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(54) NOVEL ORAL CONTRACEPTIVE REGIMENS AND PACKAGED UNIT DOSAGE FORMS THEREOF

(71) We, SYNTEX CORPORATION, a Panamanian Corporation of Apartado Postal 7386, Panama, Panama, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a method of fertility control in the human female by adherence to a novel oral contraceptive regimen. The regimen includes the administration of a combination of an estrogen and a progestogen during certain days of the reproductive cycle, and the administration of only the progestogen on certain of the other days of the cycle.

Research and development in the area of human contraception or fertility control has heretofore concentrated almost exclusively on preventative methods, whether in the form of chemical or physical diversions of or barriers to sperm transport, e.g. vaginal creams and foams, condoms, diaphragms, and intrauterine devices, or in the form of chemically based oral contraceptives. The former methods have been largely supplanted by the use of oral contraceptives which have proven to be extremely effective in the prevention of conception. This effectiveness, however, necessarily requires the administration of the oral contraceptive tablets over approximately 21 days of each reproductive cycle. During the remaining 7 days of the 28 day cycle, no hormone-containing tablets are given and it is during this period, if the reproductive cycle is accurately regulated, that normal menstrual flow takes place.

The most common form of oral contraception is based upon the daily administration of a combination of estrogen and progestogen substance for about 21 successive days, starting generally on the 5th day of the menstrual cycle. After the 21 day period, there follows a 7 day period during which neither the estrogen or progestogen substances are taken. If the reproductive cycle of the female has been properly regulated, the normal and characteristic menstrual flow is supposed to, and generally does, occur within the 7 day period.

A second method which has been developed is the "sequential" system wherein from the 5th through about the 19th day of the cycle only an estrogen is given. A different tablet containing both estrogen and progestogen substances is given for the 5 days from the 20th to the 24th day of the cycle. This regimen more closely approximates the time-related secretion by the female body of its own reproductive cycle-controlling hormones. As with the combined treatment, there are no hormonal substances given during the 7 days following the 24th day. If the reproductive cycle has been properly regulated, the normal menstrual flow will, and generally does, occur within the 7 day period.

Although oral contraceptives have proven to be extremely effective in controlling fertility, the administration of oral contraceptive formulations, like other potent drugs, has some side effects. Since the oral contraceptives maintain a pseudopregnancy condition, the most commonly occuring side effects are similar to the common symptoms observed during pregnancy. Such side effects may be attributable to the potent estrogenic and progestogenic agents administered during the course of the regimen. Accordingly, it is of continuing interest to those in this field to develop new oral contraceptive regimens which control fertility, yet do so with lower dosages of estrogen and/or progestogen agents, minimized side effects, or do so in improved manner.

Thus, Coutinho and deSouza, J. Reprod. Fert. *16*, 137—139, (1968) suggest the administration of a combined tablet containing estrogen and progestogen every other day starting on the 5th day of the menstrual cycle and ending on the 23rd day of the cycle. On intervening days between the 5th and the 23rd days of the cycle, no tablets or placebos are administered. Although it was concluded that the contraceptive effec-

tiveness of such a regimen is unaltered by extending the interval of administration to alternate days (as opposed to administration on 21 consecutive days), the reported data also shows that this was achieved with some sacrifice in cycle regulation and duration of menstrual flow. Specifically, regulation of the reproductive cycle to give menstrual flow upon termination of medication (ie, so called "withdrawal bleeding") was only effective in slightly over 50% of the cycles recorded. This loss of cycle regulation can, in turn, expose the patient to the possibility of conception during an "unprotected" period (ie, where no active medication is being taken) which does not coincide with actual menstrual flow. Additionally, the complete absence of menstrual flow (ie, amenorrhoea) increased significantly as did those instances where the duration of menstrual flow was undesirably long (ie, greater than 8 days).

The method of controlling fertility, according to the present invention, comprises administering to the human female during certain days of the reproductive cycle a combination of estrogen and progestogen, and administering during certain other days of the reproductive cycle only a progestogen. This is considered an "interrupted treatment", as distinguished from the "combined" and "sequential" treatments described above.

In the broadest aspects, the present invention relates to methods for controlling fertility in women wherein the first day of menstrual flow prior to the initiation of the administration of oral contraceptive medication is considered as day 1 of a medication administration cycle. On the 3rd, 4th, 5th, or 6th day of the cycle and every second or third day thereafter to, and including, the 23rd, 24th, 25th, 26th, 27th, or 28th day of the cycle, there is administered a combination formulation having both estrogen and progestogen substances. On the 4th, 5th, 6th or 7th day of the cycle and every day thereafter on which a combination formulation is not administered, to, and including, the 22nd, 23rd, 24th, 25th, 26th, 27th, or 28th day of the cycle, a formulation having only a progestogen substance as the active component is administered. On the remaining days of the cycle, active medication may be given in alternating or interrupted form, if desired. Generally, however, the remaining days are dosage-free or the regimen is completed by use of placebos or non-hormonal supplements. If the reproductive cycle of the female has been regulated by such a regimen, menstrual flow (ie, "withdrawal bleeding") will, and usually does, occur shortly after discontinuance of the administration of active medication.

