Topic Session 1
ORAL CONTRACEPTIVES

28 NEW ORAL CONTRACEPTIVE PROGESTINS: NORGESTIMATE

S.L. Corson

Department of Obstetrics and Gynecology, University of Pennsylvania School of Medicine, Pennsylvania Hospital, Philadelphia Fertility Institute, Philadelphia, PA, USA

Women may use contraceptive estrogen–progestin formulations for contraception and family spacing for 20 or 30 years of their reproductive life. Estrogen generally has a beneficial effect on the lipoprotein pattern, while progestins, historically, have had an opposite effect with the net change a function of potencies and dose. Certain progestins, especially those with an androgenic metabolic profile, seem to be more adverse than others.

It must also be noted that no individual oral contraceptive (OC) preparation has been shown to be more beneficial or more adverse in terms of actual cardiovascular risk except as a function of dose response for individual agents. Although a population of women exists who have been taking OCs since the 1960s, demographic long-term data are not applicable because of dramatic changes in dose reductions of both components over 25 years.

World-wide studies have documented an irrefutable correlation between low density lipoprotein bound cholesterol (LDL-C) and an inverse relationship of high density lipoprotein (HLD-C) and the risk of cardiovascular disease. Both dietary trials and drug regimens have shown that these risk factors can be altered within the general population. Therefore, it is not difficult to harbor some concern about the end effect of minor alterations in the HDL/LDL ratio caused by OCs taken for decades. The changes may be slight, and still within arbitrary limits of normal, but demographic studies show no lower threshold for the cholesterol cardiovascular relationship, which tends to be almost a linear 1% cholesterol change = 2% cardiovascular event change.

All of the passionate arguments concerning progestational effect on the lipids may soon be moot because of the development of a new generation of progestins which are essentially lipid neutral. Norgestimate is one of these new compounds. When tested against standard OC formulations, no changes in pregnancy rate or cycle control were noted. Most important, serum lipid profiles were generally improved compared with baseline. These trials will be discussed as the data are presented.

NEW PROGESTOGENS IN OCs: LIPIDS, SHBG AND ACNE

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M. op ten Berg

Organon International BV, Kloosterstraat 6, 5340 BH Oss, The Netherlands

The latest improvement in oral contraceptives is the use of more selective progestogens. This development started with the introduction of desogestrel in a monophasic pill in 1981. Desogestrel, the first of the third generation progestogens, is highly selective, with a strong progestogenic activity and weak androgenicity. Introducing a selective progrestogen in an OC has two implications: the effects of estrogen on lipid metabolism (an increase of HDL-cholesterol and a decrease of LDL-cholesterol) and on sex hormone binding globulin (SHBG) are hardly counteracted by the androgenic effects of the progestogen.

The fact that it is prudent to use OCs that have minimal effects on lipid metabolism (conclusion at the Consensus Development Meeting on metabolic aspects of OCs) is completely fulfilled by Marvelon, an OC containing 30 μg ethinyl estradiol and 150 μg desogestrel. The increase in SHBG has been shown to have positive effects on certain androgenic skin disorders like acne and hirsutism. In a study in which more than 11,000 women participated, 8.8% of the participants had acne before they started to take Marvelon for six cycles. After six cycles of use 75% of these women were completely free from symptoms. Another study has shown that the effects of Marvelon and a specific anti-acne preparation containing cyproterone acetate on acne are identical.

CLINICAL EXPERIENCE WITH A LOW-DOSE ORAL CONTRACEPTIVE CONTAINING GESTODENE

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K. Brill and B. Düsterberg

Schering AG, Berlin, Germany

The monophasic combination preparation containing 30 μg ethinyl estradiol and 75 μg gestodene was tested for contraceptive reliability, cycle control and tolerability in a total of 7 Phase III clinical studies. A total of 6,854 women were included in these studies and 69,978 cycles were monitored.

