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(54) Title: ESTROGEN/PROGESTIN/ANTIPROGESTIN METHOD AND KIT FOR ORAL CONTRACEPTION AND REGULATING MENSES

(57) Abstract

Menses regulation and, when desired, contraception is achieved at low doses of estrogen and progestin, which otherwise would create episodes of breakthrough bleeding and/or withdrawal amenorrhea, by periodically inducing menses with an antiprogestin.

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ESTROGEN/PROGESTIN/ANTIPROGESTIN METHOD AND KIT FOR ORAL CONTRACEPTION AND REGULATING MENSES

Background of the Invention

This invention relates to a method and kit for achieving oral contraception in gonadal female mammals and regulating menses and/or reducing unscheduled bleeding in pre-, para- and post-menopausal females with an estrogen, or with estrogen-progestin, in combination antiprogestin.

Although inhibition of ovulation in the form of estrogen/progestin combination oral contraceptives has been the most effective strategy for achieving reversible pharmacological fertility control in women, because of the known adverse side-effects associated with long term contraception by this method, especially in women who smoke in the 40-44 age group, over the years interest in achieving contraception at lower estrogen doses has developed.

Thus, during the over 30 year history of combined estrogen/progestin oral contraception, there has been a steady downward adjustment of the daily estrogen dosage, both for oral contraceptive purposes in premenopausal female and for estrogen replacement therapy in post-menopausal females. See, e.g., EP-A-0 253,607, which discloses, as a preferred embodiment, administering to pre-menopausal females daily a tablet containing 1 mg of 17ß-estradiol and 0.075 mg of levonorgestrel for 23 or 24 (23-26) days followed by 5 or 4 (2-5) "pill free" or blank-pill days, for a total of 28 days per cycle, and

the references cited therein, the disclosures of all of which are incorporated herein by reference.

Concurrently, although the progestin component has been lowered somewhat also, reduced androgenicity has remained an ongoing priority. Together, these adaptations of formulation have been presented in a variety of regimens, both monophasic and multiphasic. As a result, today's oral contraceptives are much safer with regard to the incidence and severity of estrogen-linked clotting disorders, as well as the cumulative impact of more "lipid friendly" progestins that maintain high density lipoprotein cholesterol levels in circulation. See, Spellacy, WN et al.,; "Am J Obstet Gynecol" 1980; 137; 109; Scott, JZ et al., "Fertil Steril" 1978; 30:141; Mishell, DR Jr. et al., "J Reprod Med." 1990; 35 (Suppl. 4): 447-481; Speroff L., "Contemp Obstet Gynecol" 1991; 36:65; Meilis GB et al., "Contraception" 1991; 43; 23; and Stamplfer MJ, Willett WC et al., "Am J. Obstet Gynecol" 1990; 163: 285.

This evolution of oral contraceptive formulations advanced most rapidly in Europe and has been steadily emerging in America as well. Indeed, the accumulating data based on oral contraceptive pills containing only 20 to 35 μg of estrogen per day spurred the Food and Drug Administration's Fertility and Maternal Health Drugs Advisory Committee to indicate low dose oral contraceptives for healthy, non-smoking women during the perimenopausal years (such as ages 35 to 50) [See Mishell (1990) and Speroff (1991)], supra; U.S. Food and Drug Administration, Advisory Committee on Maternal and Reproductive Health, 1989, Rockville, Maryland; and Rosenberg, L. et al. JAMA 1985; 253:2965. In Japan, oral contraceptives are now being evaluated for safety and efficacy criteria for the first time, with anticipation of general availability to physicians and patients within about one year.

Two principal issues are involved when considering lowering the daily dose of estrogen-progestin medications in oral contraceptives even lower, viz., (1) maintenance of contraception efficacy; and (2) avoidance of further erosion in the control of endometrial bleeding. Whereas even the lowest dose oral contraceptive products available now have demonstrated sustained contraception efficacy, overall the incidence of bleeding control problems, which manifest themselves both in breakthrough bleeding (untimely flow or spotting) or withdrawal amenorrhea during the "pill free" week (expected menses), has increased as estrogen/progestin doses are reduced. See Gray, RH. in "Endometrial Bleeding and Steroidal Contraception"; Diczfalusy E, Fraser RS, Webb FTE (Eds). Bathe, England: Pittman Press; 1990: 14-19, and Cullbey G. et al., "Contraception" 1982; 26:229.

Objects of the Invention

It is an object of this invention to solve the bleeding control problem associated with a reduction in the daily doses of estrogen, and/or of progestin when both are administered concurrently, in oral contraception and in hormone replacement therapy.

It is another object of this invention to provide a method for achieving contraception in a gonadal female mammal at ultra low estrogen and/or progestin oral doses.

Another object is to provide such a method which permits a normal menses and which regulates the onset thereof.

Still another object is to provide such a method in which the medication is self-administered.

A further object is to provide such a method which does not have the side effects associated with conventional or low oral dosage estrogen-progestin oral contraception or hormone replacement therapy.

Another object is to provide kits for practicing the method of this invention.

Another object is to provide a pharmaceutical composition effective to induce menses and/or to reduce unscheduled bleeding (breakthrough bleeding, spotting) in a female on estrogen/progestin oral contraception or estrogen and/or progestin replacement therapy.

Other objects will be apparent to those skilled in the art to which this invention pertains.

Summary of the Invention

In a method aspect, this invention relates to a method of avoiding the bleeding problems associated with administering to a female mammal dosage amounts of an estrogen, alone or in combination with a progestin, low enough to create incidents of breakthrough bleeding and withdrawal amenorrhea, which comprises periodic administration to the female of an amount of an antiprogestin effective to reduce or eliminate breakthrough bleeding and, optionally, also induce sloughing of accumulated endometrial tissue whereby menses is induced.