According to a particular regimen, the first day of menstrual flow is considered to be the first day of the initial medication administration cycle. On the 5th day and every other day to, and including, the 25th day of the cycle, there is administered a combined formulation having both estrogen and progestogen substances. On the 6th day of the cycle and every other day to, and including, the 24th day of the cycle, there is administered a formulation having only a progestogen as the active component. For the remaining 7 days of the 28 day cycle (ie, days 26—28 and days 1—4) no estrogenic or progestogenic substances are taken. Optionally, during this 7 day period, placebos with or without non-hormonal supplements can be administered to provide a continuous program of oral contraception administration over successive cycles. If the reproductive cycle of the female has been regulated by the above-described regimen, menstrual flow will, and usually does, occur shortly after the 25th day (ie, after discontinuance of the administration of the estrogenic/progestogenic substances).

The progestogen component of the oral contraceptive regimen is preferably administered daily in an amount from about 0.03 mg. to about 10.0 mg., generally from about 0.3 mg. to about 1.0 mg., throughout period of therapy. The actual amount of progestogen utilized in a daily unit dosage form will depend upon the particular progestogen utilized and its relative potency or activity, and may lie outside the above range. For example, a smaller quantity of a more potent progestogen will be required to achieve the same results as a larger quantity of a less potent progestogen. The presently preferred progestogen is norethindrone (ie, 17α - ethynyl - 17β - hydroxy - estr - 4 - en - 3 - one), as described in United States Letters Patent No. 2,744,122. Other progestogens include chlormadinone-acetate (6 - chloro - 17 - hydroxy - pregna - 4,6 - diene - 3,20 - dione acetate), norethynodrel (17α - ethynyl - 17 - hydroxy - estr - 5(10) - en - 3 - one), norgestrel (13β - ethyl - 17α - ethynyl - 17β - hydroxy - gon - 4 - en - 3 - one), medroxy - progesterone acetate (17α - acetoxy - 6α - methyl - pregn - 4 - ene - 3,20 - dione), megestrol acetate (17α - acetoxy - 6 - methyl - pregna - 4,6 - diene - 3,20 - dione), lynestrenol (17α - ethynyl - 17β - hydroxy - estr - 4 - ene), quingestrone (3 - cyclopentyloxy - pregna - 3,5 - diene - 20 - one), norethindrone acetate (17β - acetoxy 17α - ethynyl - estr - 4 - en - 3 - one), ethynodiol acetate (3β,17β - diacetoxy - 17α - ethynyl - estr - 4 - ene), and dimethisterone [17β - hydroxy - 6α - methyl - 17 - (1 - propynyl) - androst - 4 - en - 3 - one].

On those days that the estrogen component of the oral contraceptive regimen is administered it is preferably in an amount from about 0.01 mg. to about 2.0 mg., generally from about 0.03 mg. to about 0.1 mg. As with the progestogen substance, the actual amount of

estrogen substance utilized in a unit dosage form wil depend upon the particuar estrogen utilized and its relative potency or activity, and may lie outside the above range. Estrogen administration is preferably in a combined unit dosage form along with the progestogen; however, the estrogen can be administered in separate unit dosage form if so desired. The presently preferred estrogen is ethinyl estradiol (ie, 17α - ethynyl - 3,17β - dihydroxy - estra - 1,3,5(10) - triene). Other estrogens include mestranol (17α - ethynyl - 17β - hydroxy - 3 - methoxy - estra - 1,3,5(10) - triene), estradiol (3,17β - dihydroxy - estra - 1,3,5(10) - triene), estriol (3,16α, 17β - trihydroxy - estra - 1,3,5(10) - triene), estrone (3 - hydroxy - estra - 1,3,5(10) - triene - 17 - one), diethylstilbestrol, and quinestradiol (3 - cyclopentyloxy - 16α, 17β - dihydroxy - estra - 1,3,5(10) - triene.

Each of the estrogenic and progestogenic substances utilized in this regimen performs the same function or functions that it would if given, for example, in accordance with the "combined" treatment referred to above. However, it has been found that oral contraceptives, administered according to the regimen herein described, control fertility although adminstered at a substantially reduced dosage level (as compared, for example, to oral contraceptive unit dosage forms now commercially marketed by the present applicants while retaining satisfactory control over reproductive cycle length and duration of menstrual flow.

