

INJECTABLE HORMONAL
CONTRACEPTIVES:
Technical and Safety
Aspects



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PREFACE

This publication has been compiled for those who are involved in the development and management of family planning services as part of health care programmes. It deals with certain injectable hormones which are highly effective contraceptives and have an important place in many national family planning or family health programmes. The aim of this booklet is to present the problems, advantages and disadvantages associated with the use by women of injectable hormonal contraceptives and to provide information to health care administrators and planners who are interested in introducing this method of contraception into a health care programme.

The views summarized here are based on a critical review of many clinical and basic science studies and field trials. A most important source of this information has been the WHO Special Programme of Research, Development, and Research Training in Human Reproduction (in particular, its Task Force on Long-Acting Agents for Fertility Regulation), which has coordinated a large number of studies from developing countries. In fact much of the information contained in Sections 2 to 5 of this booklet has been taken from a report prepared under the Special Programme (1). This report is the result of a meeting held by WHO in October 1981, in which both animal and human data were extensively reviewed by members of the Special Programme's Toxicology Review Panel, representatives of the drug regulatory agencies of India, Mexico, Sweden, Thailand, United Kingdom and the USA, representatives from the pharmaceutical industry manufacturing these products, and expert scientists working in this field.

The present booklet does not lay down firm guidelines, but discusses various important points connected with the use of injectable hormonal contraceptives and their introduction into family planning services. It restricts itself to consideration of only the two currently available long-acting

contraceptive steroids, depot-medroxyprogesterone acetate and norethisterone enantate, i.e., to hormonal steroids with a duration of use of 2 months or longer. It should be pointed out that first-hand information is not yet available on certain aspects, such as the long-term sequelae from the use of these injectable contraceptives. Whilst various preparations have been used in monthly injections, many of these have been withdrawn in recent years and there are few countries in the world where they are readily available. Thus, they are not considered here but they remain a high priority for research and development by the Special Programme of Research, Development, and Research Training in Human Reproduction.

This publication is one in a series of technical guidelines on family planning technology, concerned with female sterilization, induced abortion, oral contraceptives, intrauterine devices, injectable contraceptives and the planning and management of family planning care.^a

^a Already published:

Female sterilization: guidelines for the development of services, Geneva, World Health Organization, 1980 (WHO Offset Publication No. 26)

Induced abortion: guidelines for the provision of care and services, Geneva, World Health Organization, 1979 (WHO Offset Publication No. 49)

Oral contraceptives: technical and safety aspects. Geneva, World Health Organization, 1982 (WHO Offset Publication No. 64)

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1. INTRODUCTION

Injectable hormonal contraceptives, when properly used, are among the most effective methods of contraception available today. It is estimated that over 10 million women have used this method and approximately 1.5 million are using it currently.

Several characteristics of injectable contraceptives have led to their widespread use: (1) they provide a highly effective contraceptive effect which lasts for 2 or more months after a single injection; (2) their use ensures periodic contact with medical and paramedical personnel; (3) their administration is simple and independent of coitus; (4) unlike most preparations of oral contraceptives, they do not contain estrogens and thus are free from adverse estrogenic effects; (5) at least one of the two available injectable hormones does not suppress lactation, an important consideration where there is a need for postpartum contraception and where infant health is dependent upon adequate breast-feeding.

However, this method of contraception is not entirely free of risks and should be used only by women who have been informed of the risks and who do not have any contraindications to its use.

2. BACKGROUND AND DESCRIPTION OF INJECTABLE HORMONES AVAILABLE AS CONTRACEPTIVES

Thus far, only two injectable hormonal contraceptives, depot-medroxyprogesterone acetate (DMPA) and norethisterone enantate (NET-EN), have been widely used. They are both progestogens but belong to different groups of steroids. Medroxyprogesterone acetate is a C₂₁ steroid while norethisterone enantate is a C₁₈ steroid.

Medroxyprogesterone acetate has been used since before 1960 for a variety of conditions including

endometriosis, threatened abortion, precocious puberty, acromegaly, endometrial carcinoma, and premature labour; doses of up to several grams have been administered without apparent adverse effects. In the mid 1960s, it was noted that women receiving DMPA for premature labour had a markedly delayed return of fertility following delivery, and clinical trials were begun in 1966 with DMPA as a contraceptive agent. Administered in a microcrystalline suspension by intramuscular injection, DMPA exerts its contraceptive effect primarily by suppression of ovulation. However, it also has an indirect effect on the endometrium and direct action on the fallopian tubes and on the production of cervical mucus, all of which may play a role in reducing fertility. DMPA as a contraceptive agent is generally given in a dosage of 150 mg every 90 days (3 months).

Norethisterone enantate (NET-EN) has been in use as a contraceptive since 1966, although it has been used less extensively than DMPA. Administered as an oily preparation (of 200 mg of the long chain ester of norethisterone) by intramuscular injection, NET-EN has a mechanism of contraceptive action that appears to include inhibition of ovulation, premature luteolysis when ovulation occurs, and progestogenic effects on the cervical mucus. Effects on tubal function and the endometrium may also be involved in reducing fertility. Clinical trials have demonstrated that it is most effective in preventing pregnancy when administered every 60 days for the first four injections over a period of 6 months, after which it may be given either every 60 days or every 84 days (in these two schedules the pregnancy rates are similar but the side-effects observed are slightly different).

DMPA has been approved for contraceptive use in 80 countries while NET-EN is registered in 25 countries and is currently being introduced into several national family planning programmes. Doubts that have been expressed regarding the safety and appropriateness of an injectable hormonal contraceptive for widespread use are

related to their possible carcinogenicity, impairment of future reproductive function, adverse metabolic effects, potential teratogenicity and other possible adverse effects on the progeny (as a result of exposure to the steroid hormone either in utero or via breast milk).

At a special meeting convened in 1978, the Toxicology Review Panel of the WHO Special Programme, together with other expert scientists and representatives of six national drug regulatory agencies, reviewed all the available animal and human data on DMPA and NET-EN. It was concluded that for DMPA:

"The available evidence does not indicate a risk of adverse effects associated with Depo-Provera (DMPA) which would preclude the use of this drug as a contraceptive. However, as shown by the experience with combined oral contraceptives, relatively uncommon complications may not be detected until a drug has been used on a large scale for prolonged periods of time. There is, therefore, a need to monitor the safety of Depo-Provera on an ongoing basis, and the Special Programme will continue to place high priority on such research." (unpublished report)

And subsequently for NET-EN:

"In the light of the findings in the monkey, beagle and rat, the Panel recommended that the current and planned clinical trials of norethisterone enantate should continue." (unpublished report)

In October 1980, the International Medical Advisory Panel of the International Planned Parenthood Federation (IPPF) reviewed the clinical data on DMPA Depo-Provera and endorsed "the recommendations of the WHO, the AID's Ad Hoc Consultation Panel on DMPA, and the Scientific Advisory Committees of USFDA that it continues to be a responsible act to make DMPA available as a contraceptive" (2).

