

[72] Inventor **Leonard Joseph Lerner**
New Brunswick, N.J.
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[73] Assignee **E. R. Squibb & Sons, Inc.**
New York, N.Y.

[54] **MODIFIED SEQUENTIAL ORAL
CONTRACEPTIVE**
5 Claims, No Drawings

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Primary Examiner—Shep K. Rose

Attorneys—Lawrence S. Levinson, Merle J. Smith and
Theodore J. Criares

ABSTRACT: This invention relates to new modified sequential oral contraceptive preparations and a method of administering them. According to this invention a regimen is followed in which a combination of estrogen and a low amount of progestogen is administered for the first 14 to 19 day phase of the cycle and a combination of estrogen and a high amount of progestogen is administered for the succeeding 4 to 7 day phase of the cycle. A 25 to 28 day cycle is completed with a 5 to 7 day hormone-free phase which may include the use of placebos or iron and/or vitamin supplement.

MODIFIED SEQUENTIAL ORAL CONTRACEPTIVE

This invention relates to a modified sequential oral contraceptive.

Oral contraceptives currently accepted are of two types. Both depend upon the administration to the nonpregnant female of a progestogen and an estrogen. In one type, which is the combination type, both a progestogen and an estrogen are prescribed for daily use over a period of 20 or 21 days, followed by a 5 to 7 day period when neither is taken, to allow for a bleeding phase, then the combination is resumed. The progestogen level is fairly high. This establishes a 25 to 28 day cycle.

The second, sequential type, also establishes a 25 to 28 day cycle but in the first phase of 15 to 16 days only an estrogen is ingested, then in the second 5 or 6 day phase a combination of progestogen and estrogen, as in the combination type, is taken. A blank period of 5 to 7 days when neither type of steroid is taken, to allow for a bleeding period, also completes this 25 to 28 cycle.

While both types have proven quite effective, each offers certain disadvantages. With the combined hormone therapy, the uterine histology does not resemble the normal proliferative or secretory picture in normal "cycling" women. Instead the endometrium is of a mixed type generally described as pseudopregnant. There is also some incidence of amenorrhea and many women do not return to normal cycles for many months after discontinuing the use of the contraceptive combination. The high cost of progestogen is also a factor.

The sequential type of administration is somewhat closer to the sequence of physiological ovarian secretion, but two separate types of tablets must be taken in proper sequence and this is confusing to some. More importantly, estrogen prepares the uterus for ova implantation in addition to inhibiting pituitary gonadotrophins. This requires strict adherence to the daily dosage schedule since deviation from the 24 hour interval of medication may result in a surge of gonadotrophin leading to ovulation and increased possibility of fertilization and pregnancy.

It is an object of this invention to provide a modified contraceptive retaining the advantages of both types and overcoming disadvantages.

According to this invention, progestogen and estrogen are administered throughout the 20 or 23 day therapy period. However, in the initial 14 to 19 day phase the amount of progestogen is sharply decreased from the amount currently supplied in the combination type of contraceptive. Then in the succeeding 4 to 7 day phase estrogen plus a high amount of progestogen is used. Then there is a 5 to 7 day bleeding period when there is no hormone administered or alternatively, a placebo or iron and/or vitamin supplement is taken to institute a one-a-day regimen during the complete 25 to 28 day cycle in order to reduce patient failure as described in my copending application Ser. No. 483,859, filed Aug. 30, 1965, now abandoned.

Thus the dosage regimen for this combination is 14 to 19 days of estrogen + low dose of progestogen, then 7 to 4 days of estrogen + high dose of progestogen followed by 5 to 7 days of no therapy or placebo or iron for a 28 day repeating cycle. Typical variations of the days in each phase of the cycle, preferably of 28 day duration, include, for example, 14 + 7 + 7, 16 + 5 + 7, 19 + 4 + 5, 17 + 6 + 5, 18 + 5 + 5. The low dose of progestogen in the first phase will tend to prevent pregnancy even if a tablet is missed by the effect of progestogen on ova transport, prevention of "rebound phenomena" induced by withdrawal of estrogen inhibition and the suppressive effect upon ovarian steroidogenesis not seen with treatment with either type of steroid alone.

The large amount of progestogen in the second 4 to 7 day phase is to insure an adequate buildup of endometrium to allow for a more effective desquamation upon withdrawal of hormone treatment.

The estrogen component of the oral contraceptive regimen is generally administered in an amount of 0.05 to 0.1 mg. daily throughout the 20 to 21 day period of therapy within the 25 to

28 day cycle. According to this invention, the low amount of progestogen combined with the estrogen during the initial 14 to 19 day phase of the cycle is about 0.25 to about 20 mg. The high amount of progestogen combined with the estrogen during the second 4 to 7 phase of the cycle is then increased to about 2 to 200 mg.

