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(54) CONTRACEPTIVE METHOD AND PACK

(71) We, SCHERING AKTIENGESELLSCHAFT, a Body Corporate organised according to the laws of Germany, of Berlin and Bergkamen, Germany, 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 is concerned with a contraceptive method and packs.

Hormonal methods of contraception have been known, and *inter alia*, the oral administration of combination preparations such, for example, as Ovulen*, Anovlar*, Lyndiol*, and similar combinations of oestrogenically and gestagenically active substances. It has also been known to administer purely sequential preparations, for example Ovanon*, with which there is administered first an oestrogen at a high dosage for 7 days without the addition of a gestagen, and then the oestrogen at the same high dosage together with a relatively large quantity of a gestagen for 15 days, and for the following 6 days the intake is discontinued to conform with the normal cycle of the woman. It has also been known to administer modified sequential preparations, for example Kombiquens*, Tri-Ervonum* and Oraconal*, with which there is administered first an oestrogen at a high dosage together with a small quantity of a gestagen for 16 days and then the oestrogen at the same dosage together with about 10 times the original quantity of the gestagen for 7 days. In conformity with the normal cycle of the woman the administration of this preparation is followed by a hormone-free period of five days, during which placebos or any other desired active substances, for example tonics and iron preparations, are administered.

There has also been known the application of two-stage combination preparations, in which is administered first a combination of an oestrogen in a small dosage and a gestagen in a small dosage for 10 to 12 days and then a combination of the oestrogen at the same dosage and the gestagen at a dosage 2 to 3 times larger for 11 to 9 days. In conformity with the normal cycle of a woman of about 28 days no oestrogens and gestagens are administered on the following 7 days. This phase is kept free from hormone intake in a known manner by administering placebos or other active substances.

Disadvantages of the administration of the aforesaid purely and modified sequential preparations are, more especially, the administration of relatively high doses of an oestrogen, which, in addition to the effects usually caused by excess of an oestrogen, for example gastro-intestinal disturbances, nausea and an increase in weight with the formation of oedemas, causes an increase in the risk of thrombo-embolic occurrences. These disadvantages have been avoided by the above mentioned two-stage combination contraceptive preparations, but it is, however, desirable to improve their tolerability and/or cycle control. This problem has now been solved by the method of contraception of the present invention as defined below.

The present invention provides a method of contraception, wherein there is administered to a human female one each of 4 to 6 (for example 6) successive days a first, low oestrogenic daily dosage of an oestrogen and a first low, gestagenic daily dosage of a gestagen, then on each of the immediately following 4 to 6 (for example 5) successive days, to complete a 10- to 12-day period, a second

* Ovulen, Anovlar, Lyndiol, Ovanon, Kombiquens, Tri-Ervonum and Oraconal are Trade Marks.

oestrogenic daily dosage of an oestrogen that is, on average, no less than, and nor more than twice, the average low oestrogenic daily dosage administered in the preceding 4 to 6 days, and a second gestagenic daily dosage of a gestagen that is, on average, no less than, and no more than 1½ times as great as, the average low gestagenic daily dosage administered in the preceding 4 to 6 days, and then on each of the immediately following 9 to 11 (for example 10) successive days, to complete a 21-day period, a third oestrogenic daily dosage of an oestrogen that is, on average, no more than the average second oestrogenic daily dosage administered in the preceding 4 to 6 days and no less than the average low oestrogenic daily dosage administered in the first 4 to 6 days, and a third gestagenic daily dosage of a gestagen that is, on average, more than the average second gestagenic daily dosage administered in the preceding 4 to 6 days and no more than 3 times as great as the average low gestagenic daily dosage administered in the first 4 to 6 days, and no oestrogen or gestagen is administered on each of the immediately following successive days, and the 28-day cycle is repeated.