Nevertheless, during the three years since 1978, considerable pressures have been put on governmental health officials throughout the world to ban the use of injectable contraceptives, particularly DMPA. This is in part due to the fact that neither DMPA nor NET-EN has been approved for use as a contraceptive in the USA. DMPA was reviewed by the US Food and Drug Administration (FDA) in 1978, and although approval was recommended by the FDA's Obstetrics and Gynecology Advisory Committee (a group of specialists who advise the FDA on technical matters), the FDA did not grant approval for its use as a contraceptive agent (3). Rather, the FDA announced that a Public Board of Inquiry would be convened. The members of this Board have recently been appointed to review the following issues:

- Whether, in comparison with other drugs approved for contraception, the benefits of DMPA in the USA outweigh its risks under conditions of general marketing.
- Whether data from beagle dog and monkey studies submitted by the Upjohn Company indicate a potential risk of breast or endometrial cancer in humans from Depo-Provera.
- Whether the human data submitted by Upjohn can, as Upjohn claims, successfully refute the risk of human cancer suggested by the animal data.
- Whether approved use of DMPA for contraception under general marketing conditions is likely to increase use of the drug as a contraceptive under conditions not stipulated in approved labelling or is likely to increase its use for unrelated indications for which safety and effectiveness have not been established (for example, for hygienic purposes in mentally retarded persons).
- Whether in the event of contraceptive failure, the use of DMPA may increase the risk of teratogenic effects to a greater extent than would other systemic contraceptives.

- Whether in view of DMPA's adverse side-effects or pharmacological effect, estrogen therapy is likely to be prescribed in addition to DMPA in a significant number of patients.
- Whether there are conditions of labelling and distribution controls which would permit marketing of DMPA as a safe and effective drug on a limited basis. (There may be certain patients in the USA for whom benefits of Depo-Provera for contraception outweigh potential risks. This population, if it exists, may be very small and may not warrant general marketing of Depo-Provera for contraception.)

Pressures have also been generated by certain consumer and women's groups in the Western world and much confusion has resulted regarding the safety of DMPA, and WHO has had numerous requests to provide a statement on the current state of knowledge of injectable hormonal contraception. Thus, in October 1981, another meeting of experts was called to re-evaluate the scientific evidence concerning the use of DMPA and NET-EN. The meeting reviewed the most recent data available and a report was prepared which is being widely disseminated by the Special Programme. The report concluded that:

"Injectable contraceptives - both DMPA and NET-EN - offer several advantages as a method of contraception, and have been shown in a number of clinical trials to be effective in preventing pregnancy and acceptable to many women. Although animal data have raised concern about the safety and long-term side-effects of DMPA and NET-EN, certain animal models and the doses used appear not to be appropriate for studying human effects of these steroids. Extensive clinical and epidemiological studies among women using these drugs have thus far demonstrated no life-threatening side-effects, including any increase in the risk of neoplasia.

"The most common side-effect is the disturbance of normal menstrual cycles, which occurs in the majority of women using injectable contraception and is the primary reason for its discontinuation. Women frequently report irregular bleeding, spotting, and amenorrhoea, but heavy or prolonged bleeding is uncommon. Studies thus far have not shown any serious short- or long-term effects of DMPA or NET-EN. However, both DMPA and NET-EN have been used for a relatively short period of time, and the potential long-term effects (more than 15 years) are not yet known.

"With regard to metabolic effects, the areas in which research should continue are on the effects and physiological consequences of long-term use of DMPA and NET-EN on carbohydrate and lipid metabolism and on blood clotting mechanisms. In addition, further research is needed regarding the risk of neoplasia among women using DMPA or NET-EN. Finally, the effects on the later development of infants who are exposed to DMPA or NET-EN in utero or through breast milk are not known; research should continue in these areas.

"In summary, DMPA and NET-EN appear to be acceptable methods of fertility regulation. Clinical evidence from more than 15 years of use as contraceptive agents shows no additional and possibly fewer adverse effects than those found with other hormonal methods of contraception. The particular advantages of DMPA and NET-EN as highly effective, long-lasting and reversible contraceptives make them important as options that should be available for women desiring a method of fertility regulation."(1)

3. PHARMACOLOGY

Although the two steroid preparations have a similar mechanism of action in inhibiting gonadotropin production by the pituitary gland and thus cause inhibition of ovulation (4), they do show certain pharmacological differences. NET-EN is prepared in an oily solution and, after injection a number of different factors affect its uptake and bioavailability (5), including the necessity for it to be hydrolysed to the biologically active steroid norethisterone (NET). In contrast, DMPA is formulated as a microcrystalline suspension of known particle size and the medroxyprogesterone acetate released into the circulation is itself biologically active.

The differences in formulation are reflected in the levels of steroid measurable in the blood. After injection of NET-EN, the blood levels of norethisterone increase rapidly and reach a peak within 5 days. With DMPA, the peak is usually reached more slowly, up to 10 days, and the peak level is lower than that observed with norethisterone enantate. After reaching the peak level the concentration of norethisterone in the blood declines rapidly and usually reaches undetectable amounts by about 70 days after injection although in some women this may be as soon as 50 days or as long as 120 days (6). Levels of medroxyprogesterone acetate decline more slowly, so that it can be measured throughout the 3-month injection interval and is sometimes detectable 200 days or more after a single injection (7-9). There is a wide variation among women in the rate of metabolism of the two steroids.

The marked difference in the pattern of blood levels of norethisterone and medroxyprogesterone acetate has one important effect - namely, upon the inhibition of ovulation. The persistence of medroxyprogesterone acetate in blood beyond the 90-day injection interval ensures inhibition of ovulation and accounts for the high efficacy of the compound. It would appear, however, that inhibition of ovulation can be achieved with doses of

DMPA of less than 150 mg (9)^a and WHO is embarking on a use-effectiveness study of a 100-mg dose. The more rapid disappearance of norethisterone from the circulation leads to a shorter period of ovulation inhibition. About 25% of women injected with norethisterone enantate will ovulate within the first 60 days after injection, and by 90 days about 60% will have ovulated (10,11).

Both steroids have a progestogenic effect on cervical mucus although the high efficacy of DMPA, given at 150 mg every 3 months, is almost certainly due entirely to suppression of ovulation for the treatment period.

