EXHIBIT 1023

Serum levels of *d*-norgestrel, luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone in women during and following ingestion of combination oral contraceptives containing *dl*-norgestrel

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Three formulations of *dl*-norgestrel were administered daily to groups of three women for five consecutive days. The serum levels of *d*-norgestrel were related to the dosage of *dl*-norgestrel ingested. Peak concentrations in the circulation of synthetic gestagen were attained a half hour to three hours after oral administration, followed by a rapid and sharp decline in levels until the next dose. Three women received 500 μg of *dl*-norgestrel and 50 μg of ethinyl estradiol for 21 days followed by six to seven days of no medication for two consecutive cycles. The gonadotropins remained suppressed for four to six days when therapy was discontinued. The daily concentrations of estradiol varied from less than 5 to 81 pg. per milliliter, and there was no difference in estrogen values during the nontreatment and treatment days. Due to the long half life of norgestrel, the one-week pill-free interval is not long enough for the complete recovery of the reproductive axis from the inhibition of oral contraceptives. (AM. J. OBSTET. GYNECOL. 129: 133, 1977.)

RADIOIMMUNOASSAY (RIA) to determine *d*-norgestrel has been used to measure serum concentrations of this gestagen following oral, intramuscular, subdermal, and intravaginal administration.[1-8] Direct measurement of the contraceptive agent in the circulation has become an important adjunct in the development and evaluation of new contraceptive modalities. In conjunction with the measurement of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone levels, RIA of the circulating gestagen levels facilitates a correlation with the function of the hypothalamus-pituitary and the ovary.

This study was undertaken to determine the profile and absolute levels of circulating *d*-norgestrel, the biologically active enantiomer, following ingestion of (racemic) *dl*-norgestrel at three commonly used dosage levels. Another aim of this investigation was to measure serum *d*-norgestrel levels in women during and after daily ingestion of 0.5 mg. of *dl*-norgestrel and 0.05 mg. of ethinyl estradiol (Ovral*) for two 21 day periods interrupted by a six- to seven-day pill-free interval. The purpose of this study was to correlate serum *d*-norgestrel levels with circulating LH, FSH, estradiol, and progesterone levels in order to assess the relationship of serum levels of this drug to suppression of hypothalamic-pituitary-ovarian function, particularly during the pill-free interval.

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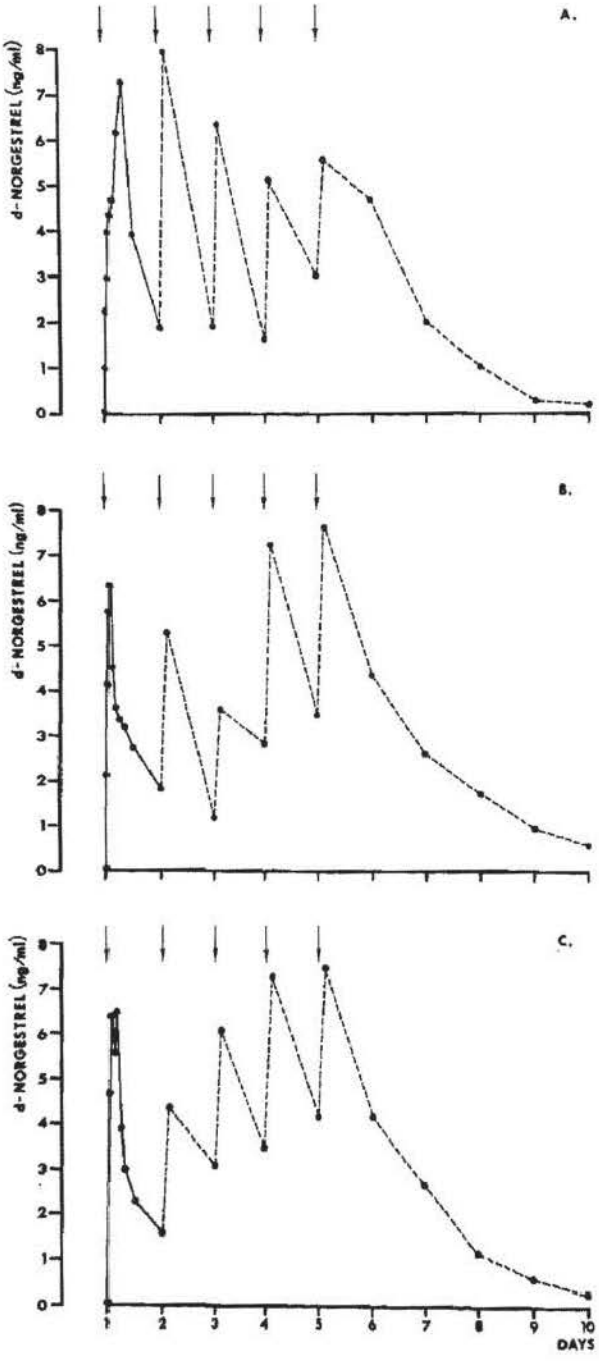

Fig. 1. Serum *d*-norgestrel levels in three subjects receiving 500 μg of *dl*-norgestrel and 50 μg of ethinyl estradiol (Ovral). Arrows indicate time of ingestion.