The process of the present invention is conventionally practiced by administration of the oral contraceptive formulations during a 28 day cycle, as described above. The formulations are prepared from the estrogenic and progestogenic agents to provide the combined estrogen/progestogen formulation and individual progestogen formulation, both as described above. The active component or components is, or are, as the case may be, in admixture with a pharmaceutically acceptable non-toxic carrier. Thus, the formulations can be appropriately compounded in any pharmaceutically acceptable non-toxic form and packaged in any manner suitable for proper delivery and use. For example, the formulations can take the form of tablets, capsules, and/or pills containing in addition to the active component or components, a number of inert materials including diluents, binders, lubricants, and/or other additives designed to improve its physical characteristics. See Remington's *Pharamaceutical Sciences*, Mack Publishing Company, Easton, Penn., 14th Edition, 1970, especially Chapter 87. As used herein, "unit dosage form" refers to the use of tablets, capsules, and/or pills, etc., by which the formulations of the present invention, including, optionally, placebos, are made available to the user thereof for daily ingestion according to the regimen herein described.

Dispensing packages according to this invention, and particularly useful herein, include those which accommodate the required formulation representing daily unit dosage form in a contiguous, sequential arrangement which, if properly used according to the instructions packaged therewith, cause the proper formulation to be taken at the appropriate time during the reproductive cycle. For example, such a dispensing package may comprise individual blister pods for the storage in each of a single unit dosage form. At the appropriate time during the reproductive cycle, the unit dosage form is manually dispensed therefrom through a frangible retaining layer. Storage of other unit dosage forms is not affected by such dispensing. Appropriate notations can be placed on the dispensing package, if desired, to guide or instruct the user thereof in the proper use of the oral contraceptive herein described. For example, day of the week, day of the cycle, miscellaneous instructions, etc., may be provided, if so desired.

Accordingly, another aspect of the present invention provides in combination, a dispensing package having oral contraceptives in unit dosage forms therein, said unit dosage forms being arranged for administration of one unit dosage form daily in a predetermined sequence during a 28 day medication administration cycle, said sequence being predetermined by the manner in which said unit dosage forms are stored in said dispensing package, said dispensing package bearing directions to take one unit dosage form daily in the directed sequence; said combination comprising a unitary member having 20—28 individual storage pods formed therein, said storage pods corresponding to the 20—28 days during which unit dosage forms are to be administered, the storage pods corresponding to the 3rd, 4th, 5th, or 6th day of said cycle and every second or third day thereafter to, and including, the 23rd, 24th, 25th, 26th, 27th or 28th day of said cycle having therein a unit dosage form having a combination of estrogen and progestogen substances, and said storage pods corresponding to the 4th, 5th, 6th, or 7th day of said cycle and every other day thereafter on which a combination formulation is not administered, to, and including, the 22nd, 23rd, 24th, 25th, 26th, 27th or 28th day of said cycle having therein a unit dosage form having only a progestogen substance as the active component; and a frangible retaining layer adapted to maintain each unit dosage form in its individual storage pod, said frangible layer being punctured only beneath an individual storage pod as the unit dosage form therein is dispensed therefrom.

The following specific description is given to enable those skilled in this art to more clearly understand and practice the present invention. It should not be considered as a limitation upon the scope of the invention but

merely as being illustrative and representative thereof.

EXAMPLE I

5,000 pink tablets having the following composition are prepared:

norethindrone	0.5 mg.
ethynyl estradiol	0.06 mg.
lactose (USP)	55.2 mg.
corn starch	19.2 mg.
polyvinylpyrrolidone	4.8 mg.
magnesium stearate	0.24 mg.
F D & C red No. 2 dye	0.007 mg.

In the following procedure, appropriate quantities of each component are utilized to give the desired number of tablets, each tablet having the composition listed above.

The norethindrone and ethynyl estradiol are dissolved in ethanol which is heated slightly. The dye is dissolved in water and both solutions are mixed. The lactose, corn starch, and polyvinylpyrrolidone are mixed and passed through a No. 40 mesh screen. The mixed solution of norethindrone and ethynyl estradiol is added to the powder mixture of lactose, corn starch, and polyvinylpyrrolidone, and granulated through a No. 12 mesh screen. This mixture is dried at 40—45°C and then passed through a No. 20 mesh screen. The magnesium stearate is passed through a No. 60 mesh screen, added to the granulated powder and mixed for three minutes. The tablets are prepared from this granulated powder by compressing portions thereof using a 6 mm. diameter flat face beveled edge punch.

EXAMPLE II

5,000 uncolored tablets having the following composition are prepared:

norethindrone	0.5 mg.
lactose (USP)	55.26 mg.
corn starch	19.20 mg.
polyvinylpyrrolidone	4.8 mg.
magnesium stearate	0.24 mg.

The method of preparing the tablets of this Example is the same as is given above in Example I, except the ethynyl estradiol and F D and C red No. 2 dye are omitted.

