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# ADVANCES IN METHODS OF FERTILITY REGULATION

Report of a  
WHO Scientific Group

WORLD HEALTH ORGANIZATION

GENEVA

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OF FERTILITY REGULATION

Geneva, 11-15 December 1972

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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 11 to 15 December 1972. The meeting was opened by Dr H. Mahler, Assistant Director-General, on behalf of the Director-General.

### 1. INTRODUCTION

An important feature of the progress in the field of fertility regulation during the past decade has been the rapidity of the pace of change resulting from continued research efforts and clinical experience with different agents. Consequently, WHO has found it valuable to convene at frequent intervals meetings of experts on various aspects of fertility regulation and its relation to general health and family planning. A list of the reports of relevant meetings held by WHO during the past few years is given in Annex 1. Other important references are given in Annex 2.

### 2. HORMONAL CONTRACEPTION

#### 2.1 Metabolic Effects of Steroidal Contraceptives

Many of the secondary effects of oral contraceptives that have concerned physicians are related to the metabolic effects of these steroids. The type of steroid, dosage, duration of use, and the individual characteristics of the user are all important factors in determining the magnitude and nature of the changes produced. This section of the report will, however, be limited to an assessment of the effects of various individual estrogens and progestogens and their combinations on protein, carbohydrate, and lipid metabolism and will be principally concerned with the types of change noted, their clinical significance and the mechanisms responsible for them.

##### 2.1.1 Proteins

Oral contraceptives generally lower certain blood amino acid levels (proline, glycine, alanine, valine, and ornithine) without significantly altering urinary amino acid excretion, thus suggesting an increased utilization. The changes are similar to those seen during pregnancy. Progesterone also lowers some blood amino acids (threonine, arginine, valine,

and ornithine) without affecting urinary levels. Most of the information available is on the combined type of contraceptive; the separate effects of synthetic progestogens have not been extensively studied and estrogens produce only minor changes.

The qualitative changes in blood protein concentrations produced by oral contraceptives are generally similar to those occurring during pregnancy, although the magnitude of such changes is usually less marked. Similar changes include an increase in blood coagulation factors (I, VII, VIII, IX, and X) and in "carrier-proteins" (cortisol-binding globulin, transferrin, ceruloplasmin) and  $\beta$ -globulin. The pre- $\beta$ -lipoprotein levels are elevated whereas the other lipoproteins are not. The unique  $\alpha_2$  "pregnancy-zone" globulin has also been found in the sera of women using oral contraceptives. Haptoglobin levels are increased and albumin levels are decreased. These changes can also be produced by the administration of estrogens alone, whereas limited studies with progestogens (chlormadinone acetate and medroxyprogesterone acetate) have shown little effect. The combined oral contraceptives may exert a synergistic effect. The changes appear to be mainly the result of a direct effect of estrogens upon the endoplasmic reticulum of the liver that alters protein production. Following discontinuation, the plasma proteins revert to their basal levels, but at different rates (e.g., transferrin in about 3 weeks; thyroid-binding globulin in about 5 weeks; "pregnancy-zone" globulin in about 8 weeks). These protein changes can affect the results of clinical laboratory tests (e.g., blood levels of copper, iron, cortisol, or thyroid hormones) but they do not generally appear to represent a medical hazard. It is important that the physician should recognize that the abnormality is a consequence of oral contraceptive use and does not necessarily represent a disease state. There are, however, 2 areas where significant clinical effects have been noted:

(a) *Blood pressure.* One effect of estrogens upon the liver is to produce an increased amount of  $\alpha_2$ -globulin (plasma renin substrate or angiotensinogen). This results in an increase in renin activity and angiotensin II levels. Normally, there is a negative feedback at the kidney to produce a decrease in renin levels. Up to 15 % of women using oral contraceptives develop hypertension (BP > 140/90), but this disappears upon stopping the drug. Women with a prior history of hypertension, for example, during pregnancy, or with excessive weight gain during administration seem more prone to this effect. These may represent subjects who are unable to decrease their renin production. Because of this potential problem, blood pressure should be determined before and during estrogen administration.

(b) *Blood coagulation.* In a previous report,<sup>1</sup> it was stated that estrogen-progestogen oral contraceptives induce many changes in the blood clotting

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1971, No. 473.

system, including a decrease in clotting time and prothrombin time and a rise in factors I, VII, VIII, IX, and X. These preparations also appear to increase the platelet count, platelet adhesiveness, and the response of platelets to aggregating agents. More recently, a number of workers have shown that estrogen-progestogen oral contraceptives also depress anti-thrombin III activity.

The estrogen component appears to be responsible for all these effects; progestogens alone have not, so far, been shown to produce adverse effects on platelets or the blood clotting mechanism. However, in contrast to epidemiological studies, which have shown a relationship between estrogen dose and thromboembolic risk, laboratory studies have not indicated a consistent association between estrogen dose and changes in the blood clotting system.

In the 1971 report,<sup>1</sup> it was stated that estrogen-progestogen oral contraceptives increase the risk of venous thromboembolism about 5 times in healthy women. The data on which this estimate was based, however, were collected at a time when oral contraceptives containing more than 50 µg of an estrogen were in widespread use. In the United Kingdom, where almost all the oral contraceptives now prescribed contain only 50 µg of an estrogen, it can be calculated that the risk in oral contraceptive users may be increased only about 3-4 times. This prediction awaits confirmation. Meanwhile, it is of interest to note that there has recently been a slight decline in the mortality from venous thromboembolic disease in women of child-bearing age in the United Kingdom.

### 2.1.2 Carbohydrates

The most widely investigated metabolic effects of oral contraceptives are those on carbohydrate metabolism. However, the extensive literature is difficult to interpret owing to the great variation in experimental method. Some experimental designs have been prospective, some retrospective, and some cross-sectional, and only a few have had adequate controls. Testing procedures have varied in complexity from single blood or urine tests to complete intravenous, oral, or cortisone-stressed oral glucose tolerance tests. The drugs under investigation have been either the sequential or combination type of oral contraceptive, or the component estrogens or progestogens alone, and have been given for varying lengths of time and at a variety of dosages. The women taking the drugs have differed in important characteristics, such as family history of diabetes, age, weight, or parity. Further, in many studies these details have not been stated or analysed separately. Although it is, therefore, somewhat hazardous at this time to draw definite conclusions, some generalizations can be made.

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1971, No. 473

#### 2.1.2.1 *Combined and sequential oral contraceptives*

(a) *Glucose* is the most widely studied blood parameter of carbohydrate metabolism. Many reports deal only with fasting blood glucose values (FBS). A slight elevation of the FBS is usually associated with the use of oral contraceptives but few investigators have noted a significantly increased incidence of abnormal values. A variety of tolerance test stimuli have been used. Generally, cortisone-provoked oral glucose tolerance tests have given the most abnormal results, followed by plain oral tolerance tests and then intravenous tolerance tests. Regardless of whether or not results are in the abnormal range, most investigators agree that there is some elevation of blood glucose while these drugs are being used. Among the 48 published studies reviewed, there were only 13 where no elevation of blood glucose levels was demonstrated, and of these, there were 7 in which a sequential type of oral contraceptive was used.

The incidence of abnormal test results in women using oral contraceptives may also depend upon the duration of use, although there is a paucity of completed long-term studies. Since the incidence of abnormal carbohydrate metabolism increases with age, this factor must also be considered in any long-term study.

(b) *Insulin*. Usage of oral contraceptives is generally associated with an elevation in levels of circulating plasma insulin as measured by immunoassay. Data suggest that the drugs affect insulin release mechanisms as well as peripheral insulin target tissues. Plasma insulin is free and not protein bound and is therefore unaffected by plasma protein changes. It is not yet certain whether the elevated insulin is all biologically active since the immunoassay system also measures the relatively inactive precursor, proinsulin. Preliminary unpublished data obtained in separation studies using Sephadex gel filtration suggest, however, that there is no elevation of proinsulin in oral contraceptive users.

#### 2.1.2.2 *Individual components of oral contraceptives*

(a) *Estrogens*. Many studies have shown that several of the estrogens can affect carbohydrate metabolism in animals. The effect is generally biphasic, with an initial deterioration and a later improvement in tolerance. The effects on carbohydrate metabolism of the two estrogens contained in oral contraceptives have been studied in menstruating women. In the few studies published, little or no consistent glucose or insulin change has been found.

(b) *Progestogens*. Relatively few studies have been made on the effects on carbohydrate metabolism of the progestogens in current use in oral contraceptives when administered without estrogens. It would appear that some have more effect than others, for example, 19-nortestosterone

derivatives appear to have a greater effect than substituted 21-progestogen derivatives. These data, although meagre and conflicting, may help to explain some of the variable results obtained with oral contraceptives containing the same estrogen but different progestogens, and the differences reported between the combination and the sequential types of drug. Thus it is important to know which progestogen is contained in the oral contraceptive under scrutiny. In addition synergism between the two steroids may be important.