Whenever used herein the term "first, low, oestrogenic daily dosage" is used to denote a total daily dosage of an oestrogen having the same oestrogenic activity as 0.02 to 0.05 mg of 17α-ethynyl-oestradiol daily. Whenever used herein the term "second oestrogenic daily dosage" is used to denote a total daily dosage of an oestrogen having the same oestrogen activity as 0.03 to 0.05 mg of 17α-ethynyl-oestradiol daily, (provided that on average the dosage is not less than, and is not more than twice, the average low oestrogenic daily dosage administered). Whenever used herein, the term "third oestrogenic daily dosage" is used to denote a total daily dosage of an oestrogen having the same oestrogen activity as 0.025 to 0.05 mg of 17α-ethynyl-oestradiol daily, (provided that on average the dosage is no more than the average second oestrogenic daily dosage administered in the preceding 4 to 6 days and no less than the average low oestrogenic daily dosage administered in the first 4 to 6 days).

The low oestrogenic daily dosages can, of course, vary slightly from day to day, provided they comply with the above definition, although they are preferably substantially uniform. Similarly, the second and third oestrogenic daily dosages can vary slightly from day to day, although they are preferably substantially uniform.

Whenever used herein, the term "first, low, gestagenic daily dosage" is used to denote a total daily dosage of a gestagen having the same gestagenic activity as 0.04 to 0.09 mg of *d*-norgestrel daily. Whenever used herein, the term "second gestagenic daily dosage" is used to denote a total daily dosage of a gestagen having the same gestagenic activity as 0.05 to 0.125 mg of *d*-norgestrel daily, (provided that on average the dosage is not less than, and not more than one and a half times as great as, the average low gestagenic daily dosage administered). Whenever used herein, the term "third gestagenic daily dosage" is used to denote a total daily dosage of a gestagen having the same gestagenic activity as 0.1 to 0.25 mg of *d*-norgestrel daily, (provided that on average the dosage is more than the average second gestagenic daily dosage administered in the preceding 4 to 6 days and no more than 3 times as great as the average low gestagenic daily dosage administered in the first 4 to 6 days).

The low gestagenic daily dosages can, of course, vary slightly from day to day, provided they comply with the above definition, although they are preferably substantially uniform. Similarly, the second and third gestagenic daily dosages can vary slightly from day to day, although they are preferably substantially uniform.

In general, the first day of the 28-day administration cycle corresponds to the first day of menstruation.

The total number of days during which the combinations of active substances are applied should always be 21, after which should follow 7 days free from hormone intake. This stage may, in a known manner, be free from intake or, alternatively, placebos or other active substances may be administered, without affecting the reliability of the method.

The present invention also provides a contraceptive pack suitable for carrying out the method of the present invention which comprises, in or on a container, card or other support member, unit dosage forms, suitable for oral adminsitration, of an oestrogen and of a gestagen, which provide

(a) a first set of 4 to 6 first, low, oestrogenic daily dosages (as hereinbefore defined),

(b) a first set of 4 to 6 first, low, gestagenic daily dosages (as hereinbefore defined),

(c) a second set of 4 to 6 second oestrogenic daily dosages (as hereinbefore defined) which, on average, are not less than, and not more than twice, the average of the first low oestrogenic daily dosages (a), completing 10 to 12 oestrogenic daily dosages,

(d) a second set of 4 to 6 second gestagenic daily dosages (as hereinbefore defined) which, on average, are not less than, and not more than one and a half times as great as, the average of the first, low gestagenic daily dosages (b), completing 10 to 12 gestagenic daily dosages,

(e) a third set of 9 to 11 third oestrogenic daily dosages (as hereinbefore defined) which, on average, are no more than the average of the second oestrogenic daily dosages (c) and no less than the average of the first low oestrogenic daily dosages (a), completing 21 oestrogenic daily dosages, and

(f) a third set of 9 to 11 third gestagenic daily dosages (as hereinbefore defined) which, on average, are more than the average of the second gestagenic daily dosages (d) and no more than 3 times as great as the average of the first low gestagenic daily dosages (b), completing 21 gestagenic daily dosages,

the sets being located in a particular order, together with indications and/or instructions, to indicate and facilitate a treatment consisting of the administration to a human female on each of 4 to 6 successive days of one of the low oestrogenic daily dosages (a) and one of the low gestagenic daily dosages (b), on each of the immediately following 4 to 6 successive days, to complete 10 to 12 days, one of the second oestrogenic daily dosages (c) and one of the second gestagenic daily dosages (d), and on each of the immediately following 9 to 11 successive days, to complete 21 days, one of the third oestrogenic daily dosages (e) and one of the third gestagenic daily dosages (f), and on each of the immediately following 7 successive days no administration of oestrogen or gestagen.