Following the commercial introduction of the preparation, further clinical data were obtained with a broader user population. In Germany it was possible to implement an extraordinarily extensive Phase IV study in a very short period of time. A total of 523,477 treatment cycles in 95,906 women were included in the analysis. So, for what is probably the first time, a prospective general clinical study for a real

contraceptive was conducted on the same magnitude as the biggest cohort epidemiologic studies.

The results of the various Phase III and Phase IB studies are in close agreement. The combination preparation containing gestodene proved to have high contraceptive reliability and gave excellent cycle control. It was well tolerated and the frequency of adverse reactions was low.

The monophasic gestodene completely fulfils the demands made of oral contraceptives today.

31 SUPPRESSION OF OVARIAN ACTIVITY WITH A MONOPHASIC GESTODENE-CONTAINING ORAL CONTRACEPTIVE: AN ULTRASOUND STUDY

H.J. Hoogland

Academic Hospital Maastricht, The Netherlands

In a longitudinal study, the suppressive activity of a monophasic gestodene-containing oral contraceptive on ovarian function was evaluated and compared with other low-dose oral contraceptives. Residual ovarian activity was monitored by ultrasound scanning, estradiol and progesterone blood levels. The extent of follicular growth and maturation and the incidence of escape ovulation were assessed in 83 women during 12 consecutive cycles.

Of these volunteers, 56 (user group) used other oral contraceptives (>6 months) in advance of this study; 27 (starter group) did not use oral contraceptives beforehand. During the study period, 1300 ultrasound investigations were performed. Residual ovarian activity was considered to be present when follicle-like structures (FLS) (mean diameter >10mm) were seen within the ovaries. In case of a detected FLS, the 17β-estradiol level was determined and the FLS growth rate was monitored by serial ultrasound investigations. In case of elevated estradiol levels or a sudden decrease in size of the FLS, the progesterone level was determined during the second half of the cycle. Based on combined serological and ultrasonographic monitoring in 996 studied cycles, no escape ovulation could be demonstrated. The highest incidence of FLS occurred during the first cycle in the starter group (26%). The incidence gradually decreased to 7% from the sixth month onward.

In the user group, before switching to the monophasic gestodene-containing pill, the last cycle of the 'old' oral contraceptive (15 different types) was also monitored by ultrasound. The incidence of FLS during this cycle was 20%. During the following six-month period with the new oral contraceptive, the FLS incidence in the user group also decreased to 6%.

OVARIAN ACTIVITY DURING ORAL CONTRACEPTION

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G. Benagiano, F.M. Primiero, C. Bastianelli, G. Abbondante, F. Grottanelli and G. Tunnera

First Institute of Obstetrics and Gynaecology, University "la Sapienza", Policlinico Umberto I°, 00161 Roma, Italy

The availability of ultrasonographic techniques for the monitoring of ovarian activity during the menstrual cycle has provided a new tool for evaluating the effects of oral contraceptives on follicular development and function. Preliminary information indicates that, in spite of their high efficacy, modern estrogen–progestogen combinations do not cause complete inhibition of ovarian activity.

To properly evaluate the effect of presently available preparations on follicular maturation and function, 62 healthy volunteers have been monitored by serial ultrasonography during a control menstrual cycle, the first and the third cycles of treatment. The following parameters have been determined: number of follicles >10 mm, size of largest follicle during each cycle and pattern of endometrial changes. This was correlated in each cycle with the hormonal profile, as determined by serial measurements of circulating FSH, LH, total estradiol, progesterone, total testosterone, androstenedione, DHEAS, prolactin and SHBG.

The following monophasic preparations were tested: ethinyl estradiol (EE) 30 μg + levonorgestrel (LNG) 150 μg; EE 35 μg + cyproterone acetate 2 mg; EE 30 μg + desogestrel (DSG) 150 μg; EE 30 μg + gestodene 75 μg; EE 35 μg + norgestimate 250 μg; EE 20 μg + DSG 150 μg. In addition, two triphasic combinations were also tested: EE + norethisterone and EE + LNG.

Subjects were divided into 8 groups of 7 women each; 6 volunteers did not complete the observation period and were replaced.

In general, all monophasic preparations tested determined a more profound ovarian inhibition, both in terms of number and size of observed follicles. It must be stressed, however, that in no case could full maturation of a follicle be detected.