#### 2.1.2.3 *Mechanism of change*

Several possible mechanisms by which steroidal contraceptives exert their effects upon carbohydrate metabolism have been suggested (altered liver function, excess production of cortisol, excess production of growth hormone, insulin binding). However, none of them completely explains all of the findings and further study is needed.

#### 2.1.2.3 *Clinical significance*

(a) *Characterization of susceptible individuals.* There have been many attempts to determine the types of women most susceptible to carbohydrate metabolic changes while using oral contraceptives. Certain characteristics of the pregnant woman that may indicate the potential or latent diabetic have now been recognized, including : previous history of abnormal blood glucose levels, family history of diabetes mellitus, delivery of excessively large infants, obesity or excessive weight gain, older age, and high parity. Women with one or more of these characteristics are not certain to develop abnormalities of carbohydrate metabolism if they use oral contraceptives but they appear to be at a greater risk of doing so when compared to a group not showing these signs. Oral contraceptive drugs should not be administered to women known to have had an abnormal glucose tolerance test. Women with any other of the above characteristics should have their blood glucose levels carefully monitored at regular intervals before and during administration.

(b) *Reversibility.* Since many women withdraw from clinical trials of oral contraceptives because they become pregnant, move away, or lose interest in the contraceptive programme, follow-up data on the reversibility of carbohydrate change are limited. Several small studies of this problem have been reported and they suggest that most of the minor alterations are reversible within 3 months of stopping the drugs.

(c) *Diabetes mellitus.* The problems of diabetes mellitus and oral contraceptive usage fall into 2 main categories : those concerning the control of existing diabetes mellitus ; and those concerning development of the disorder.

There are only a few reports of the use of oral contraceptives in women with insulin-dependent diabetes mellitus. The impression gained is that in such patients tolerance control may be more difficult initially but can be achieved, so that, given the need by diabetics for a highly effective method of contraception, combination-type oral contraceptives can be used within this disease group.

It seems clear that there is some risk of developing diabetes mellitus with continued oral contraceptive usage but the extent of the risk is unknown. Since this is a potential health problem and since the abnormalities are reversible if they are detected early in the mildly altered state, it is suggested that women who have a risk of developing diabetes (see 2.1.2.3a) while using oral contraceptives should have their carbohydrate metabolism monitored annually. The monitoring may comprise a complete tolerance test for those at greatest risk (for example, the obese woman with a strong family history of diabetes mellitus) or a single blood glucose sample (fasting or 2-hour postprandial) for others. If any abnormality is detected, the steroids should be discontinued and another means of contraception instituted.

### 2.1.3 Lipids

Estrogens elevate blood pre- $\beta$ -lipoproteins. Although occasional observations of elevated levels of cholesterol and certain phospholipids (e.g., lysolecithin) have been noted in women using oral contraceptives, a more consistent finding has been the elevation of fasting levels of circulating plasma triglycerides. The same effect can be produced by estrogens administered alone (mestranol or ethinylestradiol), but not by progestogens (megestrol acetate, chlormadinone acetate, norethisterone acetate, or etynodiol diacetate). This estrogen effect is even more marked in individuals with existing hyperlipidaemias.

Most studies have indicated that 2 mechanisms may be involved in this triglyceride change: an increased liver triglyceride production rate in response to increased circulating plasma insulin levels; and/or a decreased destruction rate due to lower lipoprotein lipase activity as measured by the post-heparin lipoprotein lipase test (PHLA), in which free fatty acid levels in the blood are measured after the intravenous injection of heparin. More recent studies correlating the fasting blood insulin and triglyceride changes in the same subject, determining the triglyceride disappearance rates after an oral fat loading meal, and carrying out the PHLA test utilizing varying dosages of heparin all suggest that other mechanisms may also be involved. Further research in this area is indicated.

Generally, the hypertriglyceridaemia is slowly reversible after the steroids have been discontinued. For the rare individual with prior congenital hyperlipidaemia, an acute vascular accident may be precipitated

during oral contraceptive use and, accordingly, an attempt should be made to recognize such women prior to administration. Where there is a family history of premature vascular accidents, blood lipid studies are indicated prior to administration. Such subjects should not be given preparations containing estrogens. The ultimate effects of elevated plasma triglyceride levels upon the vascular tree of "normal" women are unknown. Long-term prospective and epidemiologic cross-sectional studies are needed to provide more information about this critical area.

## 2.2 Long-Acting Steroidal Contraceptives

### 2.2.1 Injectable preparations

Medroxyprogesterone (17-hydroxy-6 $\alpha$ -methylpregn-4-ene-3,20-dione) is the most widely studied contraceptive that is available as an injectable long-acting preparation—depot medroxyprogesterone acetate (DMPA). Preliminary reports on clinical trials with norethisterone enantate and with a combination of dihydroxyprogesterone acetofenide and estradiol enantate have demonstrated that these injectable steroid compounds may also be effective contraceptive agents, but as they are not generally available at present, they will not be discussed in this report.

#### 2.2.1.1 *Effectiveness*

Most published data refer to the administration of DMPA in a dose of 150 mg every 3 months. These studies have taken place in clinics distributed throughout the world and, collectively, they include more than 14 000 women studied for more than 150 000 administration months. The pregnancy rate is uniformly very low, comparing favourably with the theoretical effectiveness of the combination oral contraceptives. Individual clinics with substantial numbers of patients and administration months report pregnancy rates varying from 0 to 0.35 per 100 woman-years.

As the contraceptive action of 150 mg usually lasts longer than 3 months, the effectiveness of this method of contraception is enhanced and patients who delay receiving their next scheduled injection for a few weeks may remain protected against accidental pregnancy. To increase the duration of effect it is recommended that the drug be administered by deep intramuscular injection in the gluteal region without manual massage. There are no published data concerning the efficacy of doses of less than 150 mg given at 3-month intervals.

Although doses of over 300 mg given at 6-month intervals provide effective protection, when the dose is lowered to 300 mg or less the efficacy over the 6 months appears to be reduced. In studies utilizing a dose of 300 mg administered every 6 months to more than 1 500 women studied

for more than 30 000 woman-months the cumulative pregnancy rate was approximately 1.7 per 100 woman-years.

It is not clear whether the timing of the initial injection in relationship to the menstrual cycle influences the efficacy. However, the routine practice of giving injections early in the cycle or early in the puerperium is recommended to ensure that conception has not occurred before administration is started.

#### 2.2.1.2 *Mechanism of action*

The concept of depot administration implies a continuous slow release mechanism over a period of time, to maintain a pharmacologically effective blood level. It has been postulated that DMPA acts in at least 3 different ways :

- (i) it inhibits the secretion of gonadotrophic hormones (especially the cyclic release of luteinizing hormone) and thereby inhibits ovulation ;
- (ii) it increases the viscosity of the cervical mucus, thereby forming a natural barrier to the penetration of spermatozoa ;
- (iii) it alters the secretory characteristics of the endometrium, thereby making the environment unfavourable for the implantation of the fertilized ovum.

In one study only, radioimmunoassays of DMPA blood levels were carried out in 3 women at frequent intervals following an intramuscular injection of 150 mg of DMPA. During the first 20 days following administration, blood levels of the drug fluctuated at relatively high values. Thereafter, the levels decreased and showed less fluctuation. The length of time during which these low serum levels persist and the duration of pharmacologically effective serum levels of this drug after a single 150-mg injection have not yet been definitely established.

In other studies, the mid-cycle surge of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) was inhibited for more than 90 days after injection. Daily blood levels of LH and FSH showed some fluctuation but the levels were generally similar to the levels of these hormones seen in the luteal phase of ovulatory cycles. Ovulation was inhibited as serum progesterone and urinary pregnanediol levels remained low during use. Daily serum estradiol levels showed little fluctuation and were usually in the range found in the early follicular phase of the normal menstrual cycle. The cervical mucus was scant and viscid ; whether this alteration is a primary or a secondary effect is not known.

Histological examination of the endometrium in women receiving DMPA with and without exogenous estrogen showed it to be low-lying, quiescent, or atrophic indicating that the drug has a direct effect on this tissue.

#### 2.2.1.3 *Metabolic effects*

The metabolic fate of DMPA in man is not known. Once in the blood, it seems to be metabolized mainly in the liver and the majority is excreted in the bile. Most of the metabolic studies of DMPA have been conducted just prior to the next injection at a time when tissue levels of DMPA were low.

