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ADVANCES IN METHODS OF FERTILITY REGULATION

Report of a WHO Scientific Group

A WHO Scientific Group on Advances in Methods of Fertility Regulation met in Geneva from 9 to 13 December 1974. The meeting was opened by Dr W. H. Chang, Assistant Director-General, on behalf of the Director-General.

1. INTRODUCTION

Methods of fertility regulation have constituted one of the most important areas of research during the past 15–20 years : many new drugs, devices, and techniques have been developed, and research is continuing to improve these and develop new ones ; methods of fertility control are used by individuals numbering tens of millions ; their implications for health—both immediate and long-term—are numerous ; there is interest and concern about them all over the world, in both the more and the less developed countries.

The World Health Organization, at the request of its Member States, has accordingly convened numerous meetings of experts over the past decade to assess the state of knowledge concerning methods of fertility regulation and to make recommendations for research. Several of the meetings have been devoted to comprehensive reviews of a single method, for example the hormonal pill or the intrauterine device (IUD). Others have concentrated on selected aspects of a method, for example, the effects of contraceptive steroids on intermediary metabolism.

The present meeting addressed itself to special problems that have not been extensively reviewed in the past, such as the low-estrogen combination oral contraceptive and the effects of hormonal contraceptives on vitamin metabolism, or in which significant advances have been made in the two years since the last meeting on this subject, for example low-dose progestogen contraceptives, postcoital estrogens and prostaglandins for fertility control, and the return of fertility after cessation of the use of hormonal contraceptives.

Annex 1 lists the WHO publications that have resulted from previous meetings. Further important references are given in Annex 2.

2. STEROIDAL COMBINATION ORAL CONTRACEPTIVES WITH LESS THAN 50 μg ETHINYL ESTROGEN CONTENT

2.1 Rationale for use

It is a sound general principle of therapeutics to use as low a dose of a drug as possible for as short a time as possible to produce the desired effect. It is therefore logical that continuing efforts should have been made to reduce the dose of the oral contraceptives to the minimum consistent with good clinical performance. The original "combined" formulations contained quantities of both estrogen and progestogen that, individually, were sufficient to produce the desired contraceptive effect. Subsequently, the sequential agents demonstrated the contraceptive effectiveness of ethinyl estrogens. Practical experience with mestranol by itself indicated, however, that if the dose was reduced much below 75 μg daily, or if the bioavailability was reduced by some change in the manufacturing process, higher pregnancy rates occurred.

Apart from these considerations, in 1970 concern over thromboembolism and over metabolic alterations associated with oral contraceptive use led in several countries to the recommendation that the ethinyl estrogen content should not in general exceed 50 μg daily. In view of this development, it was natural to explore further reductions in dosage, particularly as combination agents with 50 μg of estrogen taken daily were highly effective and yielded good cycle control.

Ethinyl estrogens and the various progestational agents have complex effects on the hypothalamo-pituitary-ovarian system and on other physiological mechanisms that play a role in fertility, and the interrelationships involved (e.g., synergism and antagonism) have not been systematically explored. In this context, the Group was aware that two low-estrogen combination oral contraceptives are used, apparently successfully, by very large numbers of women in the People's Republic of China. One preparation contains 35 μg of ethinylestradiol and 625 μg of norethisterone, and the other contains the same amount of ethinylestradiol combined with 1000 μg of megestrol acetate. In view of the potential of such an approach to fertility regulation in a number of developing countries, the Group thought it would be of considerable importance to assess the available information in depth. Unfortunately, with the exception of limited data presented in 1973 at a WHO Symposium,[a] the Group had no access to the relevant information.

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[a] BRIGGS, M. H. & DICZFALUSY, E., ed. *Pharmacological models in contraceptive development, WHO Symposium, Geneva, 1973*. Stockholm, Karolinska Institutet, 1974, p. 166.

linical experimentation with combination formulations containing less than 50 µg of ethinyl estrogen and decreased doses of progestogen is being pursued in other countries as well.

2.2 Potency

2.2.1 *Ethinyl estrogens*

Animal studies generally indicate that ethinylestradiol is a more potent estrogen than mestranol, the potency ratio depending on the animal species and the particular bioassay involved. Human comparisons have been complicated by problems of bioavailability, small numbers of subjects, and accuracy of the end point. Recent studies with these two estrogens prepared in an equally bioavailable form showed equal potency at dosages above 50 µg/day ; there was some evidence for a higher potency of ethinylestradiol in the lower dose range, as judged by histological studies of the endometrium and determinations of plasma progesterone and gonadotrophin levels.

2.2.2 *Progestogens*

Progestational compounds exert a large number of biological effects, such as antiovulatory, uterotrophic, antiestrogenic, androgenic, anti-androgenic, and other effects, which can be demonstrated by animal assays. However, the spectrum of activities exhibited by individual progestogens differs substantially from one compound to another. The term " progestational activity " thus has relatively little meaning unless carefully defined, and useful comparisons are difficult to make. Moreover, these various biological activities in animals may not find corresponding expression in man. Extrapolations from animal experiments may therefore not be valid.

2.2.3 *Synergism of estrogen and progestogen*

Doses of ethinyl estrogens in the range of 20–40 µg/day do not inhibit ovulation consistently. Moreover, low doses of progestogens given for 3 weeks out of 4 are not likely to have high contraceptive efficacy, although this has never been specifically investigated. Nevertheless, combinations of low doses of ethinyl estrogens and progestogens are highly effective in inhibiting ovulation and as contraceptives.

2.3 Efficacy in clinical trials

The data from multicentre clinical trials that have included at least 1000 subjects are shown in Table 1. These data must be interpreted in the context of the following discussion (section 2.4).

TABLE 1. EFFICACY IN CLINICAL TRIALS: USE-EFFECTIVENESS RATES *

	Dose in µg/day				
	ethinylestradiol + norethisterone acetate			ethinylestradiol + (±)-norgestrel [a]	
	30 + 1500 [b]	20 + 1000 [b]	30 + 600 [b]	30 + 500 [c]	30 + 300 [d]
No. of subjects	1 192	1 393	1 872	1 085	1 287
No. of cycles	14 536	15 265	20 341	7 323	11 085
Pregnancy rate/HWY [e] ± 95% confidence limit	0.58 ± 0.43	0.86 ± 0.51	1.36 ± 0.55	0.16	0.12

* Use-effectiveness rates include both pregnancies due to method failure and those due to patient failure.

[a] Formerly known as *dl*-norgestrel.

[b] Data made available by courtesy of Dr S. Preston, Parke, Davis & Company, Ann Arbor, MI, USA (1974).

[c] BYE, P. G. T. & ELSTEIN, M. *Brit. med. J.*, **2**: 389 (1973).

[d] Data made available by courtesy of Dr T. Woutersz, Wyeth Laboratories, Philadelphia, PA, USA (1974).

[e] Hundred woman-years.

2.4 Assessment of contraceptive effectiveness

2.4.1 *Bioavailability*

The general question of bioavailability of drugs has been discussed at length in a previous WHO publication.[a]

Contraceptive effectiveness is influenced by the inherent potency of the drugs, the quantity used, and also the bioavailability of the dispensed product. Bioavailability becomes increasingly important as the quantities of the drugs are reduced. Differences in manufacturing methods and quality control may be critical.

2.4.2 *Pregnancy rates*

The question of the statistical reliability of pregnancy rates observed in clinical contraceptive trials has been discussed in detail in an article by Hines & Goldzieher. Table 2, reproduced from this article, illustrates some of the considerations involved. It shows, for example, that if 2 pregnancies have been observed in 5000 cycles of experience, there is a 95% certainty that the " true " pregnancy rate per hundred woman-years (HWY) lies in the range of 0.06–1.73. Again, if 2 pregnancies have been observed in 100 cycles, it is still possible that further experience may show the agent to be of reasonable effectiveness since the lower 95% confidence limit is still only

[a] WHO Technical Report Series, No. 536, 1974.

~.9/HWY. More than 2 pregnancies in 100 cycles, if confirmed in several trials, would clearly point to an unacceptably high pregnancy rate.

Table 2 is an approximate guide only, since it takes no account of numbers of subjects studied or duration of use; effectiveness can be evaluated satisfactorily only by the use of life-table methods.

TABLE 2. THE 95% CONFIDENCE REGIONS FOR 0, 1, AND 2 PREGNANCIES OBSERVED IN A SERIES *

No. of pregnancies	No. of cycles	95% confidence region (per 100 woman-years)	
		Upper limit	Lower limit
0	100	44	0.00
1	100	67	0.30
2	100	86	2.9
0	500	8.9	0.00
1	500	13.4	0.06
2	500	17.3	0.58
0	1 000	4.4	0.00
1	1 000	6.7	0.03
2	1 000	8.6	0.29
0	5 000	0.89	0.00
1	5 000	1.34	[a]
2	5 000	1.73	0.06
0	10 000	0.44	0.00
1	10 000	0.67	—
2	10 000	0.86	0.03
0	25 000	0.18	0.00
1	25 000	0.27	—
2	25 000	0.35	—
0	100 000	0.04	0.00
1	100 000	0.07	—
2	100 000	0.09	—

* Reproduced from HINES, D. C. & GOLDZIEHER, J. *Amer. J. Obstet. Gynec.*, **105** : 450 (1969).
[a] Extremely small but not zero.

Observed effectiveness is made up of two components—drug efficacy itself and patient reliability. In many cases the latter factor may be dominant. The existence of these two factors complicates the practical assessment of drug effectiveness, especially in comparisons of 2 agents that are both highly effective to begin with. Consider, for example, a trial of a drug that yields a use-effectiveness rate of 1.20/HWY made up of a drug failure rate of 0.80/HWY and a patient failure rate of 0.40/HWY (i.e., a trial in which one-third of the total pregnancy rate is due to patient unreliability). Under these circumstances, to demonstrate that a new compound shows a twofold

increase in effectiveness over the old one would require a properly designed randomized trial involving 58 000 cycles with each compound. If a higher proportion of pregnancies were found to be due to patient failure, even greater numbers of cycles would be required for a valid trial. These considerations clearly imply that claims for superior efficacy based on small numbers of observations are unjustified.

2.4.3 *Assessment of patient reliability*

In most investigations, insufficient effort has been devoted to evaluation of patient reliability. Both the timing of tablet omissions and their total number are of importance. The usual questioning or residual package inspection is inadequate; more accurate and more reliable methods not requiring such procedures as blood or urine collection need to be developed.

2.4.4 *Controls and randomization*

It is well known that the use-effectiveness of contraceptive methods varies widely in different populations. Consequently, pregnancy rates in different studies cannot properly be compared. What is needed is a comparison group in the same population. If possible, the comparison group should be incorporated in some randomized trial design. Multicentre studies are greatly to be desired as they give an idea of the range of variation that can be expected in different population groups.

In the light of all these considerations, the data in Table 1 indicate that all the formulations listed have a reasonable level of effectiveness. However, comparisons between the formulations and with other sets of data are not justified.

