Clinical Problems

Assessment of Incremental Dosage Regimen of Combined Oestrogen-Progestogen Oral Contraceptive

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British Medical Journal, 1974, 4, 643-645

Summary

Eighty-six women of proved fertility used an incremental dosage regimen of a combined oral contraceptive for a total of 570 cycles over one year. A daily tablet containing 50 µg of ethinyloestradiol and 50 µg D-norgestrel was taken for 11 days and a daily tablet containing 50 µg ethinyloestradiol and 125 µg D-norgestrel for the next 10 days. Withdrawal bleeding occurred during the tablet-free interval of seven days. The new preparation proved to be an efficient contraceptive, well tolerated, and with few side effects. Women who had gained weight while taking other oral contraceptives lost weight when they changed to the new preparation. The regimen allowed a significant reduction in the cycle dose of progestogen, and these results suggest that a further reduction in the cycle dose of both oestrogen and progestogen may be possible without losing contraceptive efficiency.

Introduction

The ideal contraceptive should consistently prevent pregnancy, interfere as little as possible with the menstrual cycle, have no side effects in the short or long term, and not impair sexuality. Oral contraceptives come nearest to fulfilling these requirements but they are still far from the ideal. The sequential formula in which an oestrogen alone is taken during the first part of the cycle followed by a mixed oestrogen and progestogen tablet in the second part has the major disadvantage that the oestrogen to be effective as a contraceptive has to exceed 50-µg. Even at that level the regimen tends to be less efficient than the combined tablet though the formula is generally well tolerated and influences the endometrium to approximate to a normal cycle. Daily administration of a low dose of progestogen—the “mini pill”—has its advocates, but cycle control is lost, the resulting endometrium differs greatly from the normal, and contraceptive failure is higher than with the combined tablet regimen.

The most efficient contraceptive and hence the most widely used is that where a combined oestrogen-progestogen tablet is taken for 21 days of the cycle starting on the fifth day. Its disadvantages are that it is not always well tolerated and it creates an unphysiological endometrium, occasionally even atrophy and consequent amenorrhoea.

The contraceptive under trial is a “step-up” combined oestrogen-progestogen formula with which an attempt has been made to enhance the advantages and minimize the disadvantages of other preparations.

Patients and Methods

The woman is required to take a daily tablet containing 50 µg ethinyloestradiol and 50 µg of D-norgestrel for 11 days and a tablet containing 50 µg ethinyloestradiol with 125 µg D-norgestrel for the next 10 days. A woman who has not taken oral contraceptives starts the tablets on the fifth day of the first treatment cycle and thereafter begins the tablets after a seven-day interval, as do women who are changed from another oral contraceptive to the new preparation. Thus at the end of each cycle there is a tablet-free interval of seven days during which withdrawal bleeding occurs and after which the next series is begun.

Eighty-six women of proved fertility between 17 and 39 years of age took the oral contraceptive for a total of 570 cycles. Fifty-two women had changed to the new preparation from another, 31 women started the new preparation about six weeks after parturition, and the remainder were using an oral contraceptive for the first time. The women were told to keep a daily record of their tablet intake and to note the details of withdrawal bleeding and the possible occurrence of breakthrough bleeding or spotting. A routine gynaecological examination including a cervical cytology assessment was carried out before and at three to six monthly intervals during the trial. Weight and blood pressure were recorded at each clinic visit, when a general question was posed to elicit, but not to prompt, subjective complaints. With the informed consent of the patients 55 endometrial biopsies were taken at various times during treatment cycles to obtain a composite picture of the endometrium during the treatment cycle and to assess the effect, if any, of prolonged use of the preparation. The number of biopsies performed in each treatment cycle is shown in table I. The specimens were assessed¹ by one of us (W.B.R.) in ignorance of all clinical data except the fact that the specimens came from women taking a synthetic steroidal contraceptive. Correlation of histological dating with the cycle histories was done only at the end of the study. Plasma progesterone levels² were estimated at the time of endometrial biopsy.

