Injectable Contraceptives

Their role in family planning care

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The World Health Organization is a specialized agency of the United Nations with primary responsibility for international health matters and public health. Through this organization, which was created in 1948, the health professions of some 165 countries exchange their knowledge and experience with the aim of making possible the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life.

By means of direct technical cooperation with its Member States, and by stimulating such cooperation among them, WHO promotes the development of comprehensive health services, the prevention and control of diseases, the improvement of environmental conditions, the development of health manpower, the coordination and development of biomedical and health services research, and the planning and implementation of health programmes.

These broad fields of endeavour encompass a wide variety of activities, such as developing systems of primary health care that reach the whole population of Member countries; promoting the health of mothers and children; combating malnutrition; controlling malaria and other communicable diseases including tuberculosis and leprosy; having achieved the eradication of smallpox, promoting mass immunization against a number of other preventable diseases; improving mental health; providing safe water supplies; and training health personnel of all categories.

Progress towards better health throughout the world also demands international cooperation in such matters as establishing international standards for biological substances, pesticides and pharmaceuticals; formulating environmental health criteria; recommending international nonproprietary names for drugs; administering the International Health Regulations; revising the International Classification of Diseases, Injuries, and Causes of Death; and collecting and disseminating health statistical information.

Further information on many aspects of WHO's work is presented in the Organization's publications.

Front cover: "Family planning", a sculpture in wood by the Colombian folk artist Juan de la Cruz Saavedra.

Other WHO publications on contraception and family planning

	Price (Sw. fr.)
Female sterilization: guidelines for the development of services. Offset Publication, No. 26, 1976.	9.–
Induced abortion: guidelines for the provision of care and services. Offset Publication, No. 49, 1979.	6.–
Oral contraceptives: technical and safety aspects. Offset Publication, No. 64, 1982.	4.–
Intrauterine devices: their role in family planning care. Offset Publication, No. 75, 1982.	5.–
Barrier contraceptives and spermicides. Their role in family planning care. 1987.	15.–
Mechanism of action, safety and efficacy of intrauterine devices. Report of a WHO Scientific Group. WHO Technical Report Series, No. 753, 1987.	12.–
Technical and managerial guidelines for vasectomy services. 1988.	22.–
Natural family planning. A guide to provision of services. 1988.	16.–

Further information on these and other World Health Organization publications can be obtained from Distribution and Sales, World Health Organization, 1211 Geneva 27, Switzerland.

Preface

The growing interest in and demand for injectable contraceptives in many parts of the world led to the publication by WHO in 1982 of *Injectable hormonal contraceptives: technical and safety aspects* (WHO Offset Publication No. 65). The developments in the field and the experience gained in the management of family planning programmes, and in particular in the use of injectable contraceptives since that date, have made it necessary to produce the present revised and updated version of that publication. This is all the more important since, as an effective family planning method, injectable contraceptives can make an important contribution to the protection of the health of mother and child. They are compatible with the primary health care strategy, so that both the accessibility and awareness of birth spacing can be increased, since a larger number of people can be reached than would ordinarily be possible through the formal health care system.

The primary purpose of these guidelines is to assist those responsible for the development and management of family planning and health programmes in introducing or increasing the availability of injectable contraceptives. They are designed to serve the needs of various categories of health personnel, including programme managers, administrators and service providers. Essential technical information about injectables, their effects and related medical issues is included, so as to ensure that such personnel have the necessary understanding of this method of contraception. The guidelines also contain information of practical value to those initiating programmes. Thus, chapters on organizing, managing and evaluating a programme are included, together with an annex containing a model patient record form that can be adapted for use in particular settings.

The important contributions of Dr Viopapa Annandale, United Kingdom, Dr B. Affandi, Indonesia, Dr I. S. Fraser, Australia, Ms J. Hutchings, PATH, USA, Dr P. Senanayake, IPPF, United Kingdom, as well as of the members of the Task Force on Long-Acting Systemic Agents for Fertility Regulation of the Special Programme of Research, Development and Research Training in Human Reproduction, and of the many reviewers who have given unselfishly of their time in the preparation of this text, are gratefully acknowledged.

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Comments and queries on this publication should be addressed to: Maternal and Child Health, World Health Organization, 1211 Geneva 27, Switzerland.

Contents

1. Background information and programme considerations

Development of injectable contraceptives

Shortly after oral hormonal contraceptives were introduced, it was discovered that the availability of these hormones in the body could be prolonged by adding on an additional chemical group to form an ester. When injected intramuscularly, these compounds are slowly released into the circulation, and thereby provide long-lasting hormonal activity.