2.5 Side effects

The methods of assessment of side effects were discussed by a previous WHO Scientific Group.[a]

2.5.1 *Clinical effects*

Published data on the clinical consequences of administering low-dose combination oral contraceptives are difficult to interpret for a variety of reasons. The major problem is the almost invariable absence of a simultaneously run control group, let alone random assignment or a double-blind procedure. The variable character of patient populations and their reliability, differences in previous therapy, different definitions as to what constitutes a side effect, and differences in duration of observation and

[a] WHO Technical Report Series, No. 473, 1971.

...ropout rates also confound comparisons. A single, small double-blind comparison of 30 μg of ethinylestradiol + 150 μg of (+)-norgestrel [a] with 50 μg of ethinylestradiol + 250 μg of (+)-norgestrel has been reported. Control of the menstrual pattern appeared to be somewhat better with the higher dosage preparation.

2.5.2 *Metabolic effects*

No substantive data are available at this time. It would be expected that changes observed at higher dose levels would be reduced by dosage reduction, and unpublished data that were reviewed by the Group relating to one preparation suggest this to be the case. However, verification by future studies with this and other preparations is needed.

2.5.3 *Rare side effects*

The assessment of rare events, such as thromboembolism, by epidemiological methods requires extensive clinical use over a long period of time. These conditions have not yet been fulfilled and thus no comment is possible.

3. EFFECTS OF ESTROGEN-PROGESTOGEN COMBINED ORAL CONTRACEPTIVES ON VITAMIN METABOLISM

The oral contraceptives, which are now so widely used, have far-reaching metabolic effects on many tissues and organs, and these include effects on the levels and possibly the activities of various vitamins. A review of the quite extensive literature concerning their interaction with vitamins is now in order, but it must be emphasized that not all the vitamins have been studied with the same detail, nor is it always clear which component of the oral contraceptive under study is responsible for the observed changes. Most of the studies have involved various combined estrogen-progestogen pills, but the data are insufficient to permit a comparison between them. No data are available on the effects of oral contraceptives with a low estrogen content (20–40 μg of estradiol) or those containing progestogen only. This section is therefore concerned with the effects of the commonly used combined oral contraceptives considered as a group and without reference to their actual composition.

At the outset it should be emphasized that alterations in the level or distribution of vitamins in the plasma or cells are not always indicative of a significant deficiency of coenzyme function with attendant metabolic

[a] Formerly known as *d*-norgestrel.

derangement of clinical significance to the patient. It should also be emphasized that it is fairly easy to establish biochemical evidence implicating by inference a change in vitamin status but difficult to demonstrate clinical effects of such changes ; even nutritional experts differ in their interpretation of the biochemical results. This point needs to be stressed because a climate of opinion is already developing that favours the indiscriminate addition of vitamins to oral contraceptives in order to counteract the biochemical changes that have been demonstrated in users. Such an indiscriminate approach, which is superficially attractive, ignores the fact that the clinical significance of the observed changes is still unknown and that these changes may be necessary adaptations to the overall impact of the oral contraceptives on metabolic processes as a whole, rather than specific biochemical abnormalities requiring treatment. In most instances, moreover, if vitamin supplements were to be effective in correcting the observed abnormalities they would have to be given in much larger doses than the normal recommended daily intake. The uncontrolled administration of multivitamin supplements to oral contraceptive users would render more difficult the rational examination of the effect of these compounds on the health of women. In addition, the giving of vitamins in greater than normal amounts may entail dangers of its own.

To date, 6 vitamins have been studied, namely, vitamin A, vitamin B2 (riboflavin), vitamin B6 (pyridoxine), vitamin C, folic acid, and vitamin B12. There are still too few data on vitamin B1, vitamin D, niacin, pantothenic acid, and inositol to warrant any comment in this report.

3.1 Vitamin A

Mean levels of vitamin A (retinol) are elevated in the serum of oral contraceptive users, the increase being 30%–80% compared with controls. β-Carotene levels are unchanged or slightly low in users. The increase in serum vitamin A levels is due to an increase in retinol-binding protein (RBP), which is a hormonal effect probably caused by the estrogen in the oral contraceptives. It is not clear whether there is an increase in the unbound free alcohol that is the active form of vitamin A. Theoretically, it is possible that the increase in serum vitamin A is associated with a shift of the vitamin from the tissues to the blood, which could have an adverse effect on women with vitamin A deficiency, but so far there is no actual clinical evidence of such an effect in malnourished women. This should be the subject of much closer examination than has been carried out to date. It has been suggested that the elevated vitamin A levels, which take 2–3 months to return to normal after oral contraceptive use is discontinued, could constitute a teratogenic hazard in women who conceive soon after stopping the pill. This speculation

based on the known great sensitivity of the rat embryo to quite small elevations in vitamin A levels *in vitro*. There is no evidence that this mechanism has been responsible for human fetal malformations, but clearly there is a need to investigate this aspect in greater detail. Reference has already been made to the fact that the rise in vitamin A levels in oral contraceptive users is brought about by an increase in the protein-bound fraction. In this respect the *in vivo* situation differs from the *in vitro* experiments in which rat embryos were exposed to small increases in circulating free vitamin A. Nevertheless, the theoretical possibility remains that the protein-bound vitamin could also have teratogenic effects, and at least this aspect of contraceptive–vitamin A interaction would be simple to verify by appropriate animal experiments.

3.2 Vitamin B2 (riboflavin)

Riboflavin is an essential component of the flavin nucleotides (flavine-mononucleotide (FMN) and flavine-adenine dinucleotide (FAD)), which are coenzymes that, together with flavoproteins, are concerned with proton transport. FAD is the coenzyme for the flavoprotein glutathione reductase, which catalyses the reduction of oxidized glutathione. The maintenance of adequate levels of reduced glutathione is important for the integrity of the erythrocyte. Apart from the measurement of riboflavin levels in plasma, red cells, and urine, a functional test for riboflavin deficiency is provided by the measurement in red cells of the activity of erythrocyte glutathione reductase (EGR) and its stimulation *in vitro* by the addition of FAD to the incubation medium (FAD effect). Studies have shown that in oral contraceptive users, as compared with controls, riboflavin levels in plasma and red cells are lower, EGR activity in red cells is lower, and percentage stimulation of enzyme activity with the addition of FAD is greater. This evidence suggests that there is a depletion of riboflavin in women on oral contraceptives, but this is a biochemical assessment that is so far not supported by any evidence of a clinical state of vitamin deficiency induced by the steroids. One fairly widespread inherited metabolic abnormality, namely glucose-6-phosphate dehydrogenase (G6PD) deficiency, which occurs especially in tropical and Mediterranean areas, may require special consideration in relation to the use of oral contraceptives. In this condition the EGR activity in erythrocytes is considerably raised, and it is thought that this greater activity of the enzyme may partially compensate for the metabolic derangement in the G6PD-deficient red cell. If oral contraceptives caused a lower FAD saturation of the enzyme in the erythrocytes of women with G6PD deficiency, this could constitute a potential risk and increase

the clinical severity of the disease. Definitive studies of this possible effect should be carried out, together with further detailed investigations of the influence of oral contraceptives on riboflavin metabolism in malnourished women.

3.3 Vitamin B6 (pyridoxine)

A great deal of experimental work has been done on the effect of oral contraceptives on tryptophan and vitamin B6 function. It has been shown that estrogens, glucocorticoids, and pregnancy modify tryptophan metabolism as a result of the induction of the rate-limiting enzyme, tryptophan 2,3-dioxygenase, in the liver. This has the effect of diverting tryptophan down its major catabolic pathway, which is the nicotinic acid ribonucleotide pathway. Estrogens and pregnancy probably exert this effect by increasing glucocorticoid activity in the liver. Because of the enhanced metabolism of tryptophan via the niacin pathway, a number of urinary metabolites of tryptophan are increased, especially after an oral load of tryptophan. One finds, for example, increased urinary excretion of kynurenine, 3-hydroxykynurenine (HK), xanthurenic acid, and, to a lesser extent, 3-hydroxyanthranilic acid (HA). Several of the enzymatic reactions involved in the metabolic transformation of tryptophan into its excretory products require pyridoxal phosphate (PLP) as coenzyme. PLP is the coenzyme form of vitamin B6, constituting a substantial proportion of the vitamin B6 compounds present in human blood. The requirements for this coenzyme are therefore increased by the altered metabolism of trytophan. A further increase in the requirements for vitamin B6 arises from the fact that estrogen conjugates compete for PLP binding sites on the apoenzyme. Estrogen administration also increases the activities of other PLP-dependent enzymes, causing a redistribution of PLP among its apoenzymes ; this suggests an increased requirement for PLP. The urinary excretion pattern of tryptophan metabolites in women on oral contraceptives is similar to that found in nutritional vitamin B6 deficiency. Their level of plasma PLP may be reduced. In addition, tissue depletion of vitamin B6 has been confirmed by the demonstration of reduced activity and saturation with coenzyme *in vitro* of the PLP-dependent red cell aminotransferase enzymes, alanine aminotransferase and aspartate aminotransferase.

It has been shown that about 80% of women taking oral contraceptives have abnormal tryptophan metabolism suggestive of a relative vitamin B6 deficiency. About 20% of these women have an absolute deficiency of this vitamin, as demonstrated by low urinary excretion of 4-pyridoxic acid (which is the major excretory product of vitamin B6), increased urinary HK/HA ratio, and decreased activity of PLP-dependent erythrocyte alanine

nd aspartate aminotransferase enzymes. These abnormalities of tryptophan metabolism are abolished by the administration of 20–30 mg of vitamin B6 daily, which is 10–15 times the normal dietary intake of vitamin B6.

Despite the biochemical evidence of vitamin B6 deficiency induced by the oral contraceptives, skin disorders and neuropsychiatric abnormalities are the only symptoms that have been linked to this deficiency.

Perioral dermatosis has been described in association with oral contraceptive use and biochemical vitamin B6 deficiency. It is thought that the mechanism may involve inhibition of pyridoxal kinase activity.

Controversy surrounds the question of whether the pharmacological effects of oral contraceptives can produce neuropsychiatric symptoms. While in the majority of women any such symptoms may be rather trivial and shortlived, a small proportion of women taking oral contraceptives have severe depression that seems to be directly related to the use of these gonadal steroids. There are theoretical reasons for supposing that this abnormality may be due to a disorder of brain primary amine metabolism secondary to vitamin B6 depletion induced by oral contraceptives. The biochemical changes and their link with problems of mood and affect are complex.[a]

A double-blind placebo-controlled cross-over drug trial has been carried out in a group of women whose depression was judged to be due to the use of oral contraceptives. Half the women were shown to have biochemical evidence of absolute vitamin B6 deficiency ; the remainder did not have such evidence. In the vitamin B6 deficient group, the administration of vitamin B6 produced a significant amelioration in their symptoms of depression. Vitamin B6 was without significant effect in the non-deficient group.

