EXHIBIT 1005

US005552394A

United States Patent [19]

Hodgen

[11] Patent Number: 5,552,394

[45] Date of Patent: Sep. 3, 1996

[54] **LOW DOSE ORAL CONTRACEPTIVES WITH LESS BREAKTHROUGH BLEEDING AND SUSTAINED EFFICACY**

[75] Inventor: **Gary D. Hodgen**, Norfolk, Va.

[73] Assignee: **The Medical College of Hampton Roads**, Norfolk, Va.

[21] Appl. No.: **279,300**

[22] Filed: **Jul. 22, 1994**

[51] **Int. Cl.**[6] **A61K 31/56**

[52] **U.S. Cl.** **514/178**; 514/170; 514/182; 514/843

[58] **Field of Search** 514/170, 178, 514/182, 843

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,932,635	1/1976	Segre	424/239
5,010,070	4/1991	Boissonneault	514/171
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5,262,408	11/1993	Bergink	514/182

FOREIGN PATENT DOCUMENTS

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AHFS Drug Information 33, p. 2348. (1993).

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Primary Examiner—Kimberly Jordan

Attorney, Agent, or Firm—Ostrolenk, Faber, Gerb & Soffen, LLP

[57] **ABSTRACT**

A method of female contraception which is characterized by a reduced incidence of breakthrough bleeding after the first cycle involves monophasicly administering a combination of estrogen and progestin for 23–25 consecutive days of a 28 day cycle in which the daily amounts of estrogen and progestin are equivalent to about 5–35 mcg of ethinyl estradiol and about 0.025 to 10 mg of norethindrone acetate, respectively and in which the weight ratio of estrogen to progestin is at least 1:45 calculated as ethinyl estradiol to norethindrone acetate.