Each daily dosage of (a) and (b) may be combined in a single unit dosage form, each daily dosage of (c) and (d) may be combined in a single unit dosage form, and each daily dosage of (e) and (f) may be combined in a single unit dosage form, and the instructions contained in the contraceptive pack may require that there is administered on each of the first 4 to 6 successive days, the immediately following 4 to 6 successive days and the immediately following 9 to 11 successive days a single unit dosage preparation present in the pack, the single unit dosage preparation containing the total amount of the oestrogen and of the gestagen required to be administered on that day.

The pack may also include, in or on the container, card or other support member, unit dosage forms which provide 7 daily dosages free from oestrogen and gestagen, suitably each daily dosage being in a single unit dosage form, and the instructions may also, if desired, require that there is administered on each of the 7 successive days immediately following the 9 to 11 successive days a single unit dosage preparation present in the pack, the single unit dosage preparation being free from oestrogens and gestagens. All such unit dosage preparations present in the pack are arranged in an order facilitating their administration in the required manner.

Each of the unit dosage preparations in the contraceptive pack may contain the carriers, taste correctives and/or fillers normally used in galenical pharmacy, and are advantageously in a form suitable for oral administration, for example tablets or dragées.

Gestagens are also known as gestogens, progestins, progestogens and progestational hormones.

The oestrogens used in accordance with the present invention in the first, second and third stages may be the same or different (the first stage meaning the aforesaid first 4 to 6 successive days, the second stage meaning the immediately following 4 to 6 successive days and the third stage meaning the immediately following 9 to 11 days).

The oestrogen used should be administered in such doses that the quantity of the oestrogen used in accordance with the present invention on the first 4 to 6 days produces the same oestrogenic activity as that produced by the daily administration in the same way of 0.020 to 0.050 mg of 17α-ethynyl-oestradiol. The quanity of oestrogen used in accordance with the present invention on the 4 to 6 days of the second stage should produce the same oestrogenic activity as that produced by the daily administration in the same way of 0.030 to 0.050 mg of 17α-ethynyl-oestradiol. The quantity of oestrogen used in accordance with the present invention on the 9 to 11 days of the third stage should produce the same oestrogenic activity as that produced by the daily administration in the same way

of 0.025 to 0.050 mg of 17α-ethynyl-oestradiol.

As oestrogen components there are suitable besides 17α-ethynyl-oestradiol, for example 17α-ethynyl-oestradiol esters and ethers. There also come into consideration natural oestrogens, for example oestrone, oestradiol or oestriol, and esters thereof, for example oestradiol valerate. 17α-Ethynyl-oestradiol is, however, preferred.

The gestagen used is administered in such doses that the quantity of gestagen used in accordance with the present invention on the first 4 to 6 days produces the same gestagenic activity as that produced by the daily administration in the same way of 0.040 to 0.090 mg of *d*-norgestrel (18-methyl-17α-ethynyl-19-nor-testosterone). The quantity of the gestagen used in accordance with the present invention on the 4 to 6 days of the second stage should produce the same gestagenic activity as that produced by the daily administration in the same way of 0.050 to 0.125 mg of *d*-norgestrel. The quantity of gestagen used in accordance with the present invention on the 9 to 11 days of the third stage should produce the same gestagenic activity as that produced by the daily administration in the same way of about 0.100 to 0.250 mg of *d*-norgestrel.

As gestagen components there are suitable, for example, progesterone and gestagenic derivatives thereof, for example ester of 17α-hydroxy-progesterones and of 19-nor-17α-hydroxy-progesterone and their 18-methyl homologues, and gestagenic testosterone derivaties and gestagenic 19-nor-testosterone derivatives, for example 17α-ethynyl-testosterone, 17α-ethynyl-19-nor-testosterone their 18-methyl homologues, and also esters thereof.