In the preceding formulations, the polyvinylpyrrolidone can vary between 4—6%, by weight, of the total weight of the tablet, the corn starch can vary between 19—25%, by weight of the total weight of the tablet, the magnesium stearate can vary between 0.2—0.5%, by weight, of the total weight of the tablet, the coloring dye can be added as required, and the lactose is added in sufficient amount to bring individual tablets to their desired weight. Generally the lactose represents about 50—75%, by weight, of the total tablet weight.

Placebo tablets can be prepared from polyvinylpyrrolidone, corn starch, magnesium stearate, an appropriate coloring dye, and lactose in amounts, for example, as specified in the preceding paragraph.

Eleven tablets having the composition as shown in Example I, 10 tablets having the composition as shown in Example II, and 7 placebos are placed in a dispensing package. Considering the first day of menstrual flow as day one, placebos are placed in the first four individual storage pods. The eleven tablets corresponding to the composition of Example I are placed, one each, in the storage pods corresponding to the fifth day and every other day thereafter through, and including, the 25th day. The 10 tablets corresponding to the composition of Example II are placed, one each, in the storage pods corresponding to the 6th day and every other day thereafter through, and including, the 24th day. The remaining 3 placebos are placed, one each, in the 3 remaining individual storage pods corresponding to days 26—28. Appropriate notations are made on the dispensing package instructing the user thereof to take the first placebo tablet on the first day of menstrual flow. The dispensing package also includes additional instructions directing the user thereof to take the remaining tablets, at one tablet per day, in the specified sequence during the remaining days of the 28 day cycle.

In an alternate dispensing package, the 7 placebo tablets are omitted. Appropriate instructions are placed on the dispensing package directing the user thereof to consider the 1st day of menstrual flow as the day 1 of the cycle, so commence the taking of the tablets in the sequence as shown on day 5 of the cycle, and to continue taking such tablets at one tablet per day until all of the tablets have been ingested. The dispensing package also includes additional instructions directing the user thereof to wait 7 days prior to starting the next regimen with a new dispensing package of tablets.

In either case, using either the 21 or 28 tablet-containing dispensing package, the adminstration of active medication will begin for each succeeding cycle on the same day of the week as administration of active medication began during the first cycle. For as long as the patient is maintained on this regimen by the physician this 28 day cycle will be adhered to, regardless of whether menstrual flow has taken place or not during the "unprotected" period.

EXAMPLE III

81 women with proven fertility and exposed to occurrence of pregnancy, but who are not using any other means of contraceptive or fertility control, are administered the oral contraceptives of the present invention

according to the regimen described in Examples I and II above.

The results obtained in this clinical study are tabulated below in Table I. As used in Table I, "menstrual flow interval" refers to the number of days from the first day of menstrual flow for one cycle until the first day of menstrual flow for the next succeeding cycle; the "duration of menstrual flow" means the actual number of days of menstrual flow. Three patients involved in the clinical studies tabulated in Table I were on the program for too short a period of time to obtain meaningful data with regard to the interval of menstrual flow. Thus, only 78 patients are listed under that category in Table I. However, one such patient did have a bleeding episode during the time on the program and, thus, is included in the data tabulated in Table I under duration of menstrual flow.

TABLE I

	Patients		Cycles	
Menstrual Flow Interval (Days)	No.	%	No.	%
<25	14	17.9	98	18.2
25—32	49	62.9	375	69.9
>32	13	16.7	52	9.7
>60	2	2.6	12	2.2
	78		537	
Duration of Menstrual Flow (Days)				
<3	12	15.2	74	12.2
3—8	67	84.8	531	87.3
>8	—	—	3	0.5
	79		608	

No pregnancies occurred; accordingly, this represents a pregnancy rate of 0.0 per 100 woman years. As used herein, "pregnancy rate" is the number of pregnancies × 1,200 divided by the product of the number of patients observed × the months of exposure.

With regard to Table I above, the menstrual flow interval represented by 25—32 days is commonly referred to as "withdrawal bleeding". That is, it refers to the occurrence of menstrual flow shortly after the administration of active medication is terminated (ie, during the "unprotected" period during which the placebos are taken or no tablets are taken). As can be seen from the data presented in Table I, in a substantial majority (ie, approximately 70%) of the cycles tabulated to date, withdrawal bleeding has occurred as desired. In addition, the incidence of amenorrheic cycles (as categorized by a menstrual flow interval greater than 60 days) is relatively modest and, in any event, is a substantial improvement over the results reported by Coutinho et al, supra. With regard to duration of menstrual flow, the duration of a substantial majority (ie, approximately 87%) of menstrual flow episodes recorded fall within the desired 3—8 day range. Thus, these results reflect that the regimen described herein is effective in preventing conception, controlling the duration of flow, and regulating the length of the reproductive cycle, as evidence by the high incidence of "withdrawal bleeding" where the time of actual menstrual flow is desirably synchronized with the "unprotected" period. As indicated above, this is achieved with a substantial reduction in the amount of active components administered to the patient.