12 Claims, 2 Drawing Sheets

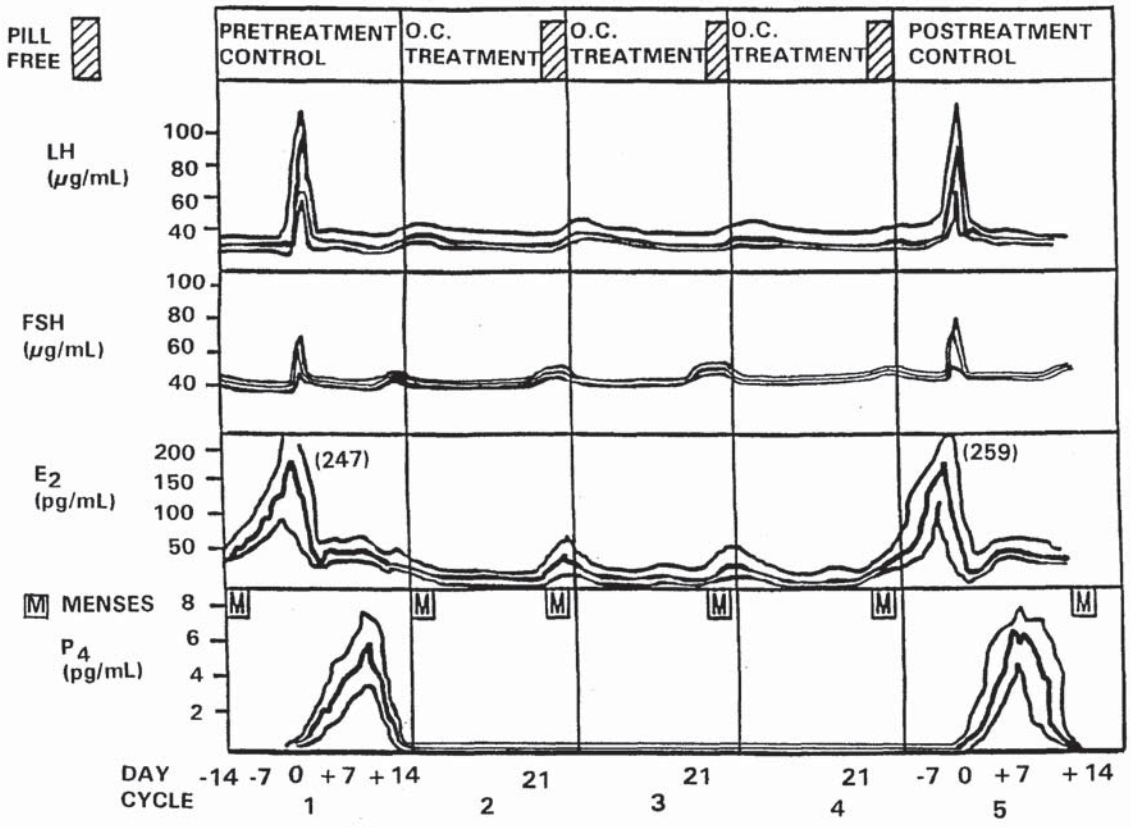

FIG. 1

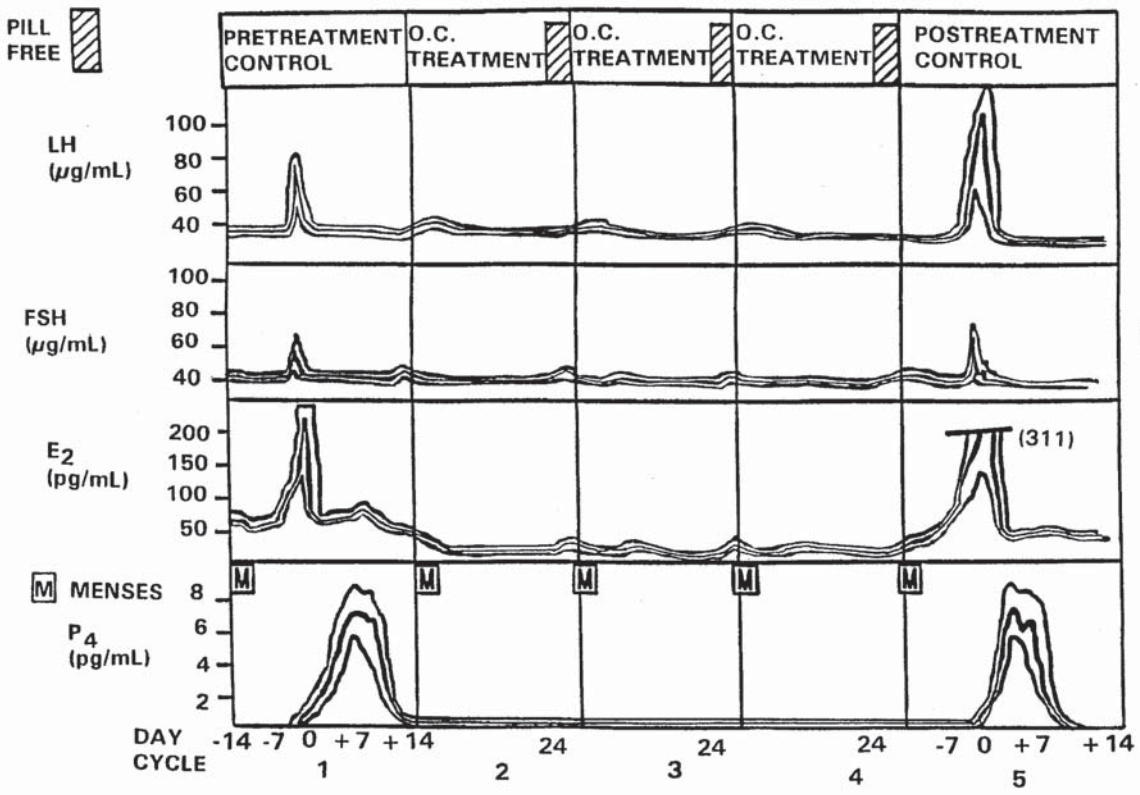

FIG. 2

LOW DOSE ORAL CONTRACEPTIVES WITH LESS BREAKTHROUGH BLEEDING AND SUSTAINED EFFICACY

BACKGROUND OF THE INVENTION

The ovarian/menstrual cycle is a complex event characterized by an estrogen rich follicular phase and, after ovulation, a progesterone rich luteal phase. Each has a duration of approximately 14 days resulting in an intermenstrual interval of about 28 days. The endometrial tissue responds to the changes in hormonal milieu.

The onset of menstruation is the beginning of a new menstrual cycle and is counted as day 1. During a span of about 5 to 7 days, the superficial layers of the endometrium, which grew and developed during the antecedent ovarian/menstrual cycle, are sloughed because demise of the corpus luteum in the non-fertile menstrual cycle is associated with a loss of progesterone secretion. Ovarian follicular maturation occurs progressively resulting in a rise in the circulating levels of estrogen, which in turn leads to new endometrial proliferation.