No statistically significant difference was observed between the two types of preparations in the levels of circulating hormones.

33 METABOLIC EFFECTS OF LOW DOSE ORAL CONTRACEPTIVE PILLS: EPIDEMIOLOGY AND CLINICAL TRIALS

T. Rabe, K. Grunwald and B. Runnebaum

Department of Obstetrics and Gynecology, Division of Gynecological Endocrinology, Vossstrasse 9, University of Heidelberg, D-6900 Heidelberg, West Germany

Inborn or acquired changes in lipid carbohydrate metabolism as well as blood clotting are supposed to be responsible for cardiovascular diseases in OC users.

Heidelberg OC multicenter trial: In an open multicenter clinical trial more than 2000 gynecologists in West Germany enrolled 59,691 healthy females and performed a standardized interview concerning risk factors in patients' family histories before prescribing a low dose oral contraceptive. The incidence of cardiovascular diseases and diabetes mellitus in family history (parents) of OC takers in West Germany ranges between 1 and 5%. In a sub-group ($n=2000$) 25% subjects showed a fasting cholesterol above 200 mg/100 ml and 19% triglycerides above 150 mg/100 ml. A similar study has been performed with 120 healthy female volunteers prior to OC administration with similar results. A cholesterol and triglyceride test before and during OC use is suggested.

Metabolic studies: Metabolic within-patient trials with low dose oral contraceptives will be described over 6 to 24 OC cycles using the following OC formulations: gestodene (75 μg gestodene/30 μg ethinylestradiol), desogestrel (30 μg gestodene/ 30 μg ethinylestradiol), norgestimate (250 μg norgestimate/35 μg ethinylestradiol). The impact on serum lipids, blood coagulation and carbohydrates will be presented by recent analysis of own long-term comparison trials. Data will be evaluated in view of clinical impact (e.g. risk of OC-dependent hypercholesterolemia, triglyceridemia, hyperinsulinemia or steroidal effect on antithrombin III, protein C and S, factors of blood clotting responsible for thromboembolism if decreased by inborn defects or drug-dependent). Metabolic effects of modern low dose OC are mild and most of them are within the normal range; therefore they are supposed to be without hazard for the individual patient.

Risk groups (e.g. age, smoking, obesity, disorders of lipids, carbohydrates and blood clotting) and laboratory screening tests will be discussed.

RANDOMIZED COMPARATIVE CLINICAL STUDY OF TWO ORAL CONTRACEPTIVES CONTAINING 30 μg ETHINYL ESTRADIOL AND EITHER 150 μg DESOGESTREL OR 75 μg GESTODENE

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S. Koetsawang *et al.*

Siriraj Family Planning Research Unit, Department of Obstetrics and Gynecology, Siriraj Hospital, Bangkok 10700, Thailand

Two oral contraceptives, one containing 30 μg ethinyl estradiol and 150 μg desogestrel (Drug A) and the other containing 30 μg ethinyl estradiol and 75 μg gestodene (Drug B) were randomly given to women requesting oral contraception at six hospitals in Thailand. A total of 500 women using Drug A and 500 women using Drug B were recruited. The efficacy, cycle control, side-effects, continuation rates and reasons for discontinuation within the first six months of use are being analyzed and will be available at the time of presentation.

ORAL CONTRACEPTION WITH NORGESTIMATE AND ETHINYL ESTRADIOL: A CLINICAL APPRAISAL

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M.E. Kafrissen

Director of Clinical Sevices, Ortho Pharmaceutical Corporation, Raritan, NJ 08869-0602, USA

