PAPERS AND ORIGINALS

Clinical and Laboratory Findings in a Trial of Norgestrel, a Low-dose Progestogen-only Contraceptive

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Summary

Norgestrel, a progestogen-only oral contraceptive, was given continually at a dose of 75 µg/day to 144 women of proved fertility. It was an efficient contraceptive with a failure rate of 2.1% (assessed by the "life-table" method) within the first 12 cycles and 3.6% within the first 30 cycles (or 2.0 conceptions per 100 woman-years when assessed by the Pearl index). The overall conception rate for the entire trial period was 2.1% and 1.3 pregnancies per 100 woman-years respectively. Norgestrel caused a high proportion of irregular and generally short bleeding intervals, about one-fifth of the cycles lasting less than 17 days. This irregularity appeared to be due to individual variance in cycle length between women rather than that between their successive cycles. No confirmed instances of thromboembolism were observed. Norgestrel apparently exerts its contraceptive action by several mechanisms: reduction in the sperm penetrability of the cervical mucus and an impairment of luteal function appear important. The serum concentrations of cholesterol and globulin were significantly reduced in women

taking norgestrel. Preliminary observations suggest that on discontinuing the medication fertility is promptly restored. Of the 144 women originally enrolled 57 (40%) withdrew for reasons connected with the method before completing 30 months on trial, over half of them because of the irregular menstrual pattern. Nonetheless, in view of its main clinical and laboratory characteristics and simple mode of administration, norgestrel appears to be a useful alternative to the combined type of pill for women unsuitable for, or unable to tolerate, oestrogen-containing preparations.

Introduction

The search for an oral contraceptive combining clinical safety with an acceptable degree of protection prompted the study of progestogens without added oestrogen taken continually in microgramme dosage. The feasibility of this type of fertility control was established in the mid-1960s in women given 0.5 mg of chlormadinone acetate daily (Rudel, Martinez-Manautou, and Maqueo-Topete, 1965; Martinez-Manautou *et al.*, 1966; Bernstein, 1971). At about the same time norgestrel, a synthetic progestogen of the 19-norsteroid type, was found to possess high anti-fertility activity at doses much lower (50 or 75 µg/day) than those needed with other progestogen-only or combined oral contraceptives (Foss, 1968; Tyler, 1969).

The clinical trials committee of the Council for the Investigation of Fertility Control therefore decided to conduct a multi-centre trial in order to assess the acceptability, efficacy, and clinical characteristics of norgestrel at a dose of 75 µg/day and to determine, where possible, changes in the composition of the blood, urine, and cervical mucus associated with its use. This paper reports the results obtained over a period of about 30 months.

Subjects and Methods

The trial was conducted in 12 clinics selected and supervised by the Council for the Investigation of Fertility Control. More than 90% of the 144 women who enlisted had previously practised some form of contraception; over half of them had

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strual periodicity was expressed in terms of conventional "cycles" rather than the more appropriate "bleeding intervals."

The frequency distributions of the cycles recorded (a) by 108 women who completed five or more cycles for a total of 1,887 cycles during the present trial, and (b) by a control group of 1,578 normal, regularly menstruating women of a similar age distribution (20-39 years) comprising 20,837 cycles (Chiazze, Brayer, Macisco, Parker, and Duffy, 1968) are shown in Fig. 2. Eighty-six cycles in women completing fewer than five cycles on trial and six other, highly abnormal cycles due to lactation, secondary amenorrhoea, etc. are excluded from the statistical analysis.

Cycle control was poor during the norgestrel trial ranging from 6 to 88 days, with a strikingly high proportion (20.6%) of cycles of 17 days or less. This compares with an incidence of under 1% of such cycles in the series of Chiazze *et al.* (1968), which is probably representative of normal women in general. On the other hand, there were marginally fewer cycles of 46 days and over (2.5%) compared with 3.6% recorded by Chiazze *et al.*

Consequently the frequency of cycle lengths of women on the trial showed a distinctly bimodal distribution, with a sharp peak in the region of 26-28 days and a second, somewhat smaller one at 12-14 days (Fig. 2).

FIG. 2—Frequency distribution of cycle lengths in 108 subjects on norgestrel (1,887 cycles) and 1,578 normal menstruating women of similar age (20,837 cycles) (Chiazze *et al.*, 1968).