Material and methods

Subjects. Twelve healthy women between 23 and 35 years of age who had regular menstrual cycles and had not used contraceptive steroids for at least three months prior to entering this study volunteered for this investigation. All 12 women ovulated during the pretreatment cycle as indicated by normal luteal phase serum progesterone concentrations.

Tablets containing 0.5, 0.3, or 0.075 mg. of *dl*-norgestrel were administered to three women every morning prior to breakfast for five consecutive days, beginning on menstrual cycle Day 5. The two higher *dl*-norgestrel doses given consisted of combination formulations (Ovral and Lo/Ovral*) containing 0.05 mg and 0.03 mg of ethinyl estradiol, respectively, while the lowest *dl*-norgestrel dose (Ovrette*) did not contain any estrogen. Antecubital venous blood was drawn prior to and ½, 1, 1½, 2, 3, 4, 6, 8, and 12 hours after ingestion of the first *dl*-norgestrel dose as well as prior to and three hours following oral intake of each of the four additional doses. Venous blood samples were also obtained each morning for the next five days from those six women who had received either one of the two combination pills.

Three other volunteers, beginning on the fifth day after the onset of menses, ingested a combination of 0.5 mg. of *dl*-norgestrel and 0.05 mg. of ethinyl estradiol (Ovral) each morning for two consecutive 21 day periods interrupted by a six- to seven-day pill-free interval. Antecubital venous blood was drawn daily three hours after oral intake or, during pill-free intervals, at the same time of the day, starting the day the first Ovral tablet was ingested and ending seven days after the last tablet of the second 21 day period of oral contraceptives had been ingested. All blood samples were allowed to clot, the serum was separated by centrifugation and stored at −15° C. until it was analyzed.

Hormone assays. Serum LH and FSH concentrations were determined by double-antibody RIA's according to previously described methods.[9, 10] A postmenopausal serum standard was used, and the results were expressed as milli–International Units per milliliter (Second International Reference Preparation of human menopausal gonadotropin).[11] Serum progesterone was measured by RIA as previously reported from this laboratory.[12] Our serum estradiol RIA[13] was modified in order to avoid measuring ethinyl estradiol in addition to estradiol. Ethinyl estradiol was found to cross react with the anti–estradiol -17β –hemisuccinate –bovine serum albumin serum employed in our standard estradiol RIA. The serum estradiol RIA used in this study consisted of diethyl ether extraction, micro-Celite column partition chromatography (which failed to separate ethinyl estradiol from the estradiol fraction), and utilization of an antiserum which we raised

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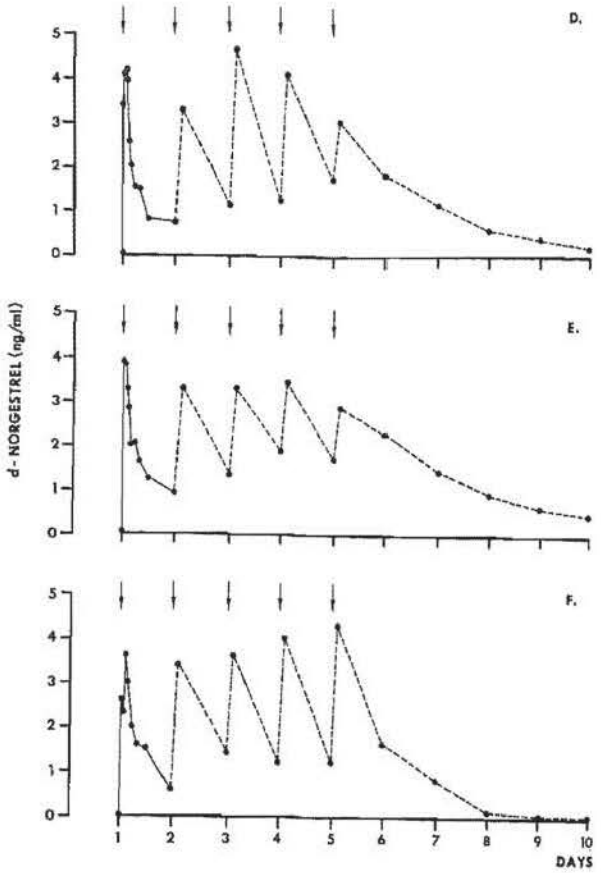