In an effort to provide an oral contraceptive that offers excellence in safety, efficacy and tolerability, the combination of norgestimate 250 μg and ethinyl estradiol 35 μg has been proposed. A review of clinical experience to date reveals that the preclinical profile of norgestimate as an effective suppressor of ovarian activity, coupled with minimal androgenicity, is predictive of desired performance. The largest clinical trial of norgestimate resulted in an actual use-efficacy Pearl Index of 0.25, based on over 400,000 cycles of experience. The metabolic profile is characterized by elevations in both HDL and HDL2. Additionally, elevation of SHBG is associated with decreases in free testosterone, DHEA, and DHEAS. Prolactin remains unchanged. The coagulation profile revealed no changes in fibrinogen, factor VII, protein C, or antithrombin III. Analysis of excretion of prostanoids found a potentially favorable increase in prostacyclin, including the dinor metabolite. Finally, tolerability, including cycle control, is found to be favorable in both objective and subjective assessment. Overall, norgestimate/ethinyl estradiol oral contraception appears to be a valuable addition to therapeutic options.

36 A MULTICENTER TRIAL WITH A NEW OC USING NATURAL ESTRADIOL AND CYPROTERONE ACETATE FOR WOMEN OVER 35

E. Hirvonen, E. Vartiainen, Y. Kulmala *et al.*

Dept. I & II, Obstetrics and Gynecology, University Central Hospital Helsinki, 00290 Helsinki, Finland

A multicenter trial was carried out by 7 Finnish gynecologists to evaluate the efficacy, cycle control and side-effects of a new biphasic oral contraceptive (OC) containing natural estradiol and cyproterone acetate (CPA). The trial comprised 288 women over 35 years of age (mean 39.3) and a total of 3929 cycles.

Serum progesterone values determined twice during the 3rd treatment cycle showed inhibition of ovulation in 95%. The contraceptive efficacy of the combination was good. The pregnancy rate was 0.4 during the first treatment year due to one pregnancy which could be attributed to a patient failure. The other pregnancy occurred during the 16th treatment cycle.

As expected, the cycle control was not as good as with the ordinary OC. Cycle control analysis in 142 women from two centers are presented in Table 1. Due to the strong progestogenic activity of CPA, bleedings became scantier in most women and were absent during the pill free week in almost 1/3 of the cases. Irregular bleeding, mainly spotting, was reported by 35.5%, 24% and 24.5% of the subjects at 3, 6 and 12 months, respectively. Still, the number of bleeding free days per cycle was relatively high (Table 1).

No significant changes in body weight or blood pressure were observed. The frequencies of subjective side-effects, such as headaches, nervousness, depression and breast tenderness, were comparable to those observed with ordinary OCs.

During the first year 72 (25.0%) discontinued the treatment because of side-effects, mainly bleeding problems, and 27 (9.4%) discontinued for personal reasons. The continuation rate at 1 year was 61.6%.

Table 1 Cycle control in 142 women

	Withdrawal bleeding				*Irregular bleeding*		
Cycle	*Absent %*	*Slight %*	*Moderate %*	*Duration % (1–5 days)*	*Spotting %*	*BTB %*	*Bleeding-free days per cycle*
3	33.5	27.8	37.1	51.4	18.1	3.6	23.8 ± 3.9
6	25.8	33.5	40.6	65.6	19.5	10.9	23.0 ± 4.3
12	28.5	28.6	39.0	72.4	13.3	1.9	23.8 ± 3.5

SAFETY AND EFFICACY OF PROGESTERONE-ONLY ORAL CONTRACEPTION IN LACTATING WOMEN: A MULTICENTER INTERNATIONAL TRIAL

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A.W. Rosman

Family Heath International, PO Box 13950, Research Triangle Park, Durham, North Carolina 27709, USA

While the progesterone-only oral contraceptive is the only oral contraceptive recommended for breastfeeding women, the efficacy (relative to the time of initiation postpartum), safety and continuation rate are not well-defined.

This non-comparative trial was conducted in 22 centers in 14 countries among 4,088 healthy, breastfeeding women <27 weeks postpartum from 1984–1988. It evaluated the efficacy, safety and reasons for discontinuation of one-year daily administration of 75 μg norgestrel. Mean age was 25.7 years and mean total of live births was 2.5. At study admission, 56% of women were fully breastfeeding, 80.8% were not menstruating, 60.2% were less than 42 days postpartum.