Further analysis of the data from the main group of 108 women showed that menstrual irregularities consisting in exceptionally short cycles occurred in apparently haphazard fashion, without any noticeable pattern in the group as a whole. Almost 74% of the women who completed an average of 15 cycles on trial experienced at least one cycle of 17 days or less, 53% three or more such cycles, and 28% five or more. By contrast only 23% had at least one long cycle (46 or more days) while on trial, 6% had three such cycles, and a mere 2% had five.

In spite of the irregular cycle pattern experienced by a majority of women mean periodicity remained fairly constant throughout the trial.

The variability of cycle length, as measured by the standard deviation for each cycle number, showed a gradual but statistically not significant decrease. The incidence of short cycles gradually decreased with time, however, mainly because women with a preponderance of such cycles tended to leave the trial.

The 43 women who had experienced at least 20 cycles on norgestrel and therefore constituted a more homogeneous group than the rest of the patients were subjected to closer analysis. When the mean length for each of their cycles from the 1st to the 20th was plotted in relation to time a highly significant upward trend (3.2 days in the course of 20 cycles, $P < 0.001$) was found.

An analysis of variance of the data from the same group of 43 women showed a highly significant difference ($P < 0.001$) in cycle length between individual women, but the variance between cycles was not significantly increased above the residual variance. Analysis thus confirmed that in spite of the wide variations in cycle length found in the trial, individual subjects retain a distinctive personal pattern of menstrual periodicity. Nonetheless, the variability in cycle length experienced by many women was such that it accounted for the withdrawal of 33 of them from the trial, or about 58% of those who withdrew for reasons connected with the method (Table I).

SIDE EFFECTS

A variety of side effects were recorded in the course of the trial in addition to those listed in Table I. Headache was common (recorded by 29 subjects in 158 cycles), but six of the seven women who had stopped combined oral contraceptives because of headaches were able to take norgestrel without experiencing them. The one who did was much less affected and continued to take the medication. Breast tenderness was reported by 11 subjects during 82 cycles, both directly norgestrel was started and later on, and spotting occurred in 55 (129 cycles). Thirteen women complained of depression (50 cycles), but none of those who had previously stopped using oestrogen-containing preparations because of depression experienced this while on norgestrel.

There was one case of suspected but not confirmed deep leg vein thrombosis. In another woman a pulmonary thrombosis was suspected, but on referral to a chest physician no evidence of thromboembolism was obtained. Both patients were taken off norgestrel.

Four additional subjects withdrew from the trial because of pains in the calf or leg over superficial veins. One complained of pain over the site of a varicose vein injection after taking only six tablets of norgestrel, while another experienced severe aching of the calf after 15 tablets. The pains disappeared when they stopped taking norgestrel, but in two women aching of the calf returned on resuming the medication.

CHANGES IN WEIGHT

Weight changes during the trial occurred in 125 women. In 57% of them the change remained within 3 lb (1.4 kg) of the weight at enrolment. In the remaining subjects it exceeded 3 lb, 25% gaining 4-31 lb (1.8-14 kg) and 18% losing weight (range 4-15 lb (1.8-6.8 kg)).

WITHDRAWALS

Of the 94 subjects who withdrew from the trial 57 did so for indications connected with the method (Table I).

RETURN OF FERTILITY AFTER DISCONTINUING NORGESTREL

Six women attached to the Birmingham clinic stopped the medication in order to conceive, and all succeeded, two within one cycle and the others in from two to six months. A seventh subject forgot to take the tablets with her while on holiday and also promptly conceived.

TABLE II—Mean Levels of Blood Constituents in 37 Women before (Pretrial) and while taking (On Trial) 75 µg Norgestrel a Day