In an article of manufacture aspect, this invention relates to a pharmaceutical composition adapted for oral ingestion and for inducing menses in a female on estrogen-progestin oral contraception or estrogen or estrogen-progestin hormone replacement medication, comprising a menses inducing amount of an antiprogestin, in admixture with amounts of an estrogen and progestin effective to achieve oral contraception when such amounts have been ingested daily without interruption by a gonadal female for at least 20 consecutive days.

In another article of manufacture aspect, this invention relates to a kit containing and arranged in a conventional manner, e.g., like Berlex Laboratories "Levien 21", at least 20 oral dosage units, each containing an estrogen and a progestin in amounts in which collectively are effective, when one dosage unit thereof is ingested daily for 20 or more days, to achieve oral contraception in a gonadal female human being but which

promote incidents of breakthrough bleeding and/or withdrawal amenorrhea.

In a first embodiment of the kit, aspect of this invention, an additional oral dosage unit, containing only a menses-inducing amount of an antiprogestin, is positioned so as to be ingested after ingestion of the 20 or more estrogen/progestin oral dosage units. In one variation of this embodiment of the kit, the number of estrogen/progestin-combination oral dosage units which precedes the antiprogestin-containing oral dosage units is increased, e.g., to 21 or more, e.g., 20 or up to 180 units. In another variation, intended for use on estrogen replacement therapy by para- and post-menopausal females, the progestin is omitted from some or all of the tablets and the antiprogestin is present in an amount to significantly reduce or eliminate breakthrough bleeding and/or to induce sloughing of accumulated endometrial tissue. These variations are for individuals who wish to extend the length of their medically regulated menstrual cycles beyond the usual 4 week term.

In a second embodiment of the kit aspect of this invention, positioned to be taken after the 20 or more oral dosage units of the first embodiment described above, e.g., like Berlex Laboratories "Levien 28", are 6 or more placebo oral dosage units to maintain a "one-pill-a-day" regimen and remind the individual when to begin a new cycle of administration.

In a third and preferred embodiment of the kit, instead of the 6 or more placebo oral dosage units described above, the kit contains 28 or 29 or 30 oral dosage units, each of which contain low dosage amounts of estrogen and progestin corresponding to the first 21 dosage units of the first embodiment. In this embodiment, the dosage unit arranged to be taken on the 22nd day also contains a menses inducing amount of the antiprogestin.

Detailed Description

This invention is based on the discovery that incidents of breakthrough bleeding and withdrawal amenorrhea the frequency of which increase when oral contraception is achieved employing lower than conventional estrogen and progestin dosages can be minimized or avoided completely by inducing menses with an anti-progestin, either during the "drug-free", i.e., estrogen- and progestin-free, week of the monthly cycle of daily for about 21 days estrogen and progestin oral administration or preferably whenever a menses is desired during uninterrupted daily estrogen and/or progestin administration.

Also, a normal menses can be achieved with an anti-progestin without interrupting a concurrent continuous low dose estrogen/progestin oral contraceptive regimen. A continuous ultra low dose estrogen/progestin oral contraception regimen in combination with periodic, e.g., at 30, 60 or 90 days intervals, administration of an anti-progestin, e.g., RU 486, provides predictable menstrual control.

The physiological rationale for this approach is to maintain a lesser degree of pharmacologic inhibition of the pituitary-ovarian-uterine axis, but by an uninterrupted regimen to avoid "follicular escape". With today's lower dose oral contraceptive products, robust ovarian follicular growth can resume more quickly during the "pill free" interval than when higher dose pills were used in former decades. In turn, enhanced endogenous estradiol secretion with rapid endometrial proliferation, all known to accelerate during the "pill-free" 7-day period, results in less intermenstrual breakthrough bleeding, and less withdrawn amenorrhea as well. The intermittent administration of the progesterone antagonist is scheduled so as to ensure sloughing of the accumulated endometrial tissue at every fourth week or at extended intervals, e.g., every 60, 90, 120, 150, 180 or

more days, without pill-free interruption of the oral contraceptive regimen.

The intermittent, i.e., about monthly or longer, e.g., di- or tri-monthly, quarterly or semi-annually, administration of an anti-progestin to induce menses according to this invention avoids abnormal bleeding problems, e.g., breakthrough bleeding and withdrawal amenorrhea, by maintaining follicular phase level of endogenous serum estradiol at a higher level than that associated with conventional low dosage estrogen/progestin oral contraception.

In the normal menstrual cycle, progesterone is produced from the corpus luteum created after ovulation. In the contraceptive method of this invention, a progestin is administered along with an estrogen, at least toward the end of each regulated cycle, e.g., during about the last two weeks of each cycle, in order to convert proliferative endometrium to the secretory phase, thereby reducing the risks of endometrial carcinomas associated with unopposed estrogen action. However, menses is achieved with the anti-progestin alone, irrespective of whether or not administration of the estrogen and/or the progestin is interrupted during the menses week of the menstrual cycle when the anti-progestin is administered.

