

HORMONAL STEROIDS IN CONTRACEPTION

Report of a WHO Scientific Group

CORRIGENDA

Page 27

For the medroxyprogesterone acetate/ethinylestradiol formulation, the quantities should read as follows :

<i>Progestogen</i>	<i>Oestrogen</i>
<i>(mg)</i>	<i>(mg)</i>
10.0	0.05
5.0	0.05
5.0	0.075

For the norethisterone/mestranol formulation, the quantities should read as follows :

<i>Progestogen</i>	<i>Oestrogen</i>
<i>(mg)</i>	<i>(mg)</i>
10.0	0.06
5.0	0.075
2.0	0.1
1.0	0.05

Page 28, table B, line 6

Delete dimethisterone 2.5 mg

Insert dimethisterone 25 mg



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HORMONAL STEROIDS IN CONTRACEPTION

Report of a WHO Scientific Group

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ON HORMONAL STEROIDS IN CONTRACEPTION**

Geneva, 23-27 October 1967

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HORMONAL STEROIDS IN CONTRACEPTION

Report of a WHO Scientific Group

A WHO Scientific Group on Hormonal Steroids in Contraception met in Geneva on 23-27 October 1967. The meeting was opened by Dr A. M.-M. Payne, Assistant Director-General, on behalf of the Director-General. Dr L. M. Hellman was elected Chairman, Dr E. Diczfalusy Vice-Chairman, and Dr R. Hertz and Dr R. P. Shearman Rapporteurs.

1. INTRODUCTION

In 1964 a WHO Scientific Group on the Mechanism of Action of Sex Hormones and Analogous Substances¹ reviewed what was then known of all the sex hormones, including steroid drugs used for contraception. In the following year, another WHO Scientific Group examined the basic and clinical aspects of oral gestogens; after reviewing the report² of this Group, the WHO Advisory Committee on Medical Research recommended that the Organization periodically evaluate developments in, and clinical experience with, contraceptives.

The primary objectives of the present meeting were to review the extensive information that had become available since the meeting of the 1965 Scientific Group and to define areas that are of continuing concern and that require further study. Thus, the two reports are complementary and should be read in conjunction.³

The present report first considers the steroid oestrogens and progestogens used in combined and sequential formulations. It is on such products, particularly combined formulations, that there has been the greatest accumulation of information since the previous report.² New oral and injectable compounds used for hormonal contraception are also considered, suggestions are made for the clinical management of

¹ See *Wld Hlth Org. techn. Rep. Ser.*, 1965, 303.

² *Wld Hlth Org. techn. Rep. Ser.*, 1966, 326.

³ Lists of selected references on particular topics covered by the present report are available, on request, from : Human Reproduction, World Health Organization, Geneva, Switzerland.

women using hormonal steroids for contraception, and general guidelines are given for preclinical studies, clinical trials, and epidemiological surveillance.

2. COMBINED AND SEQUENTIAL OESTROGENIC/PROGESTOGENIC PRODUCTS FOR ORAL CONTRACEPTION

2.1 New Drugs, Regimens, and Dosages

The outstanding developments in combined products since the last report¹ have been (1) different combinations of one of the two oestrogens, ethinylestradiol and mestranol, with the available progestogens, and (2) reduction of dosages, often resulting in changes in the relative proportions of the oestrogenic and progestogenic components. The principal developments in sequential products have been (1) an increase in the dose of oestrogen and (2) alteration in the day of the cycle on which the progestogen is added. (A list of available combined and sequential products is given in the Annex.)

The reciprocal synergistic and antagonistic action of the oestrogen and progestogen affects the clinical results obtained with all these drugs.

It is now established that the dosages of the original oral contraceptives were substantially higher than is necessary for inhibition of ovulation. An absolute reduction in dosage, without alteration of the proportions of the ingredients or the efficiency, is all to the good. It is clear that reduction of the dose of progestogen in certain combined formulations makes the absolute amount of oestrogen critical for consistent inhibition of ovulation. Where the dose of progestogen is low, it is the oestrogen that is more important as an ovulation inhibitor, whereas in sequential regimens oestrogen is all-important for that purpose.

Different modifications of formulations, such as alterations in the number or proportion of ingredients in a given contraceptive preparation, call for full and adequate evaluation of contraceptive effectiveness and of immediate and long-term effects, under different clinical and field conditions.

2.2 Mode of Action

The mode of action of contraceptive steroids is incompletely understood, partly because there is insufficient knowledge of the physiological mechanisms involved in the regulation of ovulation, fertilization, and implantation. It is, therefore, difficult to evaluate some of the pharma-

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1966, 326.

ecological effects of contraceptive steroids. Furthermore, it seems likely that different types of compound, or even the same compound at different dose levels, may act in different ways, and that the individual compounds and their combinations may exhibit multiple mechanisms of action. There is also evidence to suggest that the mode of action of contraceptive steroids in the first one or two cycles of use differs from that in later cycles.

The inhibition of ovulation produced by contraceptive steroids is mediated at least in part via the hypothalamo-pituitary system. Both oestrogens and progestogens interfere with pituitary gonadotrophic function. Detailed assessment of these effects is difficult because of individual variations and because of the problems involved in the estimation of plasma and urinary levels of follicle stimulating hormone (FSH) in the normal cycle. Furthermore, there is a lack of information on the minimum level of luteinizing hormone (LH) in plasma and urine that is compatible with ovulation. The immediate effect of the oestrogens in oral contraceptives seems to be the reduction of FSH and that of the progestogens the suppression of the midcycle peak of LH. Long-term administration of oestrogens, alone or in combination with progestogens, results in depression of both FSH and LH secretion. These changes are accompanied by morphological signs of depressed ovarian activity. The extent to which the secretion of other pituitary hormones is affected remains to be investigated.

