METHODS AND COMPOSITIONS FOR TREATING FEMALE INFERTILITY USING CLOMIPHENE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Patent Application No. 60/706,094, filed August 5, 2005 which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to female infertility. More specifically, the present invention relates to a treatment regimen for female infertility using clomiphene.

BACKGROUND OF THE INVENTION

[0003] Clomiphene citrate is well known for treatment of female anovulation. It is currently approved as a mixture of both the *cis*- and *trans*-isomers, the *cis*-isomer being present as about 30% to 50% (Merck Manual) for fertility enhancement in the anovulatory patient. Clomiphene is believed to improve ovulation by initiating a series of endocrine events culminating in a preovulatory gonadotropin surge and subsequent follicular rupture. The anti-estrogenic properties of *trans*-clomiphene have been thought to precipitate the surge of luteinizing hormone (LH) associated with ovulation.

[0004] Standard treatment regimens of up to 100 mg of clomiphene citrate for 5 days per cycle have been associated with ovulation in about 70% of patients. Nevertheless, only about 25-40% of patients treated with clomiphene citrate achieve pregnancy. London, *et al.*, Fertil. Steril. 73(3):620-626 (1999). Possible negative effects of clomiphene citrate treatment may include anti-estrogenic effects on the cervix and/or impairment of the development of the granulosa cells. The use of clomiphene citrate has also been linked to suboptimal endometrial thickness, which is associated with an elevated rate of preclinical abortion (loss of pregnancy with hCG $\geq$25 mIU prior to ultrasound observation of a sac). Dickey, et al., Hum. Reprod. 11(12):2623-2628 (1996).

[0005] The safety and effectiveness of clomiphene citrate has been widely evaluated with respect to use in the anovulatory patient. Although some studies have suggested that clomiphene citrate possesses both genotoxic and tumor enhancement effects, others have found no significant relationship between clomiphene treatment and cancer or fetal abnormalities. Clomiphene has been associated with side effects including: blurred vision,

abodominal pain, bloating, blurred vision or other vision problems, hot flashes, breast discomfort, headache, dizziness or lightheadedness, heavy menstrual periods or bleeding between periods, mental depression, nausea, vomiting, nervousness, restlessness, fatigue, and insomnia. Nevertheless, clomiphene is commonly prescribed, alone or in combination with gonadotropins such as FSH or hCG, for treatment of unexplained infertility as well as a variety of identified fertility disorders.

[0006] Methods of treating the anovulatory patient with increased rates of pregnancy and delivery are desirable.

SUMMARY OF THE INVENTION

[0007] Female infertility may be treated by administering compositions comprising clomiphene, which may comprise (*cis*, -Z-, *trans*-clomiphene) (hereinafter "*cis*-clomiphene"), (*trans*-, E-, *cis*-clomiphene) (hereinafter "*trans*-clomiphene"), and combinations thereof, or pharmaceutically acceptable salts thereof. The compositions may be administered at different times in the fertility cycle. The compositions may be administered in single or multiple daily doses, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 daily doses.

[0008] A first composition comprising clomiphene may be administered prior to ovulation. The first composition may be administered starting between approximately the second and fifth day of the menstrual cycle, at the convenience of the amenorrheic patient, or at the recommendation of the treating physician. The clomiphene of the first composition may be *trans*-clomiphene, may be comprised essentially of *trans*-clomiphene, or may be comprised of more than about 70% *trans*-clomiphene. The clomiphene of the first composition may be administered in a dose from about 0.5 to about 100 mg. The dose of the first composition may also be from about 12.5 to about 50 mg clomiphene. The dose of the first composition may also be 12.5, 25 or 50 mg clomiphene. The first composition may be administered in a single or multiple doses. The first composition may be administered for approximately five days.

[0009] A second composition comprising clomiphene may be administered starting at ovulation and up to fertilization. The second composition may comprise a mixture of *cis*- and *trans*-clomiphene, in percentage of approximately 50-80% *cis*-clomiphene and 20-50% *trans*-clomiphene. The clomiphene of the second composition may be administered in a dose from about 0.5 to about 100 mg. The dose of the second composition may also be from about 0.5 to about 10 mg clomiphene. The dose of the second composition may also be 12.5, 25 or 50 mg clomiphene. The second composition may be administered in a single or multiple

doses. If multiple dosages of the second composition are administered, at least one of the successive doses or all successive doses may have increasing percentage proportions of *cis*-clomiphene to *trans*-clomiphene.