Fig. 2. Serum *d*-norgestrel levels in three subjects receiving 300 μg of *dl*-norgestrel and 30 μg of ethinyl estradiol (Lo/Ovral). Arrows indicate time of ingestion.

against estradiol-6-(O-carboxymethyl) oxime-bovine serum albumin. The latter antiserum cross-reacted less than 0.1 per cent with ethinyl estradiol. The sensitivity of this RIA was 5 pg. of estradiol per milliliter of serum. Intra- and inter-assay coefficients of variation were less than 10 per cent.

Serum *d*-norgestrel levels were assayed by a RIA previously developed in this laboratory.[1] In this RIA, an antiserum against *d*-norgestrel-3-(O-carboxymethyl) oxime-ε-aminocaproic acid-bovine serum albumin[1] and *d*-norgestrel-3-(O-carboxymethyl) imino-(^{125}I)-iodohistamine is used. This ^{125}I-labeled *d*-norgestrel derivative renders this RIA particularly sensitive: 6 pg. of *d*-norgestrel can be measured in 0.1 ml. of serum with great precision. Intra- and inter-assay coefficients of variation were 4.4 and 4.9 per cent, respectively.

Results

Serum *d*-norgestrel levels following ingestion of five daily *dl*-norgestrel doses at three different

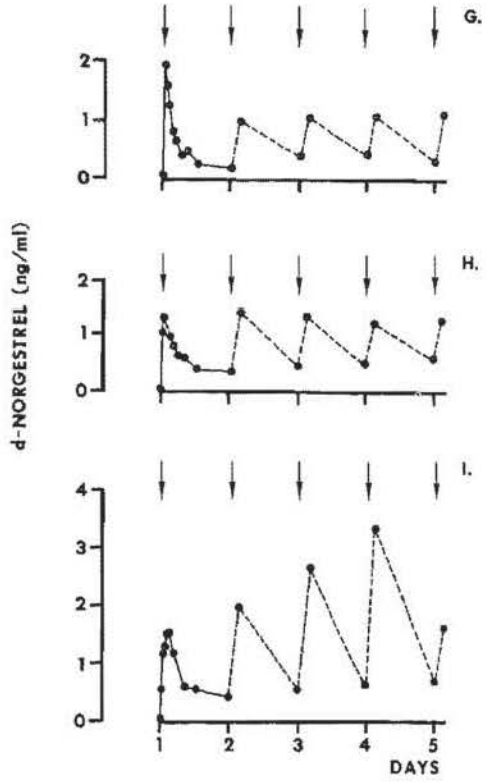

Fig. 3. Serum *d*-norgestrel levels in three subjects receiving 75 μg *dl*-norgestrel (Ovrette). Arrows indicate time of ingestion.

Table I. Ranges of maximum serum *d*-norgestrel levels and levels 24 hours after ingestion observed in three groups of three women each who received various dosages of *dl*-norgestrel

dl-Norgestrel dose (mg.)	*Maximum d-norgestrel levels (ng./ml.)*	*24-hour d-norgestrel levels (ng./ml.)*
0.5	6.3-8.0	1.6-1.9
0.3	3.6-4.2	0.6-0.9
0.075	1.5-1.9	0.2-0.5

levels. The concentrations of circulating *d*-norgestrel observed after oral intake of 0.5, 0.3, and 0.075 mg. of *dl*-norgestrel in three women at each dosage level are depicted in Figs. 1 to 3. A similar profile of serum *d*-norgestrel concentrations was observed following ingestion of all three dosages. This pattern is characterized by a rapid rise to peak levels which were attained within a half hour to three hours after ingestion in all but one of the nine volunteers studied. Serum *d*-norgestrel levels fell almost as promptly as they rose, once the peak was reached, averaging 19.6 to 25.6 per cent of the initial peak level 24 hours after ingestion of the first tablet and 28.6 to 54.1 per cent of the last peak