Inhibition of ovulation is not essential to the antifertility effect of steroids. For example, the continuous administration of low doses of progestogens does not consistently inhibit ovulation, although it offers a very high degree of protection against conception. The way in which fertility is inhibited in the presence of ovulation is incompletely understood, although it is believed to involve one or more of the factors discussed below.

Animal experiments and clinical studies indicate that certain hormonal contraceptives may, particularly when administered over long periods, alter ovarian responsiveness to gonadotrophic stimulation. There is also evidence to suggest that hormonal contraceptives interfere with the biogenesis and/or catabolism of ovarian hormones. It is not known whether this is a significant mechanism of action for all types of contraceptive steroid.

Tubal factors play an important role in ensuring fertilization and proper transport of the ovum. Both oestrogens and progestogens are known to interfere with such factors in several species; whether they do so in the human is not clear.

Animal experiments indicate that ova can be fertilized only by properly capacitated sperm. In animals, the process of capacitation — which takes place in the female genital tract — can be inhibited by the administration of progesterone. It is not known whether the inhibition of

capacitation is involved in the mechanism of action of progestogens, alone or in combination, in women.

Implantation of the fertilized ovum is regulated, in several species, by a most delicate oestrogen-progestogen balance. The nature of this balance in women is not fully understood, but it appears possible that progestogens given throughout the cycle interfere with implantation by creating changes in the endometrium (see section 2.4.1).

Some hormonal contraceptives containing progestogens induce characteristic physicochemical changes in the cervical mucus that might contribute to their contraceptive efficacy. (This is not true of sequential formulations when the progestogen is added only during the last few days.) However, more conclusive evidence will be needed before changes in cervical mucus can be regarded as a major mechanism by which progestogens induce temporary sterility.

2.3 Contraceptive Effectiveness in Clinical Practice

Contraceptive effectiveness is most frequently expressed in terms of the number of pregnancies per 100 woman years, for the following reasons. If effectiveness were reported in terms of the number of pregnancies in a given number of observed menstrual cycles, the total clinical experience would not be adequately described, since there would be no indication of the number of patients or of the length of time during which each was exposed to the contraceptive. Similarly, the expression "woman years" does not precisely convey the duration of exposure of each individual under observation, since it fails to distinguish short-term from long-term experience. Allowance should also be made for the progressive decrease in natural fertility with age, another factor that affects statistical considerations in long-term observations. In evaluating effectiveness, the "cohort approach" may be useful where there are variable patterns of reliability (i.e., in taking the pills properly and in making accurate reports) among the patients. The use of life-table methods may give further information on use-effectiveness.

There is overwhelming evidence that the different regimens and formulations of contraceptive steroids have an extremely high degree of theoretical effectiveness (i.e., effectiveness when properly used). Full evaluation of the use-effectiveness of any of these preparations is restricted by the limited reliability of patients in the taking of pills and in reporting. To permit better epidemiological analysis of the influence of side-effects on use-effectiveness, accurate information is needed on rates of use in different socio-economic groups and age-groups in different countries.

The above limitations are all the more important when efforts are made to compare the relative effectiveness of different preparations in subjects of widely varying socio-economic, cultural, and educational

level and degree of motivation; this is particularly true when there is also wide variation in the personal qualifications, attitudes, and orientations of medical and paramedical personnel.

The theoretical effectiveness of the hormonal contraceptives now in use is so great that it would be difficult to demonstrate a significant improvement in this respect. Demonstration of a two-fold increase in theoretical effectiveness would require clinical studies of between 200 thousand and 9 million cycles, depending on the reliability of the patients.

It is also difficult to compare two highly effective regimens that differ only slightly — e.g., the use of combined administration and of sequential formulations. Although published data from many parts of the world suggest that failure rates with sequential formulations exceed those with combined formulations, there is no conclusive statistical evidence of any difference in effectiveness.

The effectiveness of contraceptive drugs may also be affected by variations in different batches of drugs (e.g., in crystal size), since such variations may have an effect on the rate of absorption and clearance of the drug and on other metabolic factors.

2.4 Other Effects of Possible Clinical Significance¹

2.4.1 *Reproductive system*

Ovary

Several studies have established that some hormonal steroid contraceptives may cause ovarian changes, characterized histologically by the absence of mature follicles and fresh corpora lutea and by slight thickening of the tunica. These morphological changes are apparently associated with a reduction in ovarian steroidogenesis, and almost always disappear after use of the contraceptive is discontinued. Occasionally, corpora lutea have been seen during the first few cycles of treatment.

Fallopian tubes

Experimental evidence suggests that tubal motility, ciliary action, and tubal secretory function may be altered by hormonal contraceptives, but no direct clinical observations have been made.

Corpus uteri

Information on the histological effects of combined and sequential preparations on the endometrium has not changed since publication of

¹ Unless otherwise indicated, the discussion of the effect of oral contraceptives in this section refers to combined formulations, which have been used in most studies. There is less information on the effect of sequential formulations, and it cannot be taken for granted that the two types of product will produce the same effects in all respects.

the previous report.¹ However, limited histochemical and biochemical observations suggest that significant alterations occur in endometrial metabolism that are reflected in ultrastructural changes and that require further study. There is some evidence that when the use of sequential formulations is discontinued the endometrium returns to normal, and fertility is restored, more quickly than after the use of combined formulations.

Taking into account the natural history of fibromyomata of the uterus, it appears that hormonal steroids, in the dosages used for contraception, have no effect upon the development of such tumours. However, higher doses of progestogens, alone or combined with oestrogen, may cause rapid enlargement of, and/or degenerative changes in, fibromyomata.

