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(72) Inventeurs/Inventors:
ENGEL, JURGEN, DE;
RIETHMULLER-WINZEN, HILDE, DE;
REISSMANN, THOMAS, DE

(73) Propriétaire/Owner:
ZENTARIS IVF GMBH, DE

(74) Agent: MARKS & CLERK

(54) Titre : METHODE DE TRAITEMENT DE TROUBLES DE LA FERTILITE
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(57) Abrégé/Abstract:
In the method of therapeutic management of infertility by intrauterine insemination the improvement consisting of a) the dose-dependent suppression of endogenous gonadotropins, especially LH, with a LH-RH Antagonist allowing the maintenance of physiological oestrogen levels, b) exogeneous stimulation of the ovarian follicle growth, c) ovulation induction with HCG, native LHRH, LHRH-Agonists or recombinant LH, d) intrauterine insemination by sperm injection. The LHRH Antagonists may be preferably Cetrorelix or Antarelix. The stimulation is performed by administration of HMG or recombinant FSH with or without recombinant LH or with antiestrogens as for example Chlomiphen as well as with the combination of antiestrogens as for example Chlomiphen with gonadotropins.

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(71) Applicant: ASTA MEDICA AKTIENGESELLSCHAFT [DE/DE]; An der Pikardie 10, D–01277 Dresden (DE).

(72) Inventors: ENGEL, Jürgen; Erlenweg 3, D–63755 Alzenau (DE). RIETHMÜLLER–WINZEN, Hilde; Mittelweg 27, D–60318 Frankfurt (DE). REISSMANN, Thomas; Massbornstrasse 44, D–60437 Frankfurt (DE).

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(54) Title: METHOD FOR THE TREATMENT OF FERTILITY DISORDERS

(57) Abstract

In the method of therapeutic management of infertility by intrauterine insemination the improvement consisting of a) the dose–dependent suppression of endogenous gonadotropins, especially LH, with a LH–RH Antagonist allowing the maintenance of physiological oestrogen levels, b) exogeneous stimulation of the ovarian follicle growth, c) ovulation induction with HCG, native LHRH, LHRH–Agonists or recombinant LH, d) intrauterine insemination by sperm injection. The LHRH Antagonists may be preferably Cetrorelix or Antarelix. The stimulation is performed by administration of HMG or recombinant FSH with or without recombinant LH or with antiestrogens as for example Chlomiphen as well as with the combination of antiestrogens as for example Chlomiphen with gonadotropins.

Method for the treatment of fertility disorders

One of the ethical problems of more recent times is the increasing sterility and unwanted childlessness of many couples. With respect to the therapy of these fertility disorders, inter alia, the following treatment methods of artificial fertilization have been established:

1. Substitution therapy - applied in patients with hypogonadotropic amenorrhoea
2. Stimulation therapy - given to anovulatory patients with active, albeit deranged hypothalamic pituitary-ovarian axis
3. Regulation therapy - employed in women with POCD
4. Hyperstimulation therapy - used in IVF, gamete intrafallopian transfer (GIFT), tubal embryo transfer (TET), intracytoplasmatic sperm injection (ICSI) and intrauterine insemination (IUI).

The present invention especially relates to the improvement of the method of artificial sperm cell transfer in the uterus, i.e. the fertilization by intrauterine insemination (IUI) mentioned under item 4.

For the methods under items 2 and 4, it is necessary to stimulate follicle growth, which is achieved by the administration of gonadotropins, e.g. HMG, FSH and LH, with or without preliminary therapy with clomiphene.
It has further proved that the risk of luteinization by a premature LH surge, which leads to unfavourable implantation conditions and relatively low pregnancy rates, can be decreased by complete suppression of the endogenous gonadotropins using GnRH agonists (Garcia et al., 1984; Navot et al., 1991; Hoffmann et al., 1993).

For the control of ovarian stimulation with subsequent induction of ovulation, with the aim of obtaining fertilizable egg cells, both recombinant FSH and HMG and FSH and HMG obtained from urine are employed.

In connection with IUI, it is also desirable to control follicle growth and to specifically trigger ovulation.

The statements in the specialist literature about the therapeutic accompaniment of IUI, in particular using GnRH analogues, are mainly negative, such as, for example, the following:

1. IUI after ovarian stimulation with clomiphene may be important as the 1st choice of therapy, provided the male partner has a normal spermiogram (Hum. Reprod. 1997; July; 12(7):1458-1463).
2. GnRH agonists/HMG stimulation, however, may be ineffective in routine IUI. Treatment with GnRH agonists with maximum suppression of the endogenous gonadotropins requires a relatively long treatment period (about 3 weeks) and leads to an increased consumption of HMG and is associated with side effects.
3. Reports also exist which confirm that an increase in the pregnancy rate is not achieved by the use of GnRH agonists/HMG against HMG alone for IUI treatment in the case of unclarified infertility (Hum. Reprod. 1994 June 9(6) 1043-1047.
4. The cost differences of GnRH-a/HMG stimulation compared with clomiphene/HMG is indicated by Finnish authors in Eur. J. Obstet. Gynecol. Reprod. Biol. 1997 July 74: GnRH-a/HMG stimulation is not cost-effective in routine IUI therapy.

