Systemic contraception

International Planned Parenthood Federation

Companion volume to:

Intrauterine contraception
Vasectomy
Abortion—classification and techniques

Price $2.00 (USA) or 75p plus postage (surface or air)
Free to doctors and family planning organizations in developing countries
Available in English, Spanish and French

Printed in England by Stephen Austin and Sons, Ltd., Hertford.

INTERNATIONAL PLANNED PARENTHOOD FEDERATION

SYSTEMIC CONTRACEPTION

Edited for the IPPF Central Medical Committee
by
R. L. KLEINMAN
M.B., Ch.B., D.(Obst.)R.C.O.G.

Central Office
18–20 LOWER REGENT STREET, LONDON SW1Y 4PW, ENGLAND
Telephone: 01-839 2911 Cables: IPEPEE, London, S.W.1
1973

IPPF CENTRAL MEDICAL COMMITTEE

President of the IPPF	Dr Fernando Tamayo (*Colombia*) (*Ex officio*)
Chairman	Dr G. T. M. Cummins
Vice-Chairman	Prof. T. H. Lean
Regional Representatives	
Africa	Prof. Daniel A. Ampofo, M.B., B.S., M.R.C.O.G., M.P.H. (*Ghana*)
Europe	Prof. Pierre O. Hubinont, Ph.D., M.D. (*Belgium*)
Indian Ocean	Dr (Miss) Siva Chinnatamby, F.R.C.S., F.R.C.O.G. (*Sri Lanka*)
Middle East and North Africa	Prof. M. Sadek Foda, M.B., Ch.B., D.G.O., M.Ch. (*Egypt*)
South East Asia and Oceania	Prof. T. H. Lean, F.R.C.S., F.R.A.C.S., F.R.C.O.G. (*Singapore*)
Western Hemisphere	Dr G. T. M. Cummins, M.B., Ch.B., F.R.C.O.G. (*Barbados*) Prof. C. Gomez-Rogers, M.D. (*Chile*)
Western Pacific	Prof. E. Hyock Kwon, Ph.D., M.D., M.P.H. (*Korea*)
Co-option	Dr Alan F. Guttmacher, M.D. (*USA*)
Management and Planning Committee Representative	Dr Ruben Apelo, M.D. (*Philippines*)
Secretary to the Committee	Dr Malcolm Potts, M.A., Ph.D., M.B., B.Chir., D.(Obst.)R.C.O.G.

IPPF PANEL OF EXPERTS ON SYSTEMIC CONTRACEPTION

Regions

Africa	Dr B. K. Adadevoh (*Nigeria*) Dr J. Hayden (*Kenya*) Dr T. Ndabari (*Kenya*)
Europe	Prof. E. Diczfalusy (*Sweden*) Prof. J. Férin (*Belgium*) Dr K. Fotherby (*Britain*) Dr G. I. M. Swyer (*Britain*) Dr M. P. Vessey (*Britain*)
Indian Ocean	Dr (Miss) S. Chinnatamby (*Sri Lanka*)
Middle East and North Africa	Prof. F. Hefnawi (*Egypt*)
South East Asia and Oceania	Prof. T. H. Lean (*Singapore*) Prof. R. P. Shearman (*Australia*) Mr T. S. Sinnathway (*Malaysia*)
Western Hemisphere	Dr A. Barnes (*USA*) Dr E. Connell (*USA*) Dr C.-R. Garcia (*USA*) Dr J. W. Goldzieher (*USA*) Dr R. Hertz (*USA*) Dr J. Laragh (*USA*) Dr K. Ryan (*USA*) Dr H. Salhanick (*USA*) Dr P. Sartwell (*USA*) Dr D. Schwartz (*USA*) Dr A. Sobrero (*USA*) Dr C. Tietze (*USA*)
Western Pacific	Prof. S. Matsumoto (*Japan*)

CONTENTS

INTRODUCTION

Systemic contraception was first introduced in 1956 in the form of the combined oral contraceptive, containing a progestagen and a synthetic oestrogen. There are an estimated 30 million current users, while probably twice this number of women have taken oral contraceptives at some time or other. An enormous amount of clinical experience has been gained, and important advances have taken place in basic research into reproductive physiology since the oral contraceptive was first developed. This research was itself sometimes stimulated by clinical work on the actions of steroidal contraceptives. The experience gained and advances made provide greater insight into these actions.