There is considerable evidence for a glucocorticoid effect of this steroid in animals. Nevertheless, no consistent evidence of glucocorticoid activity has been reported in man, at the dosages used for contraceptive purposes.

Most studies demonstrate a significant gain in body weight during the use of this compound, the increase being dependent upon the duration of usage. The mechanism for this alteration has not been defined. These data are from different parts of the world and deal with women from a variety of socioeconomic groups.

Although only limited data are available, it appears that DMPA at a dosage of 150 mg every 3 months will cause a deterioration of glucose tolerance and an increase in plasma insulin levels. No apparent change in liver function or lipid metabolism has been noted. No consistent change in blood pressure has been noted.

#### 2.2.1.4 *Lactation*

An important issue in the use of hormonal contraception is the effect on lactation, particularly in countries where the survival of children is closely associated with successful breast feeding. Three published reports suggest that milk volume is probably increased and that milk composition is not affected, but more studies are needed in this area. Studies have not been undertaken to determine if the drug and/or its metabolites are excreted in the milk nor to determine if any adverse effects are produced in the neonate.

#### 2.2.1.5 *Effect on the fetus*

Animal studies have shown some teratogenicity (cleft palate) and masculinization of the fetus when the drug is given during pregnancy. No such effects have been observed in man to date but despite this, it is recommended that DMPA should be administered during, or immediately following menses or immediately postpartum (see section 2.2.1.4).

#### 2.2.1.6 *Carcinogenicity*

There is no evidence that DMPA causes an increased incidence of cancer of the breast or genital tract in women; however, adequate epidemiological studies have not been undertaken.

Several types of mammary nodule both benign and malignant are known to develop spontaneously in beagle dogs. Studies in these animals have indicated that DMPA increases the incidence of mammary neoplasms when compared with controls. Beagles developed clinically palpable nodules during the first 40 months of treatment with low and high doses of DMPA. Malignant nodules with metastases were found in 3 dogs receiving high doses (25 times the human dose) that were sacrificed in month 43 of drug administration. No such malignant nodules were found in dogs that died or were sacrificed prior to month 42 of administration, or in any of the control dogs, in either the DMPA trial or in trials with any of the other contraceptive steroids that were investigated. An increased incidence of mammary nodules has also been reported in beagles receiving continuous administration of chlormadinone acetate, but no such action has resulted from the combination type of contraceptive currently being marketed. The relevance to man of these findings in the dog is not known at the present time.

In the rhesus monkey, the data are notable for the lack of nodules both in controls and in animals treated with 1, 10, and 50 times the human dose of DMPA over a period of 36 months.<sup>1</sup>

#### 2.2.1.7 *Effects on menstruation*

It is generally agreed that once medroxyprogesterone acetate administration is started, the normal menstrual cycle is totally disrupted and irregular bleeding occurs at completely unpredictable intervals. The frequency of bleeding tends to decrease as the period of use increases and most individuals eventually develop amenorrhoea. This picture is consistent with the results of histological studies on endometrial biopsies obtained during administration. The actual number of days of bleeding per month varies among individual patients. During the first 3-month period of use the mean number of days of bleeding is almost doubled in comparison to control individuals. During the next 6 months, the number diminishes and is approximately the same as the normal number. Thereafter, the mean number of bleeding days per 3-month period progressively decreases. When bleeding does occur, it is usually not excessive and is frequently characterized as spotting.

Although less than 10% of women receiving DMPA are described as discontinuing on medical advice because of irregular or abnormal bleeding, it is not known how many discontinue the drug because such bleeding is

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<sup>1</sup> Diczfalusy, E. & Standley, C. C., ed. (1972) *The use of non-human primates in research on human reproduction. Proceedings of a Symposium organized by WHO in collaboration with the Ministry of Health of the USSR, Sukhumi, Georgia, 13-17 December 1971*, Stockholm, WHO Research and Training Centre on Human Reproduction, Karolinska Institutet.

found to be socially unacceptable and how many experience bleeding that could be considered a health hazard ; the need for endometrial curettage for serious bleeding has been reported only once.

Some investigators have added cyclical estrogens in an attempt to regulate the bleeding pattern ; however, their results are difficult to evaluate. It must be pointed out that both medical staff and patients must be aware that bleeding due to pathological causes may easily be missed if all irregular bleeding is ascribed to the effects of the drug.

Amenorrhoea has been reported to develop in about one-third to one-half of women after 6 months of administration and from one-half to three-quarters of women after 1 year. It has been suggested that this state of induced amenorrhoea may be beneficial to women with iron deficiency anaemia, but almost no data on this subject are available.

#### *2.2.1.8 Return of menstruation, ovulation, and fertility after use*

The published reports show a wide range of findings regarding the percentage of patients with a return of these 3 functions after use as well as the time intervals elapsing before such returns have been identified, and documentation is frequently vague or inaccurate.

Approximately half of the users return to a regular menstrual pattern within 6 months of discontinuing administration and about three-quarters within 1 year. There is some doubt as to whether a relationship exists between the duration of administration and the length of amenorrhoea after cessation.

The unpredictability of the return of normal menstruation and return to a state of fecundity after cessation of this method limits its use in women planning future pregnancies, unless other methods of contraception are unsuitable or contraindicated for medical or sociological reasons.

#### *2.2.1.9 Continuation of use*

The method of presentation of results in most of the studies of DMPA makes the extraction of data on continuation rates and reasons for discontinuing use extremely difficult. It is to be hoped that future studies will employ life-table methods of analysis, such as are now used routinely for analysing data on intrauterine devices, to improve this situation.

The existing data suggest that there is great variation in continuation rates : at one extreme is a study carried out in the USA in which 58% of women had discontinued the method after 1 year ; at the other is a study carried out in South Africa in which the corresponding rate was only 18% after 3 years. In both these studies 150 mg of DMPA was administered at 3-month intervals.

It has been stated that the highest discontinuation rates occur during the first 2 injection periods and that once treatment has continued for

12 months or more it is well tolerated. There are, however, few data to support this claim.

The acceptability of this method of contraception is clearly a problem that is closely related to sociocultural factors in the communities studied, especially attitudes towards menstruation, amenorrhoea, and injections. However, a most important factor in maintaining high continuation rates is the amount of personal enthusiasm, explanation, and support provided by those responsible for patient care.

#### 2.2.1.10 *Programme use of DMPA*

The decision to use injectable DMPA as a method of contraception should only be made after a careful analysis of the relative risks and benefits involved. As there is at present insufficient statistical information to permit sophisticated relative risk calculations for this method, the decision to use it will have to be based on the published information available, taking into account local needs and conditions.

### 2.2.2 **Oral preparations**

Clinical trials have been reported with only one long-acting oral steroidal contraceptive, which consists of a long-acting estrogen and progestogen that are given at the same time. The estrogen, quinestrol, is the 3-cyclopentylether of ethinylestradiol, which has prolonged activity in animals and man as a result of storage in and subsequent release from the body fat. Quinestrol remains unchanged in fat and after its release is metabolized mainly to conjugates of ethinylestradiol. The progestogen, quingestanol acetate, is the 3-cyclopentyl enol ether of norethisterone acetate. The long-acting estrogen is utilized to inhibit ovulation in the subsequent cycle and the progestogen is included to induce withdrawal bleeding after a short interval. There have been relatively few clinical studies published regarding the use of this method of contraception.

#### 2.2.2.1 *Effectiveness*

The drug is generally administered once a month. Various dosage schedules have been utilized. In most, 2 mg of quinestrol is given on the first or second day of the cycle followed 3 weeks later by the combination tablet of 2 mg of quinestrol and 2.5 mg of quingestanol acetate. The combination tablet is given every 4 weeks thereafter. Because accidental pregnancies occur with higher frequency in the first cycle of use, most investigators advise an additional contraceptive method during this period.

Approximately 1 600 women have been studied for nearly 20 000 woman-months. Pregnancy rates have varied from 0.8 to 4.0 per 100 woman-years, with lower rates if the first cycle of use is excluded. Unpublished

reports available to the Group indicate, however, that substantially higher pregnancy rates have been obtained in other clinical trials involving several hundred women followed for several thousand woman-months using the same dosage. Overall pregnancy rates in these trials were about 10 per 100 woman-years with approximately half of the pregnancies being a result of method failure.

#### 2.2.2.2 *Mechanism of action*

It has been suggested that the main mechanism of action is ovulation inhibition, but definitive studies are lacking.

