder also contains lactose and sodium hydroxide. Each ampoule is supplied with a diluent ampoule of sodium chloride solution for injections 0.9% w/v. **Indications:** Menogon is used: In the treatment of female infertility in the following groups of patients: •Infertility in women with hypo- or normogonadotropic ovarian insufficiency: stimulation of follicle growth. **Dosage and administration: Female infertility:** The dosage of HMG to induce follicle growth in normo- or hypogonadotropic women differs individually. The quantity required depends on ovarian reaction and should be monitored by ultrasonography of the ovaries and by measuring estradiol levels. If the HMG dosage is too high for the treatment individual, multiple, uni- or bilateral follicle growth can occur. Generally, HMG treatment is started with a daily dosage of 75-150 i.u. FSH plus 75-150 i.u. LH applied i.m. If the ovaries do not respond, the dosage can be gradually increased until either an increase of the estradiol secretion or follicle growth can be ascertained. The HMG dosage is maintained until the preovulatory estradiol serum level is reached. To induce ovulation, 5000 or 10000 i.u. HCG are injected one or two days after the last HMG application. Apart from large fluctuations during various treatment cycles of the same patient, a marked variation also exists between different patients in regard to the ovarian response to gonadotropins. In order to achieve a high pregnancy rate and to avoid hyperstimulation of the ovaries, a thorough monitoring of the treatment is necessary. Parameters for the control of the ovarian reaction can be: the cervical score according to Insler, the estradiol measurement of the serum or the urine as well as ultrasonographical examinations of the follicle size. **Contraindications:** Pregnancy, enlargement of the ovaries or cysts not due to polycystic ovarian syndrome, gynaecological bleeding of unknown cause, tumors in the uterus, ovaries, breasts, or testes, carcinoma of the prostate, structural abnormalities in which a satisfactory outcome cannot be expected, for example, tubal occlusion unless superovulation is to be induced for IVF, ovarian dysgenesis, absent uterus or premature menopause. **Precautions:** The following conditions should be properly treated and excluded as the cause of infertility before menotropin therapy is initiated: dysfunction of the thyroid gland and cortex of the suprarenal gland, hyperprolactinaemia, primary ovarian failure and tumors in the pituitary or hypothalamic glands. Ovarian hyperstimulation syndrome may develop in some cases. Female patients should be informed before therapy that treatment with a HMG dosage too high for the individual may lead hyperstimulation of the ovaries. In case of a moderate hyperstimulation (Grade I) with slight enlargement of the ovaries (size: 5-7 cm), excessive steroid secretion, and abdominal pain, no therapy is required, but the patient should be informed and monitored thoroughly. In case of hyperstimulation Grade II with ovarian cysts (size of ovary: 7-10 cm), abdominal pain, nausea and vomiting, clinical supervision and symptomatic treatment, if necessary an intravenous volume replacement is indicated should an increased haemo concentration prevail. In case of severe hyperstimulation (Grade III) with large ovarian cysts (ovary size more than 10 cm) accompanied by ascites, hydrothorax, distended abdomen, abdominal pain, dyspnoea, salt retention, increased haemo concentration and blood viscosity, and increased thrombocyte aggregation with the danger of thromboembolism, hospitalization is imperative. **Side effects:** Treatment with menotropin can often lead to ovarian hyperstimulation. This, however, mostly becomes clinically relevant only after hCG has been administered to induce ovulation. Treatment with HMG can often lead to a hyperstimulation of the ovaries which, however, mostly becomes clinically relevant only after application of HCG to trigger ovulation. This can lead to the occurrence of large ovarian cysts, which tend to rupture, and can cause intra abdominal bleeding. Furthermore ascites, hydrothorax, oliguria, hypotension, and thromboembolic phenomena can occur. As soon as first symptoms of hyperstimulation, such as abdominal pain and palpable enlargement in the lower abdomen, appear and are sonographically detectable, the treatment should immediately be discontinued. When a woman becomes pregnant, these side effects can intensify, be longlasting and life threatening. Unintentional multiple pregnancies occur more often during treatment with HMG. Occasionally, treatment with HMG is accompanied by nausea and vomiting. In single cases, patients may show hypersensitivity to HMG like a rash, fever or pain at the injection site. In very rare cases, long term application can cause the formation of antibodies so that no success is achieved by the therapy. **Pharmaceutical precautions:** Store at a temperature not exceeding 25 C, protected from light. **Package quantities:** 10 colorless glass ampoules of Menogon packaged together with 10 ampoules of sodium chloride solution for injections 0.9 % w/v. **Date:** June 1998.

