A RANDOMIZED, DOUBLE-BLIND STUDY OF SIX COMBINED ORAL CONTRACEPTIVES

Task Force on Oral Contraceptives

WHO Special Programme of Research, Development and Research Training in Human Reproduction

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ABSTRACT

A randomized controlled clinical trial comparing six combined oral contraceptives with 50µg or less of ethinyl estradiol was undertaken in 10 WHO Collaborating Centres for Clinical Research in Human Reproduction. A total of 2430 women entered the trial and were observed for 28,077 woman-cycles. All low-dose combined oral contraceptives demonstrated equivalent efficacy with one-year pregnancy rates of one to six percent. However, discontinuation rates for medical reasons differed significantly between the treatment groups, with the preparation containing 20µg ethinyl estradiol and that containing 400µg norethisterone acetate being associated with higher discontinuation rates due to bleeding disturbances. Even among the preparations which did not differ in discontinuation rates, the reasons for discontinuation did differ. Women receiving norethisterone preparations tended to discontinue because of bleeding disturbances while those receiving the levonorgestrel-containing preparations tended to discontinue because of complaints of nausea and vomiting.

INTRODUCTION

During the past ten years, more than 40 different combined oral contraceptive preparations have been commercially available or provided through family planning programmes in developed and developing countries. It is estimated that more than 50 million women annually now use oral hormonal contraceptives(1), for the most part combined oral contraceptive preparations containing 50µg or less of ethinyl estradiol or mestranol in combination with a progestogen.

The rationale for choosing between the many low-dose combined oral contraceptives available is not based on scientific study. Despite a plethora of clinical and laboratory reports on individual preparations, reports of clinical trials comparing the effectiveness, incidence of side-effects and rates of discontinuation for different low-dose preparations are few(1,2).

As part of its ongoing investigations into the safety and efficacy of fertility control methods, especially those issued in developing countries, the WHO Special Programme of Research, Development and Research Training in Human Reproduction has undertaken a multi-centred randomized double-blind study of six low-dose combined oral contraceptives. The preparations were selected on the basis of either their existing or expected widespread use in developing countries. In order to determine the difference between the effects of a 30µg and 50µg dose of ethinyl estradiol (EE) with a constant level of levonorgestrel (LNG), one preparation not yet commercially available was included.

Progestogens in the preparations included in the study were limited to norgestrel and norethisterone since both are known to act directly on progesterone receptors and nearly all other progestogens of the 19-norsteroid type are metabolized to norethisterone before being active in this way.

METHODS AND MATERIALS

A total of 2762 women attending family planning clinics between November 1975 and January 1979 in ten WHO Collaborating Centres for Clinical Research in Human Reproduction (CCCR's)* volunteered to participate in the study. Of these, 2430 women started in the study after satisfying the criteria for inclusion. To be included in the trial, a woman had to be healthy; to have had no contraindications for oral contraceptive use such as hypertension, heart disease, diabetes, etc.; to have been between the ages of 18 and 38, inclusive; if post-partum, to be at least 28 days post-partum and to have re-established menstruation; if lactating, to have been lactating at least 165 days and re-established menstruation; not to have used oral contraceptives within 28 days or long-acting injectable hormonal contraceptives within 90 days of starting the treatment groups; to have had regular menstrual cycles with the usual length within 21 to 35 days, inclusive. In addition, the woman must have agreed not to use any other contraceptive methods during her participation in the trial.

Women were able to withdraw from the trial at any time at their own request, and were discontinued by the clinical trial staff when pregnancy was diagnosed or when severe medical conditions developed such as cardiovascular disease, hypertension or liver disease.

Preparations

The six preparations compared were:

(1) ethinyl estradiol 50μg + levonorgestrel 150μg (EE 50 + LNG 150)
(2) ethinyl estradiol 30μg + levonorgestrel 150μg (EE 30 + LNG 150)
(3) mestranol 50μg + norethisterone 1mg (MES 50 + NET 1mg)
(4) ethinyl estradiol 50μg + norethisterone acetate 1mg (EE 50 + NAc 1)
(5) ethinyl estradiol 20μg + norethisterone acetate 1mg (EE 20 + NAc 1)
(6) ethinyl estradiol 35μg + norethisterone acetate 400μg (EE 35 + NAc 400)

The pills were produced by the manufacturers, but repackaged in twenty four 28-day cycle packets and identified by random numbers in such a way that neither the clinical trial staff nor the women knew which preparation was used by a particular woman+. At each of the centres women volunteering and eligible to participate were randomly assigned to receive one of the six oral contraceptive preparations.

In all circumstances, the pill regimen was begun on the fifth day of the menstrual cycle. The women were scheduled to return to the clinics at intervals of three cycles (84 days) for up to eight regular visits (24 cycles per woman). A woman was discontinued from the trial if the first 14 or more pills were missed in a cycle. Pregnancies occurring after discontinuation were not included in the analysis. A total of 28,077 woman-cycles were observed. Data collection was standardized and included information on age, obstetric history, previous contraceptive use, menstrual data, past medical history, current complaints and a physical examination, including a pelvic examination. On follow-up visits, complaints, significant findings on physical examination, blood pressure and weight were recorded. Menstrual diary cards were maintained by the women.