Total discontinuation percentage, including those who were lost to follow-up, was 51.6%. The accidental pregnancy rate of 1.2 ± 0.2 at 12 pill-cycle months was not affected by parity. This rate varied for subgroups with different conditions at admission: 0.0 ± 0.0 for 517 women starting pills within one week postpartum; 0.7 ± 0.2 if fully breastfeeding with or without menstruation; 0.9 ± 0.2 if not menstruating; 1.7 ± 0.4 if supplementing breastfeeding; 2.4 ± 0.7 if menstruating; and 3.4 ± 1.1 if supplementing and menstruating.

This study lends support to the safety and efficacy of progesterone-only oral contraception in breastfeeding women. Factors affecting efficacy, such as the influence of when the pill was initiated postpartum, will be presented for clinical and programmatic interest.

PROGESTOGEN-ONLY CONTRACEPTION WITH 500 μg LYNESTRENOL (EXLUTON^{R})

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H. Rekers and M. op ten Berg

Organon International BV, PO Box 20, 5340 BH Oss, The Netherlands

Progestogen-only pills (POP) have always been less popular than combined oral contraceptives (COC). For certain groups of women, however, they are more appropriate because of their lack of estrogen-related effects and because they have no effect on lactation.

A number of studies have shown that the POP containing 500 μg lynestrenol per tablet is a suitable alternative to COCs, especially for those women who would rather not or cannot use estrogens. The very high rate of ovulation inhibition seen with Exluton (80%) accounts for a pregnancy rate of 0.9% per 100 woman-years, 2–3 times better than seen with other POPs.

Cycle control with Exluton is acceptable to the large majority of users, provided that they are well informed about the irregularities that may occur during the first months of use.

The incidence of subjective side-effects is low; nausea, headache and breast tension are rare.

Finally, Exluton has been shown to have no adverse effects on blood pressure, lipid- and carbohydrate metabolism and on the hemostatic system.

Exluton therefore is a very suitable POP for lactating women and women who should not use a COC, because of:

- thrombotic pre-disposition
- (history of gestational) diabetes mellitus
- sensitivity to estrogens.

39 CLINICAL EVALUATION OF THE USE OF POP IN INDONESIA

Soedarto

Department of Obstetrics and Gynecology, Medical School Airlangga University, Jl. Darmahusada 47, Surabada, Indonesia

It is well known that breast feeding has many benefits both for the mother and the baby. Considering the benefits of breast feeding, the Indonesian Government, through the Department of Health and the National Family Planning Coordinating Board (BKKBN), promoted and encouraged the habit of lactation among Indonesian women. Despite its fertility-inhibiting effects, lactation does not postpone pregnancy indefinitely. Therefore, the use of contraception is still recommended for nursing mothers. One of the contraceptive methods suitable for nursing mothers is the progestogen-only pill (POP). In order to promote the use of POP by nursing mothers, BKKBN plans a national distribution of this contraceptive this year. Personal experience using POP (Exluton) in 60 lactating women will be presented. The total length of use was 422 months with the mean 7.4 months (SD = 3.6 months, range 2–17 months). The mean age was 24.7 years (SD = 3.7 years, range 21–31 years). Most of the women had 2 living children (range 1–3). All of the women were low socio-economic class. Continuation rate was calculated by Life Table as follows: 3 months 90%, 6 months 50.7%, 8 months 36.7%, 12 months 10%. No user stopped the pill for medical reasons. Other studies showed a better figure. No pregnancy was

found, nor significant change on the blood pressure. Half of the women underwent decrease of body weight, perhaps because of lactation without adequate nutrition. It seems the suppression effect of POP on menstruation is not strong. The women who underwent lactating amenorrhea were able to menstruate again. Women who had ever undergone menstruation still had their cycle. Other side-effects were acne and headache. Generally, breast milk volume was not affected. The growth of the babies evaluated by KMS health card was normal. Several studies done in Indonesia also showed the same results. It is concluded from the present studies in Indonesia that the POP has a good efficacy, is relatively safe with a smaller effect on menstrual pattern than injectable contraceptives, and does not influence the production of breast milk.