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(54) ORAL CONTRACEPTIVES TO PREVENT PREGNANCY AND DIMINISH PREMENSTRUAL SYMPTOMATOLOGY

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(57) **ABSTRACT**

This invention relates to a method of preventing pregnancy and treating PMS including PMDD. More particularly, the invention relates to a method, which involves administering one of several combination oral contraceptive regimens in combination with an antidepressant and a kit containing the same.

ORAL CONTRACEPTIVES TO PREVENT PREGNANCY AND DIMINISH PREMENSTRUAL SYMPTOMATOLOGY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/335,807, filed Dec. 5, 2001, the disclosure of which is hereby incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] This invention relates to oral contraceptives that prevent pregnancy and diminish or eliminate premenstrual symptomatology, including PMS and PMDD, and to a method of preventing pregnancy and diminishing or eliminating premenstrual symptomatology, including PMS and PMDD.

[0004] 2. Background Art

[0005] The human menstrual cycle involves a repetitive sequence of hormonal changes that result in episodic uterine bleeding. Normally, each menstrual cycle has a mean interval of 21 to 35 days, conventionally beginning with the first day of menstrual flow and ending on the day before the next onset of bleeding. Duration of the menstrual flow is usually 2 to 6 days with loss of 20 to 60 ml of blood.

[0006] The menstrual cycle is divided into follicular and luteal phases, each corresponding to changes occurring in the ovary. These phases may also be described as proliferative or secretory, corresponding to changes observed in the uterine endometrium. Variations in the length of the cycle are usually due to alterations in the follicular phase, because the luteal phase length remains relatively constant at 12 to 16 days.

[0007] During the follicular phase, several primary follicles are recruited for further growth and development. Granulosa cells in primary follicles posses follicle stimulating hormone (FSH) and estradiol receptors. Upon FSH stimulation, granulosa cells produce aromatase. This enzyme converts the androgens androstenedione and testosterone, made in response to luteinizing hormone (LH) by thecal cells, to estrone and estradiol, respectively. Granulosa cells respond to estradiol by undergoing mitosis to increase the number of granulosa cells and estradiol production. By day 7 of the cycle, one enlarging primary follicle is selected by unknown processes to be the follicle that will release the oocyte at ovulation.

[0008] The midcycle rise in plasma estradiol stimulates the large midcycle LH surge. This midcycle LH surge triggers resumption of meiosis within the oocyte and luteinization of the granulosa cells within the preovulatory follicle. Immediately before ovulation, the outer follicular wall begins to dissolve and an oocyte is released approximately 24 to 36 hours from the onset of the LH surge.

[0009] After ovulation, granulosa cells and the surrounding theca cells enlarge, accumulate lipid, and become transformed into lutein cells. This begins the luteal phase of the menstrual cycle. These cells form a new vascularized structure called the corpus luteum, which secretes estradiol and progesterone. LH maintains the corpus luteum during the luteal phase and, acting via the adenyl cyclase system, stimulates progesterone production. If pregnancy does not occur, lutein cells degenerate, and diminished hormone secretion precedes menstruation. Menstruation is immediately followed by the onset of another menstrual cycle.

[0010] Because endometrial proliferation serves to prepare the uterus for an impending pregnancy, manipulation of hormones and of the uterine environment can provide contraception. For example, estrogens are known to decrease FSH secretion by feedback inhibition. Under certain circumstances, estrogens can also inhibit LH secretion, once again by negative feedback. Under normal circumstances, the spike of circulating estrogen found just prior to ovulation induces the surge of gonadotropic hormones that occurs just prior to and results in ovulation. High doses of estrogen immediately post-coitally also can prevent conception probably due to interference with implantation.

[0011] Progestins can also provide contraception. Endogenous progesterone after estrogen is responsible for the progestational changes of the endometrium and the cyclic changes of cells and tissue in the cervix and the vagina. Administration of progestin makes the cervical mucus thick, tenacious and cellular which is believed to impede spermatozoal transport. Administration of progestin also inhibits LH secretion and blocks ovulation in humans.