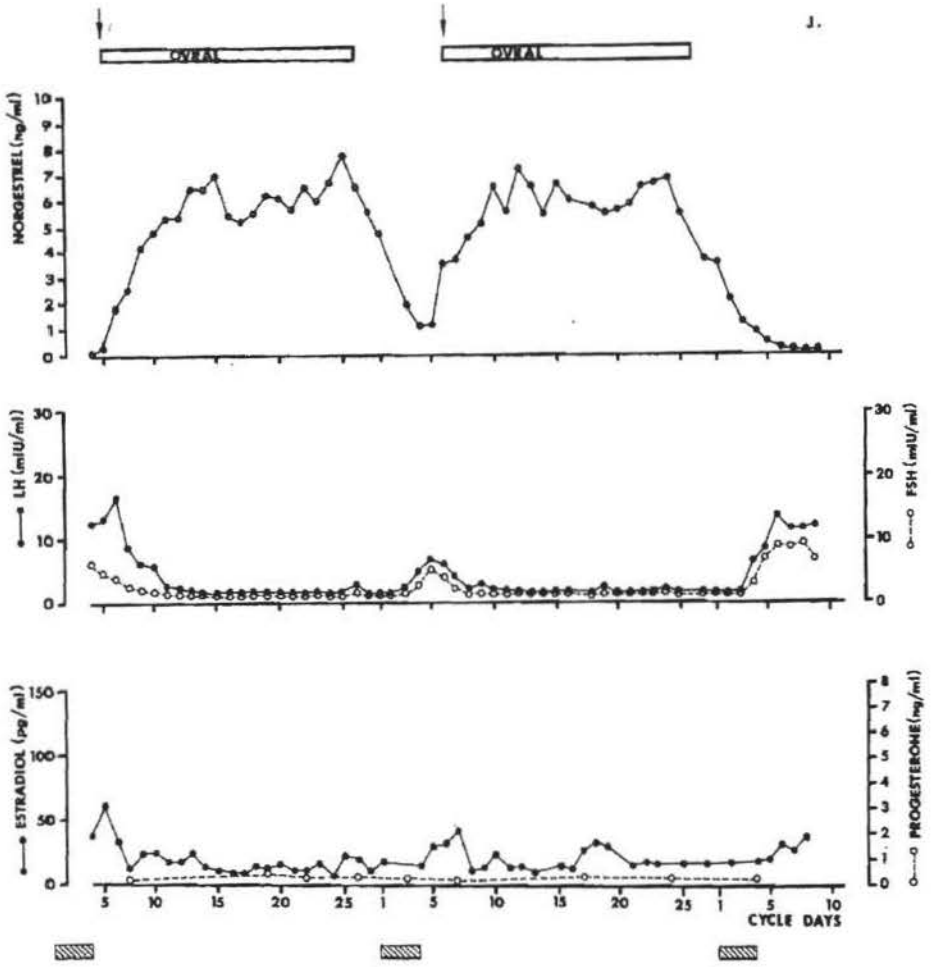

Fig. 4. Subject J.: Serum *d*-norgestrel, FSH, LH, estradiol, and progesterone levels during and following oral administration of 500 μg of *dl*-norgestrel and 50 μg of ethinyl estradiol (Ovral) for two subsequent 21 day periods interrupted by a six-day pill-free interval.

level 24 hours after the fourth tablet of 0.5, 0.3, and 0.075 mg. of *dl*-norgestrel was ingested. In the majority of the nine subjects studied, the *d*-norgestrel levels measured three and 24 hours after oral *dl*-norgestrel intake increased in a stepwise manner gradually during the five days of study.

While the profiles of circulating *d*-norgestrel levels were similar, different levels of serum *d*-norgestrel were measured after administration of the three different *dl*-norgestrel dosages. As indicated in Table I, peak as well as 24 hour *d*-norgestrel levels were related to the amount of *dl*-norgestrel ingested. Differences in drug levels at these two time intervals were distinct and did not overlap following administration of each of the three doses of the pharmacologic agent. For three days following ingestion of the last tablet of 0.5 mg. of *dl*-norgestrel, serum *d*-norgestrel levels exceeded 1 ng. per milliliter in all three women while five days after the last tablet levels were still greater than 0.2 ng. per milliliter. In all women measurable amounts of serum *d*-norgestrel were present five days after ingestion of the last tablet of each dosage (see Table I and Figs. 1 to 3).

Serum *d*-norgestrel, LH, FSH, estradiol, and progesterone levels in three women during and following ingestion of 0.5 mg. of *dl*-norgestrel and 0.05 mg. of ethinyl estradiol over two 21 day periods interrupted by six or seven pill-free days. Daily LH, FSH, estradiol, and *d*-norgestrel levels and weekly serum progesterone concentrations measured in three women during and following the oral administration of 0.5 mg. of *dl*-norgestrel and 0.05 mg. of ethinyl estradiol (Ovral) for two subsequent 21 day periods interrupted by a six- to seven-day pill-free interval are depicted in Figs. 4 to 6. Daily serum *d*-norgestrel levels rose gradually, reaching a plateau which ranged between 4 and 8

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