As esters there come into consideration esters of acids that are customarily used in steroid chemistry for esterifying steroid alcohols. There may be mentioned, for example, alkane carboxylic acids, especially alkane carboxylic acids containing 1 to 11 carbon atoms.

Preferred gestagens are, as testosterone derivatives *d*-norgestrel (18-methyl-17α-ethynyl-19-nor-testosterone) and and 17α-ethynyl-19-nor-testosterone acetate and, as progesterone derivative 6-chloro-1,2α-methylene-$\Delta^{4,6}$-pregnadien-17α-ol-3,20-dione 17-acetate (cyproterone acetate).

The gestagens used in combination with the oestrogens in accordance with the present invention (like the oestrogens) may be the same or different in the first and second or third stages.

When different gestagens (or oestrogens) are used in the first and second or third stages, the contraceptive method has, in addition to the aforesaid advantages, the further advantage of enabling the side effects of a particular gestagen (or oestrogen) to be reduced or eliminated by administering that gestagen (or oestrogen) in one stage only, and administering in one of the other stages a different gestagen (or oestrogen) that behaves competitively with respect to the side effects.

Thus, for example, in one stage the oestrogen may be used in combination with 17α-ethynyl-testosterone or 17α-ethynyl-19-nor-testosterone or an ester thereof; these (19-nor-) testosterone derivatives generally have a small androgenic side effect. Then, in one of the other stages, the oestrogen may be used in combination with a gestagen that is derived from progesterone and does not have the androgenic side effect inherent in testosterone compounds or 19-nor-testosterone compounds. Especially advantageous gestagens are those progesterone derivatives that possess, in addition to the gestagenic action, an anti-androgenic side effect (i.e. are able to neutralise partially or completely the action of androgens).

Also, for example, there may be used in one stage a gestagen in combination with an oestrogen derived from 17α-ethynyl-oestradiol. These compounds generally have a low gastric tolerability and a strong action upon carbohydrate and fat metabolism. Then, in one of the other stages the gestagen may be used in combination with an oestrogen that is derived from natural oestrogens and does not have the aforesaid side effects.

When different gestagens are used in the first and second or third stages, a preferred embodiment is to use the oestrogen in the first and second stages in combination with 17α-ethynyl-testosterone or 17α-ethynyl-19-nor-testosterone or an ester thereof and to use the oestrogen in the third stage in combination with an ester of 17α-hydroxy-progesterone, 19-nor-17α-hydroxy-progesterone or their 18-methyl homologues.

When different oestrogens are used in the first and second or third stages, a preferred embodiment is to use the gestagen in the first and second stages in

combination with a 17α-ethynyl-oestradiol derivative and to use the gestagen in the third stage in combination with an oestrogen containing no 17α-ethynyl group.

For example, there may be administered any of the following dosage combinations A to E.

	Daily dosage for each of 4 to 6 successive days (1st stage)	Daily dosage for each of the immediately following 4 to 6 successive days (2nd stage)	Daily dosage for each of the immediately following 9 to 11 successive days (3rd stage)
A	0.03 mg 17α-ethynyl-oestradiol 0.05 mg *d*-norgestrel	0.05 mg 17α-ethynyl-oestradiol 0.05 mg *d*-norgestrel	0.04 mg 17α-ethynyl-oestradiol 0.125 mg *d*-norgestrel
B	0.03 mg 17α-ethynyl-oestradiol 0.05 mg *d*-norgestrel	0.04 mg 17α-ethynyl-oestradiol 0.075 mg *d*-norgestrel	0.03 mg 17α-ethynyl-oestradiol 0.125 mg *d*-norgestrel
C	0.03 mg 17α-ethynyl-oestradiol 0.05 mg *d*-norgestrel	0.05 mg 17α-ethynyl-oestradiol 0.075 mg *d*-norgestrel	0.04 mg 17α-ethynyl-oestradiol 0.125 mg *d*-norgestrel
D	0.05 mg 17α-ethynyl-oestradiol 0.05 mg *d*-norgestrel	0.05 mg 17α-ethynyl-oestradiol 0.075 mg *d*-norgestrel	0.05 mg 17α-ethynyl-oestradiol 0.125 mg *d*-norgestrel
E	3 mg oestradiol valerate 0.05 mg *d*-norgestrel	5 mg oestradiol valerate 0.05 mg *d*-norgestrel	4 mg oestradiol valerate 0.125 mg *d*-norgestrel