#### 2.2.2.3 *Effects on menstruation*

Withdrawal bleeding begins 1–2 weeks after ingestion of the drug in about two-thirds of cycles. Cycle length has been reported to be regular in the majority of subjects. The duration of bleeding is generally increased during administration. In about one-fifth to one-third of cycles withdrawal bleeding lasts for 7 days or more. In addition, the amount of bleeding has been reported to be heavier than prior to administration in a significant number of women. This prolonged and heavy bleeding is one of the major adverse effects of this contraceptive. Another frequent side effect is breakthrough bleeding, which in one study was noted by 79% of subjects. This symptom occurs with greater frequency early in treatment, occurring in about one-fourth of the first few cycles. Amenorrhoea has also been noted in a small percentage of women.

#### 2.2.2.4 *Other effects*

Systemic effects similar to those observed with daily combination hormonal contraceptives have been reported. Nausea, vomiting, and mucorrhoea are the most frequent adverse symptoms. Headache and breast tenderness have also commonly been noted. The incidence of these symptoms has varied in different trials and no attempt has been made to compare their frequency with that occurring with other methods of hormonal contraception in the same population.

The documentation of metabolic effects appears to be scarce. One study on lipid metabolism showed triglyceride and phospholipid levels to be increased; however, serum cholesterol was unchanged.

#### 2.2.2.5 *Continuation of use*

Because of the method of presentation of data in published studies, it is difficult to determine continuation rates. Life-table methods of analysis were not used to determine continuation rates accurately. The published reports indicate that continuation rates are good, but unpublished studies to which the Group had access indicate less favourable continuation rates.

#### 2.2.2.6 *Current status*

Despite the generally favourable reports on this method of contraception, the data are too limited to allow definitive recommendations at the present time.

### 2.3 **Postcoital Contraception**

A postcoital contraceptive agent for women who have only occasional unprotected intercourse would be desirable, but adequately controlled studies would be difficult to carry out. A few studies have been done administering high dosages of estrogen for short periods of time within 3 days of intercourse. The efficacy of this method, although it appears to be favourable, is difficult to determine, because the studies have been small and follow-up data usually inadequate. The risk that large doses of estrogen may produce serious side effects, such as thromboembolism, as well as the minor problems of nausea, vomiting, and bleeding restrict the use of this method to emergency situations.

The possible mechanisms of action for this method are unknown, but suggestions include :

- (1) increased tubal transport of the fertilized ova ;
- (2) a direct effect upon the endometrium thereby inhibiting implantation of the fertilized ova ;
- (3) activation of prostaglandin F<sub>2</sub> release and/or synthesis with a possible luteolytic effect.

There are two reports of progestogens (norgestrel and quingestanol acetate) given repeatedly throughout the cycle as a postcoital contraceptive. Preliminary data have indicated that these agents have contraceptive effectiveness, but their mode of action remains to be determined. The use of progestogens in a single dose as an emergency method has not been reported.

Further studies are needed with a variety of steroids to gain more information about toxicity, dosages, delay time for effectiveness, and their mechanism of action.

### 3. **INTRAUTERINE DEVICES**

Profiting from experience gained with existing intrauterine devices, the development of newer devices has been guided by 3 principal needs : to decrease further the pregnancy rate ; to lower the expulsion rate ; and to prevent pain and bleeding disturbances that lead to removal of the IUD.

To achieve these goals modifications have been made to the size, shape, and composition of the IUDs.

Only a small number of the newly developed devices have been investigated in multicentred clinical trials, and only information about these devices will be included in this report.

### **3.1 Modifications**

#### **3.1.1 Size and shape**

Most of the IUDs available are so designed that they force the uterine cavity to adjust to their configuration, and it has been claimed that the resulting compression of the endometrium may cause pathological bleeding. In addition, the myometrium reacts to the distension by contractions that may result in expulsion of the device. In an attempt to make an IUD that will be better tolerated by the uterus, a "T"-shaped device has been designed. This device conforms more to the uterine cavity. A similar principle has been used in designing the Dalkon "Shield", manufactured from ethyl-vinyl acetate polymer, and the double coil device.

#### **3.1.2 Stiffness**

There is a significant correlation between the stiffness of the device and the expulsion rate; the most rigid device has been shown to have the lowest expulsion rate and the most pliable device the highest expulsion rate. Attempts have been made to reduce expulsion rates by the introduction of new materials; a polypropylene loop (Shell loop) has been tested clinically; stainless steel devices have also been modified (e.g., Majzlin spring) and tested in clinical trials.

#### **3.1.3 Composition**

The principle behind modifications in IUD composition is to use a device that is tolerated by the uterus as a carrier of a substance that alters the intrauterine milieu, in particular by interfering with the metabolic processes in the endometrium. The "T"-shaped device, which is well tolerated by the uterus but is associated with a high pregnancy rate when used alone, has been used as a carrier of metallic copper in the form of a thin copper wire with a total surface area of 200 mm<sup>2</sup> (Cu-T 200 device).

## 3.2 Mechanism of Action

### 3.2.1 Polyethylene devices

#### 3.2.1.1 Mobilization of leucocytes

Data from animal experiments were summarized in the 1971 report.<sup>1</sup> Since that time, studies have also been carried out in women, some of which indicate that the contraceptive effect of the IUD is directly related to the presence of increased numbers of neutrophils and macrophages in the endometrium and in uterine secretions. In a group of 36 women using the Lippes loop, endometrial aspirates were examined by light microscopy 2–16 hours after intercourse. It was concluded from these observations that the spermatozoa present in the aspirates were mostly phagocytized and were destroyed within 16 hours of intercourse.

An increased number of inflammatory cells were also reported in hysterectomy specimens from 167 women and endometrial biopsies of 202 women. The specimens, which were obtained at various intervals ranging from a few hours to 5 years after the insertion of an IUD, revealed an increase in neutrophils, mononuclear cells, and plasma cells in the endometrium. Leucocyte counts in uterine washings were studied in 38 patients prior to insertion, and 6 and 18 weeks after insertion, of an IUD. At the 6-week follow-up there was a significant increase in the total number of leucocytes and there was a further increase at 18 weeks. In addition histochemical studies revealed increased lysosomal hydrolase activity in leucocytes obtained from women using the polyethylene loop. Although no evidence of phagocytosis of spermatozoa could be found, the increased enzymatic activity was thought to reflect an increased potential for intracellular digestion by the reticuloendothelial cells in the endometrium. The suggestion that the phagocytosis of the spermatozoa might explain the mechanism of action of the polyethylene IUDs is contradictory to the observation that there is no reduction in the incidence of ovarian pregnancies in IUD-users when compared to that in the general population.

#### 3.2.1.2 Local effects on endometrial tissue

Histologically no pathological changes have been observed in the human endometrium following the insertion of a polyethylene IUD except for inflammatory changes. Biochemical sequential studies of endometrial tissue for total protein, acid-soluble nucleotide, RNA, and alkaline and acid phosphatases during the menstrual cycle have revealed an increase in the activity of acid phosphatase at midcycle in women fitted with an IUD. In addition, a peak concentration of total protein and RNA appeared

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1971, No. 473.

7 days earlier in women fitted with an IUD than in the controls, which may indicate a stimulation of the growth activity.

### 3.2.2 Copper-bearing devices

In spite of increasing data from studies in women, the mechanism of action of metal IUDs is not yet completely known. Most of the information available is from studies concerning the mode of action of copper-bearing devices. The findings are summarized below.

#### 3.2.2.1 Release rate

The release rate per day from the Cu-T 200 device (see section 3.1.3) showed some variation during the period of observation (29–430 days *in utero*). The mean release rate during the first 60 days after insertion was significantly higher than after that period. From 60 to 420 days the release rate was found to be constant at 50 µg per day.

#### 3.2.2.2 Effect on the endometrium and cervical mucus

The copper released from the device was found to be partly taken up by the endometrium. During the first 6 months, an increased copper concentration was found both in the proliferative and in the secretory endometrium, whereas only the secretory endometrium showed an increased amount of copper after 12 months. Values returned to normal within the first 2 cycles following removal of the device. The copper concentration in the cervical mucus was higher in the proliferative phase during the first 6 months with the Cu-T 200 *in utero* than before insertion. It returned to normal values shortly after removal of the device.

The copper concentration in the uterine fluid was calculated to be 4–5 times higher in the first 6 cycles than in control cycles. There is some evidence from *in vitro* studies that the increased copper concentration in the mucus and uterine fluid might influence sperm motility.

The zinc concentration was significantly decreased in the secretory endometrium after continuous exposure to the Cu-T 200 for 12 months. No change was observed in the concentration in the cervical mucus. The manganese concentration showed a decrease after 6 months and the values were significantly lower than before insertion. The significance of these changes in zinc and manganese concentration is unknown.

Studies of protein and nucleic acid levels and enzyme activities in the endometrium showed significant changes that may relate to the mechanism of action. A significant increase in acid phosphatase activity was found during the proliferative phase whereas alkaline phosphatase and β-glucuronidase activities were significantly decreased during the secretory phase. Cytochemical estimations of DNA per cell nucleus indicated that the

insertion of the Cu-T 200 device interferes with the cellular DNA in the endometrium causing a delay in the development of the S-phase of the mitotic cycle.