References: 1) Gordon UD et al ESHRE 1997; Abstract P-112. **2)** Gordon UD et al ESHRE 1997; Abstract P-108. **3)** Westergaard LG et al Hum Reprod 1996; 11 (6):1209-1213. **4)** Shoham Z et al Fertil Steril 1991; 56 (6):1048-1053. **5)** Bentick B et al Fertil Steril 1988; 50 (1):79-84. **6)** Söderström-Anttila V Hum Reprod 1996; 11 (9): 1864-1870.

FERRING PHARMACEUTICALS

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This product may not be available in all countries.

1.0 Introduction

The hypothalamic-pituitary-ovarian functional unit is characterized by a cycle of approximately 28 days which in turn consists of a follicular and a luteal phase. Under the influence of the gonadotrophins FSH (follicle stimulating hormone) and LH (luteinizing hormone), which are produced in the pituitary gland, the follicular maturation, the ovulatory, and the luteal phase take place. The hypothalamus and the pituitary gland are influenced by the maturing follicle via its main product estradiol as well as by the corpus luteum which produces progesterone (fig.1).

During the follicle-maturation phase the endometrium undergoes an estrogen-dependent proliferation. Ovulation, which is brought about by the mid-cycle-LH surge (1), marks the transition to the luteal phase which is characterized by progesterone production of the corpus luteum and by the secretory activity of the endometrium.

The follicle complex consists of theca interna, theca externa, granulosa cell layer, and oocyte passes through certain stages of growth. The differentiation of the granulosa cells is characteristic for follicular development. This process is still independent of gonadotrophins and is controlled by so far unknown intra-ovarian factors. Follicular growth becomes gonadotropin-dependent only at the time of transition of the primary follicle to the antral follicle; thereafter, the gonadotrophins are necessary for the remainder of the follicle's maturation (2, 3).

Specific receptors on the surface of theca and granulosa cells convey the effect of the gonadotrophins.

While LH receptors appear on the surface of the theca and later also on the surface of the granulosa cells, FSH receptors can only be found on granulosa cells (2, 3). Therefore androgen production is stimulated mainly by theca cells, whereas the stimulation of aromatase - an enzyme system which transforms androgens into estrogens -is caused by FSH in granulosa cells (fig. 2) (4, 5, 6). In addition, FSH stimulates the division of granulosa cells and the appearance of LH receptors on their surface. Thus, the granulosa cells of the preovulatory follicle can react to LH by producing progesterone.

Based on Falck's (7) research, the so-called two-cell-hypothesis has been suggested for the ovarian biosynthesis of estradiol, the biologically most important secretory product of the ovary during the follicular phase. According to this hypothesis, the ovarian formation of estradiol is brought about by a coordinated interaction of theca and granulosa cells layers. Consequently, a balanced ratio of FSH and LH concentrations in plasma is essential for the undisturbed development of the preovulatory follicle.

The mid-cycle LH surge terminates the follicle's maturation and results in the release of the oocyte and the formation of the corpus luteum from the remainder of the pre-ovulatory follicle (4, 6). During this process, the estradiol and androgen concentrations in circulation are reduced, whereas the synthesis of progesterone and thus the concentration of this steroid in the peripheral circulation is augmented. The decrease in estradiol concentration and the increase on progesterone concentration are accompanied by a downregulation of LH receptors in the theca cells. A decrease of the aromatase activity of the granulosa cells, which now, to a greater degree, synthesize progesterone, (8, 9), also occurs. The mitotic activity of the granulosa cells is terminated by the increase in LH, whereby the number of granulosa cells transported into the corpus luteum is determined (9).

In men, the hypothalamus-pituitary-gonadal axis regulates the testicles' endo- and exocrine functions, steroidogenesis, and spermatogenesis (fig. 3); the gonadotrophins directly influence the testicles' tubular and intertubular compartments.