It is never possible to stop asking new physiological and clinical questions, but every year knowledge on all aspects of steroidal contraceptives grows and confidence in their use becomes firmer. However, nothing can ever eliminate the possibility of new discoveries about their actions, and such discoveries might concern either beneficial or harmful actions.

The purpose of this book is to provide an up-to-date survey of knowledge concerning the actions, side-effects and clinical use of systemic contraceptives. The book expands and brings up to date Chapter 2 in the 3rd edition of the *IPPF Medical Handbook*. It covers the same basic ground as the important publication by Dr Eleanor Mears, called *Oral Contraception*, which was published by Churchill under the IPPF imprint in 1965, but of course also brings up to date the material covered in that publication. In addition this book includes material taken from the IPPF publication *Comments on Steroidal Contraception* (1970). That publication was a response to the concern about the use of oral contraceptives which became apparent in 1969 and 1970, when a number of factors combined to give particular prominence to the side-effects of oral contraception. As in that publication, care has been taken not only to present the known scientific facts concerning steroidal contraceptives, but also to underline the clinical implications of the available data.

The IPPF is grateful to Mr Max Elstein, senior lecturer in human reproduction and obstetrics at Southampton University, England, for preparing the draft on which this book is based, and to members of the IPPF Panel of Experts on Systemic Contraception for reading the draft and supplying suitable amendments.

TYPES OF SYSTEMIC CONTRACEPTIVES

Since the early 1960s hormonal contraceptives have been used on an increasingly large scale in many countries. To date there are no preparations containing steroids which have been shown to be effective and acceptable for use in men. The most widely used hormonal contraceptives are preparations containing oestrogens and progestagens. Although the variety of steroidal contraceptives which have been evaluated is extensive, the preparations consisting of a combination of oestrogen and progestagen continue to be the most popular type used.

Combined formulations

These contain an oestrogen and a progestagen (see pages 23–27) given in constant proportions and amounts for 20, 21 or 22 days, followed by an interval without medication during which uterine bleeding occurs. The commonest regimen is a 21-day course, followed by an interval of seven days when either no tablets are taken or a placebo, iron or vitamin tablets are substituted. The range of steroids used in systemic contraceptives is widening, and there is a tendency for the dose of both progestagen and oestrogen to be reduced.

Sequential preparations

In the sequential type of oral contraceptive an oestrogen is given alone for 14–16 days, followed by a combined tablet containing an oestrogen and a progestagen for five to seven days. This is followed by an interval of seven days when either no tablet is taken or a placebo is administered; during these treatment-free days there is uterine bleeding.

Continuous oral progestagens

The daily use of a small amount of one of a variety of progestagens can produce infertility without invariably inhibiting ovulation. There are no tablet-free days with this type of contraception, and the endometrium tends to break down and bleed at rather irregular intervals.

Injectable steroids

Injections of long-acting progestagens are given at intervals varying from one to six months. Uterine bleeding tends to be irregular and may be prolonged and/or heavy; there is also a tendency for prolonged periods of amenorrhoea to develop with time. The monthly injection of an oestrogen-progestagen mixture usually results in a relatively predictable pattern of bleeding, but has the disadvantage of needing repeated regular injections.

Implants

Progestagens pass slowly through the silicone polymer, silastic. It has been shown that silastic capsules of progestagen can be implanted subcutaneously or intramuscularly, or be placed as rings in the vagina or uterus from where the hormone is absorbed. Prolonged, continuous release of steroid, giving a satisfactory contraceptive effect for six to 12 months, has been demonstrated in clinical trials. It has been suggested that with technical modifications in the incorporation of the progestagen in silastic during manufacture it may be possible to extend this to encapsulated implants of pure steroid. The use of a variety of steroid mixtures is also being explored. This group of methods, especially those using the intrauterine and vaginal devices, has promise of wide application, but is still under clinical trial.