4. USE-EFFECTIVENESS

Both DMPA and NET-EN are highly effective contraceptive agents. Pregnancy rates (method failures) have been consistently low with the use of DMPA - less than 1 pregnancy per 100 woman-years of use. The pregnancy rate reported with NET-EN use has varied according to the interval between injections. A dose of 200 mg every 12 weeks resulted in a pregnancy rate that was considered to be unacceptably high (3.6 per 100 woman-years) in one clinical trial undertaken by WHO, and the trial was discontinued (12). A more recent multicentre clinical trial, conducted by WHO, included a schedule of 200 mg every 8 weeks for the initial 3 injections, and every 12 weeks thereafter. The reported cumulative pregnancy rate was less than 1 per 100 woman-years at 12 months and 1.6 at 18 months. A more frequent administration of NET-EN in the same trial, every 8 weeks throughout its use, had a lower pregnancy rate - less than 1 per 100 woman-years at 18 months(13). WHO is currently supporting field trials in the national family planning networks of six countries (Bangladesh, India, Mexico, Pakistan, Philippines, Tunisia) for further evaluation under the usual family planning clinic conditions.

^a G. Perez-Palacios - personal communication, 1981

Multicentre comparative trials have shown that for both DMPA and NET-EN the continuation rates vary markedly among different populations, ranging from 15% to nearly 90% at 1 year (12), although DMPA and NET-EN have had similar continuation rates in a given population. The most frequent reason for discontinuation, as well as the most frequently reported side-effect, of both DMPA and NET-EN is the disruption of the normal menstrual cycle that occurs in the majority of women using either of these drugs. Multicentre comparative trials of the two steroids indicate that 10-15% of women discontinue the drugs within the first year because of bleeding irregularities, and an additional 11-12% of women using DMPA discontinue because of amenorrhoea. Discontinuations because of amenorrhoea are less frequent (2-8%) among women using NET-EN.

5. SIDE-EFFECTS AND POSSIBLE LONG-TERM SEQUELAE

5.1 Bleeding problems

The majority of women using either DMPA or NET-EN experience a disruption of their normal menstrual cycle. Fewer than one-third of women receiving DMPA report having a normal menstrual cycle during the first year of use, a normal menstrual cycle being defined as a cycle of 26-35 days in which bleeding/spotting lasted from 2 to 8 days. Normal menses are slightly more common among women using NET-EN; approximately one-half of the users report at least one normal cycle during the first year (13,14). In addition to irregular episodes of bleeding and/or spotting, many women using DMPA or NET-EN experience amenorrhea. The likelihood of amenorrhoea increases with increasing duration of use of both DMPA and NET-EN. However, women using NET-EN are less likely to experience amenorrhoea than women using DMPA. Although there are no known adverse health effects of either irregular bleeding (if not heavy or prolonged) or amenorrhoea, unpredictable bleeding or spotting can be inconvenient, and prolonged amenorrhoea can lead to anxiety over an unintended pregnancy.

Severe bleeding is uncommon among users of both DMPA and NET-EN; fewer than 1 in 1000 users require dilatation and curettage for treatment (15,16). A satisfactory approach to the management of prolonged and/or heavy bleeding, with the use of injectable contraceptives, has not yet been developed. Estrogen therapy has been used to attempt to stop heavy bleeding as well as to normalize the irregular bleeding patterns. However, the extent of its use is not known, and no studies have adequately examined the usefulness of estrogen to treat bleeding problems associated with the use of only progestogens for contraception.

5.2 Metabolic effects

Oral hormonal contraceptives have been associated with effects on a variety of metabolic functions as evidenced by changes in coagulation and fibrinolytic factors, platelet function, carbohydrate and lipid metabolism, and liver, renal and thyroid function. In most instances, these effects have been considered to be a consequence of the estrogen component. This has been borne out by observations with DMPA, which have shown little or no change in the items mentioned above except for carbohydrate and lipid metabolism. Few data have been published on the metabolic effects of norethisterone enantate, but it appears that it has no influence on most metabolic functions.

Concern has recently been expressed regarding the effect of progestogens on lipid metabolism and transport. All currently-used synthetic progestogens decrease the circulating levels of high-density lipoprotein (HDL) cholesterol, which is one of the few metabolic events that can be linked to an increase in the incidence and severity of cardiovascular disease, particularly ischaemic heart disease. Both published and unpublished data (17)^a indicate that both DMPA and NET-EN lead to a decrease in HDL-cholesterol. However,

^a M.H. Briggs; K. Fotherby - personal communications, 1981.

DMPA (at the higher dosages used in postmenopausal replacement therapy) has considerably less of an effect on HDL-cholesterol than the two other synthetic progestogens, levonorgestrel and norethisterone acetate (18,19).

Carbohydrate metabolism is also affected by synthetic progestogens. DMPA has been shown by some workers to raise fasting blood glucose and insulin levels and to cause an increased response of both glucose and insulin to a glucose load as compared to pre-treatment levels (20,21). Several other studies, however, have failed to show these changes (22,23). There is also little evidence of substantive changes in carbohydrate metabolism due to NET-EN (24,25).

Although adrenal suppression has been observed when DMPA has been administered in high doses for the treatment of cancer (26) or precocious puberty (27), no cases of adrenal insufficiency or significant effects on adrenal function during contraceptive usage have been reported (28-30).

No consistent effects have been reported with regard to liver function, but most investigators have found little or no effect of DMPA or NET-EN on liver function (22,31-33). The conflicting evidence from various studies is exemplified by the fact that, in one study, DMPA has not shown any significant changes in aspartate aminotransferase (2.6.1.1), alkaline phosphatase (3.1.3.1), lactic dehydrogenase (1.1.1.27), bilirubin, or bromosulphthalein (BSP) retention (33), while another study showed some increases in the aminotransferases (34) and yet another showed no change in the aminotransferases but increased BSP retention.^a It would appear that hepatic function is not adversely affected by the two injectable contraceptives. In fact, primary biliary cirrhosis and chronic active hepatitis

^a R. Gray - personal communication, 1981

have been shown to respond to therapy with DMPA (35). Moreover, in subjects with an active liver parasitic infestation, with the liver fluke (Opisthorchis viverrini), DMPA does not give rise to any deleterious effects on liver function (36).

5.3 Possible carcinogenicity

Results from animal studies have raised concern regarding the possible carcinogenic effects of DMPA, since mammary tumours have been observed in the beagle, and two monkeys (receiving 50 times the human doses) have been shown to develop endometrial tumours. It has been concluded by the Toxicology Review Panel of the WHO Special Programme that the beagle is not an appropriate model in the study of the possible toxicity of long-acting progestogens in the human. There is evidence that healthy beagle breasts contain a reservoir of microscopic neoplasms which may grow, and occasionally become malignant, in response to overstimulation by progestogens, especially by those compounds that are particularly active in the canine species. Treatment with progesterone alone stimulates mammary gland development in the dog, but not in the rat or the human being.