Studies by light microscopy of endometrial biopsies taken on various occasions from the same women during 12 months with the Cu-T 200 *in situ* did not reveal any pathological changes in the mucosa. Except for a slight delay in the development of the midsecretory phase, no disturbances of the cyclical endometrial changes were observed. A deposit of metallic copper in the endometrium could be demonstrated histochemically during the secretory phase. An infiltration of inflammatory cells in the stroma was observed only occasionally. However, during the continuous use of the device for 1 year an increase of leucocytes was found in the glandular lumina during the secretory phase. Leucocyte counts in uterine washings did not show any increase in the proliferative phase. It seems unlikely that the limited increase in number of leucocytes is the only factor responsible for the contraceptive effect.

#### 3.2.2.3 *Systemic effects*

No systemic effects have been reported as yet in women using the Cu-T 200 device. The copper concentration in serum and plasma as well as the intracellular copper levels as estimated in peripheral blood erythrocytes remained unchanged while the device was *in utero*.

### 3.3 Use-Effectiveness and Continuation of Use

#### 3.3.1 General use

Based upon the extensive experience of the Cooperative Statistical Program for the Evaluation of Intrauterine Devices in the USA, it has been possible to use the data presented in 1970 as points of reference in the evaluation of the clinical effectiveness of the new IUDs. Published data with new IUDs that have been obtained from multicentred clinical trials are listed in Table 1 together with data obtained using the polyethylene loop.

The stiffness of the polypropylene loop, as well as the shape and tension of the stainless steel devices have resulted in a lower expulsion rate. However, the latter have an increased removal rate due to the high frequency of pain and bleeding. The removal rate for bleeding and pain for the stiffer polypropylene loop, however, is no greater than for the polyethylene loop, size D, and the pregnancy rate is lower than that with the polyethylene device. Whether it is the stiffness of the device or its different composition that accounts for these differences remains to be established. The Dalkon Shield device has a rate of expulsion lower than that of the polyethylene

TABLE 1. NET EVENT RATES PER 100 USERS FOR PREGNANCIES, FIRST EXPULSIONS, REMOVALS FOR MEDICAL REASONS, CLOSURES, AND CONTINUATION RATES, CALCULATED FOR 12 MONTHS' USE OF AN IUD

| Intrauterine device                     | Reference <sup>a</sup>   | Woman-months of use | Pregnancies | First expulsions | Removals for medical reasons |        | Closures 1st segment | Continuation rate 1st segment |
|---|--------------------------|---------------------|-------------|------------------|------------------------------|--------|----------------------|-------------------------------|
|   |                          |                     |             |                  | bleeding/pain                | others |                      |                               |
| Polyethylene loop, size D               | Tietze, 1971             | 72,046              | 2.7         | 9.5              | 11.7                         | 3.5    | 30.5 <sup>b</sup>    | 69.5 <sup>b</sup>             |
| Polypropylene loop, size D (Shell loop) | Tietze, 1971             | 12,906              | 1.0         | 3.4              | 8.7                          | 3.7    | 20.9 <sup>b</sup>    | 79.1 <sup>b</sup>             |
| Double coil                             | Tietze, 1970 a           | 12,015              | 2.3         | 14.1             | 13.2                         | 3.0    | 34.2                 | 65.8                          |
| Majzin spring                           | Tietze, 1970 b           | 14,139              | 2.2         | 3.6              | 18.0                         | 4.8    | 31.9 <sup>b</sup>    | 68.1 <sup>b</sup>             |
| Dalkon Shield                           | Snowdon & Williams, 1973 | 6,669               | 3.8         | 3.9              | 4.6                          | 0.8    | 28.6                 | 71.4                          |
| Copper-T-200 <sup>c</sup>               | Tatum, 1972              | 7,740               | 2.2         | 7.2              | 5.6                          | 4.3    | 23.5                 | 76.5                          |
| Polyethylene loop, <sup>c</sup> size D  |                          | 5,760               | 3.0         | 13.0             | 9.0                          | 2.5    | 29.8                 | 70.2                          |

<sup>a</sup> See Annex 2, Selected Bibliography, section 4, p. 40.

<sup>b</sup> Calculated from the figures given in the original.

<sup>c</sup> Double-blind multicentred trial

loop D but not lower than that of the polypropylene loop. The removal rate for bleeding and pain for the Dalkon Shield is lower than for the loops, but the pregnancy rate is not. The expulsion and removal rates for pain and bleeding are lower for women using the Cu-T 200 device than for the loop users. Nevertheless, the pregnancy rate for the Cu-T 200 device is not significantly lower. A device similar in size, shape, and composition, called the Cu-7, has been shown to have comparable event rates to the Cu-T 200.

### 3.3.2 Use in nulliparous women

No multicentred trials have been carried out in nulliparous women. The data presented refer to 2 studies, one with the Cu-T 200 device and the other with the Dalkon Shield, carried out in single-centred clinical trials. The pregnancy, expulsion, and removal rates in the Cu-T 200 study in nulliparous women are similar to those found in studies of multiparous women with the same device. The large clinical study of the Dalkon Shield device has indicated that it has a relatively high incidence of removal for bleeding and pain.

Since the Cu-T 200 device may be suitable for nulliparous women, the contraindications listed in the 1968 report<sup>1</sup> should be modified in this respect. The other indications and contraindications for the use of IUDs mentioned in the previous reports<sup>1, 2</sup> remain unchanged.

### 3.4 Miscellaneous

The current recommendations on the duration of contraceptive efficacy for the Cu-T 200 devices is 2 years. However, as studies progress or more copper is added to the device, this estimate may well be lengthened to 2 or more years.

The further information on pelvic infections related to the use of IUDs is scanty and prospective studies are needed on this aspect.

A higher incidence of uterine perforation has been reported following the insertion of the polypropylene loop and the stainless steel IUDs. The ratio for the polypropylene loop is 1 : 600, whereas the ratio for the polyethylene loop size D is 1 : 1000. One multicentred study with the Dalkon Shield has shown a perforation rate of 1 : 350. Perforations of the uterine wall and the cervix as well as complications in removal have been reported following the use of the Majzlin spring.

No increased incidence of endometrial or cervical carcinoma has been reported following the use of IUDs. However, in view of the period of time

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 397.

<sup>2</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1971, No. 473.

needed for the development of such malignant diseases it seems to be too early to draw any conclusions from the data available on the newer IUDs.

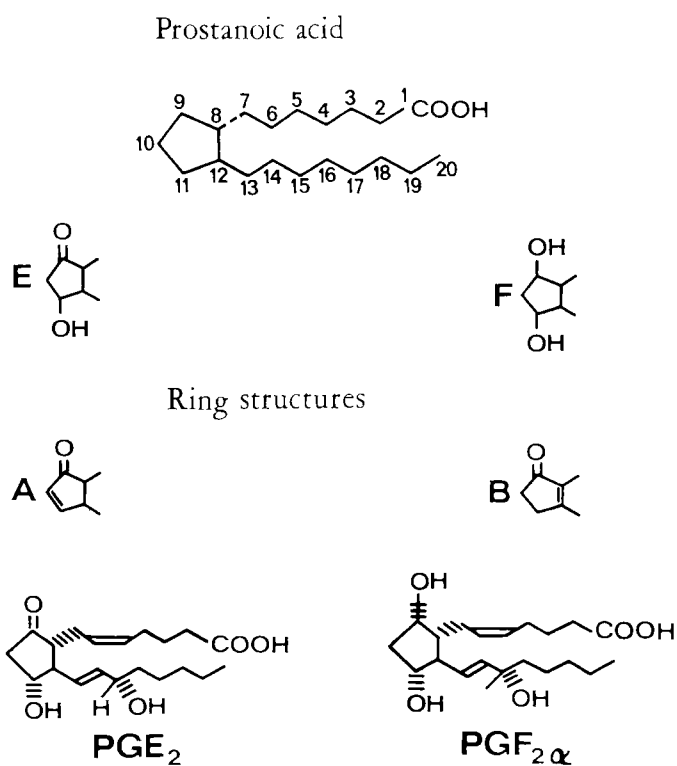
As already pointed out in a previous report,<sup>1</sup> ectopic pregnancies are relatively more frequent among the pregnancies occurring with an IUD *in situ*. Symptoms of pregnancy in a woman fitted with an IUD should alert the physician to the possibility of an ectopic gestation, and this should be kept in mind whenever termination of the pregnancy is considered.