[0010] A third composition comprising clomiphene may be administered after fertilization. The clomiphene of the third composition may be *cis*-clomiphene, may consist essentially of *cis*-clomiphene, or may be comprised of at least 50% *cis*-clomiphene. The clomiphene of the third composition may also be comprised of *trans*-clomiphene. The third composition may be administered in combination with progesterone. The clomiphene of the third composition may be administered in a dose from about 0.5 to about 100 mg. The dose of the third composition may also be from about 0.5 to about 10 mg clomiphene. The dose of the third composition may also be 12.5, 25 or 50 mg clomiphene. The third composition may be administered through part or all of the first trimester.

BRIEF DESCRIPTION OF THE DRAWING

[0011] FIG. 1 shows the chemical structure of clomiphene citrate.

DETAILED DESCRIPTION

[0012] The present invention is related to treating female infertility by administering clomiphene-containing compositions. As described above, clomiphene citrate (30-50% *cis* and 50-70% *trans*) is used in infertility treatment regimens. Although the anti-estrogenic activity of *trans*-clomiphene may be useful in stimulating ovulation, the estrogenic activity of *cis*-clomiphene may support and improve the maintenance of a fertilized embryo.

[0013] *Trans*-Clomiphene (FIG. 1) is an antiestrogen related to tamoxifen that is thought to operate in part by blocking the normal estrogen feedback on the hypothalamus and subsequent negative feedback on the pituitary. This results in an increased release of GnRH by the hypothalamus, which leads to increases in luteinizing hormone (LH) and follicle stimulating hormone (FSH). In women, these increased levels of gonadotropins are necessary for the recruitment, growth, and eventual rupture of a mature follicle (ovulation).

[0014] Ernst *et al.* have also noted that (the *trans*-isomer) is antiestrogenic (AE) while the *cis*-isomer is the more potent and more estrogenic form and has also been reported to have anti-estrogenic activity. The authors attribute the effect of clomiphene citrate on ovulatory activity to both forms stating that the mixture is more effective than *trans*-clomiphene alone.

The *trans*-isomer aids ovulation at the level of the hypothalamus. The estrogenic isomer *cis*-clomiphene contributes to enchanced ovulation elsewhere in the physiologic pathway leading to ovulation. The isomers are also reported to have different *in vivo* half-life. Furthermore the *cis* form has been reported to leave residual blood levels for in excess of one month following a single dose.

[0015] As described above, clomiphene has multiple types of activity, including but not limited to estrogenic and/or antiestrogenic effects on the pituitary, the hypothalamus, and the ovary itself. Therefore, clomiphene may have a variety of direct and indirect effects in a patient. For example, the administration of clomiphene may prevent or cure luteal defects or insufficiencies, which may be due to abnormal progesterone levels. The administration of clomiphene may also augment uterine blood flow, which may assist in development of the endometrium. Both *cis*-clomiphene and *trans*-clomiphene have been shown to raise uterine blood flow. Although both *cis*- and *trans*-clomiphene take longer to achieve peak blood flow than estradiol, the duration of the effect is greater than for estradiol. *Trans*-clomiphene may raise uterine blood flow to higher peak levels than estradiol or *cis*-clomiphene, but it must be administered at much higher doses to have this effect. The development of the endometrium may increase the likelihood of successful implantation of a fertilized egg. Additionally, the estrogenic activity of *cis*-clomiphene may prevent or improve thickening of the cervical mucus caused by the administration of *trans*-clomiphene. By counteracting the thickening of the cervical mucus often associated with the anti-estrogenic effects of clomiphene, *cis*-clomiphene may improve the hospitability of the cervix to sperm and improve the chance of fertilization.

