British Journal of Obstetrics and Gynaecology

VOLUME 86
1979

Royal College of Obstetricians and Gynaecologists
27 Sussex Place, Regent's Park, London, NW1 4RG

British Journal of Obstetrics and Gynaecology
April 1979. Vol. 86. pp 325–329

A RANDOMIZED DOUBLE-BLIND TRIAL OF TWO LOW DOSE COMBINED ORAL CONTRACEPTIVES

BY

WALLI BOUNDS,* *Medical Research Administrator*
Family Planning Association, London

M. VESSEY, *Professor*

AND

P. WIGGINS,† *Research Officer*
Department of Social and Community Medicine
Oxford University

Summary

Fifty-five women using Loestrin–20 (20 μg ethinyl oestradiol and 1 mg norethisterone acetate) as an oral contraceptive have been compared with a like number using Microgynon–30 (30 μg ethinyl oestradiol and 150 μg levonorgestrel) in a randomized, double-blind trial. Despite the small sample size, the main finding in the trial is clear-cut; Loestrin–20 provides poor cycle control and is thus less acceptable as an oral contraceptive than Microgynon–30. Although there is also a suggestion that Loestrin–20 may be less effective than Microgynon–30, the difference in the accidental pregnancy rates is not statistically significant.

IN an endeavour to minimize the risks associated with oral contraception, manufacturers have, over the years, steadily reduced the dose of the oestrogen component of the pill. Preparations containing less than 50 μg oestrogen first became available in the United Kingdom in 1973 and have now captured more than half the market (Intercontinental Medical Statistics, 1978, personal communication). Most of these low dose products contain 30 μg oestrogen, but one, Loestrin–20, contains only 20 μg ethinyl oestradiol (in combination with 1 mg norethisterone acetate). In 1974, the Family Planning Association (FPA) was asked to evaluate the use-effectiveness and acceptability of Loestrin–20. Accordingly, it was decided to conduct a multicentre randomized double-blind trial in which the new product would be compared with a pill containing 30 μg ethinyl oestradiol and 150 μg levonorgestrel (Microgynon–30) which was already in widespread use in family planning clinics.

METHODS

Seven family planning clinics (some under FPA administration, others administered by Area Health Authorities) agreed to collaborate in the trial and enrolment of patients commenced in November 1974. Owing to the slow rate of recruitment, however, the number of participating clinics was later increased to 12. At each clinic, patients were allocated to the two products at random. Neither the clinic doctor nor the patients were told the composition of the pills involved, but they were informed that both the products were combined oral contraceptives

* Present address: Margaret Pyke Centre, 27 Mortimer Street, London, W.1.
† Present address: Telecomputing Ltd., Seacourt Tower, Westway, Oxford.

containing no more than 50 μg oestrogen. This information was also given to each patient's general practitioner. The pills were supplied in pre-coded sealed envelopes containing standard unmarked 21 day blister packs.

To be eligible for recruitment, volunteers had to meet all the normal FPA requirements for oral contraceptive treatment (see FPA Clinic Handbook) but, in addition, they had to be (i) aged 16 to 39 years and of child-bearing potential, (ii) having regular sexual intercourse, (iii) menstruating regularly, (iv) prepared to accept the possibility of a slight risk of involuntary pregnancy, and (v) sufficiently reliable to keep monthly diary charts and to return to the clinic for follow-up. Women who were lactating or with a recent history of intermenstrual bleeding or spotting were specifically excluded from the trial.

At the initial visit, a history was taken, weight and blood pressure were recorded and a gynaecological examination was made. Patients were then issued (i) with an envelope containing three months' supply of the appropriate pills, (ii) with written instructions about how to take them, and (iii) with a diary card on which to note the days pills were taken and the occurrence of any bleeding (requiring sanitary protection) or spotting (not requiring sanitary protection). Trial participants were advised to take the pills according to the standard 21 days on/7 days off regimen, commencing on day 5 of the next menstrual period, and using additional contraceptive precautions during the first 14 days of treatment. Follow-up visits were arranged at 3-monthly intervals.