Clearly, further work is needed, especially to determine whether malnourished women show greater effects than women whose diet is adequate. In this context it should be remembered that both vitamin B6 intake and the availability of tryptophan (in the form of protein) need to be considered. Suggestions that vitamin B6 should be added indiscriminately to oral contraceptives to overcome the postulated deficiency in this vitamin are considered premature. In the first place, more work needs to be carried out to establish beyond doubt that the biochemical changes already described do, in fact, indicate a true vitamin B6 lack and are not due to some adaptation of metabolism secondary to estrogen administration. It is also considered unwise to add vitamin B6 because the addition of this coenzyme alone in a metabolic situation where there is a known induction of several vitamin B6 dependent enzymes concerned with amino acid metabolism

[a] See WHO Technical Report Series, No. 473, 1971.

could, on theoretical grounds at least, lead to increased loss of amino acids with unpredictable effects, especially in populations where protein intake is low.

3.4 Vitamin C

There are several biochemical studies demonstrating that women taking oral contraceptives have lower mean plasma, white cell, and platelet vitamin C levels than controls. The mean reduction in level is about 30%–40% but there is no suggestion that the levels reached are equivalent to those found in clinically scorbutic individuals. The explanation for these lowered levels of vitamin C is unknown, and it is also not clear whether they have any clinical significance. Studies suggest that it would take about 500 mg of vitamin C daily (that is, roughly 10 times the normal intake) to normalize the blood and tissue levels of vitamin C in oral contraceptive users. Further research needs to be carried out to determine the mechanisms of these changes and their pathological significance, if any.

3.5 Folic acid

While reduced mean serum and red cell folate levels have been reported by some investigators, these findings have not been consistent. Abnormal urinary formiminoglutamic acid excretion has been found in some oral contraceptive users by one investigator but this report still awaits confirmation. There are a small number of clinical reports of cases of megaloblastic anaemia that have been attributed to the use of oral contraceptives, but it is still uncertain whether these individuals were normal before starting these drugs. It is more likely that they suffered from subclinical folic acid deficiency due to unrecognized malabsorption syndromes and that the oral contraceptive was responsible for bringing these conditions to light. The mechanism producing the low folate levels in oral contraceptive users is not understood. Earlier suggestions that the gonadal steroids could impair folate absorption have not been substantiated by further studies. An interesting finding is that the serum of some pregnant women and oral contraceptive users contains a protein that binds folate ; this folate binder is probably induced by the contraceptives.

There is considerable scope for further research into the relation between oral contraceptive use and folate metabolism, particularly in those women with a nutritional deficiency state or with an increased need for folic acid—those having repeated pregnancies or suffering from chronic haemolysis, malabsorption, iron deficiency, or alimentary infestation with hookworm or other parasites. Conditions such as tropical sprue, idiopathic steatorrhoea,

coeliac disease, blind loop syndrome, and Crohn's disease need to be borne in mind. A further factor deserving consideration is that women receiving anticonvulsant drugs have an increased need for folic acid, and the combination of these drugs with oral contraceptives may consequently lead to difficulties.

3.6 Vitamin B12

There are a few reports of low serum vitamin B12 levels in women using oral contraceptives, but red cell levels are normal and there is no interference with vitamin B12 absorption. One investigation has reported extremely low values in the plasma of some women in the group under study, the levels being equivalent to those found in Addisonian pernicious anaemia. However, there are no reports of haematological abnormalities attributable to vitamin B12 deficiency. From the studies reported thus far, it would seem that the low serum levels of vitamin B12 with normal red cell and tissue levels represent a biochemical abnormality that at present has no adequate explanation. Clearly, as in the case of folic acid, more probing haematological investigations should be carried out in women on oral contraceptives.

4. POSTCOITAL ESTROGENS

A postcoital contraceptive agent would be a useful addition to current methods of fertility control. As with other methods, safety, reliability, and availability are criteria that must be satisfied if the method is to be widely used. A previous WHO Scientific Group [a] briefly reviewed the use of high dosages of estrogen as a non-repetitive interceptive measure when there is a risk of pregnancy. The report drew attention to the relatively small amount of data available, difficulties of their interpretation, and uncertainty about the mode of action.

4.1 Efficacy

Altogether there are now published data on about 4000 [b] women to whom steroidal or non-steroidal estrogens have been administered following intercourse in which either a contraceptive method was not used or there was reason to believe that the method used was ineffective. It is not possible to assess accurately the number of women who would have conceived had

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[a] WHO Technical Report Series, No. 527, 1973.

[b] About 2000 further cases are referred to in the literature but they are not considered here because of incomplete documentation.

no treatment been given. For example, some of the women might have already been pregnant when they first presented to their medical practitioner, and others may have conceived after subsequent acts of intercourse. Further, the timing of intercourse in relation to ovulation varied, the reliability of the histories of sexual exposure is open to doubt, and these subjects included very young girls and older women in whom fertility may have been relatively low. After considering the very limited literature concerning the risk of pregnancy following isolated acts of intercourse, the Group arrived at a working estimate that 150–300 pregnancies would have been expected among the 4000 women. The total number of pregnancies reported, however, was 26, and this group included some patients given doses of estrogen lower than those at present considered adequate. Even allowing for the fact that the follow-up of these patients was less than 100%, there is a good indication that the postcoital administration of estrogens can effectively prevent pregnancy.

4.2 Dosage

The dosages used have varied but those currently recommended are the oral administration, in one dose, of either 5 mg of ethinylestradiol or 50 mg of diethylstilbestrol (DES) for 5 consecutive days, to be commenced within 3 days—and preferably within 36 hours—of intercourse. There is some evidence that pregnancies occurred with greater frequency when lower doses of estrogen were used or when the interval between intercourse and treatment exceeded 72 hours. There is also evidence that the method is ineffective if implantation has occurred.

4.3 Side effects

Listed in Table 3 are the side effects reported from a study of 1942 women, two-thirds of whom were given ethinylestradiol and the remainder diethylstilbestrol. The symptoms were similar in both groups. About half the patients had no symptoms or only minor complaints. In about half the patients nausea occurred, and in about one-fifth vomiting was also a feature. Usually these symptoms were mild and did not persist for more than 24 hours or so. Occasionally, more intense gastric disturbances occurred, which usually responded to conventional antiemetic drugs. When vomiting occurred within 2 hours of administration of the steroid, the dose had to be repeated, preceded by an antiemetic. Mastalgia developed in about 20% of women but was not a reason for discontinuing treatment. In about 12% of patients the menses were delayed for several days, and prior warning about this possibility served to allay anxiety. Prolonged amenorrhoea for

TABLE 3. SIDE EFFECTS OF LARGE DOSES OF ESTROGENS ADMINISTERED AFTER UNPROTECTED COITUS *

Side effects	Women taking ethinylestradiol [a]		Women taking diethylstilbestrol [b]	
	No.	%	No.	%
Nausea	750	52.8	277	52.8
Vomiting	324	22.8	108	20.6
Tender breasts	304	21.4	74	14.1
Menorrhagia	183	12.9	42	8.0
Headache	22	1.5	15	2.8
Dizziness	8	0.5	3	0.5
Abdominal pain	21	1.4	13	2.4
Amenorrhoea (< 6 months)	7	0.4	2	0.3
Others	109	7.6	34	6.4
None	449	31.6	181	34.5
Total no. of women	1 418		524	

* Data from HASPELS, A. A. & ANDRIESSE, R. *Europ. J. Obstet. Gynec. reprod. Biol.*, **3**: 113 (1973).

[a] Dose : 5 mg daily for 5 days.

[b] Dose : 50 mg daily for 5 days.

up to 6 months was seen in 9 patients. About 12% of patients had menorrhagia with their first menstrual period. Only two subjects had persistent vomiting requiring the subsequent doses of estrogen to be given by intramuscular injection.

4.4 Safety

The immediate risks of this method seem to be negligible but the risks attributed to estrogens used in other doses and applications must be taken into account in assessing safety.[a] A woman with a history of thrombosis or a predisposition to vascular problems, or with cardiac insufficiency (especially pulmonary hypertension), systemic hypertension, liver disease, diabetes, or oedema may be at greater risk with this method but there are no data on which this risk can be assessed.

The most serious concern relates to the carcinogenic potential recently demonstrated by Herbst and co-workers [b] and confirmed by others, who have shown that diethylstilbestrol administered to women during the first trimester of high-risk pregnancy resulted in an increased incidence of vaginal adenosis and adenocarcinoma of the vagina and cervix in the female

[a] WHO Technical Report Series, No. 473, 1971 ; No. 527, 1973.

[b] HERBST, A. L. ET AL. *New Engl. J. Med.*, **284** : 878 (1971).

offspring. Other studies suggest the possibility of an increased risk of congenital malformations in the offspring of mothers who received synthetic sex hormones during the first trimester of pregnancy for a variety of reasons. In view of these findings women should be fully informed and advised to accept pregnancy termination if the postcoital estrogen therapy fails.

Finally, high-dose estrogen administration should be regarded as a once-only method, or at any rate should be repeated only infrequently. Women at risk should be given the appropriate advice and help to avoid the future necessity of emergency intervention to prevent pregnancy.

4.5 Parenteral administration

The Group received reports of studies in which estrogen was administered by intramuscular injection. A single injection of a combination of 12.5 mg of estradiol benzoate and 10 mg of estradiol phenylpropionate was used. Too few patients have been treated to permit a proper assessment of efficacy. The main advantage of the method is the much lower incidence and severity of nausea and vomiting in the patients treated thus far with this method.

5. LOW-DOSE PROGESTOGEN ORAL CONTRACEPTIVES

5.1 Rationale for use

Small doses of progestogens given continuously are used in an attempt to avoid those side effects of combined formulations believed to be attributable to the estrogen component.

Some evidence exists that low-dose progestogens given alone do not interfere with lactation. This is of particular interest for populations where prolonged breast-feeding is the normal practice.

The progestogens studied thus far are related to 17α-hydroxyprogesterone (chlormadinone acetate, megestrol acetate, and clomegestone); to 19-nortestosterone (norethisterone, norethisterone acetate, lynestrenol, quingestanol acetate, and etynodiol diacetate); or to gonane derivatives such as norgestrel.

Although chlormadinone acetate is not now commercially available as a progestogen-only oral contraceptive, the Group felt that the wide experience gained with this drug should be included in the overall assessment of progestogen-only preparations.

5.2 Efficacy

The continuous ingestion of small doses of progestogens alone has a clinical effectiveness lower than that of other oral contraceptives of either the sequential or combined type. Furthermore, the dose level is critical.

In studies where sufficiently large numbers of cycles have been collected, pregnancy rates of between 2.2 and 4.0 per 100 woman-years have been reported with 0.5 mg of chlormadinone acetate. In most studies where small numbers of cycles have been observed the rates still range from 2.0 to 4.0 per 100 woman-years, but a few indicate rates as high as 12.0 per 100 woman-years.

While there are many published studies on progestogens other than chlormadinone acetate, these were carried out on relatively small groups of patients. However, there are large amounts of unpublished data on file with pharmaceutical firms. The Group had access to some of this information, an examination of which indicates pregnancy rates ranging from 0.8 to 2.5 per 100 woman-years. However, information accumulated by manufacturers generally comes from a large number of sources and is often incompletely documented. It is possible, therefore, that these figures may underestimate the true rates.