The dominant ovarian follicle undergoes ovulation at mid-cycle, generally between menstrual cycle days 12 to 16 and is converted from a predominantly estrogen source to a predominantly progesterone source (the corpus luteum). The increasing level of progesterone in the blood converts the proliferative endometrium to a secretory phase in which the tissue proliferation has promptly abated, leading to the formation of endometrial glands or organs. When the ovulated oocyte is viably fertilized and continues its progressive embryonic cleavage, the secretory endometrium and the conceptus can interact to bring about implantation (nidation), beginning about 6 to 8 days after fertilization.

If an ongoing pregnancy is to be established via implantation, the embryo will attach and burrow into the secretory endometrium and begin to produce human chorionic gonadotropin (HCG). The HCG in turn stimulates extended corpus luteum function, i.e. the progesterone production remains elevated, and menses does not occur in the fertile menstrual cycle. Pregnancy is then established.

In the non-fertile menstrual cycle, the waning level of progesterone in the blood causes the endometrial tissue to be sloughed. This starts a subsequent menstrual cycle.

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

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

The most prevalent form of oral contraception is a pill that combines both an estrogen and a progestin, a so-called combined oral contraceptive preparation.

Alternatively, there are contraceptive preparations that comprise progestin only. However, the progestin-only preparations have a more varied spectrum of side effects than do the combined preparations, especially more breakthrough bleeding. As a result, the combined preparations are the preferred oral contraceptives in use today (Sheth et al., Contraception 25:243, 1982).

Whereas the conventional 21 day pill packs with a 7 day "pill free" or placebo interval worked well when oral contraceptives were of higher dosage, as the doses have come down, for both the estrogen and progestin components, bleeding problems have increased in frequency, especially in the early months of oral contraceptive use, but even persistently so in some patients.

Since the advent of combined estrogen-progestin medications as oral contraceptives, there has been a steady downward adjustment of the daily estrogen dosage. Concurrently, where exposure to the progestin component has also been lowered, reduced androgenicity has remained an ongoing priority. Together these adaptions in formulation have been presented in a variety of regimens, both monophasic and multiphasic. Each have their own advantages and disadvantages. All-in-all, today's oral contraceptives are much safer with regard to the incidence and severity of estrogen-linked clotting disorders as well as the suggested cumulative impact of more "lipid friendly" progestins that maintain the potentially advantageous high density lipoprotein cholesterol levels in Circulation.

U.S. Pat. No. 4,390,531 teaches a triphasic regimen in which each phase uses about 20–40 mcg ethinyl estradiol, phases 1 and 3 use 0.3–0.8 norethindrone and phase 2 doubles the amount of the norethindrone. These three phases consume 21 days of a 28 day cycle. European published application 0 226 279 states that this regimen is associated with a high incidence of breakthrough bleeding and substitutes a three phase oral contraceptive regimen using a relatively low amount of ethinyl estradiol (10–50 μg) and a relatively high amount of norethindrone acetate (0.5–1.5 mg) in each phase provided that the amount of estrogen in any two phases is never the same. A "rest" phase of about 7 days is used in this regimen.

U.S. Pat. No. 5,098,714 teaches an osmotic, oral dosage form. One "pill" is administered per day but the administration is, in effect, polyphasic. The dosage form is constructed such that it provides an initial pulse delivery of estrogen and progestin followed by prolonged delivery of estrogen.

European published patent application 0 253 607 describes a monophasic contraceptive preparation containing units having 0.008–0.03 mg of ethinyl estradiol and 0.025–0.1 mg of desogestrel (or equivalent) and a regimen where the preparation is administered over a 23–25 day period, preferably 24 days, followed by a 2–5 day pill-free period. The object of this regimen is to provide hormonal replacement therapy and contraceptive protection for the pre-menopausal woman in need thereof by supplying a low dose of an estrogen combined with a "very low dose of a progestogen."

In 1989, the accumulating data from the evolution of oral contraceptive pill formulations containing only 20–35 μg of estrogen per day spurred the Food and Drug Administration's Fertility and Maternal Health Drugs Advisory Committee to recommend indication of low dose oral contracep-

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