FSH plays a major role in the regulation of the germinal epithelium (10, 11), while LH induces and regulates the testosterone biosynthesis in the Leydig cells (12). The gonadal steroids, especially testosterone, are vitally important for induction and the maintenance of spermatogenesis (13). 17(-estradiol and estrone can be aromatized by Sertoli cells from testosterone or androstenedione. This aromatization is stimulated by FSH (14). Furthermore, FSH ensures the development and maintenance of spermatogenesis (15) by inducing the production of the androgen-binding protein (ABP) in the Sertoli cells, thus allowing them to be provided with testosterone. In addition, FSH also seems to play a role in the regulation of the Leydig cell function (16). It has not yet been unequivocally clarified whether FSH directly influences the gametes as well. There is also data which suggest that both gonadotrophins have their own individual mechanism.

One gonadotropin alone would not suffice for the complete development of the germinal epithelium: FSH controls a structural differentiation of Sertoli cells, it does not, however. influence the tubular size and the pre-existing germ and interstitial cells. Apart from the differentiation of the Leydig cells from undifferentiated mesenchymal cells. LH causes the partial maturation of the germinal epithelium as well as proliferation of the spermatogonia and the development of the primary spermatocytes. Together both gonadotrophins influence spermatogenesis, mainly indirectly through androgens. The combined action of FSH and LH may exist in the synthesis of ABP; additionally, FSH makes the Leydig cells more receptive to the effect of LH. The effect of FSH can thus be defined as building up a high androgen concentration in the lumen of the tubuli.

The lack or complete absence of FSH or LH secretion from the pituitary gland can be treated with exogenous gonadotropin substitution. In such cases Menogon®, which contains the active ingredient Menotropin (human menopausal gonadotropin, HMG), corresponding to 75 I.U. FSH and 75 I.U. LH (I.U.= international units), is appropriate.

2.0 Active ingredient

Human menopausal gonadotropin (HMG) is a mixture of glycoproteins with the hormonal effects of FSH and LH. FSH and LH consist of two sub-units, the alpha and the beta chain. The alpha chains of FSH and LH are similar and consist of 89 to 92 amino acids with 2 oligosaccaride substituents. The hormone specific beta chain of FSH consists of 118 amino acids and 2 oligosaccaride substituents and, in the case of LH, of 121 amino acids and 1 oligosaccaride substituent.

HMG, derived from the urine of postmenopausal women, is not homogenous and may contain HCG. The FSH activity in the urine of postmenopausal women is higher than that of LH. HMG contains varying quantities of isoforms which differ in their sialic acid content and their biological effect. The amount of FSH and LH (LH plus possibly HCG) is indicated in units of their biological efficacy. Minor variations in the FSH/LH ratio are possible, although they are of minimal importance for the follicle stimulating effect of HMG (17).

Menogon® as a purified lyophilized HMG is standardized in international units (I.U.) (18). One ampoule with dry substance contains the pharmaceutically effective ingredient Menotropin corresponding to 75 I.U. FSH and 75 I.U. LH as well as the additional ingredients lactose and sodium hydroxide for pH regulation. One ampoule with 1 ml solvent contains isotonic sodium chloride solution.

3.0 Pharmacological properties, pharmacokinetics, toxicology

3.1 Pharmacological properties

The target organs for the hormonal effects of HMG are the ovaries and the testes. HMG has a gametotropic and steroidogenic effect.

In the ovaries Menogon® induces, through the FSH component, an increase in the number and size of the growing follicles and stimulates their development. FSH increases the production of estradiol in the granulosa cells by aromatizing androgens which originate in the theca cells under the influence of the LH component.

In the testicles FSH induces the transformation of immature cells to the mature Sertoli cells. It primarily has a positive effect on the maturation of the seminiferous tubules and the development of spermatozoa. Intratesticularly, however, a high concentration of androgens is necessary which can be attained by a prior treatment using HCG.

3.2 Pharmacokinetics

HMG is orally ineffective; parenteral, preferably intramuscular (i.m.) injection is indicated. The biological efficacy is mainly due to FSH. The pharmacokinetics of HMG after i.m. application show vast individual variations. The maximum serum level of FSH is reached 6 to 24 hours after injection, followed by a decrease in the level with a biological half-life of 4 to 12 hours. Administered HMG is primarily discharged renally.