The daily oral doses of estrogen and progestin which are administered generally are the lowest which will achieve reliable contraception or hormone replacement therapy in women, viz., doses contraceptively equivalent to about 5 to 35 mcg. of ethinyl estradiol and about 0.5 to 1.5 mg. of norethindrone acetate. The daily doses can be the same throughout the month or can vary from week to week, as in the case of Berlex Laboratories "Tri-Levien", e.g., when a monthly menses is desired, in which case the doses of both or either can be lowered or eliminated during the menses week of the cycle. However, if administration thereof is eliminated or lowered during the menses week, the dosages thereof during the other weeks

of the cycle preferably is increased accordingly, e.g., during the second and especially during the third weeks to ensure that breakthrough bleeding does not occur prior to menses.

Similarly, when a monthly menses is not desired, e.g., in the case of post-menopausal females, the dosage of the estrogen and/or the progestin can periodically be briefly increased, e.g., at a predetermined period after the last menses, above the base-line long term dosage, to suppress isolated instances of breakthrough bleeding as a result of low levels of estrogen and/or progestin administration over a protracted period of time.

Examples of progestins which can be employed in this invention are micronized progesterone (15-50 mg/day), norethindrone and esters, e.g., acetate, thereof (0.1-0.75 mg/day), norethynodrel (0.3-0.6 mg/day); ethynodiol diacetate (0.3-0.75 mg/day), norgestrel (0.05-0.2 mg) and levo-norgestrel (0.03-0.15 mg/day), chlormadinone acetate, cyproterone, cyproterone acetate, norethindrone, desogestrel, norgestimate, dihydrospirenone, levo-norgestrel, and gestodene (Schering Ag, Berlin; U.S. Patent 4,081,537) (equivalent to 0.03-0.15 mg levo-norgestril).

For a listing of compounds see the articles from the book by B. Runnebaum et al., "Female Contraception: Update and Trends", Springer-Verlag, Berlin, 1988, pp. 64-90, 109-121, 122-128, and 129-140; which disclose progestationally active compounds. See for example, page 65 and pages 68-70 which list various progestins; pages 110 and 111 (Figure 1 and Table 1) which list synthetic progestogens; page 122, Figure 1 which list gestagens; and pages 129-133 (Figures 1-10) and page 137, Table 2 which list progestogens, or the long acting esters of estriol, described in U.S. Patents 4,681,875 and 4,738,957.

Examples of estrogens which can be employed in this invention are ethinyl estradiol and estradiol and their esters, e.g., acetate, valerate, benzoate and undecylate,

(5-15 mcg.) mestranol (20-25 mcg/day), and conjugated estrogens (5-15 mcg/day).

The progestin and estrogen can be administered in the conventional manner by any route that the selected progestin and estrogen is active, e.g., orally, by intramuscular injection, transdermally or by way of a vaginal ring. Most estrogens and the synthetic progestins are orally active and therefore are preferably administered by that route, e.g., in the form of a tablet, dragee, capsule or pill. If the progestin and/or estrogen is to be administered in tablet or dragee form, the latter, may optionally contain a pharmaceutically acceptable carrier, e.g., a binder, such as tragacanth, corn starch or gelatin; a disintegrating agent, such as alginic acid; and a lubricant, such as magnesium stearate. Also, the estrogen and/or progestin may be delivered transdermally or by way of a vaginal ring.

The estrogen and/or progestin preferably is administered without interruption, since the anti-progestin alone is effective in inducing menses, or administration thereof can be interrupted during or prior to menses, e.g., beginning on day 1 of anti-progestin administration and for up to about 6 days thereafter. Thus, the estrogen and progestin can be administered uninterrupted at lower than conventional doses for up to 6 months or longer, during which time, menses can be induced at a desired and preselected frequency, e.g., every 20, 30, 60, 90, 120, 150 or 180 days, by administrating a menses-inducing amount of the anti-progestin 1, 2 and/or 3 days prior to the desired day of onset of menses.

Examples of anti-progestins which can be employed in this invention are RU 486 ("Mifepristone", Roussel Uclaf, Paris); and "Onapristone" (Schering Ag, Berlin; U.S. Patent 4,780,461) and the steroids described in the following patents and patent applications: U.S. Patent 4,609,651, especially the compound lilopristone (11ß-(4-dimethylamino-phenyl-17ß-hydroxy-17α-(3-hydroxy-prop-1-

(Z)-enzyl-4,9(10) estradien-3-one); U.S. application Serial No. 06/827,050, especially the compounds 11ß-4-acetylphenyl)-17ß-hydroxy-17α-(1-propinyl)-4,9-estradien-3-one and 11ß-(4-acetylphenyl)-17ß-hydroxy-17α-(3-hydroxy-1(2)-propenyl)-4,9-estradien-3-one; U.S. application Serial No. 07/283,632; U.S. application Serial No. 07/541,806, corresponding to published European patent application EP-A 04042831; and other antigestations, e.g., U.S. Patent 4,891,368. The amount of the anti-progestin administered, in a single or in divided doses over a 24-72 hour period typically is about 50 to 500 mg. The minimum amount required to predictably induce menses can readily be determined by routine clinical experiments.

After the antiprogestin is administered, e.g., in a single dose or in divided doses on the same day or on successive days, menses is usually achieved within about 3-4 days thereafter.

Optionally, the antiprogestin can be administered in admixture with a daily dose of the estrogen and progestin on an appropriate day or days of the cycle, e.g., day 20 or any day thereafter, e.g., day 30, 60, 90, 120, 150 and/or 180.

In its article of manufacture embodiment, this invention relates to materials, reagents and kits for practicing the methods of this invention.