[0012] The most prevalent form of oral contraception is a pill that combines both an estrogen and a progestin, a so-called combined oral contraceptive preparation. Alternatively, there are contraceptive preparations that comprise progestin only. However, the progestin-only preparations have a more varied spectrum of side effects than do the combined preparations, especially more breakthrough bleeding. As a result, the combined preparations are the preferred oral contraceptives in use today (Sheth et al., *Contraception* 25:243 (1982)).

[0013] In establishing an estrogen-progestin regimen for oral contraceptives, two principal issues must be confronted. First, efficacy must be maintained and second, there must be avoidance of further erosion in the control of endometrial bleeding. In general, even the lowest dose oral contraceptive products commercially available have demonstrated efficacy but the overall instances of bleeding control problems have increased as the doses were reduced, as manifested both in breakthrough bleeding (untimely flow or spotting) or withdrawal amenorrhea during the "pill free" week (expected menses).

[0014] During the luteal phase of the menstrual cycle, as many as 75% of women with regular menstrual cycles experience some symptoms of premenstrual syndrome (PMS), a recurring, cyclical disorder involving behavioral, emotional, social and physical symptoms (Steiner et al., *Annu. Rev. Med.* 48:447-455 (1997)). Behavioral, emotional and social symptoms include, but are not limited to, irritability, mood swings, depression, hostility and social withdrawal. Physical symptoms include, but are not limited to, bloating, breast tenderness, myalgia, migraines or headaches and fatigue. True PMS only occurs during the luteal phase of the menstrual cycle, with a symptom-free period during the follicular phase. The etiology of PMS is still unknown.

[0015] A subgroup of women with PMS, about 2-9%, exhibit symptoms that are primarily related to a severe mood

disorder. In these women, the diagnosis of Premenstrual Dysphoric Disorder (PMDD), which is defined in the Fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) can be applied. According to the DSM-W, a woman with PMDD must have at least five premenstrual symptoms during the luteal phase, with at least one of the symptoms being an emotional or "core" symptom. The core symptoms must be irritability, anger, mood swings, tension or depression (and interfere with daily activities), and must be confirmed by a prospective daily rating for at least two cycles. Three to five percent of women with PMS report to have PMDD.

[0016] There is also a subgroup of women who experience severe PMS, which accounts for about 20% of the PMS population. These women experience severe emotional symptoms that do not fall under the strict criteria of PMDD as defined in DSM-IV but require medical attention.

[0017] Symptoms of PMDD may begin at any age after menarche, but the average age at onset appears to be around 26 years and several researchers found that symptoms, such as estrogen withdrawal symptoms, associated with the premenstrual phase gradually become worse, and perhaps more protracted, over time. It has been suggested that worsening could occur because of the recurring increases and decreases in ovarian hormones. This is supported by data from other cultures: when menstruation is infrequent, premenstrual symptoms are rare. It is also supported by data associating low parity with the risk of PMDD. Low parity yields a greater number of hormonal cycles, and, thus, a woman has more exposure to and withdrawal from massive amounts of progesterone. Further, several studies find lower rates of premenstrual symptoms among users of oral contraceptives, again suggesting that briefer exposure to peaks and troughs of endogenous progesterone is protective against PMDD (Yonkers, K., *J. Clin. Psychiatry* 58(Suppl. 14):4-13 (1997)).

[0018] Suppression of ovulation has been an important rationale for the use of hormonal treatments for PMS. One method of inhibiting ovulation is by using oral contraceptives (OCs). Combination oral contraceptives inhibit ovulation by suppressing gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). To date, only two controlled studies of the oral contraceptive treatment of PMS have been published. The results indicate that combination oral contraceptives effectively reduce physical symptoms (especially breast pain and bloating), but the response on the relief of psychological symptoms has been less clear.

[0019] Therapeutic interventions for women who meet the criteria for PMDD include selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants and anxiolytics, as well as the antidepressant alprazolam (XANAX®). These interventions have demonstrated efficacy with minimal side effects. Recent investigations of SSRI have also demonstrated success at low doses.

[0020] Antidepressants that are active at serotonin receptors include clomipramine (ANAFRANIL®), fluoxetine (PROZAC®), paroxetine (PAXIL®), sertraline (ZOLOFT®), nefazodone (SERZONE®), fenfluramine (PONDIMIN®) and venlafaxine (EFFEXOR®).