3.3 Toxicology

Toxic effects in humans are unknown, and there is no evidence of teratogenic, mutagenic, or carcinogenic activities of HMG. In isolated cases repeated cyclic application of HMG may lead to the formation of antibodies causing the treatment to be ineffectual.

4.0 Clinical details

4.1 Therapeutic indications

a) Infertility in women with hypo- or normogonadotropic ovarian insufficiency: stimulation of follicle growth.
b) Infertility in men with hypo- or normogonadotropic hypogonadism: in combination with HCG to stimulate spermatogenesis.

In general, a woman should only undergo gonadotropin treatment when pregnancy is actually desired. The disturbance of her ovarian function should be of hypothalamical-pituitary origin with low, non-detectable or normal gonadotropin levels, and viable follicles should be present.

Before beginning a treatment with gonadotrophins, the patient should be carefully examined (19, 20) in order to exclude endocrinopathies and serious general illnesses as well as fallopian tube or cervix-related fertility disturbances. At the same time, the male partner should be examined so that possible disturbances of his fertility can be excluded.

Gonadotropin treatment is indicated in infertile women with hypo- or normogonadotropic ovarian insufficiency (1, 21). The goal of this treatment is the stimulation of follicle growth. Patients with hypogonadotropic hypogonadism show low estrogen concentrations. The gonadotropin levels are low, and the pituitary reaction to GnRH is minimal or nonexistent. Patients with disturbed, but still cyclical ovarian function (corpus luteum insufficiency, anovulatory cycle, oligomenorrhea, polymenorrhea) show endogenous estrogen activity, their gonadotropin concentrations are normal, and their

reaction to GnRH is moderately to clearly demonstrable.

Gonadotropin treatment of male patients offers an opportunity to restore virility and fertility in the case of hypothalamic or pituitary hypo- or normogonadotropic hypogonadism. In combination with Choragon® (human chorionic gonadotropin, HCG), Menogon® is used to stimulate spermatogenesis. Before beginning treatment. a general anamnesis should be established (22. 23) ascertaining above all any previous infectious diseases as well as surgery or lesions to the genitals. Prior to a specific hormone therapy or to any other drug therapy of idiopathic oligospermia, sufficient diagnostic tests should be carried out which demonstrate the reproducibility of the pathological spermiogram. Somatic reasons for the fertility disturbance should be ruled out.

It should be explained to female patients that an increased percentage of multiple pregnancies is to be expected under treatment with HMG (24).

Extensive research shows that the induction of ovulation with gonadotrophins does not imply an increased risk of malformations in children, compared to the total population (25).

4.2 CONTRAINDICATIONS

Women

- pregnancy
- enlargement of the ovaries or cysts which cannot be attributed to polycystic ovary syndrome
- gynaecological bleeding of unknown origin
- endometrial, ovarian, and breast tumors

Men

- cancer of the prostate
- testicular tumors

In cases of functional disturbances of the thyroid gland and adrenal cortex, of hyperprolactinaemia and of tumors of the pituitary gland or the hypothalamus, an appropriate treatment has to be carried out prior to therapy with HMG.

4.3 Undesirable effects

Treatment with HMG can often lead to a hyperstimulation of the ovaries which, however, mostly becomes clinically relevant only after application of HCG to trigger ovulation. This can lead to the occurrence of large ovarian cysts, which tend to rupture, and can cause intraabdominal bleeding. Furthermore ascites, hydrothorax, oliguria, hypotension, and thromboembolic phenomena can occur. As soon as first symptoms of hyperstimulation, such as abdominal pain and palpable enlargement in the lower abdomen, appear and are sonographically detectable, the treatment should immediately be discontinued. When a woman becomes pregnant, these side effects can intensify, be longlasting and life threatening.

Unintentional multiple pregnancies occur more often during treatment with HMG.

Occasionally, treatment with HMG is accompanied by nausea and vomiting.

In single cases, patients may show hypersensitivity to HMG like a rash, fever or pain at the injection site. In very rare cases, long term application can cause the formation of antibodies so that no success is achieved by the therapy.

Special precautions:

Female patients with unplanned hyperstimulation of the ovaries should not be treated with HCG to induce ovulation.