Cervix uteri

In the past two years, there have been rare reports of the occurrence of cervical lesions associated with the use of combined contraceptive preparations. Such lesions consist of a focal hyperplasia of the glandular epithelium, clinically resembling cervical erosions. Ectopic columnar epithelium has been seen on colposcopic examination, but there is no cytological evidence of cellular atypia. The lesions regress when the use of steroids is discontinued, but their clinical course during sustained steroid administration is unknown.

The previous report² noted that there was some evidence of a decreased frequency of suspicious cervical smears among women using steroid contraceptives. However, more recent studies indicate that such compounds have no significant stimulatory or inhibitory effect on cellular atypia.

In cases of cervicitis with clinical manifestations, the cure rate with orthodox treatment is unaffected by the concurrent use of oral contraceptives.

Endometriosis

Hormonal steroids are not likely to be needed for contraceptive purposes by women with endometriosis, since they are frequently infertile. However, there is ample evidence that the use of the combined types of oral contraceptive in the normal dosages, given either continuously or in the usual cyclic manner, produces a subjective and objective remission rate equal to that seen in treatment with pseudo-pregnancy regimens. Nevertheless, the use of such contraceptives does not replace conventional surgery in the treatment of endometriosis associated with infertility.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1966, 326, p. 9.

² *Ibid.*, p. 11.

Primary dysmenorrhoea

Since the use of oral contraceptives by women with primary dysmenorrhoea usually produces symptomatic relief, the failure of this regimen to control symptoms is an indication that the original diagnosis should be reassessed.

Veneral disease

It is not known whether the use of combined or sequential oral contraceptives indirectly affects the prevalence of venereal disease, nor is it known whether changes in the vaginal mucosa induced by such compounds modify the clinical presentation and natural history of acute gonococcal infections in the female.

Reproductive potential

Subsequent fertility. The evidence indicates that previous levels of fertility are usually restored when treatment ceases, so that over-all fertility is neither increased nor decreased following the use of oral contraceptives. There have been some reports of persistent amenorrhoea, occasionally associated with galactorrhoea, after withdrawal of oral contraceptives, and the observed frequency of such amenorrhoea in clinical practice suggests that a causal relationship may exist. There are few data on the incidence of secondary amenorrhoea in a comparable group of women who have not received oral contraceptives, and it is not clear whether or not this post-treatment amenorrhoea is coincidental.

Subsequent offspring. There is no evidence of a relationship between the inadvertent use of hormonal steroids at oral contraceptive dosage during early pregnancy and anomalous development of the external genitalia in the newborn, although there have been some reports of masculinization of the foetus following larger doses of progestational steroids for gynaecological purposes. However, more comprehensive epidemiological studies of this effect are required. Studies should also be made of the effect of the prolonged use of hormonal contraceptives on the frequency of congenital abnormalities in subsequent offspring — e.g., a 5-year follow-up study of a sample of at least 10 000 children. In addition, further data on the frequency of twinning and on the sex ratio of subsequent offspring would be useful in evaluating possible effects on reproduction.

Menopause

The previous report¹ noted that there is no basis for the belief that long-term ovulation inhibition affects the time of onset of the natural

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1966, 326, p. 12.

menopause, and there is no reason to modify this conclusion. There appears to be no contraindication to the use of hormonal steroids for contraceptive purposes at or near the time of the climacteric. However, there is no secure basis for the use of oral contraceptives rather than oestrogen alone for the treatment of post-menopausal symptoms by general substitution therapy.

2.4.2 *Breasts*

An indeterminate proportion of women complain of breast engorgement while taking oral contraceptives. This complaint is sometimes associated with an actual change in breast size, but even the morphological basis for this change is unknown.

There are conflicting reports on the effects of hormonal contraceptives on benign breast lesions such as fibrocystic disease.

Extensive experiments in several animal species indicate that breast cancer can be induced by the sustained administration of high doses of oestrogens over a substantial part of the animal's life span. It is difficult to evaluate the pertinence of this finding to the pathogenesis of human breast cancer, particularly since some species — e.g., the monkey and guinea pig — do not develop breast cancer under comparable experimental conditions. Studies of the effect of cyclic exposure of dogs and monkeys to oral contraceptives for 7 years have been initiated recently, following the finding of breast cancer induced in dogs by one steroid preparation, and of focal mammary hyperplasia in monkeys.

It is known that in some premenopausal women breast cancer is temporarily favourably affected by ovariectomy, and it is considered that this effect is caused by a reduction in endogenous oestrogen production. Moreover, subsequent adrenalectomy affords further transient amelioration, an effect that is known to be associated with a further decrease in the production of oestrogens and other endogenous steroids. The administration of oestrogen has an unpredictable effect on breast cancer in young women, in some cases inducing remission and in others exacerbation. Conversely, the administration of oestrogens alone, or of combined contraceptive preparations, frequently induces regression of breast cancer in post-menopausal women. It is clear, therefore, that endocrine changes appreciably alter the course of breast cancer in some women.

It is now the accepted practice to withhold combined and sequential oral contraceptives from premenopausal women with diagnosed breast cancer. There is insufficient information to determine whether, or when, hormonal contraception can be used by a patient who is apparently cured.

Prolonged exposure, followed by an average latent period of about a decade, is necessary for most chemical carcinogens to take effect in the

human. The development of breast cancer in women has a long latent period and the effect of protracted cyclic steroid therapy on the pathogenic process is unknown. This situation might be clarified by studies of the comparative frequency of benign and malignant lesions, found by breast biopsy, in users and non-users of steroid contraceptives.

Large-scale studies of the effect of prolonged cyclic steroid therapy on the incidence of breast cancer in women in the reproductive age group are now in progress. The studies are designed for long-term observations under controlled conditions, and the necessary sample size is considered to be about 10 000 women. Any cases of breast cancer that might be induced by hormonal contraceptives can be expected to occur randomly over the period of study, so that some effect should be detectable before the end of the proposed period of observation.