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TABLE I—Number of Endometrial Biopsies in each Month of Treatment

Treatment cycle: No. of endometrial biopsies ..	1	2	3	4	5	6	7	8	9	10	11	12	Total
..	4	3	12	6	6	11	4	2	1	2	2	2	55

Results

No woman became pregnant during the trial period. The cycle length in most cases varied between 27 and 28 days and withdrawal bleeding began usually on the second or third day of the tablet-free interval and lasted from 3.5 to 4.5 days. Heavier than normal bleeding occurred in only one patient. The general clinical observation that the preparation was very well tolerated and acceptable to the women was borne out by the low incidence of reported side effects (table II).

TABLE II—Incidence of Side Effects. Results are Percentages

Treatment cycles:	1-3	4-6	7-13	Total
No. of cycles:	252	184	134	570
Amenorrhoea ..	1.6	0	0	0.7
Breakthrough bleeding ..	0.8	0	3.1	1.1
Spotting ..	6	3.3	1	3.9
Headache ..	2.4	2.2	0	1.8
Nervousness ..	3.6	3.3	3.1	3.2
Loss of libido ..	2.4	3.3	0	2.1
Nausea ..	1.2	0	1	0.7

Weight fluctuations of more than 2 kg above or below the initial figure after six months of treatment occurred, respectively, in 8.1% and 32.2% of the patients. There was a definite tendency to lose weight in patients who changed from other oral contraceptives to the new preparation.

Three patients withdrew during the trial because they wanted to become pregnant, eight because they preferred another contraceptive method (for non-medical reasons), three because of irregular bleeding, and four because of intolerance.

In all cases the cervical cytology smears were graded as either I or II in the Papanicolaou classification. Plasma progesterone levels were consistently below 1 µg/100 ml.

Correlation of the histological dating of the endometria with the days of the treatment cycles on which the biopsies were taken is shown in the diagram. In general the endometria were

Correlation of histological dating of endometrial biopsy specimens with corresponding days of treatment cycle.
*This patient took the tablets in the reverse order.

somewhat hypoplastic when compared with what would be expected on the corresponding days of a normal cycle. While there was a good ratio of glands to stroma the glands tended to be less well developed with more variation in luminal diameter than the normal. The endometria, however, did show unequivocal evidence of a cyclical morphology though the progestational effect was usually advanced in time with glandular subnuclear vacuolation appearing sometimes as early as the 11th day followed by apical and luminal secretion. Because of the suboptimal development of the endometria secretory activity was not as pronounced as in the normal cycle, but in some instances scalloping of glands with the typical "saw tooth" appearance could be observed. Gland exhaustion tended to occur earlier than in the normal cycle and there was little evidence of the development of a stromal predecidual reaction late in the cycle—a feature that may be quite prominent with many of the combined tablet regimens. Stromal granulocytes³ (K cells) while easily detected late in the cycle were not as numerous as in the endometrium of the late normal cycle or endometria influenced by the usual type of combined pill.⁴ One interesting feature was the development of the spiral arteries and arterioles to a more advanced stage than that seen in endometria influenced by the currently used combined pills, where venous ectasia and inhibition of arteriole development are characteristic. There was no detectable difference in the cyclical morphology of the endometria throughout the year of the study and, in particular, no tendency to endometrial atrophy with prolonged usage of the formula.

Discussion

Since the recommended limitation of the oestrogen component of oral contraceptives to a level not exceeding 50 µg daily the sequential method of administration has gradually been replaced by the combined tablet regimen though it had the advantage over the combined pill in producing a more physiological cyclical endometrium.

In contrast to the older sequential regimen, the step-up combined preparation under trial maintains the oestrogen dose at 50 µg throughout the treatment cycle but is combined with a small dose of progestogen in the first 11 days. It differs from existing formulae for the combined pills that contain D-norgestrel by a significant reduction in the total cycle progestogen dosage. For example, the total cycle dose of oestrogen is the same, at 1,050 µg, for Ovran and Eugynon as for the new preparation but the cycle dose of D-norgestrel is 5,250 µg for Ovran* and Eugynon* whereas it is only 1,800 µg for the new preparation. The low progesterone levels recorded during the trial indicate that this step-up combined regimen is an efficient ovulation inhibitor, and the histological findings showed that a form of cyclical endometrial morphology is retained. The cycle control was excellent as only three patients had to stop the preparation because of problems with cycle control. Moreover, patients who transferred from other oral contraceptives tended to lose weight. Dating of the endometria can be achieved but there is a greater margin of error than with the normal. The histopathologist knowing that he is studying endometria influenced by exogenous steroids wittingly or unwittingly makes adjustments to his assessments, and this subjective factor added to the variability of the patients' endometrial reactions to the contraceptive may occasionally produce histological dating at variance with the clinical data. Probably the antioestrogenic effect of D-norgestrel in the first half of the cycle is mainly responsible for the partial inhibition of proliferative activity and its progestational effect for the earlier appearance in the cycle of secretory activity. As the progestational effect is on a sub-optimally oestrogen-primed endometrium the secretory changes