When treating infertile women, monitoring of the ovarian activity (ultrasonography and or estradiol determination in serum) should be carried put prior to HMG application. During treatment, these examinations should be repeated daily or every other day until stimulation has been achieved. In addition, the ovarian reaction can be determined with the help of the cervical score. An intensive control during treatment is absolutely essential. Should unintentional hyperstimulation occur, treatment must be discontinued immediately.

4.4 Interactions with other medicaments

Interactions with other medicaments are unknown.

4.5 Warnings, important incompatibilities

No warnings: incompatibilities are so far unknown.

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4.6 Posology, method of administration and duration

Female infertility:

The dosage of HMG to induce follicle growth in normo- or hypogonadotropic women differs individually. The quantity required depends on ovarian reaction and should be monitored by ultrasonography of the ovaries and by measuring estradiol levels. If the HMG dosage is too high for the treatment individual, multiple, uni- or bilateral follicle growth can occur. Generally, HMG treatment is started with a daily dosage of 75-150 I.U. FSH plus 75-150 I.U. LH applied i.m.. If the ovaries do not respond, the dosage can be gradually increased until either an increase of the estradiol secretion or follicle growth can be ascertained. The HMG dosage is maintained until the preovulatory estradiol serum level is reached. To induce ovulation, 5000 or 10000 I.U. HCG are injected one or two days after the last HMG application.

Apart from large fluctuations during various treatment cycles of the same patient, a marked variation also exists between different patients in regard to the ovarian response to gonadotrophins (1, 26). In order to achieve a high pregnancy rate and to avoid hyperstimulation of the ovaries, a thorough monitoring of the treatment is necessary (1, 27, 28). Parameters for the control of the ovarian reaction can be: the cervical score according to Insler (29), the estradiol measurement of the serum or the 24 h-urine as well as ultrasonographical examinations of the follicle size.

Note:

An unintentional hyperstimulation of the ovaries after an overdosage of HMG can occur following the application of HCG.

Menogon® in combination with Choragon® (human chorionic gonadotropin, HCG) is given to women to induce ovulation and to men to induce spermatogenesis.

Male infertility:

Initially, 1500-3000 I.U. HCG three times per week is given until a normal testosterone serum level is reached, followed by an additional weekly i.m. injection of HMG (3(75-150 I.U. FSH plus 75-150 I.U. LH) over a period of several months.

Since the spermatogenesis cycle lasts approximately 90 days, treatment with a combined HCG-/HMG-therapy should extend over this period at least. Different authors recommend various dosages (23, 30, 31).

As gonadotropin therapy aims to induce or improve spermatogenesis, the occurring chances can be controlled on the basis of the spermiogram.

Menogon® is injected intramuscularly.

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4.7 EMERGENCY MEASURES, SYMPTOMS, AND ANTIDOTES

Female patients should be informed before therapy that treatment with a HMG dosage too high for the individual may lead hyperstimulation of the ovaries (32, 33).

In case of a moderate hyperstimulation (Grade I) with slight enlargement of the ovaries (size: 5-7 cm), excessive steroid secretion, and abdominal pain, no therapy is required, but the patient should be informed and monitored thoroughly. In case of hyperstimulation (Grade II) with ovarian cysts (size of ovary: 8-10 cm), abdominal pain, nausea and vomiting, clinical supervision and symptomatic treatment, if necessary an intravenous volume replacement is indicated should an increased haemo concentration prevail. In case of severe hyperstimulation (Grade III) with large ovarian cysts (ovary size more than 10 cm) accompanied by ascites, hydrothorax, distended abdomen, abdominal pain, dyspnoea, salt retention, increased haemo concentration and blood viscosity, and increased thrombocyte aggregation with the danger of thromboembolism, hospitalization is imperative.

4.8 FURTHER INFORMATION

Application during pregnancy and lactation:

There is no indication to apply HMG during pregnancy or lactation periods.

Effect on drivers and persons handling machinery:

None.

Shelf life:

Two years.

Precautions for storage:

Menogon® should be protected from light and stored at temperatures not exceeding +25°C.

Presentation and package sizes:

- Package with 5 ampoules of dry substance and 5 ampoules solvent
- Package with 10 ampoules of dry substance and 10 ampoules solvent