Once-a-month preparations

A long-acting oral oestrogen, which is stored in body fat and slowly released, is used in combination with a progestagen not stored in body fat, and is given in a single tablet at a precise time in the menstrual cycle. A regular pattern of uterine bleeding is achieved. Current evidence shows a higher pregnancy rate than with conventional or continuous oral contraceptives.

Post-coital preparations

Oestrogens have been used in high dosage, starting within 24–36 hours of unprotected intercourse. The administration continues for five days and appears to be effective in preventing pregnancy. Experiments are taking place at present in which oral progestagens are being used immediately after the time of coitus for this purpose.

HISTORICAL REVIEW

1890–1929

The research on which the use of steroidal substances for contraception is based began in the latter part of the 19th century with the observation that ovarian follicles do not develop during pregnancy. In 1897 John Beard, lecturer in comparative embryology and vertebrate morphology at the University of Edinburgh, suggested that the corpus luteum was responsible for this effect, but he thought follicle production was inhibited by pressure produced within the ovary by the corpus luteum. An endocrine function for the corpus luteum was suggested in 1898 by Auguste Prenant, professor of histology at the University of Nancy. During the next two decades Leo Loeb, of the University of Pennsylvania, provided experimental evidence that the presence of the corpus luteum inhibited ovulation in guinea-pigs; Edmund Herrmann and Marianne Stein of Vienna suppressed ovulation in rats with lipid extracts of corpus luteum; and Ottfried Fellner of Vienna showed that placental extracts would inhibit ovulation and that this might reinforce the action of the corpus luteum.

The idea that hormonal sterilization was practical first appears in the work of Ludwig Haberlandt, a physiologist at the University of Innsbruck, who published many papers on this subject from 1921 until his death in 1933. He showed that rabbits could be made infertile by the injection of extracts of corpus luteum, and mice by oral extracts of corpus luteum or placenta. He suggested that similar extracts might provide an ideal method of birth control in the human. However, his attempts to persuade clinicians to test such an extract in women were unsuccessful.

1930–1950

After Haberlandt the idea of hormonal contraception attracted little interest for 20 years, but during these years the chemical structure of the sex hormones was discovered and much knowledge accumulated about the endocrinological control of reproduction. The first three oestrogens were identified in 1929 and 1930, and progesterone in 1934.

Several workers soon found that injections of oestrogens or progesterone would inhibit ovulation in animals, but the use of these hormones was severely limited by the lengthy and elaborate processes necessary to extract them from animal material, by the need to administer them by injection, and by their brief biological activity. Nevertheless, in 1940 Sturgis and Albright reported that dysmenorrhoea could be relieved by the injection of oestrogen and that ovulation was inhibited. About the same time The *Texas State Journal of Medicine* published

an article which mentioned the use of oestrogen to suppress ovulation in the prevention of pregnancy.

The factors limiting the use of the naturally occurring hormones were overcome by the development of synthetic and semi-synthetic compounds with similar biological effects. Sir Charles Dodds and his co-workers led with the discovery in 1937 of the non-steroidal oestrogenic substance stilboestrol. Others followed with the oestrogen ethynyloestradiol and then with ethisterone, a compound with weak progesterone-like properties. These substances could be manufactured cheaply, had useful activity when given by mouth and were used by gynaecologists during the 1940s to treat conditions such as dysmenorrhoea and dysfunctional uterine bleeding.

1950 onwards

The development of potent semi-synthetic compounds with a progesterone-like activity—progestagens or progestins—occurred more slowly. No biologically effective substances apart from ethisterone became available until the early 1950s. In 1952 Frank B. Colton of Searle Laboratories synthesized norethynodrel, and Carl Djerassi of Syntex Laboratories synthesized norethisterone (called norethindrone in the USA). These steroids have many, but not all, of the biological effects of progesterone, and weight for weight are many times more active than progesterone both orally and by injection. Ways were also found of producing commercial quantities of steroids comparatively cheaply from plant sources, such as the steroid diosgenin found in yams.