#### 4. PROSTAGLANDINS IN FERTILITY REGULATION

##### 4.1 Chemical Nature

The 14 naturally occurring prostaglandins (PG) are unsaturated fatty acids with 20 carbon atoms arranged in accordance with the skeleton of the prostanic acid molecule (Fig. 1). So far 4 series of natural prostaglandins

FIG. 1. THE SKELETON OF PROSTANOIC ACID, BASIC RING STRUCTURES OF THE FOUR NATURAL PROSTAGLANDINS, AND CONFIGURATION OF THE PGE<sub>2</sub> AND PGF<sub>2α</sub> MOLECULES



<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 473.

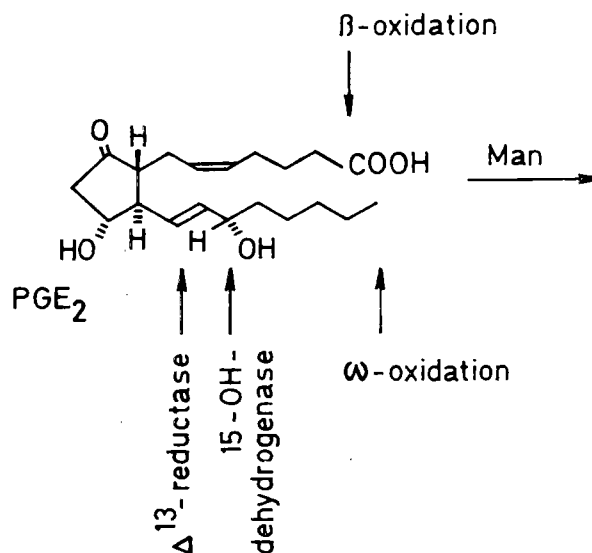
have been described and designated by the letters E, F, A, and B according to the ring structure. The 6 compounds of the E and F series constitute the "primary prostaglandins", which are of special interest in reproductive physiology. All prostaglandins have one or more double bonds in the side chains and the number of these bonds characterizes the different members of each series, e.g., E<sub>1</sub>, E<sub>2</sub>, E<sub>3</sub>, etc. Reduction of the keto group at C9 of prostaglandin E (PGE) yields 2 isomeric alcohols F<sub>α</sub> and F<sub>β</sub>. The α notation indicates that the C9 hydroxyl group is below the plane of the ring. It is possible to synthesize several of these compounds.

#### 4.2 Occurrence and Metabolism

Prostaglandins are widely distributed in the body. A variety of prostaglandins have been identified in the blood, seminal plasma, menstrual fluid, endometrium, decidua, amniotic fluid, and umbilical and placental vessels. The concentration is generally very low (a few ng/ml or less) with the exception of the seminal plasma where the levels reach 100 μg/ml.

The primary prostaglandins are rapidly inactivated and metabolized in the human body (Fig. 2). Intravenously injected prostaglandins are inactivated within a period of approximately 1 minute and the biologically inactive metabolites are rapidly excreted in the urine.

FIG. 2. ENZYMES INVOLVED IN THE METABOLISM OF PGE<sub>2</sub> IN THE HUMAN



### 4.3 Physiological Aspects and Pharmacological Action

#### 4.3.1 Ovarian function

Recent studies in animals and *in vitro* have indicated that the prostaglandins may play an important role in the regulation of ovarian function, via a variety of mechanisms (steroidogenesis, ovulation induction, and luteolysis). It has been shown that  $\text{PGF}_{2\alpha}$ ,  $\text{PGF}_{1\alpha}$ , and  $\text{PGE}_2$  are luteolytic in a number of animal species. There is also some evidence that  $\text{PGF}_{2\alpha}$  may decrease the secretion of progesterone from the corpus luteum in the rhesus monkey provided that the compound is administered in high doses into the aorta at the origin of the ovarian arteries. However, intravenous administration of  $\text{PGF}_{2\alpha}$  has not definitely been shown to influence the secretory performance of the corpus luteum in the nonpregnant primate, if given in the early or midluteal phase of the menstrual cycle. In women there is no conclusive evidence to indicate that prostaglandins have any pharmacological effects on the growing follicle or on luteal steroidogenesis. Intravenous infusion of  $\text{PGF}_{2\alpha}$  in high doses is most probably not luteolytic either in the secretory phase of the menstrual cycle or during early pregnancy.

#### 4.3.2 Fallopian tubes

The intravenous injection of  $\text{PGF}_{2\alpha}$  stimulates tubal motility in women, whereas  $\text{PGE}_2$  causes relaxation. Similar effects have been obtained by the local administration of very small doses (in the order of nanograms) directly into the tubal lumen. This indicates that ovum transport might be influenced by prostaglandins.

#### 4.3.3 Uterus

Prostaglandins have a potent stimulatory effect on uterine contractility. The compounds are active during early as well as late pregnancy and also in nonpregnant women.  $\text{PGE}_2$  is approximately 8 times as potent as  $\text{PGF}_{2\alpha}$ . Following a single intravenous injection there is a rapid dose-dependent increase in uterine tonus, which subsequently gradually returns a normal level. Constant intravenous infusion of the substances over a period of several hours alters uterine activity by increasing the frequency and amplitude of contractions both in pregnant and nonpregnant women.

Stimulation of intense uterine activity in the first or second trimester of pregnancy requires intravenous infusion of large doses of prostaglandin, which are associated with a high incidence of side effects, particularly nausea, vomiting, and diarrhoea. The frequency of side effects can be significantly reduced if the compounds are administered locally, either

by instillation into the amniotic sac via abdominal puncture or extra-amniotically between the uterine wall and the fetal membranes via a cervical catheter. Intra-amniotic administration results in a gradual elevation of uterine tonus and subsequent development of forceful coordinated contractions lasting for 10–20 hours or more, depending on the compound and the dose injected. Repeated extra-amniotic injections induce similar results. However, the effect of a single extra-amniotic injection of  $\text{PGF}_{2\alpha}$  or  $\text{PGE}_2$  lasts only 2–4 hours.

#### 4.3.4 Other systems

Prostaglandins have been shown to have a great variety of actions including effects on smooth muscle in the cardiovascular, gastrointestinal and respiratory systems, as well as effects upon gastric secretion and temperature control.

### 4.4 Clinical Application

#### 4.4.1 Induction of abortion

The primary prostaglandins are now available for use as abortifacient agents. The process of cervical dilatation and expulsion of the conceptus is the result of extensive uterine muscle contractions; however, the mechanism underlying the production of uterine stimulation is incompletely understood.

##### 4.4.1.1 Systemic administration

The efficacy of intravenously administered prostaglandins in inducing abortion is dependent upon the dose and duration of infusion. Doses of the order of 50–100  $\mu\text{g}$  of  $\text{PGF}_{2\alpha}$  or 5  $\mu\text{g}$  of  $\text{PGE}_2$  per minute have been used. The induction-abortion interval varies considerably and the infusion has to be continued for 24 hours or more in a significant number of cases. The intravenous doses of  $\text{PGF}_{2\alpha}$  or  $\text{PGE}_2$  needed for induction of abortion in the first and second trimester are very frequently associated with side effects, mainly gastrointestinal, but pyrexia, shivering, headache, and local erythema at the site of venepuncture also occur. The high frequency of these side effects, as well as the need for prolonged intravenous infusion, are major disadvantages that generally preclude the use of this method of administration. The natural prostaglandins have also been administered by the vaginal route. However, the compounds are absorbed into the systemic circulation and the incidence of side effects is apparently still too high to be acceptable.

#### 4.4.1.2 *Extra-amniotic administration*

The administration of prostaglandins into the lower uterine segment between the uterine wall and the fetal membranes produces a local stimulatory effect on the myometrium. This mode of administration eliminates the need for a high systemic concentration of the compounds. Accordingly the total dose needed for induction of abortion by the extra-amniotic method is about one-tenth to one-twentieth of the intravenous dose, and the incidence of nausea, vomiting, and diarrhoea is low.

This route of administration is mainly of use during the weeks 12–15 of gestation. Repeated injections of  $\text{PGF}_{2\alpha}$  (250–750  $\mu\text{g}$ ) or  $\text{PGE}_2$  (50–200  $\mu\text{g}$ ) are made at 2-hour intervals via a self-retaining Foley catheter introduced through the cervix into the lower uterine segment. The Foley catheter balloon is filled with 20 ml of normal saline. The catheter is left *in situ* throughout the induction and, on average, about 10 separate injections are required. Abortion occurs in 85–90% of the cases but approximately half are incomplete. The mean induction-abortion interval is about 20 hours.

The disadvantages of the method are the need for repeated instillations, and the inconvenience, especially if surgical evacuation becomes necessary, of maintaining an indwelling intrauterine catheter, with its associated risks of causing intrauterine infection.