There are many possible reasons for variations in the pregnancy rates, including the type of population studied and the care with which the study is designed and performed (cf. section 2.4). One explanation for the high failure rates reported with chlormadinone acetate in some studies conducted in the United Kingdom might be that larger doses are needed by women with a heavier body weight.

Other factors that may influence pregnancy rates include the omission of tablets and the time of tablet taking. As in any other oral contraceptive trial, the reporting of patient failure should be included in any data presented on low-dose progestogen oral contraceptives.

The difficulties of assessing efficacy in studies that do not involve sufficient numbers of observations and statistically valid comparisons with at least one other fertility regulating agent are well recognized and have already been discussed in this report. The desirability of multicentre trials has also been stressed.

5.3 Mechanism of action

The data on hypothalamic-pituitary effects and possible direct effects on the ovary are inconclusive ; histological changes are seen in the majority of endometrial biopsies but their significance with respect to implantation is uncertain. Other mechanisms such as inhibition of sperm migration have been suggested, but more investigations are needed to confirm or refute them.

5.4 Clinical side effects

5.4.1 *Cycle control*

The assessment of cycle regularity provides information of limited value unless it is related to the discontinuation rate for unacceptable bleeding. In those studies published and reviewed, discontinuation on this account represented the major proportion of withdrawals for medical reasons.

In the absence of generally agreed definitions of the normal cycle, bleeding intervals, and intermenstrual bleeding, the comparison of results between different compounds and in different studies becomes difficult and the conclusions questionable. However, there is no doubt that irregular bleeding and spotting are the most frequent complications of low-dose progestogen regimens.

While a number of studies have reported figures for those women withdrawing because of unacceptable bleeding patterns, few give details, including the numbers, of those who experience some alteration in their patterns but of insufficient severity to warrant withdrawal. Again, the lack of any standard definition makes assessment of the situation difficult. However, the frequency of irregular bleeding in the first few cycles following the initiation of medication is considerably higher than in later cycles. The mechanism responsible for the irregular bleeding is incompletely understood.

5.4.2 *Other side effects*

While non-comparative studies have suggested that side effects associated with progestogen-only oral contraceptives occur less frequently than with combined oral preparations, the two comparative studies in the literature report differences only with respect to nausea and vomiting. It should be pointed out, however, that the number of subjects in both studies was small, i.e., 70–100 per group.

5.5 Metabolic effects

5.5.1 *Carbohydrate and lipid metabolism*

The balance of evidence indicates that the low-dose progestogens exert negligible effects on carbohydrate and lipid metabolism. However, there are two reports suggesting that etynodiol diacetate and norgestrel may have a slight effect on carbohydrate tolerance. Thus far no data have been reported suggesting that orally administered compounds related to 17α-hydroxyprogesterone have a similar effect.

5.5.2 *Liver function*

The effect of various compounds on routine liver function tests has been studied. No abnormal findings have been demonstrated at these low dose levels.

Electron microscope studies of liver biopsies following the administration of chlormadinone acetate indicate certain modifications in some of the cell organelles. Similar changes have been reported in women having used estrogen-progestogen combined oral contraceptives as well as in pregnant women. No interpretation of these findings can be offered at the present time.

5.5.3 *Blood coagulation*

The limited amount of information available suggests that chlormadinone acetate and norethisterone given for 6 months do not produce changes in coagulation factors or platelet function.

5.5.4 *Lactation*

Information on the effect of low-dose progestational agents on the production and composition of milk is limited. While there are no reports suggesting a reduction in the quantity of milk, the available results are somewhat conflicting as regards milk composition. In view of the importance of lactation in many populations further studies are clearly indicated. Studies should also be conducted to determine the quantity of the various progestogens and their biologically active metabolites in the maternal milk.

5.6 Incidence of tubal pregnancy during use

The available evidence suggests that the ratio of tubal pregnancies to intrauterine pregnancies is higher than normal among women who become pregnant while taking low-dose progestogens.

6. RETURN OF FERTILITY AFTER DISCONTINUATION OF CONTRACEPTIVE STEROIDS

6.1 Estrogen-progestogen oral contraceptives

6.1.1 *Return of ovulation*

There are few detailed studies of adequate size concerning the return of ovulation after discontinuation of estrogen-progestogen oral contraceptives, as assessed by hormone assays, endometrial biopsies, or the recording of

basal body temperatures. Those studies that have been carried out suggest that about 70% of women resume ovulation in the first post-treatment cycle and that up to 95% resume ovulation within 3 cycles of stopping medication. In this context, it is worth remembering that apparently normal cycles are not always ovulatory.

6.1.2 *Return of menstruation*

Follow-up studies of women discontinuing oral contraception indicate that the length of the first post-treatment cycle is often prolonged to 6 weeks or more but that the incidence of " post-pill amenorrhoea " is low. Thus, according to all the larger studies, the incidence of amenorrhoea lasting over 6 months after discontinuation is around 1%.

Despite the reassuring findings in follow-up studies, there is now a large and complicated literature on post-pill amenorrhoea describing the clinical experience of many gynaecologists in different parts of the world. Careful examination of the individual reports shows that there are a number of features of the syndrome that are, perhaps, surprising :

(*a*) There appears to be no clear relationship between the duration of treatment with oral contraceptives and the risk of amenorrhoea after their withdrawal.

(*b*) The likelihood of amenorrhoea appears to be unrelated to the type of preparation (i.e., combination or sequential).

(*c*) Some women who develop post-pill amenorrhoea have not previously become amenorrhoeic during earlier temporary pauses in oral contraceptive treatment.

Though some women with post-pill amenorrhoea have quite unremarkable past menstrual histories, many report menstrual irregularities predating their use of the medication. The association between post-pill amenorrhoea and galactorrhoea, to which some authors have attached particular importance, is also uncertain. Secondary amenorrhoea is of course known to occur in a small proportion of healthy women in the general population in the absence of exposure to oral contraceptives. Uncontrolled observations in women discontinuing the use of the preparations are therefore extremely difficult to assess.

A recent Swedish investigation is of considerable interest.[a] In a careful study of 75 consecutive patients with amenorrhoea of at least 6 months' duration following discontinuation of oral contraception, there was a

[a] FRIES, H. On functional amenorrhoea. *Acta Universitatis Upsaliensis, Abstracts,* **207** (1974).

history of previous menstrual irregularity in 56%, an " accumulated psychiatric morbidity " (mild to severe mental illness) in 65%, recent " stressful life events " in 36%, and recent dieting in 45%. When all these factors of possible etiological importance were taken into account, there remained just 6 women in whom the only significant past history was the use of oral contraceptives. As a result of this study, it was concluded that " the earlier assumed etiological role of the oral contraceptive agents has probably been over-estimated : they may have caused or contributed to the development of prolonged amenorrhoea in some women, but in several other women the connection is merely coincidental ".

The same group also undertook an epidemiological study of a random sample of 2000 of the female population aged 18–45 years within Uppsala County.[a] Using a postal questionnaire (response rate 93%), they asked each participant whether secondary amenorrhoea of more than 3 months' duration had occurred within the preceding 12 months. They found the incidence of this disorder to be 3.3%. There appeared to be correlations between the occurrence of secondary amenorrhoea and age, marital status, residence, smoking habits, age at menarche, previous childbearing history, and oral contraception. These data indicate the complexity of the epidemiological characteristics of secondary amenorrhoea.

6.1.3 *Return of fertility*

While information about the return of ovulation and menstruation after discontinuation of oral contraception is of considerable interest, the most important point at issue is whether or not the prior use of these preparations impairs a woman's ability to conceive and bear a child. The life-table approach is essential for a valid assessment of post-contraception fertility. Information on fertility following the discontinuation of oral contraceptives is much scantier than comparable information on the intrauterine device. To be sure, a number of investigators have reported the percentage of women who conceived among those who discontinued, or the distribution of pregnancies by number of months required for conception, or even conception rates per 100 woman-years of exposure. However, none of these measures is satisfactory. The first completely neglects the duration of follow-up. The second ignores the woman who did not conceive. The third fails to take into account that the conception rate declines with time.

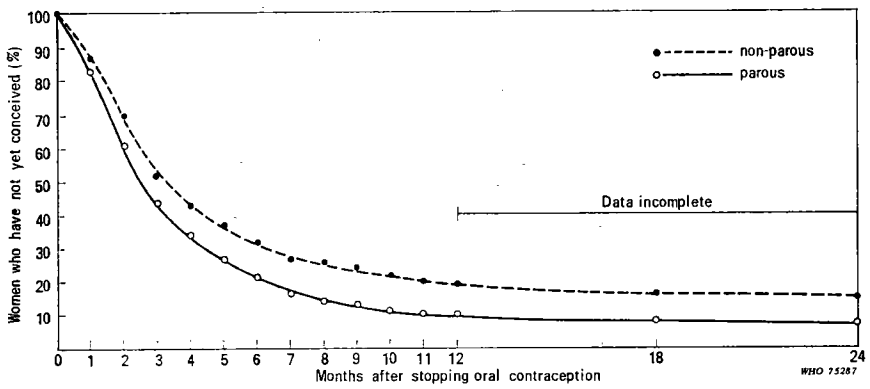
One small recent study based on the life-table method of analysis suggested, first, some delay in the restoration of fertility in previous users of combined oral contraceptives as compared with previous users of sequen-

[a] PETTERSON, F. ET AL. *Amer. J. Obstet. Gynec.*, **117** : 80 (1973).

tial preparations and, secondly, a slower restoration of fertility after long-term use of oral contraceptives than after short-term use.

Important information on the return of fertility after discontinuation of oral contraceptives has come to light in the course of the Royal College of General Practitioners prospective study. In this investigation, 2291 women stopped oral contraception because they wished to become pregnant. Fig. 1 shows the proportion of these women who had failed to conceive at

FIGURE 1. CONCEPTIONS IN 2291 WOMEN WHO DISCONTINUED ORAL CONTRACEPTION TO BECOME PREGNANT: EFFECT OF PARITY *

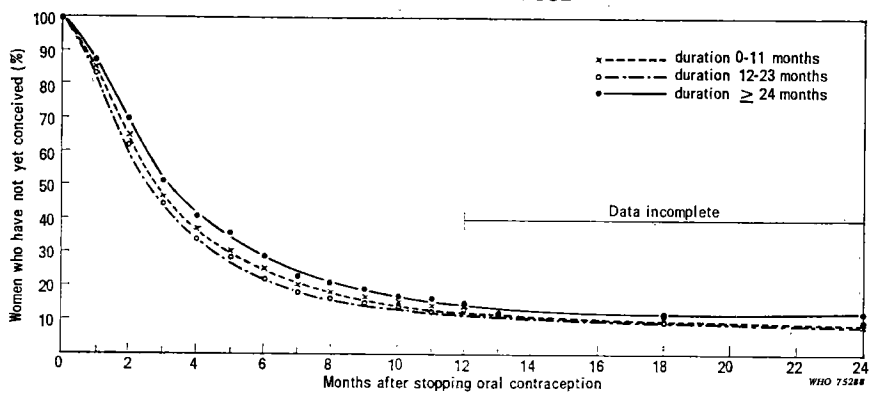


* Reproduced by courtesy of Pitman Medical Publishing Company Limited from ROYAL COLLEGE OF GENERAL PRACTITIONERS. *Oral contraceptives and health*. London, Pitman (1974).

different time intervals following cessation of oral contraception in relation to parity, and Fig. 2 shows the corresponding data in relation to duration of previous oral contraceptive usage. All these data are, of course, somewhat difficult to evaluate in the absence of control observations, but they certainly suggest that fertility following the use of oral contraceptives is unlikely to be seriously reduced.