[0021] The only approved product today for the treatment of PMDD is the SSRI fluoxetine hydrochloride (SARAFEM®). The effectiveness of fluoxetine for the treatment of PMDD was established in four randomized, placebo-controlled trials. Fluoxetine at a daily dose of either 20 mg or 60 mg proved to be superior to placebo in reducing symptoms (Steiner et al., *New Engl. J Med.* 332:1529-34 (1995)). However, the combination of oral contraceptive and fluoxetine was not examined, as women who were taking oral contraceptives were excluded from the trial.

[0022] It is the object of the present invention to provide estrogen-progestin combinations and/or regimens for oral contraceptive use, including estrogen-progestin combinations and/or regimens that contain an antidepressant, to concurrently diminish or eliminate premenstrual symptoms (PMS) including PMDD. Two regimens are proposed, the so-called 28-day regimen and the 91-day regimen. The 28-day regimen will allow women the option of maintaining the customary 13 menstrual cycles per year while diminishing or alleviating premenstrual symptoms (PMS) including PMDD. The 91 -day regimen will allow women the option of maintaining only 4 menstrual cycles per year while diminishing or alleviating premenstrual symptoms (PMS) including PMDD. Thus, the 91 -day regimen enhances compliance by involving fewer stop/start transitions per year and also results in less blood loss, and hypothetically, will diminish premenstrual symptoms, including PMDD. Having fewer menstrual intervals can also enhance lifestyles and convenience. This and other objects of the invention will become apparent to those skilled in the art from the following detailed description.

BRIEF SUMMARY OF THE INVENTION

[0023] This invention relates to female oral contraceptives that will prevent pregnancy and treat PMS including PMDD. This invention further relates to a method of preventing pregnancy and treating PMS including PMDD, by avoiding complete withdrawal of estrogen at the end of the treatment period, or between treatment periods, by administering oral contraceptives. Premenstrual symptoms are rare when menstruation is infrequent. Further, users of oral contraceptives have lower rates of premenstrual symptoms, again suggesting that briefer exposure to peaks and troughs of endogenous progesterone is protective against PMDD. More particularly, the invention relates to a method of preventing pregnancy, which involves administering one of two combination oral contraceptive regimens. Additionally, the invention relates to a method of preventing pregnancy, which involves administering one of two combination oral contraceptive regimens that contain an antidepressant.

DETAILED DESCRIPTION OF THE INVENTION

[0024] The invention relates to oral contraceptives that will prevent pregnancy and diminish or eliminate PMS including PMDD. Methods of using these oral contraceptives to prevent pregnancy and diminish or eliminate PMS including PMDD are also provided. More particularly, the methods involve administering one of several combination oral contraceptive regimens. Importantly, these regimens do not contain pill-free or placebo intervals.

[0025] One embodiment of the invention is the so-called twenty-eight day regimen that allows women the option of maintaining 13 menstrual cycles per year. In accordance

with the present invention, a women in need of contraception and treatment of PMS including PMDD, is administered a combined dosage form of estrogen and progestin, preferably monophasicly, for 21 to 26 consecutive days, preferably about 22-25 days, followed by administration of low-dose estrogen for 2 to 10 days, preferably about 3-7 days, more preferably about 2-7 days, in which the daily amounts of estrogen and progestin are equivalent to about 5-50 μg of ethinyl estradiol and about 0.025 to 10 mg, preferably about 0.05 to 1.5 mg, of levonorgestrel, respectively.

[0026] In a preferred embodiment, women will be administered an oral contraceptive on days 1 through 21 of the menstrual cycle containing 150 μg levonorgestrel and 30 μg ethinyl estradiol, followed by a dosage form on days 22-28 of the cycle, which contains 30 μg ethinyl estradiol. A typical administration schedule is illustrated in Table 1. Thus, in a 28 -day regimen schedule, there are about 13 treatment and menstrual cycles per year.