2.4.3 *General metabolic effects*

Since publication of the previous report¹ additional knowledge has been gained of the effects of steroid hormones on carbohydrate metabolism in apparently normal women. Increased plasma levels of growth hormones, sometimes accompanied by compensatory increases in plasma levels of insulin, have been observed. In some patients taking oral contraceptives, there is a statistically significant increase in the level of fasting blood glucose, accompanied by a decrease in carbohydrate tolerance and an increase in non-esterified fatty acids, serum triglycerides, and pyruvate. Because of a lack of information, the significance of these findings is not clear. The extent to which such changes are reversible after long-term administration of oral contraceptives is unknown, and follow-up studies have not yet been conducted for long enough to determine whether they are significant for the development of overt diabetes mellitus. Similarly, there is still insufficient information to reach any conclusion on the effects of oral contraceptives in women with overt diabetes mellitus.

Significant changes in plasma proteins have been demonstrated in users of oral contraceptives, as follows: an increase in serum lipoproteins and in α -1-, α -2-, and β -globulins, and a decrease in albumin.

2.4.4 *Other endocrinological effects*

Thyroid gland

The statements in the previous report² about the effects of oral contraceptives on the thyroid gland are supported and extended by recent evidence. Oral contraceptives have no apparent effect on the normal thyroid, but some important laboratory tests of thyroid function are

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1966, 326.

² *Ibid.*, p. 7.

affected. The basic change, from which all others follow, occurs in the transporting globulins. The increased level of thyroxin-binding globulin is reflected in an increased level of protein-bound iodine (PBI). Unlike the increased PBI of thyrotoxicosis, there is a fall in the resin uptake of labelled triiodothyronine (T_3), with no change in thyroidal ^{131}I uptake.

It is important that tests of thyroid function in patients taking oral contraceptives should not be misinterpreted. If such tests are deemed essential, it should be noted that ^{131}I uptake and excretion give the most significant results. The other commonly employed tests, such as T_3 resin uptake and PBI, should be used only in patients who have not taken an oral contraceptive for at least six weeks. Owing to a lack of data, no firm conclusions can be reached about the effect of concurrent use of oral contraceptives on the clinical management of hypothyroidism and hyperthyroidism.

Adrenal cortex

Little information on the effect of oral contraceptives on the adrenal cortex has been gained in addition to that noted in the previous report.¹ However, it has been shown that although the response to metyrapone may be reduced in some women taking oral contraceptives, other tests of adrenocortical responsiveness show no significant change.

Pituitary gland

Some aspects of the functional changes in the hypothalamus and pituitary gland were discussed in the previous report² and are referred to in section 2.4.8 of the present report. There is little information about the morphological changes that occur in the pituitary glands of women who have been taking oral contraceptives, and the findings are difficult to interpret. Further clarification might be obtained from studies of the function of the pituitary trophic hormones in women taking oral contraceptives.

2.4.5 *Cardiovascular system*

A few recent studies, particularly in Great Britain, have shown a slight increase in thromboembolic accidents, and even deaths, among users of oral contraceptives. Although, as noted in the previous report,³ it is difficult to estimate the magnitude of this risk on the basis of the available data, it appears to be small in comparison with the over-all risk incurred by planned and unplanned pregnancy. There are divergent

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1966, 326, p. 8.

² *Ibid.*, p. 7.

³ *Ibid.*, p. 13.

reports concerning changes in blood clotting factors; measurable factors do not seem to be indicators of clinically detectable hypercoagulability, and the changes that have been described do not appear to be related to thromboembolic accidents in patients taking oral contraceptives.

It has not been possible to assess the respective roles of particular compounds or formulations as etiologic agents, owing to the low prevalence of idiopathic thrombophlebitis in women of child-bearing age and to the smallness of the increase in incidence in patients taking oral contraceptives. Furthermore, in all studies that have been conducted it has been necessary, owing to the small numbers of patients, to group all oral contraceptives together in order to achieve statistically valid results. However, it seems that it is still justifiable to regard a history of thromboembolic disease as a contraindication to the use of steroid contraceptives.

2.4.6 *Haemopoietic system*

There is no evidence of any primary effect of hormonal steroids on haemopoiesis. Since they reduce menstrual blood loss, their use for contraceptive purposes by women with deficiency anaemias may provide a useful adjuvant to specific therapy for such disorders. Similarly, a reduction in menstrual flow is of clinical value where menorrhagia is the result of conditions such as thrombocytopenia or leukaemia. However, oral contraceptives cannot be regarded as a substitute for specific treatment of anaemias. It should be pointed out that women receiving anticoagulant therapy for reasons other than thromboembolic disease may use hormonal steroids for contraceptive purposes.

2.4.7 *Liver*

In view of the important role of the liver in such intricate aspects of steroid metabolism as conjugation, hydroxylation, dehydrogenation, and the biosynthesis of the steroid-binding proteins, more comprehensive studies of the effects of steroid contraceptives on the liver are required.

It still seems, as noted in the previous report,¹ that oral contraceptives should not be given to women with hereditary or acquired impairment of hepatic excretory function. However, the limited data available do not indicate that there is any change in tolerance to oral contraceptive steroids in patients with other forms of liver disease.

The use of steroid contraceptives is also contraindicated if there is a history of cholestatic jaundice of pregnancy, a disorder that is now recognized to be more widespread than previously thought.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1966, **326**, p. 12.

2.4.8 *Central nervous system*

That hormonal contraceptives affect the function of hypothalamic and higher centres is suggested by reports of such side-effects as headaches, migraine, convulsions, altered visual function, increased appetite, depression, and modifications in libido (see section 2.4.12). However, there is as yet no definite clinical evidence of a causal relationship between the hormonal contraceptives used and the occurrence of these manifestations of altered function of the central nervous system. Further clinical studies, using as objective criteria as possible and adequate controls, are needed.