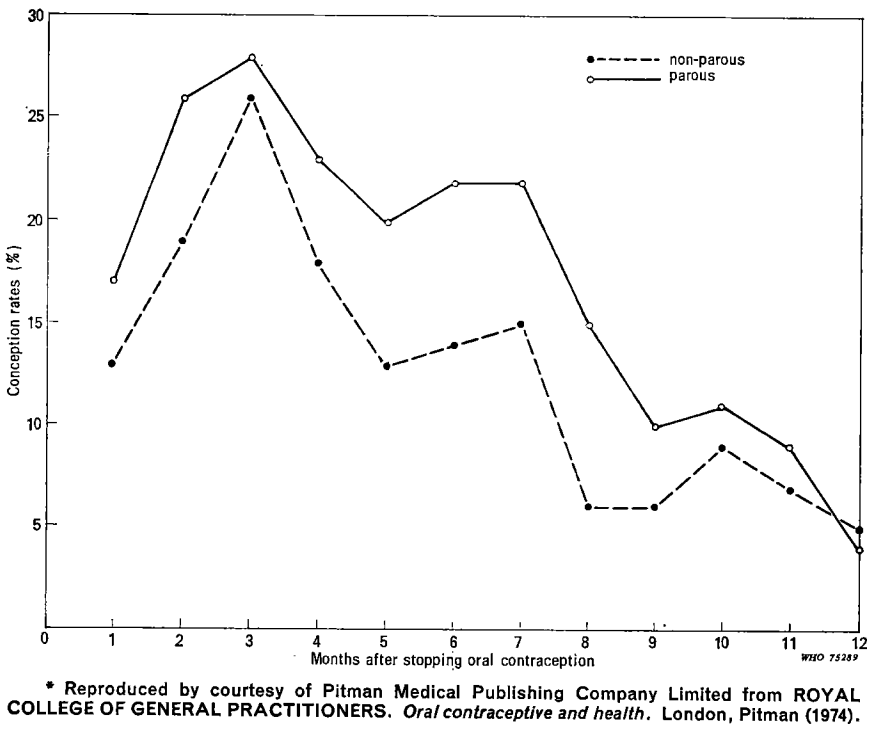
The data collected in the Royal College of General Practitioners study were also analysed by the computation of monthly conception rates, with the results shown in Fig. 3. Normally, in a population of women attempting to conceive, the most fertile are progressively selected out and there is a steady fall in conception rates plotted at monthly intervals owing to the increasing proportion of subfertile women in the nonpregnant residue. Fig. 3 provides clear evidence of a delay in conception after discontinuation of oral contraception. Why the distribution should be trimodal in form is obscure, although the second and third peaks could be due to chance.

FIGURE 2. CONCEPTIONS IN 2165 WOMEN WHO DISCONTINUED ORAL CONTRACEPTION TO BECOME PREGNANT: EFFECT OF DURATION OF PREVIOUS ORAL CONTRACEPTIVE USE*



* Reproduced by courtesy of Pitman Medical Publishing Company Limited from ROYAL COLLEGE OF GENERAL PRACTITIONERS. *Oral contraceptives and health.* London, Pitman (1974).

FIGURE 3. MONTHLY CONCEPTION RATES IN 2291 WOMEN WHO DISCONTINUED ORAL CONTRACEPTION TO BECOME PREGNANT: EFFECT OF PARITY*



* Reproduced by courtesy of Pitman Medical Publishing Company Limited from ROYAL COLLEGE OF GENERAL PRACTITIONERS. *Oral contraceptive and health.* London, Pitman (1974).

Unpublished information obtained in another large prospective study in progress in the United Kingdom was reviewed by the Group. These data also indicated a delay in conception after discontinuation.

6.1.4 *Conclusions*

Despite the extensive literature, the prior use of oral contraceptives has not been firmly incriminated as a cause of *prolonged* secondary amenorrhoea after discontinuation. Nonetheless, it seems likely that they may rarely produce this adverse effect, especially in women with a pre-medication history of menstrual irregularities. Fortunately, half or more of the patients with post-pill amenorrhoea will ovulate if treated with clomifene or, if necessary, with gonadotrophins.

On the other hand, the evidence seems clear that the use of oral contraceptives does, on average, lead to some temporary impairment of fertility after stoppage. Whether or not the preparations are also rarely responsible for permanent infertility is uncertain at the present time.

The reason for the impairment of fertility in women stopping oral contraception is not entirely clear. No doubt the delay in the restoration of ovulation plays a part, but a uterine factor may also be involved.

6.2 Progestogen-only oral contraceptives

Adequate studies concerned with the return of fertility following the discontinuation of progestogen-only oral contraceptives have not been reported.

6.3 Injectable contraceptives

6.3.1 *Medroxyprogesterone acetate (MPA)*

MPA is usually given by injection at 3-monthly intervals. Blood levels are maintained for a variable number of months after the last injection as a result of continued release of the steroid. This is in contrast to oral contraceptives, which disappear from the body much more quickly. Impairment of fertility after discontinuation of MPA injections is therefore likely to involve two components—a major one due to the high initial " pulse " and the persistence of drug activity, and a minor one similar to the delay in return of fertility that follows the withdrawal of estrogen-progestogen oral contraceptives.

(*a*) *Return of ovulation and menstruation*

Several small studies on women discontinuing the regimen of 150 mg at 3-monthly intervals reported that about one-half to two-thirds resumed menstruation within 6 months of the last injection of MPA and at least

three-quarters menstruated within 1 year. In those studies in which the occurrence of ovulation was also investigated, it was found that almost all the women had ovulated on at least one occasion within 12–18 months.

(*b*) *Return of fertility*

Only two small studies have used the life-table method to investigate the return of fertility after discontinuation of MPA. One involved 135 women and the other 188. Both indicated that about 80% of women had become pregnant within 15 months of the last injection. In the larger of the two studies, the cumulative pregnancy rate by 18 months after the last injection appeared to be similar to the corresponding rate observed in studies concerned with fertility after removal of an intrauterine device.

(*c*) *Conclusions*

Studies concerned with the return of ovulation, menstruation, and fertility after stopping injections of MPA are, in general, poor. There is usually a small number of subjects, many are lost to follow-up, and the methods used are inadequate. It seems clear, however, that the return of ovulation, menstruation, and fertility is subject to a variable degree of delay after discontinuation of medication. Whether or not MPA injections have any permanent effect on fertility in some women is unknown.

6.3.2 *Norethisterone heptanoate* [a]

Few data are available on the regimen of norethisterone heptanoate given in a dose of 200 mg every 12 weeks. In one series nearly all the women stopping the regimen re-established a normal menstrual pattern within 2–4 months of the last injection. These and other preliminary findings suggest that the effect of this contraceptive is not so long-lasting as that of MPA.

7. PROSTAGLANDINS IN FERTILITY CONTROL

Several aspects of the use of the prostaglandins for fertility regulation up to 1972 were summarized in an earlier WHO publication.[b] The present report will therefore deal mainly with advances in this field since that time.

7.1 For contraception

No reports on the use of prostaglandins as contraceptives are currently available. It may, however, be worth while to summarize some existing data that might point to possibilities for future research.

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[a] Formerly known as norethisterone oenanthate.

[b] WHO Technical Report Series, No. 527, 1973.

7.1.1 *Effects on ovulation*

Information concerning the involvement of the prostaglandins in ovulation is based entirely on animal data. The prostaglandins are probably not involved in the control of early follicular development but appear to play a direct role in follicular rupture. It has been demonstrated in some species that ovulation can be blocked by the administration of compounds that inhibit prostaglandin biosynthesis. Prostaglandins have also been used to time ovulation in animals. It is not yet known whether they are involved in the same processes in women.

7.1.2 *Regulation of corpus luteum function*

There is substantial evidence that $PGF_{2\alpha}$ is involved in regulating the lifespan of the corpus luteum in many species. The mechanism of action has not yet been established. In the human female there is no conclusive evidence that the prostaglandins exert any physiological control or have any pharmacological effect on luteal steroidogenesis during the secretory phase of the menstrual cycle. Most workers have found no changes in plasma progesterone levels after the administration of $PGF_{2\alpha}$, although others have reported a transient reduction.

Recently, the existence of specific receptors for $PGF_{2\alpha}$ has been reported in ovine and bovine corpora lutea. Evidence exists for the presence of similar receptors in the human corpus luteum. The presence of prostaglandin receptors makes possible the *in vitro* screening of different prostaglandin analogues, which may lead to the discovery of a metabolically more stable compound with a high affinity for the receptors.

7.2 For termination of pregnancy

The primary prostaglandins have been used for termination of pregnancy since 1969. Various routes of administration have been tried, including intravenous infusion, vaginal administration, intramuscular injection, and extra- or intra-amniotic instillation. The synthetic prostaglandin analogues used are mainly represented by the compounds where a methyl group has been introduced at C15. The 15-methyl derivatives of the primary prostaglandins, E_2 and $F_{2\alpha}$ or their methyl ester, are not substrates for the primary steps of inactivation by the prostaglandin-specific 15-dehydrogenase enzyme. In spite of the altered configuration of the natural molecule, the new compounds retain the smooth muscle stimulating properties both *in vitro* and *in vivo*. Another group of analogues, 16,16-dimethyl-PGE_2 and -$PGF_{2\alpha}$, has recently aroused considerable interest since these are effective orally.

2.1 *First trimester of pregnancy*

Prostaglandins cannot compete with vacuum aspiration for induction of abortion up to the twelfth week of gestation. There are, however, two clinical situations where the prostaglandins might be useful, i.e., in the early interruption of pregnancy up to the second week following the first menstruation and during the tenth to twelfth week of pregnancy. These are discussed below in sections (*a*) and (*b*) respectively.

(*a*) *Early postconceptional fertility control*

A pharmacological agent has long been needed for the interruption of pregnancy during the early postconceptional phase (up to the second week after the first missed menstruation). The ideal drug must be simple to administer, highly efficient, and unassociated with disturbing side effects. No such drug has yet been produced, but the prostaglandins constitute a promising approach.

While the systemic administration of PGE_2 or $PGF_{2\alpha}$, either intravenously or vaginally, has been shown to be effective in a proportion of cases, the treatment is associated with an unacceptably high frequency of side effects.

Using another route of administration, one group instilled 5 mg of $PGF_{2\alpha}$ or 1 mg of PGE_2 into the uterine cavity in 100 sedated patients whose last menstrual period had been delayed approximately 10–13 days. A successful complete abortion was reported in 97 of the 100, as assessed by a negative urinary pregnancy test after 10 days and the resumption of menstruation, which occurred, on average, 32 days after treatment.