In its kit aspect, this invention is directed to an otherwise conventional multiple dosage unit article of manufacture comprising 20 or 28 dosage units adapted for oral-administration. All versions contain in their first 20 or more units collectively, an amount of an estrogen and a progestin effective, when one dosage unit thereof is self-administered on 21 successive days, to block folliculogenesis for one cycle but which is less than the amount thereof effective to avoid incidents of bleeding problems. The last dosage unit of the 21 dosage units version and the 22nd dosage unit of 22 and 28 dosage

units versions contain an amount of an antiprogestin effective to prevent incidents of bleeding problems and induce menses. The 22nd to 28th dosage units of the 28 dosage units version either contain, like the first 21 dosage units, low dosage amounts of estrogen and progestin.

Preferably, the dosage units containing the estrogen and progestin and/or antiprogestin are adapted for oral administration but can alternatively be adapted for sublingual, rectal, vaginal or topical (on the skin application. Preferably also, units adapted for oral ingestion are in the form of tablets, capsules or dragees. Preferably further, the antiprogestin is contained in the same unit or units containing the estrogen and the progestin.

The pharmaceutical compositions employed in the process of this invention will usually contain the antiprogestin in conjunction with a conventional, pharmaceutically acceptably carrier. Usually, the effective dosage of the anti-progestin is from about 1.0 to about 10 milligrams per kilogram of the body weight of the host when given orally. Effective dosages will vary with the selected mode of administration and the particular species of mammal being treated.

In a pharmaceutical composition aspect, this invention relates to an oral dosage form, e.g., pill, tablet, caplet or capsule or liquid, containing a menses-inducing amount of the antiprogestin, in admixture with the amount which is orally contraceptive, when corresponding amounts thereof are ingested by a gonadal female mammal on 21 successive days, of an orally active estrogen or an orally active progestin and, optionally, a conventional pharmaceutically acceptable carrier, e.g., binder, filler or diluent in the case of a solid dosage form, or an aqueous or alcoholic liquid, e.g., as described herein above. The composition is intended to be ingested by an individual on a continuous or sequential estrogen and

progestin contraceptive regimen e.g., conventional combined daily oral estrogen and progestin ingestion, when a menses is desired.

The pharmaceutical composition of this invention permits dispensing the oral estrogen/progestin in bulk forms, e.g., in bottles of 30, 60 or 100 tablets or capsules or in bottles of liquid, since the daily dosage thereof can remain unchanged throughout the period of administration.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight.

The entire texts of all applications, patents and publications, cited above and below, are hereby incorporated by reference.

EXAMPLES

Example I: Intermittent antiprogestin administration during continuous ultra low dose contraception

Primates

Thirty-four adult female rhesus monkeys (Macaca mulatta) having regular presumptively ovulatory menstrual cycles (28.7 ± 3.4 days for the month prior to study entry) were selected. Their duration of spontaneous menses was 3.7 ± 1.6 days. These primates are worthy laboratory surrogates for investigations pertinent to human oral contraceptive use because of extensive physiologic similarities to the functions of the hypothalamic-pituitary-ovarian-uterine axis in women. See Hodgen, GD., "Fertil Steril 1982; 38:281; Danforth DR. et al., "Contraception" 1989; 39:321; and van Uem JFHM, et al., "Contraception" 1989; 40:171.

Mean body weight of the monkeys was 5.8 ± 1.6 kg (X ± SEM). They were housed individually in a controlled environment (12 hours of light and 23°C). Their diet was a commercial primate food (Purina, St. Louis, MO) with water ad libitum.

The Eastern Virginia Medical School maintains a fully accredited animal research facility which complies through its Animal Care and Use Committee with the review standards set forth in the National Institutes of Health's "Guide for Care and Use of Laboratory Animals", the Public Health Services' "Principles for the Care and Use of Laboratory Animals", and the United States Department of Agriculture's Implementation Regulations of the 1985 amendments for the Animal Welfare Act.

Study Design

The study was conducted in two parts: Part I was an adaptation interval of three oral contraceptive treatment cycles, each of which consisted of oral medication by gavage for 21 days followed by 7 no treatment days, thus

mimicking the traditional regimen of commercial oral contraceptive pill packages. This design assured that all (32 monkeys completed the course) individuals would be exposed during the initial adjustment interval, to a medication regimen for which prior human data has shown a transiently higher incidence of breakthrough bleeding than occurs among longer-term contraceptive users. See Gray (1990); Culbey et al. (1982), supra. Vaginal swabs (cotton tipped applicators moistened in 0.9% saline) and other hands-on procedures were performed daily between 7 and 9 a.m. to detect bleeding (recorded subjectively as spotting, moderate flow or overt menses). In treatment cycle 2 only, but including the antecedent week, daily blood samples were collected from a femoral vein under light ketamine anesthesia (30 to 50 mg, in Vetalar, Parke Davis, Morris Plains, NJ). Serum was harvested and frozen (-15°C) until radioimmunoassay of estradiol and progesterone (Danforth et al. (1989); van Vem et al., (1989) supra, which was completed before starting Part II of the study, thereby insuring that ovulation inhibition was achieved by the ultra low dose regimens.

In Part II, 30 of these primates were randomly assigned to five treatment groups of six each: (1) the oral contraceptive medication employed in Part I was continued (21 + 7 day regimen) for 6 months; (2) continuous (no "pill-free" interval) daily estrogen-progestin medication, with combined single day oral administration of an antiprogestin (RU 486) on treatment days 30, 60, 90, 120, 150, and 180; (3) same as group 2, except that the progesterone antagonist was given only on days 60, 120, and 180; (4) same as group 2, except that RU 486 was given only on days 90 and 180; and (5) 180 days of continuous estrogen-progestin daily therapy, but without any antiprogestin treatment. Daily monitoring to detect vaginal blood, as in Part I above, was discontinued at 187 days. Femoral blood was collected once weekly throughout in order to identify potential

breakthrough ovulation via progesterone elevations; serum values above 1.0 ng/ml were considered indicative of ovarian luteal function and possible ovulation. Likewise, these same specimens were analyzed for estradiol levels in order to monitor ongoing endogenous estrogen biosynthesis. Two monkeys, in groups 1 and 3, respectively, were dropped from the ongoing protocol, one due to a skin rash and the other because of a thumb infection requiring topical treatment. Neither incident is believed to be related to the hormonal treatments.