Between 1953 and 1957, a considerable number of esters of different estrogens and progestogens were synthesized. Some of these could be formulated only as oily solutions, whereas others could be made up as microcrystalline suspensions. The two that have come to be the most widely used as injectable contraceptives are depot-medroxyprogesterone acetate (DMPA) (a microcrystalline suspension) and norethisterone enantate (NET-EN) (an oily solution).

DMPA was first used in humans in 1960 for the prevention of premature labour and for the treatment of threatened abortion, endometriosis and endometrial carcinoma. It was then sometimes given in doses as high as 1–4 g per injection. It was soon recognized that many women who were treated during pregnancy remained infertile for many months afterwards. This led to the recognition of DMPA's contraceptive properties and proper clinical contraceptive trials were started in 1963. Three separate and independent reports appeared in 1966 indicating a very high effectiveness in preventing pregnancy,

since when it has become popular as a contraceptive and is now marketed in over 80 countries and territories.

NET-EN has been used as a contraceptive since 1966, although less extensively than DMPA. It has the disadvantages that more frequent injections are required (2-monthly as compared with 3-monthly) and that pregnancy rates are slightly higher. The discontinuation rates due to irregular bleeding are the same for both DMPA and NET-EN, but fewer women discontinue because of amenorrhoea when using NET-EN. It is now marketed in over 30 countries and territories.

It is estimated that more than 30 million women worldwide have used injectable contraceptives and, of these, over 6 million are using them at present. A list of the countries and territories in which DMPA and NET-EN are registered for use as contraceptives is given in Annex 1.

Formulation and mode of action

Injectable hormonal contraceptives, when properly used, are among the most effective methods of contraception available today, and should therefore be considered for inclusion among the family planning methods available at any clinic or other health facility offering an integrated family planning service.

NET-EN is prepared in an oily solution and, after injection, is 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. NET-EN disappears more rapidly from the circulation than DMPA and it is for this reason that it has to be given at shorter intervals.

In preventing pregnancy, both DMPA and NET-EN act essentially by:

—inhibiting ovulation;

—increasing the viscosity of the cervical secretions, thus forming a barrier to spermatozoa (and to many bacteria);

—changing the rate of ovum transport through the fallopian tubes;

—making the endometrium less suitable for implantation.

Role of injectable contraceptives in family planning programmes

The results of various studies, including the World Fertility Survey of 1980, indicate that about half of all married women in the world currently do not want any more children but that only a relatively small proportion use any form of contraception, whether modern or traditional. The need, especially for women in the developing countries, for an effective, safe, and reversible method of contraception that does not interfere with lactation, can be administered by non-physicians in remote areas, is totally independent of coitus and does not require specialized facilities or supplies can therefore hardly be overemphasized. However, every approach to fertility control has its advantages and disadvantages. None is suitable for everyone at every time. None is acceptable in every culture. Each of the currently available modern methods of contraception, including oral contraceptives and intrauterine devices (IUDs), has gained acceptance by some couples at certain stages of their reproductive life. For this reason, family planning programmes typically offer a wide range of methods to potential clients. In addition, experience suggests that a wide choice of contraceptive methods encourages acceptance and continued use, while each additional method contributes independently to the overall prevalence of contraceptive use.

Of the various methods of contraception, injectable contraceptives are particularly useful for couples who have completed their families but are not ready to accept sterilization. They are also useful as a method of spacing for couples planning a birth interval of more than 2 years, since fertility return may be delayed by an average of 6 months when the method is discontinued.

Injectables are also particularly suitable for temporary use by women who require maximum protection following immunization against rubella, for partners of men

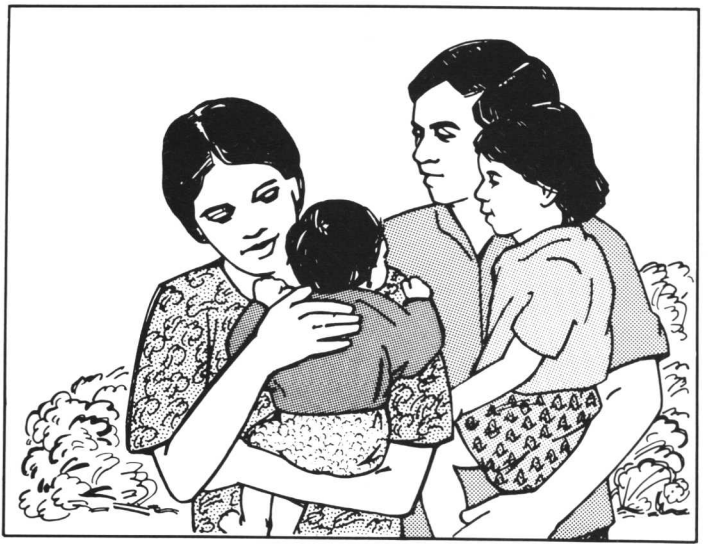

Fig. 1. Injectable contraceptives are suitable for use by couples who do not want any more children, and by those who wish to delay the next pregnancy.

undergoing vasectomy, and for postpartum women awaiting sterilization.