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\+ One woman in one centre examined her pills with a magnifying glass and was able to identify the company imprint on her pills.

At the end of the trial, the steroid content was measured in both opened and sealed unused pill samples from each of the centres. For the temperate countries, the hormone levels in pills from unopened packs ranged from 92% to 104% (mean 99.4%) of the stated dosage level; for the similar samples from the tropical countries, the range was 91.1% to 101.5% (mean 96.4%). Levels in opened packets were slightly lower.

Analysis

The statistical procedures used included standard t-tests, analysis of variance or X^2 test on contingency tables. Extensive use was made of the test for heterogeneity of counts which ignores slight differences in sample size. Net life table discontinuation rates were calculated according to the log-rank test(3,4).

Life table analysis was calculated from the first day of the menstrual period in which pills were started until the patient was terminated or completed the study after 24 cycles of use. Loss to follow-up was considered as a termination of use and was included in the "all reason discontinuation rate". Although in theory these women might be obtaining oral contraceptives from other sources, in practice the few studies that exist suggest that the majority of such women have discontinued the method(5). Since net cumulative discontinuation rate estimates involve adjustment for competing risks, the sum of the rates for specific reasons is greater than the overall discontinuation rate for "all reasons".

Definitions were standardized. A segment was defined as from the start of one menstrual-like bleeding episode to the start of the next menstrual-like bleeding episode. Bleeding disturbances derived from the menstrual diary cards were defined as follows:

amenorrhea:	longest bleeding-free segment greater than 60 days*
infrequent bleeding:	longest bleeding-free segment greater than 35 days and not over 60 days
frequent bleeding:	shortest complete segment less than 24 days
irregular bleeding:	shortest complete segment less than 24 days and longest menstrual segment greater than 35 days
prolonged bleeding:	bleeding/spotting episode longer than 7 days.

In addition to these categories derived from the menstrual diary cards, the women's complaints of bleeding disturbance were categorized and included amenorrhea, irregular bleeding, prolonged bleeding, light bleeding and spotting.

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* Although amenorrhea is commonly defined in terms of 90 days, because follow-up visits were in segments of 84 days ± 14 days, the use of 60 days for the definition was found to be more convenient in the analysis.

RESULTS

Random allocation of women participating in the trial resulted in relatively equal numbers of subjects in each of the six treatment groups (Table I). As would be expected among the 10 participating centres, there were wide differences in the characteristics of the women starting in the trial. However, as a consequence of the random allocation of subjects within each centre, of 22 variables recorded on admission, only 3 differed statistically ($p < 0.05$) between the six groups. These variables were the outcome of the last pregnancy (Table I), the length of the open birth interval and the length of the usual menstrual cycle. We considered these differences not to be of practical importance or affecting the results of the study since the magnitudes of the differences were small, and, with the number of statistical tests performed, the probability of finding three tests significant was about $p = 0.095$. Furthermore, neither these three variables nor any of the other admission characteristics correlated with the probability of continuation in the trial, pregnancy rates, side-effects or medical or personal reasons for discontinuation.

By two years, discontinuation rates for all reasons differed significantly between treatment groups, being mainly attributable to discontinuations because of side-effects or medical complications. Discontinuations because of loss to follow-up or personal reasons did not differ between groups (Table II).

Neither the one- nor two-year net life-table pregnancy rates differed significantly between treatment groups which ranged from one to six percent (Table II). Although all ten centres contributed similar numbers of subjects to the study, of the 72 pregnancies, 38 were recorded in the two Indian centres, none were recorded in one centre, and three other centres accounted for 2 to 3 pregnancies each.

One-year discontinuation rates for all reasons and for medical reasons ranged from 47.8% to 56.0% and from 23.9% to 34.7%, respectively (Table II). Discontinuations for increased blood pressure (55 cases), other cardiovascular disease (2 cases), liver dysfunction (15 cases), non-malignant breast lesions (3 cases), post-coital bleeding (1 case) or other major medical* reasons did not differ among the treatment groups.

Discontinuations for bleeding problems (200 cases) were generally more common in association with the norethisterone or norethisterone acetate preparations. The preparations containing 20ug ethinyl estradiol and 1mg norethisterone acetate had a much higher rate of discontinuations for bleeding problems (63 cases) than any of the other preparations. Discontinuations for symptoms of nausea (36 cases) and vomiting (26 cases) were more common with the two levonorgestrel-containing preparations (Table II).

Discontinuation for other minor medical complaints did not differ among groups. These included other gynaecological complaints (18 cases), other gastrointestinal complaints or perceived weight change (57 cases), skin complaints (19 cases), headache, and dizziness and other central nervous system or psychological symptoms (162 cases).

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* Other major medical reasons for discontinuation included breast malignancy (1 case), other neoplasias (1 case), pulmonary tuberculosis (5 cases), cholelithiasis (7 cases), Papinaucolou smear grade III (5 cases), pyelonephritis (3 cases), typhoid fever (5 cases), hyperthyroidism (2 cases) and one case each of migraine and seizure disorder.

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