Medications

To achieve ultra low dose oral contraception and to adjust the commercial medication used to the smaller (than human) body weight of these laboratory primates, an oral dose of 1.2 μg/day of ethinyl estradiol and 0.06 mg/day of norethindrone acetate was employed. This was achieved by grinding to a powder a commercially available pill ("Loestrin 1/20" in a conventional 21 day pack, Parke Davis, Morris Plains, NJ), contained 1 mg of norethindrone acetate and 20 μg of ethinyl estradiol per tablet.

In the Part II cycle, cycle RU 486 "(Mifepristone", Roussel Uclaf, Paris) was administered intermittently as single 50 mg tablets in combination with continuous the estrogen-progestin oral contraceptive regimen, except the group 1 and group 5 animals. Previous studies had indicated that this dose of RU 486 would be sufficient to displace natural progesterone from endometrial, myometrial and cervical receptors, thereby inducing prompt (usually within 48 hours) and complete sloughing of both uterine fundal and isthmic tissue, comparable to spontaneous menstruation. See Healy DL, et al., "Fertil Steril" 1983; 40:253; Danforth DR et al., Contraception 1989; 40:199. Because the estrogen and progestin components were already combined, progestin was included even during the intervals of RU 486 administration.

In terms of comparison to human dose equivalents, the daily dose received by the monkeys, with a monkey's body weight about 6 kg and a woman's at 60 kg, was about 12 μg of ethinyl estradiol and 0.6 mg of norethindrone acetate. Thus, this ultra low dose oral contraceptive formulation presented a 40% reduction in daily estrogen-progestin exposure compared to one of the lowest dose combination oral contraceptives commercially available today in America or Europe. Even taking into account that when a continuous ultra low dose regimen was used, versus the traditional 21 + 7 day protocol, that there would be 92 more treatment days on an annualized basis, the treatment reduced the annual rate of exogenous estrogen-progestin exposure by more than 20%.

Statistical Evaluations and Results

Differences between group results in study Part I, calculated as the means and standard errors, were compared using the F statistic, testing at $P < 0.05$ level of significance.

Although two of the menstrual factors monitored (breakthrough bleeding rates and duration of withdrawal ("pill-free") menses did not reveal any significant differences ($P > 0.05$), certain trends were observed, viz., (1) the breakthrough bleeding rates were noticeably lower in cycles 2 and 3; and (2) the duration of withdrawal menses in the "pill-free" interval was slightly less each month. In turn, the incidence of withdrawal amenorrhea (the third menstrual factor which was monitored) at the time of expected withdrawal menses did increase significantly ($P < 0.05$) in treatment cycle 3 versus 1. Circulating levels of estradiol and progesterone reflected indirectly the inhibitory actions of the estrogen-progestin medication on pituitary gonadotropin secretion. Although serum estradiol rose clearly during the "pill-free" intervals adjacent to the treatment days in cycle 2, follicular maturation was curtained by

reinstitution of medication, as indicated by highest levels around 60 pg/ml without therapy and suppression to near 25 pg/ml on day 21. Since serum progesterone levels remained at or near the lower detection limits of the assay throughout, the data firmly indicate that ovulation probably was blocked reliably in all 32 monkeys.

Data derived from Part II of the study was listed by treatment group with the profiles of endometrial bleeding through six treatment cycles to 180 days. Mean (+ SEM) number of days for breakthrough bleeding or menses was calculated by dividing the total number of incidents recorded (per treatment cycle in the case of group 1 or 30 days intervals for groups 2 to 5) by the number of individuals observed in the group. In the tabulation of data, menses (withdrawal or induced bleeding at expected intervals) was scored for vaginal blood detected within the "pill free" interval for group 1 or within seven days after the intermittent administration of RU 486 during continuous ultra low dose oral contraception (groups 2 to 4). Similarly, failure to observe vaginal bleeding during these times of expected menses, either withdrawal of the oral contraceptive medication or soon after giving the progesterone antagonist, was scored as withdrawal amenorrhea.

For group 1, the incidence of breakthrough bleeding changed little from the 1st to 6th treatment cycle. However, the data overall obtained in Part II compared to that in Part I showed a 2.4 fold reduction ($P < 0.05$) in the breakthrough bleeding rates, progressively. Statistical significance ($P \leq 0.05$) was reached also in treatment cycles 3 and 6 of Part II versus treatment cycle 1 of Part I.

For groups 2 to 4 in association with the intermittent single doses of RU 486 at 30, 60, or 90 days intervals, the overall breakthrough bleeding incidence was reduced by 57% ($P < 0.05$) when the statistical comparison was made for total combined data from groups 2 to 4

versus group 1. However, group 5 manifested a unique response to continuous ultra low dose oral contraception. The frequency of breakthrough bleeding rose moderately in the 5th and markedly in the 6th 30-day interval compared to all other study groups ($P < 0.05$).