The oestrogenically and gestagenically active components are preferably administered orally together, buy they may, however, also be administered separately or parenterally. For this purpose the active substances may be worked up into the usual forms for administration with the additives, carrier substances and/or taste correctives normally used in galenical pharmacy by methods known *per se*. For oral administration, which is preferred, there may be mentioned, more especially, tablets, dragees, capsules, pills, suspensions or solutions, and for parenteral administration, more especially, oily solutions, for example solutions in sesame oil or castor oil, which may also, if desired, contain a diluent, for example benzyl benzoate or benzyl alcohol.

The contraceptive pack may be constructed, for example, in the form of a clear vision-package containing, for example, 6 dragees of the first stage, 5 dragees of the second stage, 10 dragees of the third stage and 7 placebos, one of which unit dosage preparations can be taken out each day over a period of 28 days.

The following Examples illustrate the invention:—

Example 1.

Composition of one dragée for each stage of method of contraception

1st Stage (6 dragées)	0.030 mg	of 17α-ethynyl-oestradiol
	0.050 mg	of *d*-norgestrel
	33.170 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of 6 successive days.

2nd Stage (5 dragées)	0.050 mg	of 17α-ethynyl-oestradiol
	0.050 mg	of *d*-norgestrel
	33.150 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of the immediately following 5 successive days.

3rd Stage (10 dragées)	0.040 mg	of 17α-ethynyl-oestradiol
	0.125 mg	of *d*-norgestrel
	33.085 mg	of lactose
	18.00 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of the immediately following 10 successive days.

Example 2.

Composition of one dragée for each stage of method of contraception

1st Stage (6 dragées)	0.030 mg	of 17α-ethynyl-oestradiol
	0.050 mg	of *d*-norgestrel
	33.070 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	0.100 mg	of magnesium stearate
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of 6 successive days.

2nd Stage	0.040 mg	of 17α-ethynyl oestradiol
	0.075 mg	of *d*-norgestrel
	33.035 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	0.100 mg	of magnesium stearate
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of the immediately following 5 successive days.

3rd Stage (10 dragées)	0.030 mg	of 17α-ethynyl-oestradiol
	0.125 mg	of *d*-norgestrel
	32.995 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	0.100 mg	of magnesium stearate
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of the immediately following 10 successive days.

Example 3.

Composition of one dragée for each stage of method of contraception

1st Stage (6 dragées)	0.030 mg	of 17α-ethynyl-oestradiol
	0.050 mg	of *d*-norgestrel
	33.070 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	0.100 mg	of magnesium stearate
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of 6 successive days.

2nd Stage (5 dragées)	0.050 mg	of 17α-ethynyl-oestradiol
	0.075 mg	of *d*-norgestrel
	33.025 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	0.100 mg	of magnesium stearate
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of the immediately following 5 successive days.

3rd Stage (10 dragées)	0.040 mg	of 17α-ethynyl-oestradiol
	0.125 mg	of *d*-norgestrel
	32.985 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	0.100 mg	of magnesium stearate
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of the immediately following 10 successive days.

Example 4.
Composition of one dragée for each stage of method of contraception

1st Stage (6 dragées)	0.050 mg	of 17α-ethynyl-oestradiol
	0.050 mg	of *d*-norgestrel
	33.050 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	0.100 mg	of magnesium stearate
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of 6 successive days.

2nd Stage (5 dragées)	0.050 mg	of 17α-ethynyl-oestradiol
	0.075 mg	of *d*-norgestrel
	33.025 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	0.100 mg	of magnesium stearate
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of the immediately following 5 successive days.