EXAMPLES IV AND V

The compositions of Examples I and II are repeated except 0.5 mg. of norethindrone acetate is substituted for the 0.5 mg. norethindrone in each instance.

EXAMPLES VI AND VII

The compositions of Examples I and II are repeated except 6.0 mg. of dimethisterone is substituted for the 0.5 mg. norethindrone in each instance.

EXAMPLES VIII AND IX

The compositions of Examples I and II are repeated except 0.5 mg. of norethynodrel is substituted for the 0.5 mg. norethindrone in each instance.

EXAMPLES X AND XI

The compositions of Examples I and II are repeated except 0.5 mg. of ethynodiol acetate is substituted for the 0.5 mg. norethindrone in each instance.

EXAMPLES XII AND XIII

The compositions of Examples I and II are repeated except 0.25 mg. of norgestrel is substituted for the 0.5 mg. norethindrone in each instance.

EXAMPLES XIV AND XV

The compositions of Examples I and II are repeated except 5.0 mg. of medoxyprogesterone acetate is substituted for the 0.5 mg. norethindrone in each instance.

EXAMPLES XVI AND XVII

The compositions of Examples I and II are repeated except 0.5 mg. of chlormadione acetate is substituted for the 0.5 mg. norethindrone in each instance.

The present invention has been particularly described above with reference to not only an effective regimen, but one that conforms to an accepted mode of administration of oral contraceptives to a large number of women of varying backgrounds, intelligence, inclinations, etc. That is, the regimen has been based upon a medication administration cycle requiring 21 days on medication and 7 days off medication, whereby in each succeeding cycle the administration of active medication begins on the same day of the week as in the first or preceding cycle. However, from a theoretical point of view without regard to the convenience of use aspect, the present invention can be modified in certain particulars which are considered to be within the broad concepts of this invention.

For example, a combined formulation having both estrogen and progestogen substances can be administered on the 3rd day of the medication administration cycle and a progestogen formulation administered on the 4th day of the cycle. This is followed by the 21 days of medication administration as described above, whereby active medication is administered on 23 days of a 28 day cycle.

Alternatively, administration of the interrupted regimen can be as given above with the exception that no medication is given on the 25th day. In this aspect of the invention, administration of active medication ends on the 24th day with the administration only of the progestogen substance.

In a further aspect of the invention, once again considering the first day of menstrual flow prior to the initiation of administration of medication as day one, the administration of active medication can begin on the 3rd, 4th, 5th, or 6th day of the cycle with the administration of a combined estrogen and progestogen formulation. The combined formulation, however, is only administered every third day. On intervening days, only a progestogen substance is administered.

Thus, in the broadest aspects of the invention, combined estrogen and progestogen formulations are administered on the 3rd, 4th, 5th, or 6th, day of the cycle and every second or third day thereafter through, and including, the 23rd, 24th, 25th, 26th, 27th, or 28th day of the cycle. On the 4th, 5th, 6th, or 7th day of the cycle and every day thereafter on which a combination formulation is not administered, through, and including, the 22nd, 23rd, 24th, 25th, 26th, 27th, 28th day of the cycle, formulation having only a progestogen substance as the active component is administered. On the remaining days of the cycle, the regimen may be completed by additional active medication or placebos, etc., as indicated above. Generally, however, active medication will be given for only a period of 20—23 days.

Dispensing packages accommodating the novel oral contraceptive regimen of this invention, with or without placebos, are also considered a part of the present invention. As indicated above, such packages include instructions directing the user thereof to take a single unit dosage form daily in the desired sequence, whereby the proper formulation is ingested on the proper day during the medication administration cycle. Suitable packages include those shown by Applezwig U.S. No. 3,409,721, and those oral contraceptive packages now marketed by the present applicants. A further package has one row of combined estrogen/progestogen unit dosage forms, and a second row of unit dosage forms having only progestogen as the active component. One unit dosage form is taken from one row and the next unit dosage form is taken from the other row, and so on, alternating back and forth. Placebos may be added at the beginning and/or end of each row, if so desired.

WHAT WE CLAIM IS:—

1. A method of controlling fertility in women wherein the first day of menstrual flow prior to the initiation of the administration of medication is considered as day 1 of a 28 day cycle, said method comprising administering on the 3rd, 4th, 5th, or 6th day of said cycle and every second or third day thereafter to, and including, the 23rd, 24th, 25th, 26th, 27th, or 28th day of said cycle a combination formulation having both estrogen and progestogen substances, and administering on the 4th, 5th, 6th, or 7th day of said cycle and every day thereafter on which a combination formulation is not administered, to, and including, the 22nd, 23rd, 24th, 25th, 26th, 27th or 28th day of said cycle a formulation having only a progestogen substance as the active component.