The main advantage of the method is its applicability in the early stage of the second trimester when termination of pregnancy is difficult by other methods in current use.

#### 4.4.1.3 *Intra-amniotic administration*

Probably the most successful method of administration of prostaglandins for the induction of late second trimester abortion is by intra-amniotic injection. Transabdominal puncture of the amniotic sac in weeks 15–20 of gestation is generally a simple procedure and the introduction of a thin polyethylene catheter through the needle allows repeated drug injections. Different dose schedules have been applied in an attempt to reduce the number of injections and to obtain optimum results. A dose of 25 mg of  $\text{PGF}_{2\alpha}$  repeated once after 24 hours if necessary, gives an abortion rate of approximately 95% with a mean induction-abortion interval of 28 hours. At least 40–50% of the abortions are complete. The incidence of gastrointestinal side effects is of the order of 2 episodes per abortion. A second dose given 6 rather than 24 hours following the first injection results in the same high success rate, and a shortening of the mean induction-abortion interval to 18–20 hours. However, the incidence of gastrointestinal side effects approximately doubles. Clinical trials have also been conducted using a single injection of 40–50 mg of  $\text{PGF}_{2\alpha}$ . There is a high success

rate but limited information is available with regard to side effects. The high dose method has the advantage of involving only a single injection but needs to be tested in a larger group of women.

#### **4.4.2 Prostaglandin analogues**

Prostaglandin analogues with structural modifications aiming at slower metabolic degradation and better target organ specificity could result in less frequent administration and lower the incidence of side effects. Prostaglandin-specific 15-dehydrogenase does not inactivate the 15-methyl derivatives (see Fig. 2) of the primary prostaglandins  $E_2$  and  $F_{2\alpha}$ . Recent clinical studies with these compounds suggest increased potency and duration of action. Preliminary data indicate that the number of extra-amniotic injections can be significantly reduced and that abortion might be induced by a single intra-amniotic injection, with a lowered incidence of side effects. These prostaglandin analogues are not generally available because extensive clinical and toxicological tests have yet to be conducted.

#### **4.4.3 Preoperative dilatation of the cervix**

Curettage remains the method of choice for the termination of first trimester pregnancies. However, primary instrumental evacuation at the end of the first trimester is associated with an increased incidence of complications, particularly in cases where the size of the uterus is large and information on the period of amenorrhoea is uncertain. Repeated extra-amniotic administration of  $PGF_{2\alpha}$  given over a short period of time at doses of 300–500  $\mu\text{g}$  induces cervical dilatation preoperatively in the late stages of the first trimester. Surgical evacuation of the uterus following this treatment is a simple procedure with a minimum of blood loss.

#### **4.4.4 Postconceptional use of prostaglandins**

Studies of fertility control by the administration of  $PGE_2$  and  $PGF_{2\alpha}$  in the period up to 4 weeks after ovulation have been conducted but the results have not been encouraging.

### **5. METHODS OF TUBAL OCCLUSION FOR FERTILITY REGULATION**

New methods of achieving tubal occlusion for fertility regulation must be viewed against the background of well established surgical techniques, especially in regard to their complications and their effectiveness. Unfortunately documentation in the past has been unsatisfactory.

### 5.1 Abdominal Surgical Approach

The common techniques by the abdominal approach are the Madlener operation (1.4% failure rate), the Pomeroy ligation (0.4% failure rate), and resection of the tubal isthmus (0.2% failures). These and other techniques involve surgical immobilization of the woman for several days, and carry with them morbidity rates varying from 5 to 10%. The mortality rate is extremely low. Attempts to minimize these disadvantages have been made successfully in the following ways :

- (1) by employing the abdominal approach early in the puerperium ;
- (2) by performing "interval" (non-puerperal) sterilization through a small suprapubic incision and elevating the uterus and tubal isthmii by means of a cannula fixed into the uterus via the vagina ; hospital stay is reduced to a minimum of 2-3 days ; the effectiveness of the technique is improved by adopting diathermic division of the tubes under direct visual control ;
- (3) by taking steps to avoid sterilization in the presence of infection or suspected infection ; in doubtful cases, prophylactic chemotherapy should be considered.

### 5.2 Endoscopic Methods

These techniques have been introduced to reduce patient disturbance to a minimum. In well trained and skilled hands, they have been successful by both the abdominal (laparoscopic) and vaginal (culdoscopy) routes. The methods may be used either on out-patients or on day patients (i.e., patients admitted to hospital for a period of less than 24 hours), but full surgical facilities must always be available. Culdoscopy does not usually require general anaesthesia, but laparoscopy does, since attempts to perform the procedure with local anaesthesia alone increase the risks of serious complications. Sterilization by laparoscopy and tubal diathermy has produced excellent results and can be performed both in association with therapeutic abortion and in the puerperium as early as the third day. Tubal diathermy alone is not sufficiently effective. Culdoscopy is generally restricted to "interval" cases and is best accompanied by culdotomy. The visual accuracy afforded by the culdoscope allows effective occlusion to be achieved either by ligation, cauterization, or the application of tantalum clips. The long-term effectiveness of the latter is not yet established. It is mandatory in endoscopic techniques that the pelvis should be free from active inflammation and that in the case of culdoscopy the rectovaginal pouch should not exhibit any pathological signs. Both laparoscopy and culdoscopy require little preoperative preparation of the patient. However,

the surgeon must be well trained in these techniques and the instruments need good care and maintenance. The establishment of well equipped day surgical centres staffed by personnel trained in endoscopic techniques would be an important addition to established methods of fertility control.

### **5.3 Vaginal Surgical Approach**

Surgical methods of opening the vagina anteriorly or posteriorly in order to approach the pelvic cavity have been employed extensively in some centres. Variations in techniques and methods of reporting make it difficult to evaluate the morbidity, mortality, and failure rates given. However, a review of the available data suggests that the methods are associated with a morbidity rate varying from 0.5% to 10% and with a failure rate of up to 1%.

In view of these results, the adoption of this route must be carefully weighed, taking into account local conditions and the availability of personnel who are well trained in vaginal surgery.

### **5.4 Selection of Patients**

These techniques should be applied only to those patients who desire permanent sterilization and who do not have any gynaecological disease that might necessitate hysterectomy. Exclusion of the latter patients will reduce the incidence of postoperative morbidity requiring subsequent hysterectomy.

### **5.5 Long-Term Effects**

Effective tubal occlusion by the above techniques probably permits only limited possibilities of reversal. True reversal implies the re-establishment of fertility. So far, the selection of patients for tubal occlusion has precluded any single investigator from having more than very small numbers requesting tubal reconstruction. The comparative success of such reconstruction is not yet known, and there is a need for international collaborative studies to provide sufficient cases for conclusions to be drawn. It is possible that occlusion of the oviducts by the application of tantalum clips may offer an important advance towards true reversibility.

Limited retrospective reports covering small numbers of cases and variable techniques are available regarding the incidence of poststerilization menorrhagia. These reports suggest that there is an incidence of up to approximately 30% following tubal occlusion. Further prospective studies would be valuable.

## 5.6 Recent Alternative Surgical Methods

Tubal occlusion by approaching the interstitial part of the tubes by means of a hysteroscope is being conducted in a few centres. The hysteroscope can be passed through the cervix under local anaesthesia and the oviducts can be cauterized under direct visual control. Insufficient information is available regarding the difficulties, dangers, degree of electrocoagulation needed, and the long-term success rate. However, this approach may prove to be a very attractive method of achieving sterilization since it can be performed under local anaesthesia in a short period of time as an out-patient procedure. The method does require special instrumentation and training. Since hysteroscopic methods may offer other advantages over the blind intrauterine coagulation techniques, it is suggested that both techniques should be evaluated in multicentred trials.

## 5.7 Conclusion

The need for surgeons to be properly trained in both diagnostic and operative endoscopic procedures cannot be too strongly emphasized. It is desirable to establish training centres and mobile training teams so as to introduce the techniques safely into communities where they are needed.

The ideal technique for tubal occlusion should be an easy out-patient procedure that is readily and successfully reversible. Such a technique has not yet been achieved although considerable advances have been made by the introduction of endoscopic methods.

## 6. NEW APPROACHES

### 6.1 Transvaginal Chemical Sterilization

The use of various chemical agents to produce tubal occlusion has been reported. An aqueous suspension containing 1.5 g of mepacrine hydrochloride in 5 ml of water has been instilled transvaginally once in the immediate postmenstrual period in each of 2 consecutive cycles. The instillation of 2-4 ml of this suspension is performed with a syringe and biopsy cannula with minimal pressure. Tubal occlusion, determined by tubal insufflation, was induced in 93% of the 134 women studied. So far, the incidence of pregnancy in this group of women has been low and no ectopic pregnancies have occurred. In view of its simplicity, this approach merits further investigation with regard to frequency of administration, delivery systems, and new compounds.