3rd Stage (10 dragées)	0.050 mg	of 17α-ethynyl-oestradiol
	0.125 mg	of *d*-norgestrel
	32.975 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	0.100 mg	of magnesium stearate
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragee of this composition is administered on each of the immediately following 10 successive days.

Example 5.

Composition of one dragée for each stage of method of contraception

1st Stage (6 dragées)	3.000 mg	of oestradiol valerate
	0.050 mg	of *d*-norgestrel
	30.200 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of 6 successive days.

2nd Stage (5 dragées)	5.000 mg	of oestradiol valerate
	0.050 mg	of *d*-norgestrel
	28.200 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of the following 5 successive days.

3rd Stage (10 dragées)	4.000 mg	of oestradiol valerate
	0.125 mg	of *d*-norgestrel
	29.125 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of the immediately following 10 successive days.

WHAT WE CLAIM IS:—

1. A method of contraception, wherein there is administered to a human female one each of 4 to 6 successive days a first, low oestrogenic daily dosage (as hereinbefore dfined) of an oestrogen and a first low, gestagenic daily dosage (as hereinbefore defined) of a gestagen, then on each of the immediately following 4 to 6 successive days, to complete a 10- to 12-day period, a second oestrogenic daily dosage (as hereinbefore defined) of an oestrogen that is, on average, no less than, and no more than twice, the average low oestrogenic daily dosage administered in the preceding 4 to 6 days, and a second gestagenic daily dosage (as hereinbefore defined) of a gestagen that is, on average, no less than, and no more than one and a half times as great as, the average low gestagenic daily dosage administered in the preceding 4 to 6 days, and then on each of the immediately following 9 to 11 successive days, to complete a 21-day period, a third oestrogenic daily dosage (as hereinbefore defined) of an oestrogen that is, on average, no more than the average second oestrogenic daily dosage administered in the preceding 4 to 6 days and no less than the average low oestrogenic daily dosage administered in the first 4 to 6 days, and a third gestagenic daily dosage (as hereinbefore defined) of a gestagen that is, on average, more than the average second gestagenic daily dosage administered in the preceding 4 to 6 days, and no more than 3 times as great as the average low gestagenic daily dosage administered in the first 4 to 6 days, and no oestrogen or gestagen is administered on each of the immediately following successive days, and the 28-day cycle is repeated.

2. A method as claimed in claim 1, wherein on each of the first 4 to 6 successive days, on each of the following 4 to 6 successive days and on each of the

Example 5.
Composition of one dragée for each stage of method of contraception

1st Stage (6 dragées)	3.000 mg	of oestradiol valerate
	0.050 mg	of *d*-norgestrel
	30.200 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of 6 successive days.

2nd Stage (5 dragées)	5.000 mg	of oestradiol valerate
	0.050 mg	of *d*-norgestrel
	28.200 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of the following 5 successive days.

3rd Stage (10 dragées)	4.000 mg	of oestradiol valerate
	0.125 mg	of *d*-norgestrel
	29.125 mg	of lactose
	18.000 mg	of maize starch
	2.100 mg	of polyvinylpyrrolidone
	1.650 mg	of talcum
	55.000 mg	total weight, which is made up with the usual sugar mixture to about 90 mg.

A single dragée of this composition is administered on each of the immediately following 10 successive days.

WHAT WE CLAIM IS:—

1. A method of contraception, wherein there is administered to a human female one each of 4 to 6 successive days a first, low oestrogenic daily dosage (as hereinbefore dfined) of an oestrogen and a first low, gestagenic daily dosage (as hereinbefore defined) of a gestagen, then on each of the immediately following 4 to 6 successive days, to complete a 10- to 12-day period, a second oestrogenic daily dosage (as hereinbefore defined) of an oestrogen that is, on average, no less than, and no more than twice, the average low oestrogenic daily dosage administered in the preceding 4 to 6 days, and a second gestagenic daily dosage (as hereinbefore defined) of a gestagen that is, on average, no less than, and no more than one and a half times as great as, the average low gestagenic daily dosage administered in the preceding 4 to 6 days, and then on each of the immediately following 9 to 11 successive days, to complete a 21-day period, a third oestrogenic daily dosage (as hereinbefore defined) of an oestrogen that is, on average, no more than the average second oestrogenic daily dosage administered in the preceding 4 to 6 days and no less than the average low oestrogenic daily dosage administered in the first 4 to 6 days, and a third gestagenic daily dosage (as hereinbefore defined) of a gestagen that is, on average, more than the average second gestagenic daily dosage administered in the preceding 4 to 6 days, and no more than 3 times as great as the average low gestagenic daily dosage administered in the first 4 to 6 days, and no oestrogen or gestagen is administered on each of the immediately following successive days, and the 28-day cycle is repeated.