2.4.9 *Skin*

It is now apparent that the development of chloasma in women taking oral contraceptives is more widespread geographically than indicated in the previous report.¹ The condition is not uncommon in Australia, New Zealand, and other parts of the world.

There is now ample evidence that the elevated plasma levels of testosterone and androstenedione seen in some patients with certain types of hirsutism may be suppressed by contraceptive steroids of either the combined or the sequential type. The use of hormonal contraceptives by women with hirsutism and acne is not contraindicated, and these conditions may in fact improve as a result of such medication.

2.4.10 *Skeletal growth*

The effect of oral contraceptives on the growth rate of immature girls is not known. The finding of elevated plasma levels of growth hormones suggests that the production of such hormones may be increased by oral contraceptives. Although it is known that epiphyseal closure may be accelerated in some girls by massive doses of oestrogens, the evidence is contradictory and not all investigators agree that these drugs always produce this effect, particularly when taken in the amounts contained in oral contraceptives. Since the use of oral contraceptives by growing girls is increasing, the effect of oestrogens and progestogens on linear growth requires further study.

2.4.11 *Weight*

Some women gain weight when taking oral contraceptives. In some women, this weight gain is the result of fluid retention in early cycles, whereas in others it is caused by the accumulation of fat. Published data show that weight gain of both types is a significant problem

¹ *Wld Hlt Org. techn. Rep. Ser.*, 1966, 326, p. 15.

with combined products in the higher dosage range, but is less frequently encountered with lower doses of the same progestogens or with sequential preparations. The evidence suggests that long-term weight gain is related to stimulation of appetite in susceptible women, and that this was more common with the earlier preparations that contained a relatively larger amount of progestogen.

2.4.12 *Complaints by the patient*

The side-effects of the use of hormonal contraceptives most commonly reported by the patient are nausea or vomiting, headache, weight gain, altered libido, intermenstrual bleeding, failure of menses on cyclic withdrawal or on discontinuation of use, reduction or increase in menstrual flow, and mastalgia. Idiosyncratic responses, such as urticaria, arthralgia and myalgia, are occasionally noted. All the complaints noted above can frequently be corrected by the use of a different preparation or by other individual adjustments.

In assessing the frequency of most of these complaints, the observer must necessarily rely on reports made by patients. Such reports are materially affected by the interrogator and his manner of interrogation and by what the patient feels he wants her to say. As a result, any determination of the relative frequency of these side-effects is highly unreliable, and of little value in comparing one group of women with another or the side-effects of one preparation with those of another. Even if reliable, such information is relevant only if the prevalence of comparable complaints among non-users of oral contraceptives is known.

Properly controlled double-blind studies may provide more reliable information than is now available, but even they are of somewhat doubtful value.

2.4.13 *Interactions with other drugs*

Laboratory experiments have shown interactions at the enzyme level between massive doses of corticosteroids or barbiturates and contraceptive hormonal steroids. However, there is no evidence that these results have any relevance to the woman who is taking hormonal steroids at oral contraceptive dosage.

There is insufficient information on the interaction of oral contraceptives with drugs used in the long-term treatment of chronic illnesses. Concurrent chemotherapy for tuberculosis has no apparent influence on the effectiveness of oral contraceptives, nor do they in turn appear to modify the effectiveness of the anti-tuberculosis treatment. It is not known whether the contraceptive hormones interact with drugs used in the treatment of other conditions, such as malaria and schistosomiasis.

2.4.14 *Effects under special circumstances*

Malnutrition

Further studies of the effects of oral contraceptives in women with different types of malnutrition are necessary. The situation is complicated by the fact that there are many types of malnutrition, of varying distribution throughout the world.

Studies in Ceylon showed that 60% of the women taking oral contraceptives were suffering from general malnutrition on a weight basis, and that half of this group experienced a significant gain in weight when taking oral contraceptives. In Mexico, where protein deficiency is common, it has been found that the taking of oral contraceptives has no apparent adverse effect on women with this condition. In one Mexican population that was studied, deficient protein intake was frequently associated with chronic liver disease. Nevertheless, studies of BSP retention and transaminase levels before and after 4-6 years of contraceptive use showed that no significant changes occurred.

Lactation

In many parts of the world adequate lactation is of paramount importance for the survival and normal growth of infants. Circumstantial evidence suggests that in some lactating women taking oral contraceptives there is a dose-related reduction in the amount of milk secreted and/or in the duration of lactation. No major effect on milk quality has been reported, but more detailed information is necessary. The entire subject of the effect of oestrogens and progestogens on lactation requires further study.

Contraceptive steroids and/or their metabolites are to some extent excreted into breast milk. In order to assess the possible effects of these compounds on infants, further studies are necessary to determine the extent of such excretion and the chemical and biological properties of the compounds that are excreted.

2.5 Indications and Contraindications

2.5.1 *Indications*

In women with certain gynaecological disorders such as dysmenorrhoea and hypermenorrhoea, the use of hormonal steroids is preferable to other methods of contraception, provided it is acceptable to the patient. Those women who have excessive or prolonged menstrual blood loss will usually derive greater benefit from a combined than from a sequential oral contraceptive. Where avoidance of pregnancy is of paramount

clinical importance, the use of oral contraceptives is preferable to other methods, provided that it is acceptable to the patient and that there are no specific contraindications (see below).

Data from populations where comparable statistics are available indicate that the use of combined or sequential oral contraceptives is the most efficacious method available for reversible contraception. In countries where family planning is only now becoming more widely used, there are not yet sufficient data on acceptability and use-effectiveness to indicate whether or not the use of oral contraceptives is preferable to other methods.