With regard to pill withdrawal or RU 486 induced menses, the ultra low dose oral contraceptive, administered in a traditional 21 + 7 day regimen, resulted in fewer ($P < 0.05$) days of menstrual flow than in the pretreatment spontaneous menstrual cycle (1.7 ± 0.5 days, overall versus 3.7 ± 1.6 days, respectively); menses after RU 486 was of longer duration (3.1 ± 0.8 day; $P < 0.05$) than with the interrupted pill cycle alone. There were no significant differences in bleeding profiles among RU 486 treated groups ($P > 0.05$). Lastly, those primates receiving an uninterrupted course of ultra low dose oral contraceptive medication for 180 days (group - 5) demonstrated a longer duration of withdrawal menses than other treated group (4.9 ± 3.5 days, $P < 0.05$). However, the degree of individualism observed prevented achieving statistical significance ($P > 0.05$) from findings in the pretreatment cycle.

The incidence of amenorrhea in Part II was noticeably reduced when RU 486 was added intermittently to the continuous oral contraceptive regimen. In fact, no monkeys failed to bleed after RU 486, although for some the presence of vaginal blood was as brief as one or two days. In contrast, when either the 21 + 7 day conventional regimen or continuous administration of the ultra low dose oral contraceptive alone were used, the incidence of amenorrhea ranged between 20 and 30% overall ($P < 0.05$).

Throughout Part II, weekly serum progesterone levels remained below 1.0 ng/ml, except for one instance when a value of 1.4 ng/ml was found. Reassay of this specimen produced a concentration of 0.26 ng/ml, suggesting that the initial value may have resulted from a spurious

assay, rather than indicating possible elevated ovarian follicular or luteal activity. Concurrently, overall serum estradiol concentrations during the 180 day study were 37 ± 19, 23 ± 7, 27 ± 7, 22 ± 5, 25 ± 3 and 26 ± 6 pg/ml for groups 1 to 5, respectively, illustrating overall significantly ($P < 0.05$) lower estrogen levels during continuous ultra low dose oral contraceptive regimens, irrespective of RU 486.

These findings are consistent with the ultra low dose oral contraceptive employed being sufficient to block ovulation when using either a conventional regimen of 21 days of medication plus 7 "pill free" days or uninterrupted treatment for 180 days. However, the incidence of bleeding problems, either breakthrough bleeding or withdrawal amenorrhea in the "pill free" interval was increased, irrespective of whether the treatment regimen was the traditional 21 + 7 days scheme or was extended continuous therapy, compared to when RU 486 was given in conjunction with the estrogen/progestin therapy.

Addition of the antiprogestin RU 486 intermittently at 30, 60, or 90 day-intervals was associated with two improvements in the bleeding profiles. Reduced breakthrough bleeding in the intermenstrual intervals and reliable menstrual induction at the expected time was observed, thus eliminating withdrawal amenorrhea. Also, overall, the duration of induced menstrual flow was slightly greater after RU 486. When continuous oral contraceptive treatment was used without RU 486, the frequency of breakthrough bleeding rose measurably in the 5th and, especially, the 6th 30 day interval. Like-treated females that received single administrations of the progesterone antagonist at 30, 60, or 90 day intervals consistently experienced the lowest (57% less) breakthrough bleeding rates compared to findings when the traditional 21 + 7 day scheme or continuous dosing, but without the anti-progestin.

The frequency of breakthrough bleeding among women beginning oral contraceptive use is known to be higher in the initial pill cycles than subsequently. It is believed that this often reported observation may reflect both a biological effect of hormonal adjustment to the medication as well as unreliable user compliance among women not experienced with oral contraceptives. The results of the above-described experiments in this primate model are consistent with such opinions in part; viz., a progressive decline in breakthrough bleeding incidence was observed through the initial 3 to 4 months of treatment with an ultra low dose oral contraceptive administered in a conventional 21 + 7 day regimen. Although the observed absolute frequency of breakthrough bleeding was lower than that often reported in women, this may be due to enforcement of compliance experimentally on the monkeys and/or other differences related to dose, regimen or species. Moreover, having stabilized these primates on this cyclic treatment schedule for three cycles in Part I before segregating them into the five groups of Part II may have improved our insight into the impact of RU 486 on bleeding control problems associated with low dose oral contraceptive use. Not only was RU 486 consistently related to significantly less breakthrough bleeding, but the antiprogestin reliably induced some bleeding in all instances within 72 hours, whether administered at 30, 60 or 90 day intervals. Without intermittent RU 486 treatment, the incidence of amenorrhea at expected bleeding times was elevated with both the 21 + 7 conventional regimen and the 180 day continuous treatment alone (group 5). The latter data suggest that continuous oral contraceptive regimens require occasional sloughing of the endometrial to avert cumulative bleeding irregularities.

From the foregoing data, several possible explanations can be given for the improved bleed control during the continuous ultra low dose regimen of oral contracep-

tion plus intermittent RU 486. For example, serum estradiol levels were almost unvarying, hovering near 25 pg/ml, and absence of the secretory bursts of estradiol that characterize the "pill free" interval during transient "follicular escape" when traditional 21 + 7 day regimens are used RU 486 treatment may act in three ways: (1) constraint by its antimutagenic properties on endometrium, on modulating rapid endometrial proliferation; (2) negating an excessive degree of progestin over estrogen dominance (here the ratio of norethindrone acetate: ethinyl estradiol is 50:1); and (3) extended continuous oral contraceptive regimens that cause accumulation of endometrial tissue, and ultimately higher breakthrough bleeding rates, can be offset by occasional sloughing of tissue.