	Glucose (mg/100 ml)	Creati- nine (mg/100 ml)	Urea (mg/100 ml)	Sodium (mEq/l.)	Potas- sium (mEq/l.)	Alkaline Phospha- tase (units/ 100 ml)	Bili- rubin (mg/100 ml)	Calcium (mg/100 ml)	Iron (µg/100 ml)	Uric Acid (mg/100 ml)	Albumin (g/100 ml)	Glo- bulin (g/100 ml)	As- partate Amino- trans- ferase (units/ ml)	Choles- terol (mg/100 ml)	P.B.I. (µg/100 ml)
No. of women:	37	37	37	36	36	37	37	37	37	37	37	37	37	37	25
Pretrial value (S.D.) ..	85.4 (13.1)	0.90 (0.22)	26.8 (4.8)	142.4 (2.1)	4.3 (0.32)	6.4 (1.62)	0.51 (0.23)	9.90 (0.26)	90.6 (29.2)	4.01 (1.04)	4.75 (0.33)	2.71 (0.39)	8.3 (6.4)	218.9 (35.6)	5.26 (1.09)
On-trial value (S.D.) ..	82.4 (13.9)	0.87 (0.18)	26.4 (6.0)	142.1 (2.0)	4.2 (0.28)	6.1 (1.75)	0.52 (0.17)	9.92 (0.29)	86.8 (39.2)	4.07 (0.82)	4.68 (0.21)	2.52 (0.36)	7.13 (4.2)	198.2 (36.3)	5.50 (0.89)
Mean difference (S.D.)	3.0 (2.5)	0.03 (0.04)	0.4 (1.0)	0.3 (0.4)	0.1 (0.05)	0.3 (0.2)	-0.01 (0.03)	-0.02 (0.05)	3.8 (7.2)	-0.06 (0.12)	-0.07 (0.04)	0.19 (0.06)	1.2 (0.5)	20.7 (5.0)	-0.24 (0.13)
P*	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	<0.01	<0.05	0.001	N.S.

* Significance of difference between pretrial and on-trial means assessed with the Wilcoxon test.
N.S. = Not significant.

Special Investigations

BIOCHEMICAL FINDINGS IN BLOOD

Tests comprising 15 determinations were performed in 37 women, but the serum protein-bound iodine (P.B.I.) was estimated in only 25 of them (Table II).

The findings obtained during the control (pretrial) cycles were within the ranges to be expected in normal women of comparable age and parity. In 13 of the 15 determinations the on-trial data (recorded after not less than four and usually after six or seven months on norgestrel) showed either non-significant or barely significant ($P > 0.05$) differences when using Wilcoxon's signed rank test (Bradley, 1968). In two of them, however, the difference between the control and on-trial findings was highly

or very highly significant (globulin, cholesterol). The most interesting one was the change in cholesterol. The mean control value was 218.9 ± 35.6 (S.D.) mg/100 ml, but during treatment it fell to 198.2 ± 36.3 mg/100 ml ($P < 0.001$). The reduction in serum globulin from a pretrial mean of 2.71 ± 0.39 g/100 ml to 2.52 ± 0.36 g/100 ml on trial was also highly significant ($P < 0.01$) and equally unexpected; there was no corresponding change in albumin.

URINARY EXCRETION OF OESTRONE AND PREGNANEDIOL

Only specimens obtained between days 17 and 25 and from cycles within an overall range of 25-36 days were analysed. The results are shown in Fig. 3.

The mean excretion ($\pm$ S.D.) of oestrone for 20 specimens examined during the pretrial period was 14.0 ± 9.0 µg/24 hr, and 18.0 ± 18.0 µg/24 hr for 12 samples collected from subjects on norgestrel; the difference was not significant. The mean pregnanediol excretion ($\pm$ S.D.) for 39 pretrial control samples was 3.5 ± 1.8 mg/24 hr, and 2.0 ± 1.4 mg/24 hr for 17 samples collected during treatment; the difference between the control and trial series was highly significant ($P < 0.01$). This finding is

FIG. 3—Urinary excretion of pregnanediol and oestrone in 24-hour samples collected between days 18 and 28 of the cycle. One on-trial value, determined on cycle day 17, is excluded. (see text). ● = Pretrial. ○ = On trial.

FIG. 4—Sialic acid and alkaline phosphatase content of cervical mucus related to sperm migration index (see text). ● = Pretrial. ○ = On trial.

consistent with previous ones (Fotherby, Svendsen, and Foss, 1968; Mukherjee, Wright, Davidson, and Fotherby, 1972), showing that women on norgestrel at a dose of 50-75 µg daily have a diminished pregnanediol excretion, the values obtained often being less than those normally associated with an ovulatory menstrual cycle.