Although the pattern of occurrence of endometrial carcinoma in monkeys is unknown, it has been reported to the Toxicology Review Panel that similar lesions have been observed to occur spontaneously in animals in other unrelated studies. There is evidence to suggest that the tumours arose from a cell type found in the endometrial plaque. These plaques are known to be progestogen-dependent in the rhesus monkey and such plaque formation is not observed in the human. The same view is held by the United Kingdom Committee on Safety of Drugs. The surrounding endometrium was atrophic and showed no evidence of preneoplastic change. Moreover, it must be noted that progestogens, and particularly DMPA, are used extensively in the treatment of human endometrial cancer.

Epidemiological studies in women receiving DMPA have thus far demonstrated no increase in the incidence in any type of cancer. At least five clinical studies have examined the relationship between DMPA and breast cancer (6). Only two of them had a comparison group of women who did not receive DMPA; however, in all five studies there was no evidence of an increase in breast cancer among women using DMPA. Studies conducted to examine the risk of cervical neoplasia among DMPA users have suffered from a variety of methodological problems; no studies, however, have demonstrated an increased risk of invasive carcinoma of the cervix (37). In many countries, including the USA, endometrial carcinoma is one of the few indications for which DMPA is approved for use. However, because of certain findings in monkeys, a study was conducted in Chiang Mai, Thailand, in which women admitted to the hospital for endometrial carcinoma were questioned regarding previous DMPA use. Although 16 of the 27 women came from areas where DMPA was widely used, none of the women reported previous use of DMPA (38).

In addition to these completed studies, WHO is currently conducting a multinational case-control study to examine the relationship between steroid contraceptives (including DMPA and NET-EN) and the risk of selected neoplasms, including carcinoma of the breast, cervix, endometrium, ovary, and hepatobiliary system. Because of the potentially long latent period of cancer, and because injectable contraceptives have been used for only about 15 years, it is important to continue to monitor the development of neoplasms among women who have used DMPA or NET-EN, especially those who used them many years ago.

5.4 Return of fertility

The presence of MPA in the circulation (following cessation of DMPA) appears to continue to inhibit ovulation for a varying period of time. A large study conducted in Thailand showed that women discontinuing DMPA became pregnant some 5.5 months (average) after the

treatment period. The average delay to conception was somewhat less for both IUD and oral contraceptive users, but at one year after discontinuation the proportion who had not yet conceived was similar for both DMPA and IUD users. At two years, more than 90% of previous DMPA users had become pregnant (39,40). A study is currently being initiated in India by WHO to examine the return of fertility among women who discontinue NET-EN.

5.5 Effects on progeny

5.5.1 In utero exposure to injectable hormones

No studies have systematically followed up the health and development of infants who had been exposed in utero to DMPA. When given after pregnancy has begun, DMPA does not appear to increase the risk of spontaneous abortion or stillbirths. Three cases of clitoral hypertrophy have been reported among infants exposed to DMPA in utero and a number of studies have suggested a teratogenic effect of progesterone received in utero. However, other studies have not confirmed these findings (41). No large increase in congenital malformations has been observed among women who have received DMPA while pregnant, unlike the tragic and dramatic effect seen with thalidomide. If any increase in risk of congenital anomalies exists with DMPA - and there is no clear evidence that it does - it must be quite small. In addition, if proper precautions are observed in administering the drug, that is, if it is given during the first 5 days of the menstrual cycle, the potential problem of infants exposed to DMPA in utero should be minimal.

No studies have examined the outcome of pregnancy after exposure to NET-EN.

5.5.2 Exposure of infants via breast milk

Unlike the oral contraceptives (containing both estrogen and progesterone), DMPA does not appear to have any deleterious effects on the quantity or nutritive

value of breast milk. In fact, some studies have suggested an increase in the quantity of breast milk with the use of DMPA (42). DMPA is present in the breast milk in approximately the same concentration as in the mother's serum (43). It can be estimated that the breast-feeding infant would receive less than 0.5% of the maternal dose and it is likely that only a portion of the steroid is absorbed in the infant's gut. The effects of DMPA on the breast-fed infant have only been studied - and in a very limited number of children - up to 13 years of age, during which period growth and development appear to proceed normally (44,45)^a. Animal data have suggested a possible effect on reproductive development (46), but adequate data are not yet available on children exposed to DMPA via breast milk and followed up through puberty. Studies have not as yet adequately examined the effects of use of NET-EN during lactation.

5.6 Other side-effects

Several other side-effects have been reported infrequently with the use of DMPA or NET-EN. These include headaches, weight gain, abdominal discomfort, and anxiety or nervousness.

The cardiovascular effects associated with the use of estrogen-containing preparations of oral contraceptives have not been found with the use of injectable progestogen-only contraceptives. There appear to be no significant changes in blood coagulation or the incidence of thromboembolic disease. The effects on blood pressure are minimal, with several studies reporting slight decreases.

6. CLINICAL MANAGEMENT

A woman who requests either DMPA or NET-EN should be questioned to determine if there are any contraindications to the use of the drug, or if she has any

^a Upjohn Company - personal communication, 1981

special problems which require the assistance and supervision of trained medical personnel when DMPA or NET-EN is the chosen method of contraception.

6.1 Contraindications to the use of DMPA

These include cancer of the breast; all genital cancers (except as treatment for endometrial cancer); undiagnosed abnormal uterine bleeding; and a suspected pregnancy.

6.2 Contraindications to the use of NET-EN

Contraindications to the use of NET-EN include all those (given above) for DMPA. In addition, since insufficient data are available on the use of NET-EN during lactation, other methods of contraception should be considered for use during lactation.

6.3 Special problems that require medical assistance

These include an undiagnosed breast lump; abnormal liver function or recent history of liver disease; history or evidence of cardiovascular disease; congenital hyperlipidaemia; history of infrequent bleeding, amenorrhoea or late menarche in nulliparous women; diabetes mellitus or history of gestational diabetes; and age over 40 years.

An undiagnosed breast lump may be malignant, and should be evaluated prior to beginning any hormonal contraceptive.

It is not known whether the increased risk of benign liver tumours found with the use of combined oral contraceptives is due to the progestogen or estrogen component or both. Thus women with liver disease should preferably have their liver function monitored, if they choose to use injectable progesterone contraceptives.

Similarly, the increased risk of cardiovascular disease associated with the use of combined oral contraceptives is thought to be due primarily to the estrogen component. However, until it has been demonstrated that progestogens do not play a role in the development of cardiovascular disease, women who have either current evidence or a history of cardiovascular disease should preferably be monitored for any change in their cardiovascular condition, if they receive either DMPA or NET-EN.