In speaking of "low" and "high" amounts of progestogen, it will be appreciated that these are related to the potency of the particular progestogen selected. Progestational agents which are effective in conventional contraceptive preparations are administered in amounts of about 1 to 25 mg. per day depending upon their potency. Thus in speaking of a low amount it is intended that about 10 to about 25 percent of that amount which would be administered according to prevailing practice in the currently used combination type of preparation or of that amount used in the second phase of the cycle. Similarly, the high dosage is the amount of progestogen required daily for an adequate development of a secretory endometrium preparatory to desquamation, i.e., in the range of about 2 to 250 mg. The low dosage of a given progestogen is insufficient to adequately produce this condition and may be regarded as a subpotent amount.

Thus, for example, if chlormadinone acetate is used as the progestogen, this highly potent substance would be used according to conventional practice in an amount of about 3 mg. per day. According to this invention, about 0.25 to 0.5 mg. of chlormadinone is used in the first or low phase and about 2 to 5 mg. in the second or high phase.

Similarly, 16 α ,17 α -dihydroxyprogesterone acetophenone, a less potent progestational agent, is conventionally used at a dosage of about 50 to 250 mg. per day. According to this invention, the initial low amount is about 10 to 20 mg. per day and the later high dosage is about 50 to 200 mg. per day. The estrogens similarly vary in potency and are used according to this invention in the range of about 0.05 to 0.1 mg. (per day), preferably 0.075 to 0.1 mg. in both phases.

The contraceptives of this invention may be made up by conventional procedures in any form for oral administration, capsules, tablets and the like, but tablets are the preferred mode of administration.

The dosage units are preferably packaged in a dispensing device, e.g., a folder or sequential plastic dispenser, and arranged in a manner which facilitates the orderly daily administration in sequence and aids the woman in keeping track of her regimen. Color variations may be used as an aid in this respect.

In order to provide further aid in maintaining the regimen, the 21 to 23 tablets or capsules containing the hormones may be followed with a sequence of 5 to 7 similar placebo units, or units containing an iron and/or vitamin supplement for use during the nontherapy bleeding portion of the cycle to complete the 28 day period. In this manner, a tablet or capsule is taken every day and it is easier to keep track of the schedule and maintain regularity.

Estrogens which may be used according to this invention include 17 α -ethynylestradiol 3-methyl ether, 17-ethynylestradiol and any other orally active estrogens.

Progestogens include ethynodiol diacetate, megestrol acetate, 16 α ,17 α -dihydroxyprogesterone acetophenone, 17-hydroxy-19-nor-17 α -pregn-5(10)-en-20-yl-3-one, 19-nor-17 α -pregn-4-en-20-yne-3 β ,17-diol, 17-hydroxy-19-nor-17 α -pregn-4-en-20-yl-3-one and its acetate, 17-hydroxy-6 α -methyl-pregn-4-ene-3,20-dione and its acetate, 6 α ,21-dimethyl-17-hydroxy-pregn-4-en-20-yne-3-one, 6-chloro-17 α -hydroxy-pregna-4,6-diene-3,20-dione, 9 β ,10 α -pregna-4,16-diene-3,20-dione, and any other orally active progestogen.

A preferred regimen includes 14 tablets containing 5 to 20 mg. of 16 α ,17 α -dihydroxyprogesterone acetophenone + 75 to 100 mcg. of ethinyl estradiol followed by 7 tablets containing 25 to 50 mg. of 16 α ,17 α -dihydroxyprogesterone acetophenone + 75 to 100 mcg. of ethinyl estradiol. This may be followed by 7 placebo tablets or 7 tablets each con-

taining supplemental iron in any of the conventionally available forms, e.g., 5 to 50 mg. daily (as elemental iron), with or without a maintenance multivitamin formula of conventional constitution including vitamins A, B complex, C, D, etc.

The following examples are illustrative of the invention.

EXAMPLE 1

a. 1,000 capsules are prepared from the following ingredients:

16 α ,17 α -dihydroxyprogesterone acetophenonide	10 gm.
Ethinyl estradiol	75 mg.
Lactose	326 gm.
Talc	10.5 gm.
Magnesium stearate	3.5 gm.

The ethinyl estradiol is dissolved in chloroform and dispersed on the lactose, then let dry. This is admixed with the acetophenonide, talc and magnesium stearate. The mixture is subdivided and filled into 1000 No. 2 red gelatin capsules each containing 10 mg. of the acetophenonide and 75 mcg. of ethinyl estradiol.

b. 1,000 No. 2 uncolored capsules are prepared from the same ingredients as in part (a) except that 50 gm. of 16 α ,17 α -dihydroxyprogesterone acetophenonide and 286 gm. of lactose are used. Each capsule contains 50 mg. of the acetophenonide and 75 mcg. of ethinyl estradiol. Fourteen capsules from part (a) and 7 capsules from part (b) are placed in individual, plastic covered compartments in rows in a folder with directions to take one per day of the red capsules for 14 days beginning with day 5 from onset of menstruation and then one per day of the white capsules for 7 days.