2. The method of Claim 1 wherein active medication comprising said formulation is administered for 20—23 days.

3. The method of Claim 1 further including administering placebos on those days of said cycle on which a progestogen substance is not administered, said placebos containing neither estrogen nor progestogen substances.

4. The method of Claim 1 further including repeating said 28 day cycle of medication administration at least one further time, the first day of the next succeeding cycle following directly after the 28th day of the preceding cycle.

5. The method of Claim 1 wherein said combination of estrogen and progestogen substances is administered every second day.

6. The method of Claim 5 wherein said

EXAMPLES XVI AND XVII

The compositions of Examples I and II are repeated except 0.5 mg. of chlormadione acetate is substituted for the 0.5 mg. norethindrone in each instance.

The present invention has been particularly described above with reference to not only an effective regimen, but one that conforms to an accepted mode of administration of oral contraceptives to a large number of women of varying backgrounds, intelligence, inclinations, etc. That is, the regimen has been based upon a medication administration cycle requiring 21 days on medication and 7 days off medication, whereby in each succeeding cycle the administration of active medication begins on the same day of the week as in the first or preceding cycle. However, from a theoretical point of view without regard to the convenience of use aspect, the present invention can be modified in certain particulars which are considered to be within the broad concepts of this invention.

For example, a combined formulation having both estrogen and progestogen substances can be administered on the 3rd day of the medication administration cycle and a progestogen formulation administered on the 4th day of the cycle. This is followed by the 21 days of medication administration as described above, whereby active medication is administered on 23 days of a 28 day cycle.

Alternatively, administration of the interrupted regimen can be as given above with the exception that no medication is given on the 25th day. In this aspect of the invention, administration of active medication ends on the 24th day with the administration only of the progestogen substance.

In a further aspect of the invention, once again considering the first day of menstrual flow prior to the initiation of administration of medication as day one, the administration of active medication can begin on the 3rd, 4th, 5th, or 6th day of the cycle with the administration of a combined estrogen and progestogen formulation. The combined formulation, however, is only administered every third day. On intervening days, only a progestogen substance is administered.

Thus, in the broadest aspects of the invention, combined estrogen and progestogen formulations are administered on the 3rd, 4th, 5th, or 6th, day of the cycle and every second or third day thereafter through, and including, the 23rd, 24th, 25th, 26th, 27th, or 28th day of the cycle. On the 4th, 5th, 6th, or 7th day of the cycle and every day thereafter on which a combination formulation is not administered, through, and including, the 22nd, 23rd, 24th, 25th, 26th, 27th, 28th day of the cycle, formulation having only a progestogen substance as the active component is administered. On the remaining days of the cycle, the regimen may be completed by additional active medication or placebos, etc., as indicated above. Generally, however, active medication will be given for only a period of 20—23 days.

Dispensing packages accommodating the novel oral contraceptive regimen of this invention, with or without placebos, are also considered a part of the present invention. As indicated above, such packages include instructions directing the user thereof to take a single unit dosage form daily in the desired sequence, whereby the proper formulation is ingested on the proper day during the medication administration cycle. Suitable packages include those shown by Applezwig U.S. No. 3,409,721, and those oral contraceptive packages now marketed by the present applicants. A further package has one row of combined estrogen/progestogen unit dosage forms, and a second row of unit dosage forms having only progestogen as the active component. One unit dosage form is taken from one row and the next unit dosage form is taken from the other row, and so on, alternating back and forth. Placebos may be added at the beginning and/or end of each row, if so desired.

WHAT WE CLAIM IS:—

1. A method of controlling fertility in women wherein the first day of menstrual flow prior to the initiation of the administration of medication is considered as day 1 of a 28 day cycle, said method comprising administering on the 3rd, 4th, 5th, or 6th day of said cycle and every second or third day thereafter to, and including, the 23rd, 24th, 25th, 26th, 27th, or 28th day of said cycle a combination formulation having both estrogen and progestogen substances, and administering on the 4th, 5th, 6th, or 7th day of said cycle and every day thereafter on which a combination formulation is not administered, to, and including, the 22nd, 23rd, 24th, 25th, 26th, 27th or 28th day of said cycle a formulation having only a progestogen substance as the active component.

2. The method of Claim 1 wherein active medication comprising said formulation is administered for 20—23 days.

3. The method of Claim 1 further including administering placebos on those days of said cycle on which a progestogen substance is not administered, said placebos containing neither estrogen nor progestogen substances.

4. The method of Claim 1 further including repeating said 28 day cycle of medication administration at least one further time, the first day of the next succeeding cycle following directly after the 28th day of the preceding cycle.

5. The method of Claim 1 wherein said combination of estrogen and progestogen substances is administered every second day.

6. The method of Claim 5 wherein said

estrogen is 17α - ethynyl - 3,17β - dihydroxy - estra - 1,3,5(10) - triene.