TABLE 1

Administration schedule for a 28-day regimen

Days	Hormone	Antidepressant
1–21	150 μg levonorgestrel and 30 μg ethinyl estradiol	none
22–28	30 μg ethinyl estradiol	none

[0027] In another embodiment of the invention, a women in need of contraception and treatment of PMS including PMDD, is administered a combined dosage form of estrogen and progestin, preferably monophasicly, for 21 to 26 consecutive days, preferably about 22-25 days, followed by administration of low-dose estrogen for 2 to 10 days, preferably about 3-7 days, more preferably about 2-7 days, in combination with the antidepressant fluoxetine hydrochloride, in which the daily amounts of estrogen and progestin are equivalent to about 5-50 μg of ethinyl estradiol and about 0.025 to 10 mg, preferably about 0.05 to 1.5 mg, of levonorgestrel, respectively, and the fluoxetine hydrochloride is in an amount of about 5-120 mg. Oral contraceptives with initial doses of fluoxetine at either 5 mg or 10 mg/day can be started to avoid any activating side effects that may lead to noncompliance. The dose can then be increased as needed. Fluoxetine can also be given intermittently during the late luteal phase, which is typically 1-2 weeks before menses. In addition, a one-time or once-weekly dose of about 90 mg of fluoxetine can be administered.

[0028] In a preferred embodiment, women will be administered an oral contraceptive on days 1 through 21 of the menstrual cycle containing 150 μg levonorgestrel and 30 μg ethinyl estradiol, followed by a dosage form on days 22-28 of the cycle, which contains 20 mg fluoxetine hydrochloride and 30 μg ethinyl estradiol. A typical administration schedule is illustrated in Table 2. Thus, in a 28 -day regimen schedule, there are about 13 treatment and menstrual cycles per year.

TABLE 2

Administration schedule for a 28-day regimen with an antidepressant

Days	Hormone	Antidepressant
1–21	150 μg levonorgestrel and 30 μg ethinyl estradiol	none
22–28	30 μg ethinyl estradiol	20 mg fluoxetine hydrochloride daily OR a one-time dose of 90 mg fluoxetine hydrochloride OR a once-weekly dose of 90 mg fluoxetine hydrochloride

[0029] An additional embodiment of the invention is a long-term regimen that allows women the option of limiting their menstrual periods to about four times per year. In accordance with the present invention, a women in need of contraception and treatment of PMS including PMDD, is administered a combined dosage form of estrogen and progestin, preferably monophasicly, for 60 to 110 consecutive days, preferably about 81 to 89 days, followed by administration of estrogen for 2 to 10 days, preferably about 5 to 8 days, in which the daily amounts of estrogen and progestin are equivalent to about 5-50 μg of ethinyl estradiol and about 0.025 to 10 mg, preferably about 0.05 to 1.5 mg, of levonorgestrel, respectively.

[0030] In a preferred embodiment, the 91 -day regimen, women will be administered an oral contraceptive on days 1 through 84 of the menstrual cycle containing 150 μg levonorgestrel and 30 μg ethinyl estradiol, followed by a dosage form on days 85-91 of the cycle, which contains 30 μg ethinyl estradiol. A typical administration schedule is illustrated in Table 3. Thus, in a 91 -day regimen, there are only four treatment and menstrual cycles per year.

TABLE 3

Administration schedule for a 91-day regimen

Days	Hormone	Antidepressant
1–84	150 μg levonorgestrel and 30 μg ethinyl estradiol	none
85–91	30 μg ethinyl estradiol	none

[0031] In an additional embodiment of the invention, a women in need of contraception and treatment of PMS including PMDD, is administered a combined dosage form of estrogen and progestin, preferably monophasicly, for 60 to 110 consecutive days, preferably about 81 to 89 days, followed by administration of low-dose estrogen and fluoxetine hydrochloride for 2 to 10 days, preferably about 5 to 8 days, in which the daily amounts of estrogen and progestin are equivalent to about 5-50 μg of ethinyl estradiol and about 0.025 to 10 mg, preferably about 0.05 to 1.5 mg, of levonorgestrel, respectively, and the fluoxetine hydrochloride is in an amount of about 5-120 mg. Oral contraceptives with initial doses of fluoxetine at either 5 mg or 10 mg/day can be started to avoid any activating side effects that may lead to noncompliance. The dose can then be increased as needed. Fluoxetine can also be given intermittently during the late luteal phase, which is typically 1-2 weeks before menses. In addition, a one-time or once-weekly dose of about 90 mg of fluoxetine can be administered.

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