A total of 133 patients was recruited between November 1974 and September 1976. Of these, 23 have been excluded from the analysis: 11 who had taken Loestrin–20 or Microgynon–30 before entering the trial, 7 who never commenced taking their pills, and 5 who did not return to the clinic after their initial visit and could not be traced. The present report thus concerns 110 patients, of whom 55 were admitted to each of the two treatment groups. All but 6 of these subjects (3 in each treatment group) were successfully followed either until they discontinued the trial pill or up to the study closure date (31st December, 1976).

RESULTS

The characteristics of the subjects in the two treatment groups are summarized in Table I. Although there are some minor differences, none approaches statistical significance and there is no suggestion that the randomisation procedure was in any way unsatisfactory.

Table II shows the *net* cumulative discontinuation rates per 100 women at selected ordinal months of use computed by the standard methods described by Tietze and Lewit (1974). *Gross* discontinuation rates were also calculated, and differences in these rates between the two treatment groups were tested for statistical significance by the log-rank method described by Azen *et al* (1977). It can be seen from Table II that women using Loestrin–20 discontinued treatment because of abnormal bleeding far more often than women using Microgynon–30 ($\chi_1^2 = 10{\cdot}1$, $P < 0{\cdot}01$) but that the rates of discontinuation for other reasons were closely similar in the two treatment groups. Of the 13 women who stopped taking Loestrin–20 because of abnormal bleeding, 6 complained of oligomenorrhoea or amenorrhoea while the other 7 complained of irregular bleeding. Of the 2 women who stopped taking Microgynon–30

TABLE I

Characteristics of the subjects in the two treatment groups on admission to the trial

Characteristic	Loestrin–20	Microgynon–30
Mean age (years)	25·3	26·1
Nulliparous (per cent)	45	35
Irregular periods (per cent)	13	13
Usual cycle length > 30 days (per cent)	11	20
Usual duration of bleeding > 7 days (per cent)	0	7
Using combined pill as last contraceptive (per cent)	65	62
Number of subjects in group	55	55

TABLE II

Net cumulative discontinuation rates per 100 women by reason for discontinuation at selected ordinal months of use

Reason for discontinuation	Treatment group	Ordinal months of use 4	8	12	Significance of difference*
Accidental pregnancy	L	1·8	4·1	4·1	NS
	M	0·0	1·9	1·9	
Abnormal bleeding	L	7·5	17·8	27·0	$\chi^2_{(1)} = 10{\cdot}1$
	M	3·7	3·7	3·7	$P < 0{\cdot}01$
Other side effects	L	12·9	17·0	20·0	NS
	M	9·3	17·5	20·6	
Planning pregnancy	L	1·9	6·0	11·8	NS
	M	1·9	4·1	7·2	
Other personal reasons	L	3·7	10·0	10·0	NS
	M	5·6	7·6	14·1	
Continuation rate	L	72·2	45·1	27·1	—
	M	79·4	65·2	52·4	
Woman-months of use (cumulative)	L	189	288	333	—
	M	191	331	400	

L = Loestrin–20 M = Microgynon–30

* Log rank method using gross rates (see Azen *et al*, 1977)

because of disturbances of bleeding, one complained that bleeding was irregular and the other that it was prolonged.

In analysing the data on bleeding patterns recorded on the diary cards, we defined 'menstrual bleeding' as *any* bleeding of sufficient severity to require sanitary protection, irrespective of whether it occurred on days when tablets were taken or during the 7 day tablet-free intervals. This, of course, implies that the terms 'breakthrough bleeding' or 'intermenstrual bleeding' are inapplicable to our analysis. On this basis, the overall distribution of menstrual cycle length in the two treatment groups is given in Table III. A few women in each of the groups failed to complete their diary cards properly and have, therefore, not contributed to the table, but this is unlikely to be of any consequence. The results shown in Table III indicate quite clearly that Loestrin–20 provides much less satisfactory cycle control than Microgynon–30; in view of these data the pattern of discontinuation of use of the two products shown in Table II is not surprising.