7. The method of Claim 5 wherein said progestogen is 17α - ethynyl - 17β - hydroxy - estr - 4 - en - 3 - one.

8. The method of Claim 1 wherein said combination of estrogen and progestogen substances is administered every third day.

9. A method for controlling fertility in women wherein the first day of menstrual flow prior to the initiation of the administration of medication is considered as day 1 of a 28 day cycle, said method comprising administering on the 5th day of said cycle and every other day to, and including, the 25th day of said cycle a combination formulation having both estrogen and progestogen substances, and administering on the 6th day and every other day to, and including, the 24th day of said cycle a formulation having only a progestogen substance as the active component.

10. The method of Claim 9 further including administering placebos on the 7 consecutive days following the 25th day of said cycle, said placebos containing neither estrogen nor progestogen substances.

11. The method of Claim 9 wherein no estrogenic or progestogenic medication is administered during days 1—4 and 26—28 of said cycle; said method further including repeating said 28 day cycle of medication administration at least one further time, the first day of the next succeeding cycle following directly after the 28th day of the preceding cycle.

12. The method of Claim 9 wherein said progestogen is administered daily from the fifth day of said cycle to, and including, the 25th day of said cycle in an amount from 0.03 mg. to 10.0 mg.

13. The method of Claim 9 wherein said progestogen is 17α - ethynyl - 17β - hydroxy - estr - 4 - en - 3 - one.

14. The method of Claim 9 wherein said estrogen is administered every other day from the fifth day of said cycle to, and including, the 25th day of said cycle in an amount from 0.01 mg. to 2.0 mg.

15. The method of Claim 9 wherein said estrogen is 17α - ethynyl - 3,17β - dihydroxy - estra - 1,3,5(10) - triene.

16. The method of Claim 9 wherein 0.06 mg. of 17α - ethynyl - 3,17β - dihydroxy - estra - 1,3,5(10) - triene is administered as said estrogen.

17. The method of Claim 9 wherein said combination formulation comprises a combination of 17α - ethynyl - 17β - hydroxy - estr - 4 - en - 3 - one and 17α - ethynyl - 3,17β - dihydroxy - estra - 1,3,5(10) - triene.

18. The method of Claim 9 wherein said combination formulation comprises 0.5 mg. 17α - ethynyl - 17β - hydroxy - estr - 4 - en - 3 - one and 0.06 mg. 17α - ethynyl - 3,17β - dihydroxy - estra - 1,3,5(10) - triene.

19. The method of Claim 9 wherein 0.5 mg. 17α - ethynyl - 17β - hydroxy - estr - 4 - en - 3 - one is administered every other day from the sixth day of said cycle to, and including, the 24th day of said cycle.

20. In combination, a dispensing package having oral contraceptives in unit dosage forms therein, said unit dosage forms being arranged for administration of one unit dosage form daily in a predetermined sequence during a 28 day medication administration cycle, said sequence being predetermined by the manner in which said unit dosage forms are stored in said dispensing package, said dispensing package bearing directions to take one unit dosage form daily in the directed sequence; said combination comprising a unitary member having 20—28 individual storage pods formed therein, said storage pods corresponding to the 20—28 days during which unit dosage forms are to be administered, the storage pods corresponding to the 3rd, 4th, 5th, or 6th day of said cycle and every second or third day thereafter to, and including, the 23rd, 24th, 25th, 26th, 27th or 28th day of said cycle having therein a unit dosage form having a combination of estrogen and progestogen substances, and said storage pods corresponding to the 4th, 5th, 6th, or 7th day of said cycle and every other day thereafter on which a combination formulation is not administered, to, and including, the 22nd, 23rd, 24th, 25th, 26th, 27th or 28th day of said cycle having therein a unit dosage form having only a progestogen substance as the active component; and a frangible retaining layer adapted to maintain each unit dosage form in its individual storage pod, said frangible layer being punctured only beneath an individual storage pod as the unit dosage form therein is dispensed therefrom.

21. The combination of Claim 20 wherein there are 20—23 unit dosage forms containing either a progestogen substance or a combination of progestogen and estrogen substances.

22. The combination of Claim 20 wherein said unitary member has 28 individual storage pods, said combination further including a single placebo unit dosage form in each of said storage pods not holding a progestogen-containing unit dosage form, said placebo unit dosage forms including neither estrogen nor progestogen substances.

23. The combination of Claim 20 wherein said storage pods corresponding to the 3rd, 4th, 5th, or 6th day of said cycle and every second day thereafter to, and including, the 23rd, 24th, 25th, 26th, 27th, or 28th day of said cycle have therein a unit dosage form having a combination of estrogen and progestogen substances.

24. The combination of Claim 20 wherein said storage pods corresponding to the 3rd, 4th, 5th, or 6th day of said cycle and every third day thereafter to, and including, the

23rd, 24th, 25th, 26th, 27th, or 28th day of said cycle have therein a unit dosage form having a combination of estrogen and progestogen substances.