In another study of 16 patients, a 100% success rate was reported following the intrauterine instillation of either 1 mg of PGE_2 or 4 mg of $PGF_{2\alpha}$. Side effects of the treatment included vomiting (6 women) and uterine cramps (12 women). Uterine bleeding was initiated within 2–5 hours and lasted from 4 to 14 days in 15 of the women. In the remaining patient, who experienced continued bleeding, curettage was performed.

It is hoped that these results can be improved upon by one of the new prostaglandin analogues, which might show better discrimination in favour of uterine (rather than gastrointestinal) stimulation. Such a compound might increase the efficiency of, for example, vaginal administration, which would be more practical than intrauterine instillation when used on a large scale. Studies on these analogues must, however, include a thorough follow-up, and any pregnancy occurring after treatment must be interrupted until the possible teratogenic effects of the compounds have been elucidated.

(*b*) *Preoperative cervical dilatation*

Primary instrumental evacuation of the uterus between the tenth and twelfth weeks of gestation is associated with an increased complication rate and may also be hazardous in cases where the uterus is large. In addition, it has been suggested that forceful cervical dilatation might have late sequelae in the form of an increased prematurity rate in subsequent pregnancies.

Partial or full cervical dilatation can be achieved preoperatively by repeated extra-amniotic instillations of $PGF_{2\alpha}$ as summarized previously.[a] Similar results may be obtained with one single extra-amniotic instillation or repeated intramuscular injections of the analogue 15-methyl $PGF_{2\alpha}$.

Limited success has also been reported with the administration of vaginal suppositories containing 50 mg of $PGF_{2\alpha}$. However, prostaglandins administered vaginally are absorbed into the general circulation, entailing a concomitant increase in gastrointestinal side effects.

7.2.2 *Second trimester of pregnancy*

$PGF_{2\alpha}$ and PGE_2 administered extra- and intra-amniotically are in routine use in several countries for the induction of second-trimester abortion.

(*a*) *Extra-amniotic administration*

Appraisal of the extra-amniotic use of the primary prostaglandins has not changed significantly since the last report.[a]

The major drawbacks of the method have been the need for repeated instillations and the inconvenience of an indwelling catheter, which harbours a potential risk of causing intrauterine infection. To avoid these problems the possibility of a single injection method has been explored, with two different regimens. One of these utilizes one 10-mg dose of $PGF_{2\alpha}$ instilled into the extra-amniotic space. The other is based on the use of 0.75-1.0 mg of the 15-methyl $PGF_{2\alpha}$. Although these approaches are promising, more experience is needed before they can be evaluated.

(*b*) *Intra-amniotic administration*

The intra-amniotic administration of prostaglandin is probably the most successful method tested thus far for induction of second-trimester abortion. It has been found that doses of the order of 5–15 mg $PGF_{2\alpha}$ need to be repeated one or more times to accomplish a second-trimester abortion.

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[a] WHO Technical Report Series, No. 527, 1973.

it has also become evident that a single intra-amniotic injection of 25 mg of $PGF_{2\alpha}$ is not sufficient.

These observations have led to a dose schedule involving an initial injection of 25 mg of $PGF_{2\alpha}$ repeated after 24 hours if abortion is not imminent. The success rate with this schedule of administration is high, generally of the order of 95%. The mean induction–abortion interval is approximately 28–30 hours (Table 4).

TABLE 4. REPEATED INTRA-AMNIOTIC ADMINISTRATION OF 25 mg OF PROSTAGLANDIN $F_{2\alpha}$ FOR INDUCTION OF SECOND-TRIMESTER ABORTION

No. of cases	Interval between injections (hours)	No. of abortions	Induction–abortion interval (hours)
34 [a]	24	33	28.0
101 [b]	24	101 [f]	33.2
20 [c]	24	20	27.5
21 [d]	24	18	26.6
20 [e]	24	16	26.5
20 [c]	6	20	21.3
18 [a]	6	18	18.3

[a] BYGDEMAN, M. ET AL. *Advances in the Biosciences*, **9**: 525 (1973).
[b] NYBERG, R. *Advances in the Biosciences*, **9**: 533 (1973).
[c] GILLET, P. G. ET AL. *Advances in the Biosciences*, **9**: 545 (1973).
[d] SEPPÄLÄ, M. ET AL. *Prostaglandins*, **2**: 311 (1972).
[e] BALLARD, C. A. & QUILLIGAN, E. J. *Advances in the Biosciences*, **9**: 551 (1973).
[f] Includes patients aborting after more than 48 hours. First dose varied between 25 and 35 mg.

If the second 25-mg dose is injected after an interval of 6 hours the same high success rate is obtained and the induction–abortion interval is reduced to approximately 20 hours (Table 4). It is likely that, at least in some cases, the concentration of $PGF_{2\alpha}$ becomes too low to induce efficient uterine contractions if there is a 24-hour wait before the second injection. This might explain the shortening of the induction–abortion interval when the two 25-mg doses are injected 6 hours apart.

There have been recent attempts to achieve a single-injection procedure by increasing the dose to 40 or 50 mg of $PGF_{2\alpha}$. The results obtained with one injection of 40 mg are somewhat conflicting. According to some authors additional treatment is necessary to obtain a high success rate (more than 90%) with an observation period of 48 hours, while other investigators have been more successful with this treatment schedule (Table 5).

The 15-methyl derivatives of PGE_2 and $PGF_{2\alpha}$ and their methyl esters are currently under investigation. One intra-amniotic administration of 2.5 mg of 15(S) 15-methyl $PGF_{2\alpha}$ has the same effect as repeated instillations of the parent compound in inducing a second-trimester abortion

TABLE 5. SINGLE INTRA-AMNIOTIC ADMINISTRATION OF PROSTAGLANDIN $F_{2\alpha}$ OR 15-METHYL PROSTAGLANDIN ANALOGUES FOR INDUCTION OF SECOND-TRIMESTER ABORTION

No. of cases	Compound	Dose (mg)	No. of abortions	Induction-abortion interval (hours)
82 [b]	$F_{2\alpha}$	40	82 [a]	24.9
33 [c]	$F_{2\alpha}$	40	25	18.5
30 [d]	$F_{2\alpha}$	40	29	25
20 [e]	$F_{2\alpha}$	40	20	16.2
40 [f]	$F_{2\alpha}$	50	38	19.1
50 [c]	15-me $F_{2\alpha}$	2.5	49	18.8
20 [g]	15-me E_2 methyl ester	0.1	18	16.5

[a] Approximately 30 % of these patients required additional treatment to complete the abortion process.

[b] ANDERSON, G. G. ET AL. *Advances in the Biosciences*, **9**: 539 (1973).

[c] WIQVIST, N. ET AL. *Contraception*, **8**: 113 (1973).

[d] CORLETT, R. C. & BALLARD, C. A. *Amer. J. Obstet. Gynec.*, **118**: 353 (1974).

[e] LAUERSEN, N. H. & WILSON, K. H. *Amer. J. Obstet. Gynec.*, **118**: 210 (1974).

[f] BRENNER, W. E. ET AL. *Prostaglandins*, **4**: 485 (1973).

[g] AMY, J. J. ET AL. *J. Obstet. Gynaec. Brit. Cwlth*, **80**: 101 (1973).

(Table 5). This procedure seems to be more effective than one intra-amniotic injection of 40 mg of $PGF_{2\alpha}$ but it remains to be established whether it is superior to a single dose of 50 mg of $PGF_{2\alpha}$.

The experience with intra-amniotic administration of PGE_2 is more limited than that with $PGF_{2\alpha}$. Dose schedules involving 10–20 mg of PGE_2 have been successful. No randomized studies comparing $PGF_{2\alpha}$ and PGE_2 have been carried out.

(*c*) *Intramuscular and vaginal administration*

Successful studies with 15(S) 15-methyl PGE_2 methyl ester and 15(S) 15-methyl $PGF_{2\alpha}$ administered intramuscularly and/or vaginally have been reported. These analogues appear to have a lower frequency of side effects than their parent compounds. However, further similar studies with these analogues are still needed.

7.3 Comparison between hypertonic saline and prostaglandins for termination of pregnancy

Hypertonic saline injected intra-amniotically is commonly used for termination of second-trimester pregnancy. A multicentre randomized investigation has recently been carried out comparing the injection of 200 ml

of 20% saline with 2 intra-amniotic injections of 25 mg of $PGF_{2\alpha}$ given at 6-hour intervals. This and other studies are discussed in the following sections.

7.3.1 *Efficacy*

Of the 1513 patients participating in the study, 717 were treated with $PGF_{2\alpha}$ and 796 with saline. In the prostaglandin group 85.4% aborted within 48 hours of the first injection. In the hypertonic saline group the corresponding figure was 80.5% ($P < 0.05$). The mean induction–abortion interval was significantly shorter in the prostaglandin group than in the saline group : 19.7 *versus* 30.4 hours ($P < 0.001$). The cumulative abortion rate also showed that the abortion process was much faster after prostaglandin administration. The difference was most pronounced during the first 24-hour period, when approximately 65% of the prostaglandin-treated patients aborted compared with some 20% of the saline-treated patients. The frequency of complete abortion was the same in the two groups (approximately 60%).

7.3.2 *Complications*

The rapid metabolism of the prostaglandins gives them a distinct advantage over hypertonic saline in the event any of the administered abortifacient enters the systemic circulation.

(*a*) *Vomiting and diarrhoea*

The average number of vomiting episodes per patients was 1.5 with prostaglandin and 0.4 with hypertonic saline. The corresponding figures for diarrhoea were 0.4 and 0.0 respectively. Both differences are highly significant ($P < 0.001$).

(*b*) *Cervical rupture*

It seems clear that cervical rupture is more common following the intra-amniotic administration of $PGF_{2\alpha}$ than following hypertonic saline. In one report the frequency of this side effect was 1% for $PGF_{2\alpha}$ and 0.1% for hypertonic saline. An incidence of approximately 1% with PGE_2 has also been reported. The patients in whom cervical rupture occurred were mainly young primigravidae in whom an oxytocin infusion was given simultaneously to reduce the induction–abortion interval. It is possible that the synergism between prostaglandin and oxytocin resulted in overstimulation of the uterus.

(*c*) *Epileptic seizures*

In one study [a] 5 out of 320 patients aborted with intra-amniotic $PGF_{2\alpha}$ experienced " epileptiform convulsions " following the injection of the compound. In the above-mentioned randomized study this complication was not encountered after $PGF_{2\alpha}$ administration. Several other publications also support the conclusion that if convulsions are side effects of prostaglandin administration, they occur extremely rarely.

(*d*) *Myometrial necrosis*

Inadvertent injection of hypertonic saline into the myometrium has been shown to cause substantial necrosis of the muscle. Necrosis does not occur under similar circumstances with prostaglandin.

7.3.3 *Mechanism of action of hypertonic saline*

Recent studies on the mechanism of action of hypertonic saline suggest that stimulation of uterine contractility might in part be due to endogenous release of prostaglandin. Moreover, the administration of inhibitors of prostaglandin biosynthesis (indometacin and acetylsalicylic acid) resulted in a significant prolongation of the time taken to abort following saline instillation.