TABLE III

Distribution of cycle length in the two treatment groups

Cycle length (days)	Loestrin–20 No. of cycles	per cent	Microgynon–30 No. of cycles	per cent
–17	60	21·7	28	6·1
18–24	14	5·1	10	2·2
25–31	150	54·4	397	86·5
32–38	11	4·0	7	1·5
39–	41	14·8	17	3·7
Total	276	100·0	459	100·0

Table IV provides data on the duration of menstrual bleeding in the two treatment groups. Again, Loestrin–20 appears to be less satisfactory than Microgynon–30, its use being associated with an excess of both short (up to 3 days) and prolonged (7 or more days) episodes of bleeding. Table V summarizes the information on spotting, both that occurring immediately before or immediately after menstrual bleeding

TABLE IV

Distribution of duration of menstrual bleeding in the two treatment groups

Duration of menstrual bleeding (days)	Loestrin–20		Microgynon–30	
	No. of cycles	per cent	No. of cycles	per cent
1–3	143	51·8	187	40·7
4–6	110	39·9	258	56·3
7–9	21	7·6	12	2·6
10–	2	0·7	2	0·4
Total	276	100·0	459	100·0

TABLE V

Distribution of duration of spotting in the two treatment groups

Number of days of spotting	Loestrin–20		Microgynon–30	
	No. of cycles	per cent	No. of cycles	per cent
'Linked' to menstrual bleeding				
0	160	58·0	273	59·5
1–2	96	34·8	159	34·6
3–	20	7·2	27	5·9
Total	276	100·0	459	100·0
'Unlinked' to menstrual bleeding				
0	244	88·4	436	95·0
1–2	19	6·9	16	3·5
3–	13	4·7	7	1·5
Total	276	100·0	459	100·0

('linked' spotting) and that occurring at other times in the cycle ('unlinked' spotting). Differences between the treatment groups are small but, on balance, somewhat in favour of Microgynon–30.

We examined the nature of the 'other side effects' (depression, headache, nausea, etc.) leading to discontinuation of Loestrin–20 and Microgynon–30 (see Table II) but could discern no indication of any differences between the groups. It may be noted, however, that the one woman who developed a deep vein thrombosis during the trial did so during the fourth month of treatment with Microgynon–30. We also analysed the limited data available on body weight and blood pressure; no significant changes in either measurement occurred in either contraceptive group during the course of treatment.

Accidental pregnancies

Two women had accidental pregnancies while taking Loestrin–20, one during the second cycle and one during the seventh cycle. Neither woman admitted to having missed any pills, but both stated that they might have taken a pill several hours late during the cycle in which they conceived. Both women carried their pregnancy to term, and both gave birth to normal healthy infants (one male, one female).

The woman who became pregnant while taking Microgynon–30 did so during the fifth cycle. She claimed to have taken all her pills exactly in accordance with the instructions. The pregnancy was terminated at 8 weeks gestation.

One of the 23 women excluded from the analysis is also known to have had an accidental pregnancy (proven by two positive pregnancy tests) while taking Loestrin–20. The pregnancy occurred during the third cycle, was not associated with any irregularity in the taking of pills, and ended in a spontaneous abortion at 8 to 10 weeks gestation.

DISCUSSION

Despite the small sample size, the main finding in this clinical trial seems to be clear-cut: Loestrin–20 provides poor cycle control and, as a result, is a less acceptable contraceptive than Microgynon–30. There is also a suggestion that Loestrin–20 might be less effective than Microgynon–30, but the difference between the accidental pregnancy rates does not reach statistical significance.

Other published data about the efficacy and acceptability of Loestrin–20 seem to be limited to those described by Preston (1972). This author reported the results of a study in which the experience of 1218 subjects receiving Loestrin–20 who were followed for a total of 8284 cycles was compared with the experience of comparable numbers of subjects receiving different dosage combinations of ethinyloestradiol and norethisterone acetate. While Loestrin–20 was only a little less effective than the pills containing higher dosages of the con-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.