2. A method as claimed in claim 1, wherein on each of the first 4 to 6 successive days, on each of the following 4 to 6 successive days and on each of the

following 9 to 11 successive days, the daily dosages are substantially uniform dosages.

3. A method as claimed in claim 1 or claim 2, wherein on each of the days the oestrogen and the gestagen are administered together.

4. A method as claimed in any one of claims 1 to 3, wherein on each of the days the oestrogen and the gestagen are administered orally.

5. A method as claimed in any one of claims 1 to 4, wherein the first oestrogenic daily dosage and the first gestagenic daily dosage are administered on each of 6 successive days, the second oestrogenic daily dosage and the second gestagenic daily dosage are administered on each of the immediately following 5 successive days, and the third oestrogenic daily dosage and the third gestagenic daily dosage are administered on each of the immediately following 10 successive days.

6. A method as claimed in any one of claims 1 to 5, wherein the same oestrogen is administered on each of the first 4 to 6 successive days, the immediately following 4 to 6 successive days and the immediately following 9 to 11 successive days.

7. A method as claimed in any one of claim 1 to 5, wherein the oestrogen administered on each of the second 4 to 6 successive days or the oestrogen administered on each of the 9 to 11 successive days is different from the oestrogen administered on each of the first 4 to 6 successive days.

8. A method as claimed in any one of claims 1 to 7, wherein the or one of the oestrogens is 17α-ethynyl-oestradiol.

9. A method as claimed in any one of claims 1 to 8, wherein the or one of the oestrogens is oestradiol valerate.

10. A method as claimed in any one of claims 1 to 9, wherein the same gestagen is administered on each of the first 4 to 6 successive days, the immediately following 4 to 6 successive days and the immediately following 9 to 11 successive days.

11. A method as claimed in any one of claims 1 to 9, wherein the gestagen administered on each of the second 4 to 6 successive days or the gestagen administered on each of the 9 to 11 successive days is different from the gestagen administered on each of the first 4 to 6 successive days.

12. A method as claimed in any one of claims 1 to 11, wherein the or one of the gestagens is *d*-norgestrel.

13. A method as claimed in any one of claims 1 to 12, wherein the or one of the gestagens is cyproterone acetate.

14. A method as claimed in any one of claims 1 to 13, wherein the or one of the gestagens is 17α-ethynyl-19-nor-testosterone acetate.

15. A method as claimed in any one of claims 2 to 5, wherein there is administered any one of the dosage combinations A to E herein.

16. A method as claimed in claim 5, carried out substantially as indicated in any one of Examples 1 to 5 herein.

17. A contraceptive pack suitable for carrying out the method claimed in claim 1, which comprises, in or on a container, card or other support member, unit dosage forms, suitable for oral administration, of an oestrogen and of a gestagen, which provide

(a) a first set of 4 to 6 first, low, oestrogenic daily dosages (as hereinbefore defined),

(b) a first set of 4 to 6 first, low, gestagenic daily dosages (as hereinbefore defined),

(c) a second set of 4 to 6 second oestrogenic daily dosages (as hereinbefore defined) which, on average, are not less than, and not more than twice, the average of the first low oestrogenic daily dosages (a), completing 10 to 12 oestrogenic daily dosages,

(d) a second set of 4 to 6 second gestagenic daily dosages (as hereinbefore defined) which, on average, are not less than, and not more than one and a half times as great as, the average of the first, low gestagenic daily dosages (b), completing 10 to 12 gestagenic daily dosages,