Overall, the findings of this primate study are consistent with the feasibility of (1) further reductions in the daily dose of estrogen-progestin oral contraceptives; (2) continuous ultra low dose oral contraceptive regimens, wherein the daily pill-taking interval is extended to 30, 60, and 90 days without interruption; and (3) a single intermittent dose of an antiprogestin in combination with continuous oral contraceptive regimens to reduce intermenstrual breakthrough bleeding rates and to insure avoidance of withdrawal amenorrhea, both of which are known to be associated with today's lower dose oral contraceptive regimens.

Thus, the present invention is useful in increasing oral contraceptive safety, user satisfaction and user compliance, without comprising contraceptive efficacy. Moreover, because contraceptive efficacy in women is not sacrificed and may, in fact, be enhanced by a continuous estrogen/progestin regimen which does not require user memory of stop-start days, as with a 21 day cycle pill package and the major patient compliant of menstrual nuances is meaningfully reduced by intermittent inclusion of an antiprogestin, ultra low dose estrogen/progestin

oral contraceptives thus become increasingly desirable for sexually active women from their teenage years through menopause.

Additionally, although some women desire from their cyclic oral contraceptive medication a regular withdrawal menses every 4 weeks (13 times annually), others would prefer a less frequent menstrual flow, assuming a safe and efficacious product designed to insure menses less often, such as only 4 times per year, existed. The present invention, which employs a combination of low dose estrogen-progestin pill in a continuous regimen, in combination with an antiprogestin administered only at extended intervals, when a menses is desired or medically indicated, provides such a product.

Also, withdrawal menses in some post-menopausal women, whether using sequential or concurrent estrogen-progestin therapy is a major cause of failed user compliance. A therapeutic regimen in accordance with this invention can overcome the patient disfavor of frequency cyclical vaginal bleeding without sacrificing safety and effectiveness, by the use of continuous estrogen replacement therapy, in conjunction with a progestin with intermittent use of antiprogestin to shed accumulated endometrial tissue only a few times yearly, motivates post-menopausal patients, via less frequent menses, to remain on hormone replacement therapy with its apparent long-term advantages to cardiovascular integrity and bone maintenance.

In the case of hormone replacement therapy the major patient compliant of breakthrough bleeding is significantly reduced by intermittent inclusion of an antiprogestin due to its antimitotic activity which may supplement the inhibitory effects of progestin itself on endometrium growth and its beneficial action on the vascular bed of the endometrium. The withdrawal bleeding following antiprogestin administration may not necessarily occur because of the lack of endometrial transformation by a progestin.

Example II: **Intermittent antiprogestin during estrogen and estrogen plus progestin replacement therapy**

Primates

Twenty previously ovariectomized cynomolgus monkeys (Macaca fascicularis) have implanted for 281 days a single-estradiol containing subcutaneous capsule. Estradiol release from this capsule results in serum estradiol concentrations of approximately 75 pg/ml. A subcutaneous progesterone capsule is implanted on day 191 and remain in place until day 281. Progesterone release from this capsule results in serum progesterone concentrations of approximately 4 ng/ml. The study takes place in the animal research facilities of the Eastern Virginia Medical School as described in Example I.

Study design

The purpose of this study was to evaluate breakthrough bleeding prior to and after onpristone treatment in ovariectomized monkeys receiving estrogen and estrogen plus progesterone replacement therapy. The twenty monkeys were assigned to the following four groups: Group 1 receives onapristone vehicle (saline) on days 30, 60, 90, 120, 150, 180, 210, 240, 270. Group 2 receives 3 mg/kg i.m. onapristone on days 30, 60, 90, 120, 150, 180, 210, 240, 270. Group 3 is treated with 10 mg/kg i.m. onapristone on the same days. Group 4 receives 30 mg/kg i.m. onapristone on the same days. Vaginal swabs are performed daily from day 1 to 281. The primary parameter for evaluation in this study is the occurrence of vaginal bleeding.

Preliminary results of ongoing study

The progressing duration of estradiol treatment results in the increasing rate of breakthrough bleeding in the vehicle treated group (Group 1). Onapristone treatment in Groups 2-4 does not induce bleeding but it lowers

the incidence of breakthrough bleeding. Once combined estradiol and progestin treatment has been initiated, onapristone induces vaginal bleeding.

Kit Example

A kit is provided which contains 28 unit doses convention tablets adapted for oral ingestion, each containing 12 mcg. of the estrogen ethinyl estradiol and 0.6 mg of the progestin norethindrone acetate.

(a) In one embodiment, the tablets are arranged in a conventional circular or elongated "racetrack" oval configuration, with indicia corresponding to the days of the week, so that compliance with the daily intake regimen can readily be confirmed by the patient.

For an example of such products, see Berlex Laboratories "Levien-28". The tablet arranged to be taken on the 21st or later day contains, in addition to the ethinyl estradiol and norethindrone acetate, 500 mg. of the anti-progestin RU 486 ("Mifepristone", Roussel Uclaf).

(b) In another embodiment, 20 or more e.g., 20, 23, 24, 30, 60, 90 or 120, tablets containing only the estrogen and progestin or only the estrogen are packaged loosely in a container, e.g., a bottle with flat faces or a flat metal box with a snap open top such as is conventionally used to hold aspirin tablets, or like container. Packaged separately, e.g., in an accessible cavity in the bottle cap or in a bubble pack adhesively affixed to one face of the bottle or the metal box, is a tablet containing the anti-progestin alone or in admixture with the estrogen and progestin. On the package for this tablet is provided space for the physician (or patient) to write the day and the month when the tablet instead of (when the tablet contains both the anti-progestin and the estrogen and progestin) or in addition to the other tablets (when the tablet contains only the anti-progestin) should be taken to induce menses. The kit contains the

number of tablets required to provide continuous estrogen/progestin therapy for one menstrual cycle of 28, 30, 60, 90 or 120 days duration.