25. In combination, a dispensing package having oral contraceptives in unit dosage forms therein, said unit dosage forms being arranged for administration of one unit dosage form daily in a predetermined sequence during a 28 day medication administration cycle, said sequence being predetermined by the manner in which said unit dosage forms are stored in said dispensing package, said dispensing package bearing directions to take one unit dosage form daily in the directed sequence; said combination comprising a unitary member having 21 or 28 individual storage pods formed therein, said storage pods corresponding to the 21 or 28 days during which unit dosage forms are to be administered, the first of said storage pods corresponding, in the 28 pod-containing unitary member, to the 1st day of said cycle and, in the 21 pod-containing member, to the 5th day of said cycle, said storage pods corresponding to the 5th day of said cycle and every other day thereafter to, and including, the 25th day of said cycle having therein a unit dosage form having a combination of estrogen and progestogen substances, and said storage pods corresponding to the 6th day of said cycle and every other day thereafter to, and including, the 24th day of said cycle having therein a unit dosage form having only a progestogen substance as the active component; and a frangible retaining layer adapted to maintain each unit dosage form in its individual storage pod, said frangible layer being punctured only beneath an individual storage pod as the unit dosage form therein is dispensed therefrom.

26. The combination of Claim 25 wherein said unitary member has 28 individual storage pods, said combination further including a single placebo unit dosage form in each of said storage pods corresponding to days 1—4 and days 26—28 of said cycle, said placebo unit dosage forms containing neither estrogen nor progestogen substances.

27. The combination of Claim 25 wherein each of said combined estrogen and progestogen unit dosage forms includes 0.01 mg. to 2.0 mg. estrogen and 0.03 mg. to about 10.0 mg. progestogen.

28. The combination of Claim 25 wherein each of said combined estrogen and progestogen unit dosage forms includes 17α - ethynyl - 17β - hydroxy - estr - 4 - en - 3 - one as said progestogen and 17α - ethynyl - 3,17β - dihydroxy - estra - 1,3,5(10) - triene as said estrogen.

29. The combination of Claim 25 wherein each of said combined estrogen and progestogen unit dosage form includes 0.06 mg. 17α - ethynyl - 3,17β - dihydroxy - estra - 1,3,5(10) - triene and 0.5 mg. 17α - ethynyl - 17β - hydroxy - estr - 4 - en - 3 - one.

30. The combination of Claim 25 wherein said estrogen in each of said combined estrogen and progestogen unit dosage forms comprises 17α - ethynyl - 3,17β - dihydroxy - estra - 1,3,5(10) - triene.

31. The combination of Claim 25 wherein said progestogen in each of said combined estrogen and progestogen unit dosage forms comprises 17α - ethynyl - 17β - hydroxy - estr - 4 - en - 3 - one.

32. The combination of Claim 25 wherein said unit dosage forms containing only progestogen as the active component include 0.03 mg. to 10.0 mg. of said progestogen.

33. The combination of Claim 25 wherein each of said unit dosage forms containing only progestogen as the active component include 17α - ethynyl - 17β - hydroxy - estr - 4 - en - 3 - one as said progestogen.

34. The combination of Claim 25 wherein said unit dosage forms containing only progestogen as the active component include 0.5 mg. 17α - ethynyl - 17β - hydroxy - estr - 4 - en - 3 - one.

35. The method of Claim 1 wherein said progestogen is selected from norethindrone, norethindrone acetate, chlormadinone acetate, norethynodrel, norgestrel, medroxyprogesterone acetate, megestrol acetate, lynestrenol, quingestrone, ethynodiol acetate, and dimethisterone.

36. The method of Claim 9 wherein said progestogen is selected from norethindrone, norethindrone acetate, chlormadinone acetate, norethynodrel, norgestrel, medroxyprogesterone acetate, megestrol acetate, lynestrenol, quingestrone, ethynodiol acetate, and dimethisterone.

37. The combination of Claim 20 wherein said progestogen in said unit dosage forms is selected from norethindrone, norethindrone acetate, chlormadinone acetate, norethynodrel, norgestrel, medroxyprogesterone acetate, megestrol acetate, lynestrenol, quingestrone, ethynodiol acetate, and dimethisterone.

38. The combination of Claim 25 wherein said progestogen in said unit dosage forms is selected from norethindrone, norethindrone acetate, chlormadinone acetate, norethynodrel, norgestrel, medroxyprogesterone acetate, megestrol acetate, lynestrenol, quingestrone, ethynodiol acetate, and dimethisterone.

39. A method according to claim 1 substantially as described herein.

* C L M S *

40. A method according to claim 9 substantially as described herein.

41. A dispensing package according to claim 20 substantially as described herein.

42. A dispensing package according to claim 25 substantially as described herein.

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