EXAMPLE 2

a. 1,000 tablets of 90 mg. each are prepared from the following ingredients:

Mestranol	80 mg.
Chlormadinone	500 mg.
Spray dried lactose	43.52 kg.
Microcrystalline cellulose (Avicel)	45.0 kg.
Stearic acid	900 mg.

The mestranol and chlormadinone are dissolved in chloroform. The solution is poured onto the microcrystalline cellulose while mixing, then this is allowed to dry. The dried mixture, lactose and stearic acid are blended, then compressed into tablets using a 3/4-inch standard concave die. The tablets are undercoated with shellac, dried and pan coated with FD & C Red No. 3. Each tablet contains 0.5 mg. of chlormadinone and 80 mcg. of mestranol.

b. 1,000 tablets of 90 mg. each are prepared from the same ingredients as in part (a) except that 3 grams of chlormadinone and 41.02 kg. of spray dried lactose are used. The tablets are left uncoated. Each contains 3 mg. of chlormadinone and 80 mcg. of mestranol.

Nineteen tablets from part (a) and 4 tablets from part (b) are placed in sequence in a plastic dispenser dispensing one tablet at a time with directions as in example 1 except for appropriate changes in the number of days to 19 and 4, respectively.

EXAMPLE 3

One thousand tablets of 90 mg. each are prepared from the following ingredients:

Lactose	44.1 gm.
Microcrystalline cellulose (Avicel)	45.0 gm.
Stearic acid	0.9 gm.

The tablets are compressed as in example 2 and coated with FD & C Blue No. 1.

Five tablets prepared as above are added to a dispenser as in example 2 with further directions to take one blue tablet each

day for 5 days following the white tablets.

EXAMPLE 4

One thousand tablets of 145 mg. each are prepared from the following ingredients:

5 Ferrous sulfate	25 gm.
Sucrose	100 gm.
Lactose	20 gm.

The above materials are granulated with 3 percent of a polyvinyl pyrrolidone-alcohol solution, dried and admixed with 3 percent by weight of starch and 1 percent by weight of stearic acid, then compressed and coated as in example 2 (FD & C Blue No. 1). Five of these iron tablets are used in place of the placebos in example 3.

I claim:

1. A packaged sequential combination of contraceptive composition which comprises unit dosage forms for oral administration of one unit dosage form daily in sequence during a 25 to 28 day cycle, each of the first 14 to 19 of said unit dosage forms comprising as the essential components a first phase combination of estrogen in a daily dosage amount of from 0.5 mg. to 0.1 mg., said amount preparing the uterus for ova implantation in addition to inhibiting pituitary gonadotrophins, which daily estrogen dosage if omitted during a 24 hour interval may result in a surge of gonadotrophin leading to ovulation, with a subpotent dosage of a given species of progestogen, each of the next 4 to 7 unit dosage forms comprising as the essential components a second phase combination of estrogen with an increased dosage of progestogen, the amount of the same species of progestogen in the initial 14 to 19 unit dosage forms being about 10 to about 25 percent of the amount in each of the subsequent 4 to 7 unit dosage forms, said daily sequential unit dosages being placed in consecutive sequence in individual covered compartments in a dispensing package bearing direction to take one per day and adapted for dispensing one at a time each day, said subpotent, first phase dosages of a given species of progestogen being insufficient to adequately produce the development of a secretory endometrium and tending to prevent pregnancy if a daily dosage is missed by the effect of progestogen on ova transport, prevention of rebound phenomena induced by withdrawal of estrogen inhibition and suppressive effect on ovarian steroidogenesis not seen with treatment with either type of steroid alone, said second phase high dosages of the same species of progestogen being the amount required daily for insuring an adequate development of a secretory endometrium preparatory to desquamation upon withdrawal of hormone treatment.

2. A combination of tablets as in claim 1 comprising a first series of 14 to 19 tablets each containing about 0.05 to about 0.1 mg. of estrogen and about 0.25 to about 20 mg. of progestogen and a second series of 4 to 7 tablets each containing about 0.05 to about 0.1 mg. of estrogen and about 2 to about 200 mg. of progestogen.

3. A combination of tablets as in claim 1 wherein the first 14 to 19 tablets contain about 75 mcg. of ethinyl estradiol and about 10 mg. of 16 α ,17 α -dihydroxyprogesterone acetophenonide and the next 4 to 7 tablets contain about 75 mcg. of ethinyl estradiol and about 50 mg. of 16 α ,17 α -dihydroxyprogesterone acetophenonide.

4. A combination of tablets as in claim 3 wherein the first 14 to 19 tablets contain about 75 mcg. of ethinyl estradiol and about 10 mg. of 16 α ,17 α -dihydroxyprogesterone acetophenonide, the next 4 to 7 tablets contain about 75 mcg. of ethinyl estradiol and about 50 mg. of 16 α ,17 α -dihydroxyprogesterone acetophenonide and a third series of 5 to 7 tablets to complete the 25 to 28 unit cycle contains about 5 to 50 mg. of iron in each.

5. A combination as in claim 1 wherein an additional 4 to 7 unit dosage form comprises iron supplement or nonmedicinal ingredients.