However, the use of long-acting (i.e., effective for two or three months) injectable steroids is associated with menstrual disturbances and a slower return to fertility as compared with IUDs and oral contraceptives. It is also relatively labour-intensive in the sense that health personnel have to provide repeat injections at 2- or 3-monthly intervals, as well as counselling for menstrual disturbances and other minor side-effects. Programme administrators must therefore weigh these disadvantages of injectables against the fact that they provide a long-acting, reversible method of contraception that is totally independent of coital activity, does not require specialized facilities or supplies and can be administered by a non-physician.

Controversy associated with injectable contraceptives

The controversy associated with long-acting hormonal contraceptives has centred around DMPA and the

application to market it as a contraceptive in the USA. A major aspect of this controversy has been the interpretation of data from animal toxicology studies, particularly those relating to possible carcinogenic effects. Because of this, numerous reviews have been undertaken by both national and international bodies, the most important of which are summarized below.

In 1978, the Toxicology Review Panel of the WHO Special Programme of Research, Development and Research Training in Human Reproduction, together with other scientists and representatives of six national drug regulatory agencies, reviewed the results of animal and human experiments with DMPA and NET-EN, and 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 . . . There is 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."

For NET-EN, the Panel recommended that: "in the light of the findings in the monkey, beagle and rat . . . the current and planned clinical trials of norethisterone enantate should continue."

DMPA was reviewed by the Food and Drug Administration (FDA) in the USA in 1978, and although approval for use as a contraceptive agent 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 such approval.

The International Medical Advisory Panel of the International Planned Parenthood Federation met in 1980 and endorsed the recommendations of WHO, the Ad Hoc Consultative Panel on DMPA of the Agency for International Development, and the Scientific Advisory Committee of the US Food and Drug Administration, that it "continues to be a responsible act of making DMPA available as a contraceptive."

WHO then convened another meeting of experts in 1981,[a] who concluded that:

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[a] Facts about injectable contraceptives: Memorandum from a WHO Meeting. *Bulletin of the World Health Organization*, **60**: 199–210 (1982).

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.

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 time, and the potential long-term effects (over more than 15 years) are not yet known.

With regard to metabolic effects, research should continue on the effects and physiological consequences of long-term use of DMPA and NET-EN on carbohydrate and lipid metabolism. In addition, further research is needed regarding the long-term 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 are 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 for women desiring a method of fertility regulation.

Eventually the FDA constituted a Public Board of Inquiry which, in its report of October 1984, stated that the available information on DMPA "does not provide sufficient basis from which FDA can determine that DMPA is safe for general marketing in the United States".

Subsequently the company withdrew its application for marketing.

The concern over DMPA first arose because of the increased incidence of breast cancer it produced in beagle bitches. Animals treated with doses of DMPA ranging from the human equivalent dose to up to 50 times this dosage for periods of up to 7 years developed a larger number of benign and malignant breast nodules than control animals. Since that time, a large amount of data, from both animals and humans, has been accumulated showing the beagle bitch to be a poor model for predicting the risk of breast cancer in humans. For this reason, the United Kingdom Committee for the Safety of Medicines and other drug regulatory bodies in western European countries no longer require the use of this animal model in the toxicology testing of hormonal contraceptives. Since the application for a licence to market DMPA as a contraceptive in the USA was withdrawn, the FDA has reviewed its requirements for testing of steroid hormones, dropping the need for testing in the monkey, and reducing the period of testing in the beagle from 7 to 3 years.

WHO has published the results from an interim analysis of a 3-country case–control study of DMPA and cancer, which included a total of 427 cases of breast cancer and 5951 controls.[a] The relative risk of breast cancer among women who had used DMPA was 1.0, suggesting that no association exists between DMPA use and breast cancer. However, since few women use DMPA for more than 1 or 2 years, it is difficult to draw any firm conclusions about long-term DMPA use and breast cancer.

Concern also arose from animal toxicology studies when a small number of malignant and premalignant endometrial lesions were observed in rhesus monkeys treated with DMPA and NET-EN. Again, there is evidence that these findings are not predictive of a risk of endometrial cancer in humans and, in fact, there is reason to expect that administration of these progestogens will actually reduce the risk of endometrial cancer in women. The interim results from the WHO study mentioned above showed a relative risk of 0.3 for endometrial cancer which, although

[a] Depot-medroxyprogesterone acetate (DMPA) and cancer: Memorandum from a WHO Meeting. *Bulletin of the World Health Organization*, **64**: 375–382 (1986).