COMPOSITION OF CERVICAL MUCUS

Samples of cervical mucus were obtained from 15 women during the pretrial control period and from 19 women on trial with norgestrel (Fig. 4). Ten of the control samples and six of the on-trial samples were collected between days 11 and 16—that is, the ovulatory phase—of cycles ranging from 26 to 36 days. The mean concentration ($\pm$ S.D.) of sialic acid in the 10 control samples was 1.6 ± 1.1 µg/g of mucus, and that in the six on-trial samples 2.5 ± 1.0 µg/g. Thus the sialic acid concentration of cervical mucus from women treated with norgestrel tended to be higher than that of samples obtained during a control cycle, although the difference did not reach a statistically significant level. The difference between the alkaline phosphatase activity of nine samples from control cycles (mean 5.3 ± 2.3 mU/hr/g of mucus) and six on-trial cycles (mean 7.2 ± 8.6 mU/hr/g of mucus) was also not significant. There was, however, a highly significant difference ($P < 0.002$) in the sperm penetrability of the cervical mucus. In 10 on-trial samples the mean sperm migration index ($\pm$ S.D.) was 1.0 ± 1.5 compared with 5.2 ± 2.4 in six pretrial samples (Fig. 4). Thus treatment with norgestrel tended to render the cervical mucus less penetrable to spermatozoa, possibly as the result of raising its sialic acid content.

BLOOD PRESSURE AND CERVICAL SMEARS

No pronounced or consistent changes in either blood pressure or cervical smear picture were seen in women on trial.

Discussion

The practical usefulness of any method of contraception depends on its use-effectiveness—that is, the protection from unintended pregnancy that can be achieved with it under ordinary ("real-life") conditions (Tietze, 1971)—and long-term acceptability. The main limiting factor of low-dose progestogen-only preparations is their pronounced tendency to cause irregular and abnormal bleeding. Apart from this norgestrel has been found to be a valuable and generally acceptable contraceptive (Foss, 1968, 1971; Tyler, 1969; Hernandez-Torres, 1970). In the present trial many women reported spontaneously that they were satisfied and felt "positively well" while taking the compound. Others liked it enough to continue with it in spite of abnormal bleeding.

Fertility Control.—The trial has shown that 75 µg of norgestrel a day taken continually in accordance with instructions provides a degree of protection which is probably acceptable to most women. The adjusted conception rate (see above) was 2.1% within the first nine months (assessed by the life-table method), corresponding to one of 1.3 pregnancies per 100 woman-years (in terms of the Pearl index). This compares with a calculated method failure rate of about 0.8 per 100 woman-years reported by Foss (1968, 1971) in British women (4,278 cycles) on a daily dosage of 50 µg, and rates of 0 and 0.4 per 100 woman-years, respectively, seen in the U.S.A. (813 cycles; Tyler, 1969) and Puerto Rico (2,767 cycles; Hernandez-Torres, 1970). These findings indicate that the fertility control exerted by norgestrel, while not as complete as that produced by combined oral contraceptives, compares favourably with that obtained with other progestogen-only preparations and intrauterine devices (Tietze, 1971).

Menstrual Periodicity.—Variable and imperfect cycle control appears to be a characteristic feature of contraception with

norgestrel and other progestogen-only preparations (Foss, 1968; Christie, 1969), and the present trial was no exception (see Fig. 2). A somewhat lower incidence of menstrual irregularities has been reported from norgestrel trials in other countries—for example, in the U.S.A. by Tyler (1969), and in Puerto Rico by Hernandez-Torres (1970). Also, in both of these series relatively more women appeared to have accepted the inconvenience of imperfect cycle control and did not withdraw from the trial. In assessing the importance of frequent or irregular bleeding as a reason for withdrawal it should be noted that there is a not inconsiderable drop-out rate from all oral contraceptive trials run for prolonged periods.

Side Effects.—In contrast to the frequency of menstrual complaints side effects were relatively slight and tolerable. Their large variety suggests that some at least were due to individual factors. Headaches or depression, even when previously experienced with combined oral contraceptives, were generally absent during the present trial, and the only subject troubled by headache while taking norgestrel was not severely affected and continued with the drug. Two instances of thrombosis were suspected on clinical grounds (see above) but no proof of its occurrence was obtained in either subject. Tenderness of the calf and leg or over superficial veins was an unexpected complaint; it appeared to be specific to the medication.