*A series of 21 tablets of Ovran and of Eugynon contains 10,500 µg DL-norgestrel as a racemic mixture of the D and L forms.

should be less pronounced than those seen in a normal post-ovulatory endometrium. Nonetheless, the endometrium does undergo cyclical changes resembling normal ones, and these changes are probably sufficiently different from the normal to prevent nidation should "escape" ovulation and fertilization occur.

We thank Wyeth, Belgium, and Schering, Berlin, for supplying the contraceptive preparation for this trial. The laboratory facilities are supported in part by grant No. 20.035 from the Belgian

Research Council. We are indebted to Miss M. R. Puttemans who performed all the technical work.

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Today's Treatment

Blood and Neoplastic Diseases

Management of Solid Tumours—Surgery, Radiotherapy, and Chemotherapy

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British Medical Journal, 1974, 4, 645-647

The traditional mainstays of cancer treatment have been surgery and radiotherapy and more recently chemotherapy. Immunotherapy offers hope, but is at present largely experimental. Until recently these disciplines were often found in isolation from each other and some patients were given treatments which were inappropriate for their disease. An important introduction into the investigation and management of cancer has been the concept of oncology as a specialty.

Surgery

Cancer surgery has reached a level of technical achievement beyond which it is unlikely that important advances will be made. Its established role in palliation is, of course, vital, and a newer role in the pathological staging of several tumour types has developed. The use of irradiation as an adjunct in the surgical management of tumours of borderline operability or inoperable tumours at several sites is being intensively investigated. Chemotherapy as an adjunct to surgery in tumours with a high propensity for metastatic spread may be of value in some cases—for example, in osteogenic sarcoma and carcinoma of the breast.

Radiotherapy

During the past two decades rapid technological advances have occurred in radiotherapy; kilovoltage machines have been superseded by megavoltage apparatus generating penetrating beams of high energy x-rays at high dose rates, and the precision, ease, and adaptability of treatment planning methods have been

improved by the introduction of simulators, mould room facilities, and computers. These developments, together with improved tumour localization techniques, have facilitated the treatment of most deep-seated tumours with a high degree of accuracy.

Successful radiotherapy must be based on precise tumour localization. Isotope scanning has achieved some success, ultrasonic scanning now shows considerable promise for obtaining details of tumour localization and volume for planning treatment.

Surgical staging procedures have been particularly useful in Hodgkin's disease, demonstrating occult splenic involvement in about 40% of patients with apparently localized nodal disease. There may be room for further improvement in achieving precise distribution of radiation dose within these accurately identified structures. For example, the possibility of employing proton beams together with x-ray beams to treat inaccessible sites such as the pancreas and the advantages of using beams of negative pi-mesons to achieve the same end is currently under discussion.

When optimal dose distribution has rarely posed a problem—for example, in skin cancer—the cure rate with irradiation has been excellent. The same is true for glottic cancer. Significant advances have, however, also been made in Hodgkin's disease,¹ based on two factors: tumour localization, and the ability to give tumoricidal doses to deeply placed nodes—for example, in the mediastinum and retroperitoneal areas. In bladder cancer radical radiotherapy was impracticable before the introduction of supervoltage irradiation, which can cure about 20% of advanced lesions,² a proportion which is likely to be considerably improved by the planned sequential use of irradiation and surgery. In advanced carcinoma of the cervix, improvements in stage IIB and IIIa have been recorded after the introduction of supervoltage irradiation.³ In localized carcinoma of the prostate, a site previously ignored by the radiotherapist, the Stanford group have reported a five year disease free rate of 72%.⁴ Successive improvements in the curability of testicular tumours have resulted from the introduction of modern treatment and investigative techniques.⁵ About 40% of children with medulloblastoma can be cured using techniques which irradiate the entire neuraxis.⁶

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