Since the return of fertility following the use of either DMPA or NET-EN has not been thoroughly studied among nulliparous women, any indication of potential subfertility or anovulation, such as irregular menses or late menarche, should ideally be evaluated before commencing either DMPA or NET-EN. Both of these preparations inhibit ovulation and frequently disrupt menstrual patterns.

Although neither DMPA nor NET-EN has been shown to cause overt clinical diabetes mellitus, changes in carbohydrate metabolism have been shown to occur, including increased insulin requirements and a slight deterioration in glucose tolerance. Thus, women known to have diabetes or a history of gestational diabetes may experience noticeable changes in glucose tolerance and insulin needs. They should therefore have their glucose tolerance and/or glucose levels monitored if they receive DMPA or NET-EN.

The use of DMPA or NET-EN by women over the age of 40 is discussed in section 8.5.

6.4 History and physical examination

The history and physical examination necessary for women either to start or to continue DMPA or NET-EN should include at least the minimum information required to identify those who have contraindications for its use or who present special problems that require medical intervention or supervision.

Information should be obtained on age, recent menstrual history, and whether there is a history of jaundice, other liver disease, cardiovascular disease or diabetes.

The information on menstruation should preferably contain data on age at menarche, regularity and length of cycle, duration and amount of menstrual flow, occurrence of abnormal bleeding, and date of last menstrual period.

The obstetrical history should contain information regarding parity, abortions, date of last delivery, present lactational status, and gestational diabetes.

The physical examination should include inspection for the presence of jaundice. When the local circumstances permit, examination of the urine for the presence of sugar, auscultation of the heart, blood pressure measurements, and breast and pelvic examination should also be included. The Papanicolaou smear is an optional examination to be performed when indicated and when resources permit.

6.5 Selection of the type of injectable progestogen

Both DMPA and NET-EN are highly effective methods of contraception, with similar side-effects and contraindications. However, since a few differences have been observed between the two steroids, there are situations in which one of the two may be more appropriate as a contraceptive method.

As mentioned above, the lack of data on the use of NET-EN during lactation would suggest that DMPA should be the injectable steroid of choice for use when the woman is breast-feeding her infant.

A slightly lower pregnancy rate (failure rate) has been reported with DMPA, as compared to NET-EN, so that when avoiding pregnancy is of particular importance, DMPA may be preferred over NET-EN. However, amenorrhoea is

more frequent with the use of DMPA so that women who want to avoid this fairly common side-effect may wish to use NET-EN rather than DMPA.

NET-EN is given at more frequent intervals than DMPA. The preference of an 8-weekly or 12-weekly injection interval may also affect which contraceptive is chosen.

6.6 Duration of use

If a periodic clinical evaluation does not reveal any adverse effects, the medication may be continued for several years. In healthy young women the associated risks are minimal. DMPA or NET-EN should be used primarily for spacing pregnancies in younger women, and sterilization or other forms of contraception should be considered for women not desiring any more pregnancies. Beyond 40 years of age, other forms of contraception should be considered (see section 8.5).

6.7 Indications for discontinuation

If any of the contraindications to use appear, further injections of the drug should not be given. Similarly, if any of the special problems requiring medical supervision should develop, the advice of trained medical personnel should be sought prior to giving additional injections.

In countries where a screening programme for cervical cytology exists, DMPA and NET-EN users should be encouraged to take the opportunity to have such a screening every 2 years. Discovery of cervical dysplasia should be handled according to standard gynaecological practice.

An annual examination of the pelvis and of the breasts is recommended.

6.8 Administration of DMPA and NET-EN and follow-up

The initial injection of both DMPA and NET-EN should be given during the first 5 days of the menstrual period. This timing of the initial injection is very important, to avoid administering the contraceptive hormone during an early, still undiagnosed pregnancy. Failure to observe this rule may result in the exposure of the unborn fetus to the progestogen.

The woman should be re-examined for the development of any problems, and to receive the next injection, every 3 months if using DMPA, and every 8-12 weeks if using NET-EN (depending on the dosage schedule being followed).

The technique of injection is important. For the microcrystalline formulation (DMPA), it is essential (in order to ensure that the correct dose is administered) that the vial should be well shaken before aspirating the suspension into the syringe. NET-EN is formulated in a viscous oily solution which needs special care when aspirating it into the syringe, and during injection in order to ensure that all the material is ejected from the syringe and that no leakage occurs around the needle. If the vial should have been stored in low temperature, it is advisable to warm it before giving the injection. The preparation should be given by deep intramuscular injection, preferably into the gluteal muscles, although in many cases the upper arm may be more convenient. The injection site should not be massaged.

6.9 Treatment of bleeding problems

A majority of women who receive either DMPA or NET-EN will experience a change in the pattern of their usual menstrual cycle. Adequate counselling on the anticipated side-effects (including bleeding problems), when the contraceptive is begun is essential for minimizing unnecessary concern on the part of the woman receiving the contraceptive. A woman who has been informed of the

possible side-effects and their probable health importance will be less alarmed, and will be better able to judge when she should consult her physician or health worker. The importance of side-effects should not be minimized, however, and she should be instructed to consult her physician or health worker if she experiences prolonged or heavy bleeding.

Each woman who does return with prolonged or heavy bleeding should be evaluated for anaemia. If she is found to have iron-deficiency anaemia, she should receive appropriate iron therapy, such as ferrous sulfate.

Many clinicians administer estrogen preparations as treatment for bleeding disorders associated with injectable progestogen contraceptives. However, no comparative study has demonstrated the effectiveness of this approach to treatment, nor has any other approach been studied and shown to be effective either. The World Health Organization currently takes the following approach to the treatment of bleeding disorders in its clinical trials of both DMPA and NET-EN, recognizing, however, that its effectiveness has not been adequately demonstrated.

If the bleeding is heavy or prolonged, the following regimen is recommended:

(a) The woman should first be evaluated for possible causes of the bleeding (other than the steroid) and also tested for anaemia. Ferrous sulfate should be given, if indicated.

(b) A woman experiencing moderate and prolonged - or heavy - bleeding due to the steroid should be given 25 µg of estradiol, one tablet 3 times daily for 3 days.

(c) If this therapy is ineffective, or if the woman initially presents with very heavy bleeding, she should be given 5 mg of estradiol cypionate in an oily suspension intramuscularly; and this dose should be

repeated once if the bleeding does not stop within 24 hours. Additional medical advice may be indicated at this stage.

(d) If, after having received 10 mg of estradiol cypionate intramuscularly, the bleeding continues, the woman should be referred for possible dilatation and curettage.