In a study by Diedrich et al. from 1994 Hum. Reprod. 1994 May; 9(5), the suppression of the undesired, premature LH surge by cetrorelix during ovarian stimulation with HMG and the on-time induction of ovulation was described in the context of a COS-ART study.

It was possible to shorten the length of the treatment period using this LHRH antagonist and the partial dose-dependent suppression of the endogenous gonadotropins additionally proved advantageous, since it was possible

to reduce the consumption in comparison to the use of agonists of HMG.

The object of the invention is therefore to improve, i.e. to make inexpensive and more effective, the treatment method of intrauterine insemination known per se and thus in the end to fulfil the desire for children of many couples.

According to one embodiment, the present invention provides a composition for suppressing an endogenous gonadotropin level prior to intrauterine insemination, said composition comprising a luteinising hormone-releasing hormone (LH-RH) antagonist and a pharmaceutically acceptable carrier.

According to another embodiment, the present invention provides use of a luteinising hormone-releasing hormone (LH-RH) antagonist in the manufacture of a medicament for suppressing of an endogenous gonadotropin level, wherein the medicament is formulated for administration prior to an intrauterine insemination.

According to yet another embodiment, the present invention provides a kit for preparing a subject for intrauterine insemination, said kit comprising:

a) a LH-RH antagonist for suppressing an endogenous gonadotropin level such that a physiological oestrogen level is maintained;

b) a composition for stimulating ovarian follicle growth;

c) a composition for inducing ovulation, and

d) a set of instructions for administering components a, b and c to the subject prior to intrauterine insemination.

It has now been found that the treatment method of IUI can be improved by carrying out a partial suppression of the endogenous gonadotropins, which can only be achieved by means of LHRH antagonists, preferably cetrorelix or antarelix. At the same time, follicle growth is stimulated by means of urinary or recombinant FSH, HMG or clomiphene, or a combination thereof. Subsequently, ovulation can be triggered at a desired time by means of HCG, native LHRH, LHRH agonists or recombinant LH. Surprisingly, this takes place when the dominant follicle has reached a diameter of about 16-18mm. Intrauterine sperm injection then takes place with the aim of intracorporeal fertilization. It is possible in this way to carry out a stimulation treatment which is less stressful for the patient and guarantees a high degree of safety with respect to the ovulation time and leads to a saving in cost.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A composition for suppressing an endogenous gonadotropin level prior to intrauterine insemination, said composition comprising a luteinising hormone-releasing hormone (LH-RH) antagonist and a pharmaceutically acceptable carrier.

2. A composition according to claim 1, wherein the endogenous gonadotropin is luteinising hormone (LH).

3. A composition according to claim 1 or 2, wherein the LH-RH antagonist is cetrorelix or antarelix.

4. A composition according to any one of claims 1 to 3, wherein said composition maintains a physiological oestrogen level.

5. Use of a luteinising hormone-releasing hormone (LH-RH) antagonist in the manufacture of a medicament for suppressing of an endogenous gonadotropin level, wherein the medicament is formulated for administration prior to an intrauterine insemination.

6. The use according to claim 5, wherein the LH-RH antagonist is cetrorelix or antarelix.

7. The use according to claim 5 or 6, wherein the medicament is formulated for a dose-dependent suppression of the endogenous gonadotropin level such that a physiological oestrogen level is maintained.

8. A kit for preparing a subject for intrauterine insemination, said kit comprising:

a) a LH-RH antagonist for suppressing an endogenous gonadotropin level such that a physiological oestrogen level is maintained;

b) a composition for stimulating ovarian follicle growth;

c) a composition for inducing ovulation, and

d) a set of instructions for administering components a, b and c to the subject prior to intrauterine insemination.

9. A kit according to claim 8, wherein said set of instructions includes a dosage schedule for administering the LH-RH antagonist to achieve a dose-dependent suppression of the endogenous gonadotrophin level.

10. The kit according to claim 8 or 9, wherein the intrauterine insemination is achieved by sperm injection.

11. A kit according to any one of claims 8, 9 or 10, wherein the composition for stimulating ovarian follicle growth comprises a urinary or recombinant follicle-stimulating hormone (FSH) or human menopausal gonadotrophin (HMG), with or without recombinant LH.

12. A kit according to any one of claims 8, 9 or 10, wherein the composition for stimulating ovarian follicle growth comprises an antioestrogen.

13. A kit according to claim 12, wherein the antioestrogen is a clomiphene or a gonadotropin, or both.

14. A kit according to any one of claims 9 to 13, wherein the composition for inducing ovulation comprises a human chorionic gonadotrophin (HCG), a native LH-RH, a LH-RH agonist or a recombinant luteinising hormone (LH).