Gelatin-resorcinol-formaldehyde, a surgical adhesive, has been used experimentally in animals for permanent tubal occlusion, however, no data are available on its use in women.

A liquid silastic preparation has been introduced transcervically for mechanical blockage of the fallopian tube in women. Experience with this method is very limited.

## 6.2 Silastic Vaginal Ring

Since the 1971 report<sup>1</sup> only limited clinical studies have been performed using a progestogen-containing silastic ring that is placed in the vagina. Two of these studies used the principle of inserting the devices for intervals of 3 weeks per month with the object of inhibiting ovulation. The devices used contained 100 mg of medroxyprogesterone acetate. Sufficient amounts of the drug were absorbed to inhibit ovulation in nearly all cycles studied during a trial period of 6 months. The devices were removed for 1 week to allow withdrawal bleeding, which usually occurred within a few days of the removal and was similar in amount and duration to normal menses. Breakthrough bleeding or spotting occurred with less frequency than has been reported with oral low-dose progestogens and other systemic side effects were minimal. Superficial vaginal ulceration occurred in a few women who were fitted with devices of a uniform size. These healed spontaneously within 1 week. In a subsequent study, using different-sized devices initially fitted by a physician, no vaginal ulceration occurred. In both studies, after initial fitting, the patients were able to insert and remove the devices themselves. No dyspareunia was reported and acceptance by the couple was good.

An alternative approach was also studied in a few women using devices of different design containing chlormadinone acetate. These devices were constructed with the intention that the daily release rate of drug would prevent pregnancy without inhibiting ovulation. Results of this preliminary study were promising and they encourage further trials with vaginal devices releasing a low dose of various progestogens for periods of several months without removal of the device.

## 6.3 Progestogen-Containing Subdermal Devices

Since the 1971 report, only a few more additional studies using this contraceptive approach have been published. In these studies either 4 or 5 dimethylpolysiloxane capsules, each containing about 25 mg of megestrol acetate, were inserted in one subcutaneous location. With 4 implants the pregnancy rate varied between 6 and 12 per 100 woman-years and the duration of effect lasted for 9-12 months. With 5 implants the

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1971, No. 473.

pregnancy rate varied between 1 and 3 per 100 woman-years and the contraceptive effect was extended to 15 months. The main side effect was intermenstrual bleeding that, although frequent initially, decreased after a few cycles and was rarely of sufficient concern for the subjects to request removal of the capsule. Restoration of fertility appeared to be prompt following removal. An increased incidence of ectopic gestations was noted in one clinic, but no ectopic pregnancies were reported in the other studies. Because the initial trials were promising, further trials with the subdermal administration of this and other progestogens are now being undertaken.

#### **6.4 Progesterone-Releasing Intrauterine Devices**

Since the 1971 report, only a few clinical studies have been published on progesterone-releasing devices. These small studies have encouraged the development of a "T"-shaped device that releases progesterone into the uterine cavity at the rate of 50 µg per day. This device is currently undergoing clinical trials.

### **7. RECOMMENDATIONS**

The Group made the following recommendations :

#### **1. Data analysis**

(a) The life-table method of analysis should be applied whenever possible ; its use is *not* limited to studies of intrauterine devices.

(b) Studies are needed on the reasons for the marked variations in the findings reported from various centres particularly in multicentred investigations of oral contraceptives and intrauterine devices.

#### **2. Metabolism and mode of action**

(a) All of the studies reviewed in this report should be repeated and extended to populations living in many areas of the world under different nutritional and socioeconomic conditions.

(b) In particular, further studies should be carried out on :

(i) various C<sub>18</sub> and C<sub>21</sub> progestogens, estrogens (mestranol and ethinylestradiol), and their various combinations, at different dosages and for different lengths of administration, to determine their effects on the metabolism of proteins, carbohydrates, lipids, vitamins, trace elements, and on certain hormones especially prolactin. The reversibility of these effects should be assessed further ;

- (ii) clinical implications of any metabolic changes that are found ;
- (iii) the effects of oral contraceptives on hypertension and alterations in the renin-angiotensin system ;
- (iv) the effects of various types and doses of estrogen on blood coagulation factors and the incidence of thromboembolic disease.

### **3. Long-acting injectable steroidal contraceptives**

(a) Further studies should be undertaken on the effects of DMPA and of other injectable formulations on the volume of breast milk and on the growth curve of breast fed neonates. Investigations are also needed on the excretion in breast milk of the steroids injected and of their metabolites.

(b) Studies should be undertaken on the metabolism of DMPA, especially during the 8 weeks following injection, and on the effects of this steroid on lipid metabolism and glucocorticoid activity.

(c) Further epidemiological studies are needed on the occurrence of neoplasms in women receiving DMPA and on the potential teratogenic effects of this steroid.

(d) Further studies should be made of the acceptability of amenorrhoea, breakthrough bleeding, and uterine blood loss, especially in populations prone to iron deficiency anaemia.

(e) Return of fertility following cessation of administration should be investigated.

(f) Other drugs and formulations should be developed and evaluated as long-acting injectable steroidal contraceptives.

### **4. Long-acting oral contraceptives**

(a) Further clinical trials are necessary to determine the efficacy and acceptability of long-acting oral contraceptives.

(b) More studies are needed on the short-term and long-term metabolic effects of long-acting estrogens.

### **5. Postcoital contraceptives**

(a) Well controlled studies are needed to assess the efficacy and acceptability of the emergency use of estrogens as postcoital agents.

(b) Studies are also needed on the effectiveness of progestogens as postcoital agents with special emphasis on dose, timing, and frequency of administration.

(c) Further investigations are required on the mechanism of action of both estrogens and progestogens when used as postcoital agents.

## 6. Intrauterine devices

Studies are required on :

(a) Contraceptive efficacy and mechanism of action of various types of IUDs. Studies are needed especially on the influence of various co-polymers used in IUDs and the effect of IUDs on spermatozoa.

(b) Genital tract secretions, including prostaglandins, in IUD users.

(c) Cytology, including karyotype estimations of the endometrium and cervix, following the long-term use of IUDs.

(d) Incidence of pelvic inflammation and venereal disease in IUD users and in users of other contraceptives.

(e) Duration of action of existing and new copper-bearing devices.

(f) The absorption and distribution of copper released from intra-uterine devices as compared to those of ingested copper.

(g) The significance of altered concentrations of trace elements in the endometrium and plasma of women using copper-bearing IUDs.

(h) Trace elements in the endometrium and myometrium with the stainless steel device *in situ*.

## 7. Prostaglandins

Controlled studies are required on :

(a) Levels of prostaglandins and their metabolites in plasma and uterine tissue during pregnancy, the normal menstrual cycle, and in subjects taking prostaglandin inhibitors.

(b) The influence of endogenous prostaglandins and their metabolites on ovarian function.

(c) Evaluation and study of synthetic and naturally occurring prostaglandin antagonists and their role in fertility control.

(d) Use of prostaglandins and their analogues as fertility regulating agents in the pre-implantation period.

(e) Use of intra-amniotically administered prostaglandins and their analogues in the induction of abortion as compared with the use of saline and other abortifacients, e.g., urea, formaldehyde, etc.

(f) Blood coagulation factors in saline-induced and prostaglandin-induced abortions, as well as in spontaneous abortions.

## 8. Tubal occlusion

(a) Studies should be undertaken on the mechanism of action of mepacrine and allied compounds in producing tubal occlusion.

(b) The potential of intratubal devices in fertility regulation should be explored.

(c) The use of tantalum clips applied by laparoscopy or other techniques should be investigated.

(d) The hysteroscopic technique of tubal instillation of occlusive chemicals should be compared with that of electrocoagulation and with the so-called "blind" technique.

(e) Studies are required on ovarian function following tubal occlusion by surgical methods.

(f) Prospective studies are needed on the morbidity, mortality, and side effects of surgical methods of sterilization.

**Annex 1**

**REPORTS OF MEETINGS ON VARIOUS ASPECTS  
OF FERTILITY REGULATION PUBLISHED IN THE WHO  
TECHNICAL REPORT SERIES**

*WHO Scientific Group Reports*

- No. 334 (1966) Immunological aspects of human reproduction
- 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. 435 (1969) Biological components of human reproduction
- No. 442 (1970) Health aspects of family planning
- No. 461 (1970) Spontaneous and induced abortion
- No. 473 (1971) Methods of fertility regulation : advances in research and clinical experience

*WHO Expert Committee Report*

- No. 476 (1971) Family planning in health services

## Annex 2

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