8. RECOMMENDATIONS

In addition to endorsing the recommendations and research needs identified in recent previous reports [b] on the methods of fertility control under review, the Group made the following recommendations.

8.1 General

1. There is a need to standardize definitions of menstrual cycle phenomena including " normal cycles ", " bleeding intervals ", " intermenstrual bleeding ", " spotting ", " latent period ", and " post-pill amenorrhoea ".

2. Further studies are needed on lactating women using all types of hormonal contraception to investigate the reported appearance of steroids and their metabolites in the milk and to determine whether these small amounts have a demonstrable effect on the nursing infants.

3. The effects of hormonal contraceptives on the outcome of pregnancy, should be thoroughly investigated.

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[a] LYNEHAM, R. C. ET AL. *Lancet*, **2**: 1003 (1973).

[b] WHO Technical Report Series, No. 473, 1971 ; No. 527, 1973.

4. Properly designed comparative studies should be carried out on continuation rates with different methods of fertility regulation in different parts of the world.

5. The present status of sustained release contraceptives requires critical review.

6. Sequential monitoring techniques using the life-table approach should be developed for assessing the efficacy and side effects of contraceptives. If possible, such methods should take account of patient reliability.

7. In order to assess pregnancy rates and side effects, properly designed multicentre studies involving contemporaneous comparison groups, preferably with random allocation, are needed. Provision should be made for a high level of follow-up.

8. The Group noted that patient reliability is an important factor to be taken into account when assessing oral contraceptive efficacy. Methods of medication monitoring would therefore be useful. The feasibility of developing nonintrusive methods of medication monitoring should be explored.

8.2 Steroidal combination oral contraceptives with less than 50 μg ethinyl estrogen content

1. The metabolic effects, rare adverse effects (such as thromboembolism, hypertension, and post-treatment amenorrhoea), and effects on lactation of these formulations should be studied.

2. Further studies are needed to assess the relative antifertility potencies of estrogens in general and various progestogens in relation to their metabolic effects.

8.3 Effects of estrogen-progestogen combined oral contraceptives on vitamin metabolism

1. Studies of the effects of oral contraceptives on vitamin metabolism are important and should be encouraged.

2. Data are lacking or incomplete in relation to vitamins B1 and D and the appropriate investigations should therefore be carried out.

3. Insufficient attention has so far been directed to the effects of individual steroids, dose-response relationships, and the influence of steroidal combinations on vitamin metabolism.

4. The clinical relevance of the effects of oral contraceptives on vitamins is the most important consideration. Future studies should emphasize this aspect, which has thus far received insufficient attention.

5. In connexion with the preceding recommendation, it should be pointed out that vitamins, which are coenzymes, have an impact on amino acid and protein metabolism. This field of investigation needs greater attention.

6. The effects of oral contraceptives on vitamins concerned with the haematological system are of great concern. Appropriate studies are urgently needed.

7. Studies of the influence of oral contraceptives on riboflavin metabolism should be carried out on subjects with glucose-6-phosphate dehydrogenase deficiency.

8. The possible teratogenic effect of elevated vitamin A levels induced by oral contraceptives needs careful study.

8.4 Postcoital estrogens

1. The development of various postcoital methods of fertility control is considered most important.

2. Randomized controlled studies of the postcoital use of estrogens are needed with special attention to dose, efficacy, safety, and the reduction of side effects.

3. Evaluation of the postcoital estrogen method is important. In particular, the outcome of any pregnancy should be carefully recorded. The offspring should if possible undergo special surveillance because of concern about adenocarcinoma of the vagina and cervix.

4. The immediate metabolic effects of postcoital estrogens should be evaluated in view of the numerous effects known to be associated with the use of existing estrogen-containing oral contraceptives.

5. The impact of postcoital estrogens on physiological processes, including the cardiovascular system, should be evaluated because of the theoretical possibility that untoward effects may be produced in women with pre-existing disease who require emergency intervention to prevent pregnancy.

8.5 Low-dose progestogen oral contraceptives

1. The testing of low-dose progestogens, which may have spectra of action including low hypothalamic inhibitory activity and which could provide better cycle control, should be encouraged.

2. Studies should be carried out on the effects of these formulations on hypothalamic, pituitary, and ovarian function.

3. Further comprehensive studies are required to ascertain which endometrial events are compatible with implantation and how these events are modified by the various types of progestogens.

4. Endometrial events associated with irregular bleeding require further studies.

5. Additional studies on the effects of these preparations on lipid and carbohydrate metabolism are needed.

6. The administration of these compounds at different times during lactation should be studied to determine the effects on duration of anovulation, postpartum amenorrhoea, and subsequent cycle regularity.

8.6 Return of fertility after discontinuation of contraceptive steroids

1. Carefully designed studies should be carried out on the return of menstruation, ovulation, and fertility after cessation of the use of long-acting formulations.

8.7 Prostaglandins

1. Studies should be undertaken to ascertain the role of the prostaglandins in the regulation of the human menstrual cycle.

2. Further studies are needed on the use of prostaglandins and their analogues for the termination of early pregnancy.

3. Randomized studies comparing the use of prostaglandins and prostaglandin analogues and other methods in general use for termination of pregnancy are warranted.

4. Rare side effects associated with the use of prostaglandins and their analogues, such as cervical rupture and convulsions, require further investigation.

5. It is important that complications associated with the routine and research use of prostaglandins and prostaglandin analogues be reported and evaluated.

6. New prostaglandin analogues with specific uterine and luteolylic activities need to be developed.

7. The mode of action of these compounds in the stimulation of uterine contractility should receive further study.

Annex 1

REPORTS OF WHO SCIENTIFIC GROUPS ON VARIOUS ASPECTS OF FERTILITY REGULATION PUBLISHED IN THE WHO TECHNICAL REPORT SERIES

No. 360 (1967) Biology of fertility control by periodic abstinence

No. 386 (1968) Hormonal steroids in contraception

No. 397 (1968) Intra-uterine devices : physiological and clinical aspects

No. 424 (1969) Developments in fertility control

No. 461 (1970) Spontaneous and induced abortion

No. 473 (1971) Methods of fertility regulation : advances in research and clinical experience

No. 527 (1973) Advances in methods of fertility regulation

Annex 2

SELECTED BIBLIOGRAPHY *

1. Steroidal combination oral contraceptives with less than 50 µg ethinyl estrogen content (section 2)

BRIGGS, M. H. & DICZFALUSY, E., ed. *Pharmacological models in contraceptive development, WHO Symposium, Geneva, 1973.* Stockholm, Karolinska Institutet, 1974, p. 166

BYE, P. G. T. & ELSTEIN, M. Clinical assessment of a low-oestrogen combined oral contraceptive. *Brit. Med. J.*, **2** : 389–392 (1973)

DIONNE, P. & VICKERSON, F. A double blind comparison of two oral contraceptives containing 50 mcg and 30 mcg ethinyl estradiol. *Curr. ther. Res.*, **16** : 281–288 (1974)

HINES, D. C. & GOLDZIEHER, J. W. Clinical investigation. A guide to its evaluation. *Amer. J. Obstet. Gynec.*, **105** : 450–487 (1969)

WHO Technical Report Series, No. 473, 1971 *(Methods of fertility regulation : advances in research and clinical experience)*

WHO Technical Report Series, No. 536, 1974 *(Bioavailability of drugs : pharmacokinetic aspects)*

2. Effects of estrogen-progestogen combined oral contraceptives on vitamin metabolism (section 3)

Vitamin A

BRIGGS, M. ET AL. Steroid contraceptives and plasma carotenoids. *Contraception*, **6** : 277–280 (1972)

GAL., I. ET AL. Effects of oral contraceptives on human plasma vitamin A levels. *Brit. med. J.*, **2** : 436–438 (1971)

MORRISS, G. M. & THOMSON, A. D. Vitamin A and rat embryos. *Lancet*, **2** : 899–900 (1974)

WILD, J. ET AL. Vitamin A, pregnancy, and oral contraception. *Brit. med. J.*, **1** : 57-59 (1974)

Vitamin B2 (Riboflavin)

SANPITAK, N. & CHAYUTIMONKUL, L. Oral contraceptives and riboflavine nutrition. *Lancet*, **1** : 836–837 (1974)

Vitamin B6

ADAMS, P. W. ET AL. Effect of pyridoxine hydrochloride (vitamin B6) upon depression associated with oral contraception. *Lancet*, **1** : 897–904 (1973)

* For the convenience of the reader references are grouped under headings corresponding to certain sections of the report.

ADAMS, P. W. ET AL. Vitamin B6, depression and oral contraception. *Lancet*, **2** : 516–517 (1974)

ROSE, D. P. Aspects of tryptophan metabolism in health and disease : a review. *J. clin. Path.*, **25** : 17–25 (1972)

ROSE, D. P. ET AL. Experimental vitamin B6 deficiency and the effect of oestrogen-containing oral contraceptives on tryptophan metabolism and vitamin B6 requirements. *Clin. Sci.*, **42** : 465–477 (1972)

Vitamin C

BRIGGS, M. & BRIGGS, M. Oral contraceptives and vitamin nutrition. *Lancet*, **1** : 1234–1235 (1974)

CLEMETSON, C. A. B. Caeroplasmin and green plasma. *Lancet*, **2** : 1037 (1968)

RIVERS, J. M. & DEVINE, M. M. Plasma ascorbic acid concentrations and oral contraceptives. *Amer. J. clin. Nutr.*, **25** : 684–689 (1972)

SAROJA, N. ET AL. Effect of estrogens on ascorbic acid in the plasma and blood vessels of guinea pigs. *Contraception*, **3** : 269–277 (1971)

Folic Acid

CHANARIN, I. V. Recent advances in megaloblastic anaemia. *In :* Walker, G., ed. *Ninth Symposium on Advanced Medicine*. London, Pitman, 1973, p. 272

DA COSTA, M. & ROTHENBERG, S. P. Appearance of a folate binder in leukocytes and serum of women who are pregnant or taking oral contraceptives. *J. Lab. clin. Med.*, **83** : 207–214 (1974)

SHOJANIA, A. M. ET AL. Oral contraceptives and folate metabolism. *Lancet*, **1** : 886 (1969)

SHOJANIA, A. M. ET AL. The effect of oral contraceptives on folate metabolism. *Amer. J. Obstet. Gynec.*, **111** : 782–791 (1971)

STEPHENS, M. E. M. ET AL. Oral contraceptives and folate metabolism. *Clin. Sci.*, **42** : 405–414 (1972)

Vitamin B12

BRIGGS, M. & BRIGGS, M. Endocrine effects on serum-vitamin-B_{12}. *Lancet*, **2** : 1037 (1972)

SHOJANIA, A. M. Effects of oral contraceptives on vitamin-B_{12} metabolism. *Lancet*, **2** : 932 (1971)

WERTALIK, L. F. ET AL. Decreased serum B_{12} levels with oral contraceptive use. *J. Amer. med. Ass.*, **221** : 1371–1374 (1972)