2.5.2 Contraindications

As mentioned above, the use of sequential or combined contraceptives is contraindicated in pre-menopausal women in whom cancer of the breast has been diagnosed. Owing to the lack of information, no definite statement can be made on the advisability of oral contraception in cases of genital tract carcinoma in which appropriate treatment does not impair the reproductive potential — e.g., some cases of carcinoma in situ of the cervix.

As previously noted, the use of oral contraceptives is contraindicated if there is a history of thromboembolic disease or of cholestatic jaundice of pregnancy or certain other forms of hepatic excretory impairment.

The increasing use of oral contraceptives augments the probability of encountering patients in whom the occurrence of a certain disease will raise the possibility that the disease may be caused by the contraceptive in use. A wide variety of such diseases was listed in the previous report,¹ but subsequent experience justifies the view that most, if not all, of these conditions are not drug related. Nevertheless, it is necessary to continue surveillance of such conditions in those taking oral contraceptives, in case they should be the result of adverse reactions to the drugs.

2.6 Extent of Use

It is difficult to estimate the number of women throughout the world who are taking oral contraceptives. From the available information it is apparent that the rate of usage varies widely from one country to another. Much of this variability may be related to socio-cultural and religious factors, cost, and government attitudes. In some countries the sale of oral contraceptives is illegal, in many they are available only on the prescription of a qualified medical practitioner, and in others they may be bought readily without any medical intermediary.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1966, 326, p. 19.

The available information on the increase in use of oral contraceptives in countries where they have been used for some years is somewhat more valuable than an attempt to estimate the total number of women who are using them. The rapid increase in use of oral contraceptives is indicated by the figures in Table 1, and the extent to which they are used in the different age-groups in the USA is shown in Table 2. It remains to be

TABLE I
USE OF ORAL CONTRACEPTIVES IN DIFFERENT COUNTRIES *

Country	Number of "cycle packs" ^a sold yearly per 1 000 fertile women							
	1959	1960	1961	1962	1963	1964	1965	1966 ^b
Australia			122	349	937	1 707	2 346	2 796
Belgium				31	140	230	485	781
Brazil				7	24	109	228	383
Colombia				11	78	224	375	682
Federal Republic of Germany				24	31	201	279	378
France				20	25	34	79	134
Italy						1	20	59
Spain						6	42	72
United Kingdom			4	25	72	251	426	500
USA	16	22	79	251	409	812	1 178	1 524

* After van Keep, P. A. (1967) *Advanc. Fert. Control*, 2, 1.

^a A "cycle pack" is a packet that contains enough pills for use during one cycle.

^b Estimated.

TABLE 2
USE OF ORAL CONTRACEPTIVES BY MARRIED WOMEN IN THE USA, 1965 *

Category	Estimated numbers (in thousands) and percentages in the following age-groups :											
	Under 45		Under 20		20-24		25-29		30-34		35-44	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Past and present users												
Now using	3 815	15.5	258	28.5	1 241	30.5	1 042	22.4	628	13.3	646	6.3
May use again	1 341	5.4	89	9.8	419	10.3	373	8.0	206	4.3	254	2.5
Will not use again	1 232	5.0	42	4.6	246	6.1	311	6.7	326	6.9	307	3.0
Non-users												
May use	4 676	19.0	261	28.8	852	21.0	1 050	22.6	931	19.7	1 582	15.4
Will not use	12 794	51.9	242	26.7	1 188	29.2	1 795	38.6	2 502	52.8	7 067	68.7
Ignorant of method	787	3.2	13	1.4	119	2.9	75	1.6	143	3.0	437	4.2
Total	24 645		905		4 065		4 646		4 736		10 293	

* After Ryder, N. B. & Westoff, C. F. (1966) *Science*, 153, 1199; data from US Bureau of the Census (1965) *Population characteristics*, Washington, D.C. (Ser. P-20, Publication No. 144). The figures given are for married women living with their husbands.

seen whether countries in which the large-scale use of oral contraceptives was more recently accepted will show changes comparable to those shown in Table 1; there are no data on which significant projections can be based. Furthermore, there is a lack of accurate information on rates of use in different socio-economic groups and age-groups in different countries.

Studies in certain countries have shown that the extent to which a given oral contraceptive preparation is used is largely fortuitous, depending partly on the time when it was introduced and the intensity with which it was promoted.

3. OTHER HORMONAL CONTRACEPTIVE FORMULATIONS

3.1 Oral Progestogens Alone

An important recent development is the use of a progestogen taken orally in small daily doses without interruption. Many progestogens are now being tested for this purpose in clinical trials, but it is too early to assess the results adequately.

The mechanism of action of progestogens given in this manner is incompletely understood (see section 2.2). In some women, ovulation is inhibited, but ovulation can be detected in at least some cycles in 30% or more of the subjects. Studies of the endometrium and of pregnanediol excretion have given results that are consistent with ovulation in some cases and with anovulation in others.

Changes in sperm penetration of the cervical mucus may be involved in the contraceptive effect; however, in some women taking progestogens of this type, motile spermatozoa have been demonstrated in the fundus uteri.

It seems, therefore, that the mechanism of action of continuous low-dose progestogen therapy may involve any combination of effects upon ovum release, tubal transport, implantation, and cervical penetration by spermatozoa.

Use-effectiveness data are so far available for only one preparation, chlormadinone acetate, given orally in a dose of 500 µg daily. In 26 000 cycles of use, the pregnancy rate was found to be 3.3 per 100 woman years.

The only side-effect for which significant data are available is that of bleeding, which occurred in about 18% of all the cycles studied. The cycle length was also found to be more variable than usual.

There is as yet insufficient information on potential toxicity, indications for use, or contraindications to the use of continuous low-dose progestogens. However, preliminary evidence indicates that this form of contraception has little, if any, effect on the quantity of milk or duration of lactation.