1. Compositions and Activity

[0016] A first composition comprising clomiphene may be administered prior to ovulation. The clomiphene of the first composition may be comprised of at least about 70% of *trans*-clomiphene. Prior to ovulation, the use of *trans*-clomiphene may be an effective means of increasing LH while potentially decreasing the side effects suffered by the patient during traditional clomiphene citrate treatment. The first composition may be administered in one or more doses.

[0017] A second composition comprising clomiphene may be administered starting at ovulation and up to fertilization. The clomiphene of the second composition may be comprised of *cis*- and *trans*-clomiphene. The second composition may be administered in one or more doses. If multiple doses of the second composition are administered, at least one

or each successive dose may be comprised of increasing proportions of *cis*-clomiphene relative to *trans*-clomiphene. The second composition may provide improved hospitability of the cervix to sperm, which may lead to improved fertilization, and increased uterine blood flow, which may improve the susceptibility of the endometrium to implantation by the fertilized ovum. The skilled clinician may consider, for example, the patient's estradiol levels and endometrial thickness to determine the proper dosage. The second composition may be useful in patients having lower than normal estradiol levels and/or insufficient endometrial thickness. The second composition may also treat a luteal insufficiency.

[0018] A third composition comprising clomiphene may be administered beginning at fertilization, which may be by intercourse or artificial insemination, or upon the transfer of embryos into the patient's uterus. The clomiphene of the third composition may be comprised of at least 50% *cis*-clomiphene.

[0019] The third composition may provide increased uterine blood flow, which may improve the susceptibility of the endometrium to implantation by the fertilized ovum. The skilled clinician may consider, for example, the patient's estradiol levels and endometrial thickness to determine the proper dosage, but it is contemplated that the third composition will be especially useful in patients having lower than normal estradiol levels and/or insufficient endometrial thickness.

[0020] The third composition may comprise *trans*-clomiphene, which may be beneficial , such as in cases where the patient's progesterone levels are insufficient, or where a prior luteal insufficiency is not fully resolved.

2. Dosing and Administration Regimen

[0021] The first composition may be administered as part of an ovulation induction regimen. The clomiphene of the first composition may be consisting of *trans*-clomiphene, may be comprised essentially of *trans*-clomiphene, or may be comprised of at least about 70% *trans*-clomiphene. The dosage in which the clomiphene of the first composition is administered may be about 25-200 mg/day, for about five days, starting at or around days 2-5 of the menstrual cycle, at the convenience of the amenorrheic or oligomenorrheic patient, or at the recommendation of the treating physician.

[0022] The second composition may be administered starting at or after ovulation as detected by basal body temperature, LH surge, or by other means. Dosages of clomiphene may range from about 10 μg/kg to10 mg/kg to more than 10 mg/kg. The second composition may comprise both *cis*- and *trans*-clomiphene and may comprise more than about 50% *cis*-

clomiphene. The second composition may comprise multiple formulations throughout the treatment regimen, with at least one to each subsequent formulation having an increased proportion of *cis*-clomiphene. For example, where the second composition is administered in two formulations, one formulation may comprise less than about 50% *cis*-clomiphene and the other formulation may comprise more than about 50% *cis*-clomiphene. In another example, where the second composition is administered in three formulations, one formulation may comprise about 50% *cis*-clomiphene, while a second formulation may comprise about 75% *cis*-clomiphene, and a third formulation may comprise about 75% *cis*-clomiphene. Other formulations and dosage regimens are also contemplated and will be understood by one skilled in the art.

[0023] The third composition may be administered starting at or after insemination or fertilization as detected by hCG ≥25mIU, or by ultrasound. The third composition may comprise *cis*-clomiphene or consist essentially of *cis*-clomiphene. In some patients, the third composition may further comprise one or more additional components. For example, some patients whose corpus luteum is insufficient (i.e., does not produce adequate progesterone) it may be beneficial to augment progesterone through some or all of the first trimester until the placenta is able to produce adequate progesterone to support the pregnancy. In such cases, *cis*-clomiphene could be administered alone, in combination with small amounts of *trans*-clomiphene, or, alternatively, in combination with progesterone. Dosages may range from about 10 μg/kg to 10 mg/kg to more than 10 mg/kg clomiphene. The duration of treatment may be determined based on the patient's hormone levels, medical history, and/or the discretion of the treating physician.