7. COUNSELLING

Each woman, preferably with her partner, should be informed of the various contraceptive methods available, and the risks and benefits of each method should be clearly explained. The final choice of method should be hers, unless absolute contraindications exist. If her choice is an injectable hormone - either DMPA or NET-EN - then the nature and type of the common side-effects should be explained, with an emphasis on their transient nature. She should be assured that she is welcome to return to the clinic at any time to discuss problems and any doubts that may arise. It is a recommended practice to make the woman aware of the possible side-effects of DMPA or NET-EN, rather than to let her believe it to be free of any problems. Discontinuation because of side-effects is less common among well-informed women.

In normal practice, the woman should receive her first injection during the first 5 days of menstruation, as described above. This rule helps to ensure that she is not pregnant when receiving the injection and maximizes the contraceptive efficacy during the first month. Subsequent injections should be administered every 12 weeks (+ 5 days) for DMPA. In the case of NET-EN, the injections should be given every 8 weeks (+ 5 days) for the initial 3 injection intervals, and then every 8-12 weeks.

Irregular bleeding (including prolonged bleeding, spotting and amenorrhoea) is the common cause for

discontinuation of injections by patients. If the woman is duly forewarned and reassured, she is less likely to stop the method because of the side-effects. However, she should be advised to return to the clinic if the bleeding is heavy or prolonged.

One of the main problems associated with the use of DMPA or NET-EN, particularly in countries where health care is not readily accessible, is to ensure that the woman returns to receive her injection at the appropriate time intervals. Health workers should thus particularly emphasize the need to return at the designated time, for the next injection.

Counselling should be given by informed personnel, including trained auxiliaries, social workers, nurses, midwives and physicians. It can be given in private or in group meetings, at outpatient clinics, in lying-in wards, consulting rooms or conference rooms, or in the home.

7.1 Package insert for women on injectable contraceptives: an example

The package insert should be worded as simply as possible to make it easy to understand. The essential information should be presented objectively and should not arouse apprehension or anxiety on the part of the consumer.

The use and design of a package insert should comply with local programme policies and conform to the legal requirements of the country.

The package insert should never be considered as a substitute for the education and counselling that must be given by the family planning personnel.

The following is an example of the "instructions for use" which should be given in such a package insert. Obviously, the example will have to be modified and adapted to suit the sociocultural setting:

"Product X is an injectable contraceptive preparation that contains a hormone similar to one which occurs naturally in women. It has been shown to be highly effective in preventing pregnancy when taken as prescribed.

"In a very small number of women, potentially serious side-effects may occur. Your doctor or attending health worker is in the best position to decide whether or not any conditions are present that pose a risk to you.

"If you have elected to use "product X", periodic medical supervision is recommended.

"You should receive the first injection during the first five days of your menstrual period, and the next injections as indicated by the health worker. It is important to receive the injection exactly at the times designated, otherwise you may become pregnant. It is extremely rare for pregnancy to occur when the injections are received regularly.

"Most women who receive an injectable contraceptive do not have regular menstrual periods, especially during the first months of use. You may experience irregular bleeding, spotting, or no bleeding at all. None of these conditions is harmful to your health if the bleeding is not very heavy or prolonged. If you should have no bleeding for more than two months, you should consult your health worker to be certain you are not pregnant.

"Other less common side-effects experienced by some women include headache, dizziness and weight gain.

"You should contact your doctor or other health worker if you develop heavy or prolonged bleeding or symptoms of pregnancy (apart from the absence of menstruation).

"Never take an injectable contraceptive when you suspect you are pregnant. It will not cause abortion but may interfere with the normal development of your baby.

"If you wish to become pregnant, you may simply stop receiving injections of the contraceptive. Some women experience several months' delay before they become pregnant, once they have stopped injectable contraceptives".

8. SPECIAL PROBLEMS

8.1 Conception while using DMPA or NET-EN

Although both DMPA and NET-EN are extremely effective as contraceptives, a very small number of women will become pregnant while using one of these steroids. Since the pregnancy would be unplanned, the woman may wish to consider terminating it, as an elective abortion, depending upon her own feelings about the pregnancy and about abortion, and depending upon the availability of abortion in her country.

If she continues the pregnancy (as a result of conception using DMPA), there does not appear to be any increased risk of spontaneous abortion. Although a few congenital anomalies have been reported among women who received progestogens while pregnant, the increased risk of abnormalities in the infant exposed to DMPA in utero appears to be minimal (41). Even with a several-fold increase in dose, major congenital anomalies are generally very uncommon, and the risk would still be quite small. No studies have examined the effect on the outcome of pregnancy as a result of conception while using NET-EN.

8.2 Postabortion and postpartum use

Either DMPA or NET-EN can be given immediately following an abortion. For women who are not

breast-feeding their infants, either contraceptive can also be used immediately postpartum. However, for women who are breast-feeding their infants, it is not yet advisable to use NET-EN, because there is little information on its effects during lactation.

DMPA does not appear to have any deleterious effect on either the quantity or the composition of breast milk, and some studies have demonstrated an increase in the amount of breast milk produced and in the duration of breast-feeding. The breast-feeding infant receives less than 0.5% of the maternal dose of DMPA and probably absorbs only a portion of that dose. Infants whose mothers received DMPA while breast-feeding appear to develop normally, both physically and mentally, at least till the age of 13 years.

8.3 Conception after discontinuation of injections

Following discontinuation of DMPA, most women experience a delay in the return of ovulation, the length of delay varying considerably among individual women. Thus, women who attempt to become pregnant after discontinuing DMPA will probably have a delay of at least several months before conceiving. The average time between the last injection and conception is about 9 months, including the 3 months of intended contraception; more than 90% of women become pregnant within 2 years of discontinuing DMPA.

No information is available on conception following discontinuation of NET-EN.

8.4 Use among young adolescents

The consequences for sexual development of interrupting pituitary activity in the first few years of adolescence are not fully understood and concern has occasionally been expressed about the administration of hormonal contraceptives to young girls. However, if sexually active adolescents are not able to use other

methods, an injectable hormonal method may be prescribed, since the social, medical and psychological consequences of unwanted pregnancy and abortion outweigh any physiological reservations that currently exist. Until further knowledge is gained, it is advised that (if possible) hormonal contraceptives should be avoided within the first 2 years of the menarche. In such cases, advice on other methods must be given.

8.5 Use among women over the age of 40

Although the adverse cardiovascular effects associated with the use of combined oral contraceptives have not been demonstrated for the injectable progestogens, there are other potential problems associated with the use of DMPA and NET-EN by women older than 40. In particular, the irregular menstrual periods (including amenorrhoea) that occur among most women receiving either DMPA or NET-EN may be mistaken for premenopausal signs, and the injections may unwisely be discontinued. In these women, it is difficult to determine the onset of menopause and the concurrent cessation of the need for contraception, because of the irregular bleeding patterns caused by the drug.