3.2 Oestrogens Alone

Although the cyclic administration of oestrogens alone is the oldest form of hormonal contraception, it is rarely used.

The post-ovulatory use of large doses of oestrogens for contraception is being assessed. Information is too scanty for any conclusions to be reached on the mechanism of action, reliability, acceptability, and safety of this approach, or on indications for, or contraindications to, its use. Experiments in animals seem to indicate that it acts by preventing implantation.

3.3 Long-Acting Oral Formulations

Preliminary studies of a combination of a long-acting oestrogen and a progestogen, given in the form of one pill each month, are in progress. However, the results are as yet insufficient to justify further comment.

3.4 Long-Acting Injectable Formulations

Long-acting injectable progestogens, with or without long-acting oestrogen esters, are at present undergoing clinical trials. Such injections are sometimes supplemented by the oral administration of oestrogens at regular intervals. Preliminary information from studies in which 150 mg of medroxyprogesterone acetate in aqueous suspension was administered intramuscularly every 90 days indicates that the pregnancy rate was 0.5% for 14 000 woman months. Other regimens, in which other progestogens with or without oestrogen are administered monthly or every 6 months, have also been used. The evidence suggests that long-acting injectable preparations are effective in preventing conception.

The principal immediate side-effect of long-acting preparations is irregular uterine bleeding. The major long-term problem is the unpredictability of the interval between cessation of treatment and the re-establishment of ovarian function and ovulation, which in some instances may be as much as 14 months.

The acceptability of this type of treatment will probably be determined by the type of individual to be treated. For those who envisage later pregnancies the variable duration of the infertile interval following cessation of treatment is a disadvantage. However, selected samples of women who desire no more children may find the method acceptable.

The mechanism of action of long-acting injectable formulations is not clear, nor is enough known about their absorption after injection. The factors that determine the length of the interval between cessation of treatment and resumption of menses are also obscure.

4. GUIDELINES FOR THE USE AND STUDY OF STEROID CONTRACEPTIVES

4.1 Clinical Management

In some countries the increasing use of oral contraceptives, together with the fact that they are usually available only on prescription, has permitted the application of certain public health measures to an increasingly large group of women. In many areas it is usual for physicians to take full medical histories and carry out complete physical examinations before they prescribe oral contraceptives. As a result, opportunities for the detection of cancer (e.g., by examination of the breasts and study of exfoliated cervical cells) have reached a larger proportion of women than might otherwise have been possible. In the same areas, it is accepted practice for women using oral contraceptives to undergo medical review at regular intervals of 6 or 12 months, affording an opportunity for repeated examination of breasts and study of cervical cytology. Such examinations are considered necessary not because the women are taking oral contraceptives, but because they are a health measure that is applicable to all women.

Even in areas that have the standards of medical care noted above, the use of oral contraceptives is undertaken with an awareness of the substantial limitations in our knowledge of their immediate and ultimate effects. The guidelines outlined above may have to be modified to permit the use of hormonal steroids for contraception in given countries, regions, or localities where cultural and other factors may differ. When such modifications are necessary, an assessment should be made of the risks of steroid contraception in comparison with those of other methods and with those of not using contraception at all. Consideration should also be given to the possibility of using paramedical personnel; when such personnel are employed they should be properly instructed and supervised.

4.2 Preclinical Studies

The extrapolation to women of data derived from dose and duration studies in experimental animals is of questionable validity and may be misleading, particularly when it is impossible to assess the comparability of dosages and lifespans. In the light of these considerations, the interpretation of such data is extremely difficult. There is no evidence to justify recent emphasis on the presumed advantages of observations in subhuman primates and in canines. It is most important that, in the study of hormonal contraceptives, administratively imposed selection of

experimental conditions and of particular animal species be based on detailed technical advice from qualified personnel.

4.3 Clinical Trials

A clinical trial should be designed in accordance with basic statistical requirements and with the specific objectives of the trial (e.g., the determination of factors such as use-effectiveness, acceptability, and safety). Consideration should also be given to the training of the personnel who are to carry out the tests. In clinical pharmacological studies it is necessary to have an understanding of the principles of controlled study and of the fact that a certain sample size is required to obtain statistical significance. The emphasis placed on such considerations will vary widely, depending upon whether the objective of the study is to determine small differences in relatively rare events or differences in frequent occurrences.

4.4 Epidemiological Surveillance

There are few areas where there is epidemiological surveillance for adverse reactions to hormonal contraceptives steroids. Furthermore, there is at present no way of ensuring that reports of such surveillance are complete and unbiased. Continued study of the effects of hormonal contraceptives is obviously necessary.

Ideally, surveillance should provide a means of giving an early warning if action should be necessary. However, it should be emphasized that with simple surveillance systems there can be no assurance that, if an adverse reaction is reported, it is caused by the drug concerned; nor is there any assurance that such reporting is complete and accurate. In order to determine their significance, stringent statistical criteria must be applied to reports of such adverse effects.

Efforts should be made to improve the way in which adverse reactions are reported. For each type of adverse reaction, the crucial data are the number of reactions (numerator) and the number of users (denominator), together with comparable data for a control group made up of non-users of oral contraceptives. Better methods for collecting and interpreting such data are urgently needed.

5. RECOMMENDATIONS FOR RESEARCH

Throughout this report attention has been drawn to areas where further investigation is necessary. Both long-term and short-term studies of these problems should be carried out in different populations. For

convenience, the needs are listed below, although not in any order of priority.

(1) The development of new formulations and regimens that are safer, more specific in action, better tolerated by the subject, and more acceptable.

(2) Studies of the metabolism of steroids used for contraception, with special emphasis on absorption, plasma levels, tissue distribution, catabolism, and excretion.