(c) In another version of the above-described kits otherwise corresponding to the first embodiment (s), amounts of the estrogen and progestin vary, i.e., in the first 7 tablets, the amounts thereof are 35 mcg. and 1.5 mg. per tablet, respectively,; in the next 7, they are 30 mcg. and 0.8 mg. per tablet, respectively; in the next 7, they are 20 mg. and 0.6 mg. per tablet, respectively; and in the last 7, they are 5 mcg. and 0.4 mg. per tablet, respectively.

(d) In variations of each of the kits described hereinabove, the norethindrone acetate in the tablets is replaced by 25 mcg. of gestodene.

(e) In other variations of each of the kits described hereinabove, the estrogen therein is replaced by 20 mcg. of mestranol.

(f) In other variations of each of the kits described above, the antiprogestin therein is replaced by 500 mg. of onapristone.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A method of avoiding the bleeding problems associated with administering to a female mammal dosage amounts of an estrogen low enough to create incidents of breakthrough bleeding and withdrawal amenorrhea, which comprises periodic administration to the female of an amount of an antiprogestin effective to reduce or eliminate breakthrough bleeding and, optionally, also induce sloughing of accumulated endometrial tissue whereby menses is induced.

2. The method of claim 1, wherein the female mammal is a gonadal human desiring contraception and the estrogen is administered in combination with a progestin in amounts effective to block folliculogenesis and thereby creating a contraceptive state therein and inducing menses upon the administration of the antiprogestin.

3. The method of claim 1, wherein the antiprogestin is administered about monthly.

4. The method of claim 1, wherein the female is a postmenopausal woman on hormone replacement therapy.

5. The method of claim 2, wherein the estrogen is administered in combination with progestin in an amount effective to suppress endometrial proliferation.

6. The method of claim 1, wherein the antiprogestin is administered at longer than monthly intervals.

7. The method of claim 2, wherein the administration of the progestin and estrogen is continued uninterrupted throughout the cycle, including during menses.

8. The method of claim 1, wherein the administration of the progestin and estrogen is interrupted proximate the day of antiprogestin administration.

9. The method of claim 1, wherein the antiprogestin is administered orally.

10. The method of claim 1, wherein the antiprogestin is mitepristone.

11. The method of claim 1, wherein the estrogen is ethinyl estradiol.

12. The method of claim 1, wherein the progestin is norethindrone acetate.

13. The method of claim 1, wherein the female mammal is a gonadal human and the amounts of estrogen and progestin administered are effective to block folliculogenesis and thereby create a contraceptive state therein; wherein the antiprogestin is administered orally; and wherein the administration of the progestin and estrogen is continued uninterrupted throughout out the cycle, including the menses.

14. The method of claim 12, wherein the antiprogestin is administered about monthly.

15. The method of claim 12, wherein the antiprogestin is administered at longer than monthly intervals.

16. A kit containing at least about 20 estrogen and progestin-containing tablets, which collectively are effective when 21 thereof are taken on successive days to achieve continuous oral contraception in a gonadal female human being but which contain amounts thereof which are too low to avoid breakthrough bleeding incidents where administration of the tablets is interrupted for a week during each monthly cycle to induce menses; and containing a tablet, arranged in the kit so as to be taken after at least 20 of the estrogen and progestin-containing tablets have been taken, which contains an amount of an antiprogestin effective to induce menses.

17. A kit according to claim 15, containing 28 of the estrogen and progestin containing tablets, arranged to be taken sequentially with the anti-progestin containing tablet positioned as the 20th or later tablet in the sequence.

18. A kit according to claim 15, wherein the estrogen is ethinyl estradiol, the progestin is norethindrone acetate and the antiprogestin is mifepristone.

19. A kit according to claim 15, wherein the estrogen is ethinyl estradiol, the progestin is gestodene and the antiprogestin is onapristone.

20. A pharmaceutical composition in solid oral unit dosage form comprising amounts of an estrogen and of a progestin contraceptively equivalent to 5 mcg. to 35 mcg. of ethinyl estradiol and 0.5 mg. to 1.5 mg. of norethindiol acetate, respectively, and an amount of an

antiprogestin effective to induce menses in a female human being who has ingested daily for at least 20 days corresponding amounts of the estrogen and progestin.

21. A pharmaceutical composition according to claim 19, containing 0.5 to 35 mcg. ethinyl estradiol, 0.5 to 35 mg norethindrone acetate and 50 to 500 mg. of mifepristone.

22. A pharmaceutical composition according to claim 19, containing 0.5 to 35 mcg. ethinyl estradiol, 10 to 15 mcg. gestodene and 50 to 500 mg. of onapristone.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01931

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/56 -
US CL :514/178,179,182

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS & Cas Online: estradiol, norethindrone acetate, gestodene, Rh486, onapristone, estrogen, pagest?, contracept?, blood?, bleed?, withdrawl amenorrhea, spotting, menses

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A, 0,253,607 (AMERICAN HOME PRODUCTS CORP.) 20 JANUARY 1988, See abstract.	1-22
Y	Chemcial Abstracts, Volume 105, no.1, Chillik et al, "RU486-induced manses in cynomogus monkeys in uniformity of endometrial sloughing," abstract no. 897;, Fertil. Steril., 1986, 45(5), p. 708,712.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 01 May 1993	Date of mailing of the international search report 01 JUN 1993
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