Women who have had their desired number of children should be advised to consider sterilization. If doubt exists regarding the status of their menopause, hormonal methods can be replaced by other methods of contraception that do not interfere with ovulation.

9. PROGRAMME IMPLICATIONS

Injectable hormonal contraceptives should be included among the family planning methods available at the clinic or other health facility offering an integrated family planning service. Their simple delivery makes them suitable for administration by trained auxiliary health workers who (with appropriate training) can carry out the counselling, selection and follow-up. For this purpose

it is advantageous to prepare suitable checklists since these will ensure that the procedures are carried out efficiently and safely (with no important points being overlooked) and will facilitate the decision whether a medical opinion is necessary (see section 9.2 below).

Before a decision is taken to use a nonclinical, nonmedical system for the distribution of injectable contraceptives, the following should be considered:

- (1) The decision must be taken by the programme authorities and accepted at every level of operation. This sometimes necessitates a revision of the regulations governing health professionals, or legislative changes.
- (2) The distribution system must be under the supervision of the national family planning programme.
- (3) The proper training of all the personnel involved must be guaranteed, and this training should be supervised by the national family planning programme.
- (4) Supplies and proper channels for distribution are needed and should be in operation.
- (5) The necessary drugs and facilities for the management of bleeding problems should be available (see section 6.9).
- (6) Such a system requires the support of medical facilities to cope with the special clinical problems.

9.1 Training of personnel

The training given to personnel who will be responsible for providing injectable contraceptives in any family planning system must ensure that the participants:

- understand the concepts and rationale of family planning;
- are capable of describing the different contraceptive methods available and their risks and benefits;
- identify the cases that present a contraindication to the use of the injectable contraceptives or special problems that require medical intervention and/or supervision;
- know how to instruct the women effectively on the expected side-effects and on the need to return for follow-up;
- recognize the complications and make the necessary referrals;
- maintain basic records for management of patients and programme evaluation.

The duration of this kind of training will be determined by the level of basic knowledge and experience of the trainees and by the capacity of the clinical facilities where they are to be taught.

9.2 Checklists

Checklists have been developed for auxiliaries primarily for the screening of women who can be given injectable contraceptives without being examined by the physician; they can also be utilized in follow-up visits. Once established, the same checklist should be used by all categories of personnel, who should be trained in its use.

An acceptable checklist must permit the detection of all those with contraindications to the injectable contraceptive or with problems that require medical intervention or supervision. An example of a checklist for nonphysicians is given in Annex 1.

10. CONCLUSIONS

Injectable contraceptives provide a highly effective and acceptable means of fertility regulation with certain advantages for women in both developed and developing countries. As far as the short-term use of long-acting progestogens is concerned, the main disadvantage for most women is the disturbance of the menstrual pattern, but the principal concern is with their long-term safety. Although there is no long-term experience with NET-EN, that with DMPA so far gives little cause for concern except for the as yet unresolved question of carcinogenic risk, a question common to all steroidal contraceptives. The incidence of many diseases varies markedly throughout the world and the risks from steroidal contraceptives are likely to be different for different populations. The risks attached to the use of injectable preparations in any country must therefore be carefully evaluated and weighed against the benefits they confer.

REFERENCES

1. Bulletin of the World Health Organization (1982) 60 (in press).
2. International Planned Parenthood Federation (1980) IPPF International Medical Advisory Panel meeting - October 1980. IPPF Med. Bull., 14, No 6.
3. Federal Register, (1978) 43: 28555-28556.
4. Perez-Palacios, G., et al. (1981) On the mechanism of action of progestins. Acta endocrinol., 97: 320-328.
5. Fotherby, K. (1981) Factors affecting the duration of action of the injectable contraceptive norethisterone enantate. Contracept. Deliv. Syst., 2: 249-257.
6. Sang, G.W. et al. (1981) Pharmacokinetics of norethisterone enantate in humans. Contraception, 24: 15-27.
7. Kirton, K.T. & Cornette, J.C. (1974) Return of ovulatory cyclicity following an intramuscular injection of medroxyprogesterone acetate. Contraception, 10: 39-45.
8. Ortiz, A. et al. (1977) Serum MPA concentrations and ovarian function following intramuscular injection of Depo-Provera. J. clin. Endocrinol. Metab., 44: 32-38.
9. Fotherby, K., Koetsawang, S. & Mathrubutham, M., (1980) A pharmacokinetic study of different doses of Depo-Provera. Contraception, 22: 527-536.
10. Fotherby, K., et al. (1980) A preliminary pharmacokinetic and pharmacodynamic evaluation of depot-medroxyprogesterone acetate and norethisterone enantate. Fertil. Steril., 34: 131-139.

11. Benagiano, G., et al., (1980) Return of ovarian function and endometrial morphology in women treated with norethisterone enantate: A pilot study. Fertil. Steril., 34: 456-460.
12. WHO Expanded Programme of Research, Development and Research Training in Human Reproduction (1977) Multinational comparative clinical evaluation of two long-acting injectable contraceptive steroids: Norethisterone enantate and medroxyprogesterone acetate. 1. Use-effectiveness. Contraception, 15: 513-533.
13. WHO Special Programme of Research, Development and Research Training in Human Reproduction (1981) Multinational comparative clinical trial of long-acting injectable contraceptives: norethisterone enantate and depot-medroxyprogesterone acetate. A preliminary report. Contraception, 24 (in press)
14. WHO Expanded Programme of Research, Development and Research Training in Human Reproduction (1978) Multinational comparative clinical evaluation of two long-acting injectable contraceptive steroids: Norethisterone enantate and medroxyprogesterone acetate. 2. Bleeding patterns and side effects. Contraception, 17: 395-407.
15. Parveen, L., Chowdhury, A.Q., & Chowdhury, Z. (1977) Injectable contraception (medroxyprogesterone acetate) in rural Bangladesh. Lancet, 2: 946-948.
16. Koetsawang, S. (1980) Present management of abnormal bleeding associated with steroid contraceptives. In: Diczfalusy, E. et al., ed., Endometrial bleeding and steroidal contraception, Pitman, Bath, pp. 50-58.
17. Kremer, J., de Bruijn, H.W.A. & Hindriks, F.R. (1980) Serum high density lipoprotein cholesterol levels in women using a contraceptive injection of depot-medroxyprogesterone acetate. Contraception, 22: 359-367.