(e) a third set of 9 to 11 third oestrogenic daily dosages (as hereinbefore defined) which, on average, are no more than the average of the second oestrogenic daily dosages (c) and no less than the average of the first low oestrogenic daily dosages (a), completing 21 oestrogenic daily dosages, and

(f) a third set of 9 to 11 third gestagenic daily dosages (as hereinbefore defined) which, on average, are more than the average of the second gestagenic

daily dosages (d) and no more than 3 times as great as the average of the first low gestagenic daily dosages (b), completing 21 gestagenic daily dosages, the sets being located in a particular order, together with indications and/or instructions, to indicate and facilitate a treatment consisting of the administration to a human female on each of 4 to 6 successive days of one of the low oestrogenic daily dosages (a) and one of the low gestagenic daily dosages (b), on each of the immediately following 4 to 6 successive days, to complete 10 to 12 days, one of the second oestrogenic daily dosages (c) and one of the second gestagenic daily dosages (d), and on each of the immediately following 9 to 11 successive days, to complete 21 days, one of the third oestrogenic daily dosages (e) and one of the third gestagenic daily dosages (f), and on each of the immediately following 7 successive days no administration of oestrogen or gestagen.

18. A contraceptive pack as claimed in claim 17, wherein each of the daily dosages (a) and (b), each of the daily dosages (c) and (d) and each of the daily dosages (e) and (f) is of substantially uniform dosage.

19. A contraceptive pack as claimed in claim 17 or claim 18, wherein the daily dosage of each of (a) and (b) is combined in a single unit dosage form.

20. A contraceptive pack as claimed in any one of claims 17 to 19, wherein the daily dosage of each of (c) and (d) is combined in a single unit dosage form.

21. A contraceptive pack as claimed in any one of claims 17 to 20, wherein the daily dosage of each of (e) and (f) is combined in a single unit dosage form.

22. A contraceptive pack as claimed in any one of claims 17 to 21, which includes, in or on the container, card or other support member, unit dosage forms which provide 7 daily dosages free from oestrogen and gestagen.

23. A contraceptive pack as claimed in any one of claims 17 to 22, wherein there are 6 daily dosages of each of (a) and (b) and 5 daily dosages of each of (c) and (d).

24. A contraceptive pack as claimed in any one of claims 17 to 23, wherein the same oestrogen is present in each of the daily dosages (a), (c) and (e).

25. A contraceptive pack as claimed in any one of claims 17 to 23, wherein the oestrogen present in each daily dosage (c) or (e) is different from the oestrogen present in each daily dosage (a).

26. A contraceptive pack as claimed in any one of claims 17 to 25, wherein the or one of the oestrogens is 17α-ethynyl-oestradiol.

27. A contraceptive pack as claimed in any one of claims 17 to 26, wherein the or one of the oestrogens is oestradiol valerate.

28. A contraceptive pack as claimed in any one of claims 17 to 27, wherein the same gestagen is present in each of the daily dosages (b), (d) and (f).

29. A contraceptive pack as claimed in any one of claims 17 to 27, wherein the gestagen present in each daily dosage (d) or (f) is different from the gestagen present in each daily dosage (b).

30. A contraceptive pack as claimed in any one of claims 17 to 29, wherein the or one of the gestagens is *d*-norgestrel.

31. A contraceptive pack as claimed in any one of claims 17 to 30, wherein the or one of the gestagens is 17α-ethynyl-19-nor-testosterone acetate.

32. A contraceptive pack as claimed in any one of claims 17 to 31, wherein the or one of the gestagens is cyproterone acetate.

33. A contraceptive pack as claimed in any one of claims 18 to 23, wherein the unit dosage forms provide any one of the dosage combinations A to E herein.

34. A contraceptive pack as claimed in any one of claims 17 to 33, wherein each unit dosage preparation is in the form of a tablet.

35. A contraceptive pack as claimed in any one of claims 17 to 33, wherein each dosage preparation is in the form of a dragée.

36. A contraceptive pack as claimed in claim 23, wherein the unit dosage forms are substantially as indicated in any one of the Examples 1 to 5 herein.

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