3. Postcoital estrogens (section 4)

BAČIČ, M. ET AL. Failure of large doses of ethinyl estradiol to interfere with early embryonic development in the human species. *Amer. J. Obstet. Gynec.*, **107** : 531–534 (1970)

HASPELS, A. A. Post-coital oestrogens in large doses. *Int. Planned Parenth. Fed. med. Bull.*, **6** : 2 (1972)

IASPELS, A. A. & ANDRIESSE, R. The effect of large doses of estrogens post coitum in 2000 women. *Europ. J. Obstet. Gynec. reprod. Biol.*, **3** : 113–117 (1973)

HERBST, A. L. ET AL. Clear-cell adenocarcinoma of the vagina and cervix in girls. Analysis of 170 Registry cases. *Amer. J. Obstet. Gynec.*, **119** : 713–724 (1974)

KUCHERA, K. K. Post-coital contraception with diethylstilbestrol—updated. *Contraception*, **10** : 47–54 (1974)

MORRIS, J. M. & VAN WAGENEN, G. Interception : the use of postovulatory estrogens to prevent implantation. *Amer. J. Obstet. Gynec.*, **115** : 101–106 (1973)

4. Low-dose progestogen oral contraceptives (section 5)

ABDEL-KADER, M. M. A. ET AL. Clinical, biochemical, and experimental studies on lactation. *Amer. J. Obstet. Gynec.*, **105** : 1168–1175 (1969)

ADAMS, P. W. & WYNN, V. The effects of a progestogen, megestrol acetate, on carbohydrate and lipid metabolism. *J. Obstet. Gynaec. Brit. Cwlth*, **79**, 744–752 (1972)

BONNAR, J. Progestogen-only contraception and tubal pregnancies. *Brit. med. J.*, **1** : 287 (1974)

BROGDEN, R. N. ET AL. Progestogen-only oral contraceptives : a preliminary report of the action and clinical use of norgestrel and norethisterone. *Drugs*, **6** : 169–181 (1973)

BUTLER, C. Pregnancy and chlormadinone acetate. *Brit. med. J.*, **4** : 686 (1969)

CONNELL, E. B. Low dosage approach to oral contraception. *In :* Hoffman, R. & Kleinman, R., ed. *Advanced concepts in contraception*. Amsterdam, Excerpta Medica, 1968, pp. 52–55

DICZFALUSY, E. ET AL. Pituitary and ovarian function in women on continuous low dose progestogens ; effects of chlormadinone acetate and norethisterone. *Acta endocr. (Kbh.)*, **62** : 679–693 (1969)

GOLDMAN, J. A. & ECKERLING, B. Effect of a progestogen oral contraceptive compound on carbohydrate metabolism. *Israel J. med. Sci.*, **8** : 1724–1727 (1972)

GOLDZIEHER, J. W. & RICE-WRAY, E. *Oral contraception*. Springfield, IL, Thomas, 1966

GOLDZIEHER, J. W. ET AL. A placebo-controlled double-blind crossover investigation of the side effects attributed to oral contraceptives. *Fertil. and Steril.*, **22** : 609–623 (1971)

HAWKINS, D. F. Progestogen-only contraception and tubal pregnancies. *Brit. med. J.*, **1** : 387 (1974)

HOWARD, G. ET AL. Low-dose continuous chlormadinone acetate as an oral contraceptive. *Lancet*, **2** : 24–26 (1969)

JAFFE, R. B. & MIDGLEY, R. A., JR. *In :* Moyer, D. L., ed. *Progress in conception control*. Philadelphia, Lippincott, 1968, p. 16

KAMAL, I. ET AL. Clinical, biochemical, and experimental studies on lactation. *Amer. J. Obstet. Gynec.*, **105** : 314–334 (1969)

KARIM, M. R. ET AL. Injected progestogen and lactation. *Brit. med. J.*, **1** : 200–203 (1971)

LARSSON-COHN, U. ET AL. Glucose tolerance and insulin response during daily continuous low-dose contraceptive treatment. *Acta endocr. (Kbh.)*, **62** : 242–250 (1969)

LARSSON-COHN, U. ET AL. Effects of continuous daily administration of 0.5 mg of chlormadinone acetate on the plasma levels of progesterone and on the urinary execretion of luteinizing hormone and total oestrogens. *Acta endocr. (Kbh.)*, **63** : 705–716 (1970)

MARTÍNEZ-MANAUTOU, J. Low level progestogens. *In :* Diczfalusy, E. & Borell, U., ed. *Nobel symposium 15. Control of human fertility*. Stockholm, Almqvist & Wiksell, 1971, pp. 53–69

MARTÍNEZ-MANAUTOU, J. ET AL. The ultrastructure of liver cells in women under steroid therapy. II. Contraceptive therapy. *Acta endocr. (Kbh.)*, **65** : 207–221 (1970)

MEARS, E. ET AL. Preliminary evaluation of four oral contraceptives containing only progestogens. *Brit. med. J.*, **2** : 730–734 (1969)

POLLER, L. ET AL. Effects of progestogen oral contraception with norethisterone on blood clotting and platelets. *Brit. med. J.*, **4** : 391–393 (1972)

SMITH, M. ET AL. Progestogen-only oral contraception and ectopic gestation. *Brit. med. J.*, **4** : 104–105 (1974)

SPELLACY, W. N. ET AL. Norgestrel and carbohydrate lipid metabolism : glucose, insulin and triglyceride changes during six months time of use. *Contraception*, **9** : 615–625 (1974)

VESSEY, M. P. ET AL. Randomised double-blind trial of four oral progestogen-only contraceptives. *Lancet*, **1** : 915–927 (1972)

5. Return of fertility after discontinuation of contraceptive steroids (section 6)

EL MAHGOUB, S. & KARIM, M. The long term use of injectable norethisterone enanthate as a contraceptive. *Contraception*, **5** : 21–29 (1972)

FRIES, H. On functional amenorrhoea. Etiological & epidemiological aspects, with special reference to oral contraceptive treatment and anorexia nervosa. *Acta Universitatis Upsaliensis, Abstracts*, **207** (1974)

GOLDITCH, I. M. Postcontraceptive amenorrhoea. *Obstet. and Gynec.*, **39** : 903–908 (1972)

GOLDZIEHER, J. W. An assessment of the hazards and metabolic alterations attributed to oral contraceptives. *Contraception*, **1** : 409–445 (1970)

LARSSON-COHN, U. The length of the first three menstrual cycles after combined oral contraceptive treatment. *Acta obstet. gynec. scand.*, **48** : 416–422 (1969)

MCDANIEL, E. B. & Tieng, P. Return of menstruation and fertility in Thai women after contraceptive injections. *J. biosoc. Sci.*, **3** : 209–222 (1971)

MCDANIEL, E. B. & TIENG, P. Depot-medroxyprogesterone acetate as a contraceptive agent: return of fertility after discontinuation of use. *Contraception*, **8** : 407–414 (1973)

PETTERSSON, F. ET AL. Epidemiology of secondary amenorrhea. I. Incidence and prevalence rates. *Amer. J. Obstet. Gynec.*, **117** : 80–86 (1973)

RICE-WRAY, E. ET AL. Return of ovulation after discontinuance of oral contraceptives. *Fertil. and Steril.*, **18** : 212–218 (1967)

ROYAL COLLEGE OF GENERAL PRACTITIONERS. *Oral contraceptives and health*. London, Pitman, 1974

SCHWALLIE, P. C. & ASSENZO, J. R. Contraceptive use-efficacy study utilizing medroxyprogesterone acetate administered as an intramuscular injection once every 90 days. *Fertil. and Steril.*, **24** : 331–337 (1973)

CHWALLIE, P. C. & ASSENZO, J. R. The effect of depot-medroxyprogesterone acetate on pituitary and ovarian function, and the return of fertility following its discontinuation : a review. *Contraception*, **10** : 181–202 (1974)

SCUTCHFIELD, F. D. ET AL. Medroxyprogesterone acetate as an injectable female contraceptive. *Contraception*, **3** : 21–35 (1971)

SHEARMAN, R. P. & SMITH, I. D. Statistical analysis of relationship between oral contraceptives, secondary amenorrhoea and galactorrhoea. *J. Obstet. Gynaec. Brit. Cwlth*, **79** : 654–656 (1972)

STEELE, S. J. ET AL. Amenorrhoea after discontinuing combined oestrogen-progestogen oral contraceptives. *Brit. med. J.*, **4** : 343–345 (1973)

TYLER, E. T. ET AL. Present status of injectable contraceptives : results of seven-years study. *Fertil. and Steril.*, **21** : 469–481 (1970)

VENNING, G. R. Secondary amenorrhoea following oral contraception—causal or coincidental ? *Proc. roy. Soc. Med.*, **66** : 569–570 (1973)

ZAÑARTU, J. & NAVARRO, C. Fertility inhibition by an injectable progestogen acting for 3 months. A clinical survey of 130 fertile women treated with norethisterone enanthate. *Obstet. and Gynec.*, **31** : 627–633 (1968)

6. Prostaglandins in fertility control (section 7)

BALLARD, C. A. & QUILLIGAN, E. J. Midtrimester abortion with intramuscular injection of 15-methyl-prostaglandin E_2. *Contraception*, **9** : 523–529 (1974)

BERGSTRÖM, S., ed. *Advances in the biosciences*. Vol. 9, *The International Conference on Prostaglandins, Vienna, September 1972*. Oxford, Pergamon Press, 1973

BEHRMAN, H. R. & ANDERSON, G. C. Prostaglandins in reproduction. *Arch. intern. Med.*, **133** : 77–84 (1974)

BRENNER, W. E. ET AL. Coagulation changes during abortion induced by prostaglandin $F_{2\alpha}$. *Amer. J. Obstet. Gynec.*, **117** : 1080–1087 (1973)

BYGDEMAN, M. ET AL. The influence of prostaglandin metabolites on the uterine response to $PGF_{2\alpha}$. A clinical and pharmacokinetic study. *Life Sci.*, **14** : 521–531 (1974)

BYGDEMAN, M. ET AL. Reassessment of systematic administration of prostaglandins for induction of midtrimester abortion. *Prostaglandins*, **8** : 157 (1974)

CSAPÓ, A. I. Prostaglandin impact for menstrual induction. *Population Report Series G*, No. 4, pp. G. 33–44 (1974)

KARIM, S. M. M., ed. *The prostaglandins*. Oxford, Medical and Technical Publishing, 1972

LOWENSOHN, R. & BALLARD, C. A. Cervicovaginal fistula : An apparent increased incidence with prostaglandin $F_{2\alpha}$. *Amer. J. Obstet. Gynec.*, **119** : 1057–1061 (1974)

POWELL, W. S. ET AL. Prostaglandin $F_{2\alpha}$ receptor in human corpora lutea. *Lancet*, **1** : 1120 (1974)

WIQVIST, N. ET AL. Intra-amniotic prostaglandin administration. A challenge to the currently used methods for induction of mid-trimester abortion. *Contraception*, **8** : 113–131 (1973)