18. Silfverstolpe, G., et al. (1979) Lipid metabolic studies in oophorectomized women. Effects of three different progestogens. Acta. obstet. gynec. scand., Suppl. no. 88, pp. 89-95.
19. Hirvoran, E., Mälkönen, M. & Manninen, V. (1981) Effects of different progestogens on lipoproteins during post-menopausal replacement therapy. New Eng. J. Med., 304: 560-563.
20. Spellacy, W.N. et al. (1972) The effects of medroxyprogesterone acetate on carbohydrate metabolism: Measurement of glucose, insulin and growth hormone after twelve month's use. Fertil. Steril., 25: 239-243.
21. Vermuelen, A. & Thiery, M. (1976) Hormonal contraceptives and carbohydrate tolerance. II. Influence of medroxyprogesterone acetate and chronic oral contraceptives. Diabetologia, 10: 253-259.
22. Amatayakul, K. (1979) Oral contraceptives and nutrition. The effects of Depo-Provera on carbohydrate lipids and vitamin metabolism. J. Steroid Biochem., 11: 475-481.
23. Beck, P., Zimmerman, D.E. & Eaton, R.P. (1977) Effect of contraceptive steroids on arginine-stimulated glucagon and insulin secretion in women. III. Medroxyprogesterone acetate. Metabolism, 26: 1193-1198.
24. Howard, G., Myatt, L. & Elder, M.G. (1977) The effects of intramuscular norethisterone enantate used as a contraceptive on IV glucose tolerance and blood coagulation factors. Brit.J.Obstet.Gynaec., 84: 618-621.
25. Dhall, K. et al. (1977) Short-term effects of norethisterone enantate and medroxyprogesterone acetate on glucose, insulin, growth hormone and lipids. Fertil. Steril., 28: 156-158.

26. Hellman, L. et al. (1976) The effect of medroxyprogesterone acetate on the pituitary-adrenal axis. J. clin. Endocrinol. Metab., 42: 912-917.
27. Sadeghi-Nejad, A., Kaplan, S.L. & Grumbach, M.M. (1971) The effect of medroxyprogesterone acetate on adrenocortical function in children with precocious puberty. J. Pediat., 78: 616-624.
28. Horowski, R. et al. (1978) Influence of depot-progestogens on anterior pituitary and adrenocortical hormones. Acta endocrinol., 87, Suppl. 215, p.98.
29. Aedo, A.R., Landgren, B.M. & Diczfalusy, E. (1981) Studies on ovarian and adrenal steroids at different phases of the menstrual cycle. III. Steroid and lutropin levels before and after the administration of a single contraceptive dose of depot-medroxyprogesterone acetate (DMPA). Contraception, 24: 117-135.
30. Aedo, A.R., Landgren, B.N. & Diczfalusy, E. (1981) Studies on ovarian and adrenal steroids at different phases of the menstrual cycle. IV. The effect of dexamethasone suppression and subsequent ACTH stimulation at different phases of the menstrual cycle and following the administration of 150 mg of depot-medroxyprogesterone acetate (DMPA). Contraception, (in press.)
31. Garcia, C.R. & Wallach, E.E. (1968) Liver function studies and progestogen contraception. Fertil. Steril., 19: 172-185.
32. Bergstein, N.A.M. & Muste-Zevenaar, H. (1970) Liver functien derzock bij vrouwen met medroxyprogesteron acetaat 150 mg (Depot-Provera). Geneeskund Gids (New Series), 8: 289-291.

33. Amatayakul, K., Sivassomboon, B. & Singkamani, R. (1980) Effects of medroxyprogesterone acetate on serum lipids, protein, glucose tolerance and liver function in Thai women. Contraception, 21: 283-297.
34. Adlercreutz, H. & Tenhunen, R. (1970) Some aspects of the interaction between natural and synthetic female sex hormones and the liver. Amer.J.Med., 49: 630-648.
35. Sotaniemi, E.A., et al. (1978) Effects of medroxyprogesterone on the liver function and drug metabolism of patients with primary biliary cirrhosis and chronic active hepatitis. J. Med., 9: 117-128.
36. Grossman, R.A., et al. (1979) Effects of the injectable contraceptive depot-medroxyprogesterone acetate in Thai women with liver fluke infestation: final results. Bull.Wld.Hlth.Org., 57: 829-837.
37. WHO Scientific Group on Steroid Contraception and the Risk of Neoplasia (1978) Report. World Health Organization, Geneva, Technical Report Series No. 619.
38. McDaniel, E.B. (1979), Endometrial carcinoma survey in Thailand. IPPF Med. Bull. 13: 3.
39. Pardthaisong, T., Gray, R.H., & McDaniel, E.B. (1980) Return of fertility after discontinuation of depot-medroxyprogesterone acetate and intra-uterine devices in Northern Thailand. Lancet, 1: 509-511.
40. Pardthaisong, T. & Gray, R.H. (1981) The return of fertility following discontinuation of oral contraceptives in Thailand. Fertil. Steril., 35: 532-534.
41. Schardein, L. (1980) Congenital abnormalities and hormones during pregnancy: a clinical review. Teratology, 22: 251-270.

42. WHO Scientific Group on the the Effect of Female Sex Hormones on Fetal Development and Infant Health (1980) Report, World Health Organization, Geneva, Technical Report Series No. 657.
43. Saxena, B.N., Shrimanker, K. & Grudzinskas, J.G. (1977) Levels of contraceptive steroids in breast milk and plasma of lactating women. Contraception, 16, 605-613.
44. Karim, M., et al. (1971) Injected progestogen and lactation. Brit.Med.J., 1: 200-203.
45. Huber, D.A., et al. (1980) Oral and injectable contraceptives: Effects on breast milk and child growth in Bangladesh. In: Zatzuchni, G. et al., ed., Research frontiers in fertility regulation, Hagerstown, Harper & Rowe, pp. 127-135.
46. Satayashit, N., Tankeyoon, M., & Chaudhury, R.R. (1976) The effect of medroxyprogesterone acetate, administered to the lactating rat, on the subsequent growth, maturation, and reproductive function of the litter. J. Reprod. Fertil. 46, 411-412.

Annex 1

Checklist for auxiliary workers for the prescription of
injectable contraceptives to eligible women

Check the following by history and examination:

	<u>Yes</u>	<u>No</u>
Above 40 years of age
Above 35 years of age and a heavy smoker
Seizures
Severe pain in the calves or thighs
Symptomatic varicose veins in the legs
Severe chest pains
Unusual shortness of breath after exertion
Severe headaches and/or visual disturbances
Lactating (Yes = for less than 6 months)
Intermenstrual bleeding and/or bleeding after sexual intercourse
Amenorrhoea
Abnormally yellow skin, eyes
Blood pressure (Yes = above 140 mm Hg (18.7 kPa) systolic and/or 90 mm Hg (12 kPa) diastolic)
Mass in the breast
Swollen legs (oedema)

Instructions

If all the above are negative, the women may be given injectable contraceptives. If any are positive, she must first be seen by a doctor.