Chemical Findings in Blood.—The most striking finding emerging from the analysis of blood constituents was the significantly lower concentration of cholesterol during norgestrel treatment ($P < 0.001$; Table II). It has been shown that serum cholesterol tends to rise in women taking oestrogen-containing oral contraceptives (Wynn, Doar, and Mills, 1966) and continues to do so with increasing length of exposure (Briggs, Pitchford, Staniford, Barker, and Taylor, 1970). It is therefore interesting that continuous treatment with a daily dose of 75 µg of norgestrel far from raising the blood cholesterol level may actually reduce it. The slight lowering in the concentration of blood glucose in women on norgestrel should also be mentioned. The significance of this observation is increased by the report that glucose tolerance tests and serum alanine transferase levels remained normal in women receiving norgestrel at a dosage of 50 µg/day (Foss, Holton, and Lewis, 1970). By contrast there is considerable evidence that combined oral contraceptives can impair glucose tolerance (Spellacy, 1969; Briggs *et al.*, 1970).

Urinary Steroid Excretion.—Previous studies have shown that the pregnanediol excretion in women treated with 50 or 75 µg of norgestrel a day may be either similar to or considerably lower than that seen during normal ovulatory cycles (Fotherby *et al.*, 1968). The former pattern indicates that the contraceptive action of norgestrel is not, or not always, due to a suppression of ovulation but may be attributed to other mechanisms of action, such as effects on the cervical mucus (Roland, 1968; Tyler, 1969; see also below) or endometrium (Foss, 1968). In the present trial a significantly lower mean excretion of pregnanediol was seen during the administration of norgestrel compared with that in pretrial control cycles (Fig. 3). This is consistent with earlier suggestions that norgestrel treatment interferes with luteal function and the biosynthesis of progesterone rather than with the development of the corpus luteum (Fotherby *et al.*, 1968; Mukherjee *et al.*, 1972). By contrast the urinary excretion of oestrone was not significantly altered in women on trial.

Effects on Cervical Mucus.—It is generally assumed that norgestrel, like other progestogens, exerts its major contraceptive effect by altering the physicochemical properties of the cervical mucus. As a result the mucus becomes scanty, thick, and tenacious and less penetrable to spermatozoa, so that they can no longer be recovered during postcoital aspiration of the uterine cavity (Roland, 1968, 1971; Moghissi and Marks, 1971). The tests undertaken in the present trial confirm that penetrability of the cervical mucus to spermatozoa is reduced and its sialic acid content increased during norgestrel treatment (Fig. 4). An inverse relation between the sialic acid concentration of cervical mucus and its sperm receptivity was previously shown

by Carlborg, Johansson, and Gemzell (1969), penetrability increasing as the sialic acid content decreased. Other workers have also reported a higher alkaline phosphatase activity of cervical mucus at mid-cycle (Pincus, 1965; Smith, Hunter, and Spadoni, 1970), but in the present study there was no correlation between alkaline phosphatase activity and the sperm migration index. It would thus seem that norgestrel at dose levels of 50-75 µg/day exerts its antifertility action at several sites and by various mechanisms. Among these are effects on the cervical mucus, which is rendered less penetrable to sperm, associated with an increase in the sialic acid content of the mucus, and on the corpus luteum, the progesterone secretion of which (but probably not that of oestrogen) is reduced in some women.

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Survey of Cervical Cytology in General Practice

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Summary

In a practice in an industrial area a cervical cytology service was offered to women, and in the years 1967-70 280 cervical smears were carried out. In 1971 all women born between 1 January 1920 and 31 December 1935 who had not had a cervical smear taken in the preceding four years were sent a letter explaining the service and inviting them to attend. Those who did not attend received a second letter and, if necessary, a visit by a nurse in an effort to persuade them to do so.

Eventually 88.4% of the women in this age group who could be traced attended, and 16 abnormal cervical smears were reported. As a result of cone biopsy 12 women were found to have carcinoma in situ.

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Introduction

During 1967-70 235 cervical smear tests were carried out in a practice in north-east England. In 1970 fewer than half of the women eligible had availed themselves of the service. A direct approach was therefore made to these patients to persuade them to undergo this test and to ascertain the reason for their reluctance.

The practice is situated in a heavy industrial area of north-east England, and looks after 8,250 patients. Because of its origin as a panel practice there is a loading of patients in social classes III and IV (skilled and semiskilled). Four partners are assisted by a midwife and a practice nurse attached to the practice. One senior receptionist, who also acts as the practice secretary, and two junior receptionists staff the main surgery, and a part-time receptionist helps at a branch surgery.

It had always been practice policy to offer cervical smear tests freely. Smears had been taken at postnatal examinations, at all gynaecological examinations, and at yearly intervals from all patients on the "pill." In addition a policy of persuasion to take the test was used with all women patients aged 35 years or more.