(3) Morphological, biochemical, and physiological studies of the reproductive tract of women using hormonal contraceptives for different lengths of time. Such studies are particularly important during the post-treatment period.

(4) Assessment of normal levels of FSH and LH and of the relationship of changes in these levels to ovulation.

(5) Information on the prevalence of primary, secondary, and post-partum amenorrhoea in women of reproductive age in different populations.

(6) Elucidation of the endocrine mechanisms involved in post-treatment amenorrhoea.

(7) Studies of the reproductive history of ova released from the ovaries of former users of oral contraceptives.

(8) Long-term study of the occurrence and course of malignancy of the breast and genital tract in women using hormonal contraceptives.

(9) Studies of general metabolic effects in women using steroid contraceptives, with special emphasis on carbohydrate, fat, protein, and mineral metabolism.

(10) Studies of the mechanisms leading to vascular thrombosis in general, including predisposing factors.

(11) Comprehensive studies of hepatic effects of hormonal steroids.

(12) Studies of the effects of hormonal steroids on the central nervous system and on pituitary function, with special attention to hypothalamic releasing factors and higher nerve centres.

(13) Controlled studies of the psychosocial aspects of hormonal contraception.

(14) Studies of the possible effects of hormonal contraceptives on skeletal growth in young girls.

(15) Further analysis of the influence of hormonal contraception on the incidence, pathogenesis, and clinical course of different diseases, including diabetes, parasitic infestations, neoplastic disease, various

types of malnutrition, venereal infections, pelvic pathology, and psychiatric disorders.

(16) Further studies of the interaction between hormonal steroids used for contraception and other drugs.

(17) Further study of the effects on lactation, the amount of hormonal steroids excreted in breast milk, the chemical nature of the metabolites, and the possible effects on breast-fed babies. Efforts should be made to distinguish the effects of oestrogen and progestogen used separately and in combination, and the effects of different ratios of these two components when they are used in combination.

(18) The development of improved epidemiological methods for the assessment of safety, short-term and long-term effects, use-effectiveness, and acceptability of hormonal steroid contraceptives.

(19) Further research in normal human reproductive physiology, covering basic, clinical, and epidemiological aspects. The lack of understanding of such physiology is in large part responsible for the deficient understanding of all factors involved in the use of contraceptive steroids.

In addition, the Scientific Group endorses the recommendations made in the previous report,¹ and urges greater support of programmes for the training of workers in the field of normal human reproductive physiology.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1966, 326.

Annex

CURRENTLY MARKETED ORAL CONTRACEPTIVES

A. COMBINED FORMULATIONS

<i>Progestogen (mg)</i>	<i>Oestrogen (mg)</i>
etynodiol acetate ¹	mestranol ²
1.0	0.1
lynestrenol ³	mestranol
5.0	0.15
2.5	0.075
medroxyprogesterone acetate ⁴	ethinylestradiol ⁵
10.0	0.5
5.0	0.5
5.0	0.075
megestrol ⁶ acetate	ethinylestradiol
4.0	0.05
2.0	0.1
megestrol acetate	mestranol
5.0	0.1
norethisterone ⁷	mestranol
10.0	0.6
5.0	0.075
2.0	0.1
1.0	0.05
norethisterone acetate	ethinylestradiol
4.0	0.05
3.0	0.05
2.5	0.05
1.0	0.05
noretynodrel ⁸	mestranol
10.0	0.15
5.0	0.075
2.5	0.1
norgestrel ⁹	ethinylestradiol
0.5	0.05
norgestrienone ¹⁰	ethinylestradiol
2.0	0.05

(Notes: see p. 20)

B. SEQUENTIAL REGIMENS

<i>Composition</i>	<i>Days</i>
chlormadinone acetate ¹¹ and mestranol :	
mestranol 0.08 mg	15
mestranol 0.08 mg + chlormadinone acetate 2 mg	5
dimethisterone ¹² and ethinylestradiol :	
ethinylestradiol 0.1 mg	16
ethinylestradiol 0.1 mg + dimethisterone 2.5 mg	5
megestrol acetate and ethinylestradiol :	
ethinylestradiol 0.1 mg	16
ethinylestradiol 0.1 mg + megestrol acetate 5 mg	5
inert tablets	7
noretynodrel and mestranol :	
mestranol 0.1 mg (days 5-19)	15
mestranol 0.075 mg + noretynodrel 5 mg (days 20-24)	5

¹ Proposed international non-proprietary name (INN) for 19-nor-17 α -pregn-4-en-20-yne-3 β ,17-diol diacetate.

² Proposed INN for 17-ethynyl-3-methoxy-1,3,5(10) estratrien-17 β -ol.

³ Proposed INN for 19-nor-17 α -pregn-4-en-20-yn-17-ol.

⁴ Proposed INN for 17 α -hydroxy-6 α -methylpregn-4-ene-3,20-dione acetate.

⁵ Proposed INN for 17-ethynyl-estra-1,3,5(10)-triene-3,17 β -diol.

⁶ Proposed INN for 17-hydroxy-6-methylpregna-4,6-diene-3,20-dione.

⁷ Proposed INN for 17 α -ethynyl-17 β -hydroxyestr-4-en-3-one.

⁸ Proposed INN for 17-hydroxy-19-nor-17 α -pregn-5(10)-en-20-yn-3-one.

⁹ Proposed INN for 13-ethyl-17-hydroxy-18,19-dinor-17 α -pregn-4-en-20-yn-3-one.

¹⁰ Proposed INN for 17-hydroxy-19-nor-17 α -pregna-4,9,11-trien-20-yn-3-one.

¹¹ Proposed INN for 6-chloro-17-hydroxypregna-4,6-diene-3,20-dione acetate.

¹² Proposed INN for 6 α ,21-dimethyl-17-ethynyl-17 β -hydroxyandrost-4-en-3-one.