3. Formulations

[0024] Suitable pharmaceutical compositions or unit dosage form may be in the form of solids, such as tablets or filled capsules or liquids such as solutions suspensions, emulsions, elixirs or capsules filled with the same, all for oral use. The compositions may also be in the form of sterile injectable solutions or emulsions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions.

[0025] Compositions according to the present invention may also be administered by the intravenous, subcutaneous, buccal, transmucosal, intrathecal, intradermal, intracisternal or other routes of administration. During the course of treatment, hormone levels may be measured as described above and dosages may be altered to achieve a sufficient change in

FSH, LH, estrogen, progesterone or other hormones to achieve the desired physiological results associated with pregnancy described above. The compositions may be administered daily, non-daily or episodic. For example, the compositions may be administered at a dosing regimen of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days between administrations.

[0026] The following Example is meant to be illustrative of the invention and is not intended to limit the scope of the invention as set out is the appended claims.

EXAMPLE 1

Use of Clomiphene Compositions in an Infertility Treatment Regimen

[0027] A first composition comprising purified *trans*-clomiphene (50 mg) is administered daily to an anovulatory adult female for 5 days starting on the third day of the menstrual cycle. The second composition is administered in two daily 0.5 mg doses starting at ovulation as detected by basal body temperature. The first dosage of the second composition comprises approximately 51% *cis*-clomiphene and 49% *trans*-clomiphene. The second dosage of the second composition comprises approximately 75% *cis*-clomiphene and 25% *trans*-clomiphene. When the patient's hCG levels reach levels associated with pregnancy (hCG $\geq$25mIU), the third composition is administered in a single dosage.

[0028] Upon completion treatment with the first, second, and third clomiphene compositions, the adult female successfully achieves and sustains a pregnancy.

CLAIMS

1. Use of clomiphene in the manufacture of a plurality of compositions for treating female infertility by administration to a patient in need thereof, namely;
   a. a first said composition, wherein the clomiphene is comprised of at least about 70% *trans*-clomiphene, for administration to the patient prior to ovulation.
   b. a second said composition, wherein the clomiphene is comprised of *trans*-clomiphene and *cis*-clomiphene, for administration to the patient between ovulation and fertilization; and optionally
   c. a third said composition, wherein the clomiphene is comprised of at least about 50% *cis*-clomiphene, for administration to the patient after fertilization.
2. Use accordingly to claim 1, wherein the compositions are administered in a single or multiple daily doses.
3. Use according to claim 2, wherein the number of daily doses is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10.
4. Use according to claim 1, wherein the first composition is administered starting at about day 2 to about day 5 of the patient's menstrual cycle.
5. Use according to claim 1, wherein the clomiphene of the first composition consists essentially of *trans*-clomiphene.
6. Use according to claim 1, wherein the clomiphene of the first composition is *trans*-clomiphene.
7. Use according to claim 2, wherein the first composition is administered in multiple doses.
8. Use according to claim 2, wherein the first composition is administered in a single dose.
9. Use according to claim 1, wherein the clomiphene of the second composition is comprised of about 50-80% of *cis*-clomiphene and about 20-50% of *trans*-clomiphene.
10. Use according to claim 2, wherein the second composition is administered in multiple doses.
11. Use according to claim 10, wherein at least one successive dose comprises an increased percentage of *cis*-clomiphene compared to the previous dose.

12. Use according to claim 2, wherein the second composition is administrated as a single dose.
13. Use according to claim 1, wherein the clomiphene of the third composition consists essentially of *cis*-clomiphene.
14. Use according to claim 1, wherein the clomiphene of the third composition is *cis*-clomiphene.
15. Use according to claim 1, wherein the clomiphene of the third composition comprises *trans*-clomiphene.
16. Use according to claim 1, wherein the third composition further comprises progesterone.
17. Use according to claim 2, wherein the third composition is administered in a single dose.
18. Use according to claim 2, wherein the third composition is administered in multiple doses.
19. Use according to claim 1, wherein the third composition is administered throughout the first trimester to the patient's pregnancy.