By the end of 1955, the effects of these new progestagens on animals had been investigated by Francis J. Saunders of Searle Laboratories and by Gregory Pincus and his associates at the Worcester Foundation for Experimental Biology in Boston, USA. Studies using norethynodrel were begun in women by a team led by John Rock, and in 1956 Rock, Garcia and Pincus demonstrated the effectiveness of norethynodrel in suppressing ovulation. The same workers, with Edris Rice-Wray, organized successful trials with larger numbers of women in Puerto Rico. The original preparation of norethynodrel contained oestrogen as a contaminant, and it was soon found that the occasional bleeding from the endometrium while norethynodrel was being taken could be minimized by adding more of the same oestrogen—mestranol. The combination of 10 mg of norethynodrel and 150 μg of mestranol was called Enovid (Enavid in the UK)* by Searle

*Where unavoidable, brand names are used in this book. These are names commonly in use in either Britain or the USA and in many other countries. However, in some countries different brand names are used for the same product, as mentioned on page 62, and a check for the correct name or the constituents of a particular product can be made in the *IPPF Directory of Contraceptives.*

Laboratories and, after trials in both Los Angeles and Puerto Rico in which its contraceptive effectiveness was amply confirmed, it was officially approved in 1959 for use in the USA as the first combined oral contraceptive.

The amounts of steroid in Enovid proved to be unnecessarily high, and by 1964 it was shown that contraceptive efficiency could still be secured with the dose of norethynodrel ranging down to 2·5 mg and the accompanying mestranol to 100 μg. The combined method pioneered with Enovid, now spread to a great variety of preparations, continues to be the most widely used form of systemic contraception.

Development of new formulations

Following the first generation of commercial combined oral contraceptives, such as Enovid, Ortho-Novum and Lyndiol, a second group, such as Anovlar, Ovulen and Lyndiol 2·5, was introduced, and again the progestagen content was reduced by approximately half. At a later time, further reductions in dosage of both progestagen and oestrogen were made, resulting in preparations such as Minovlar, Eugynon, Norinyl-1 and Demulen.

The development of oral contraceptives preceded the introduction of liberal abortion laws in many countries. The knowledge that a pregnancy could not be terminated if a woman in a trial became pregnant prevented clinicians from carrying out a titration of the minimum dose of hormone necessary to prevent pregnancy. The inability to carry out these tests necessitated an over-generous use of steroids and has probably been responsible for creating an unfavourable image for oral contraceptives as a result of the relatively high incidence of side-effects found with the oral high-dose preparations.

A further group of combined tablets was introduced in 1970 following the evidence published by the British Committee on Safety of Drugs (now the Committee on Safety of Medicines) that the incidence of thromboembolic disorders in users of oral contraceptives was lower when the tablets contained less than 75 μg of oestrogen. Currently recommended formulations contain 50 μg of oestrogen, which is either ethynyloestradiol or the slightly less active mestranol, and recently a combined tablet with only 30 μg of ethynyloestradiol has been introduced. These combined low oestrogen-low progestagen oral contraceptives have provided virtually complete contraception and in general have satisfied the majority of users. They are also a little cheaper than the higher dose tablets. In a minority of women preparations containing larger amounts of steroid have been

necessary to control certain side-effects, particularly breakthrough bleeding.

SEQUENTIAL METHODS

Other methods of administering oral contraceptives have been developed, but to date have not proved as satisfactory as the use of the combined method. Sequential formulations, mimicking to some extent the natural occurrence of the ovarian steroids during a normal menstrual cycle, were first suggested in the 1940s for the treatment of menstrual dysfunction, but used injections of natural progesterone rather than the still undiscovered progestagens. Robert B. Greenblatt suggested in 1961 that oral contraception could be achieved with sequential formulations, and in 1963 Joseph Goldzieher and his associates published a clinical trial of the sequential method. Certain side-effects were less common, but contraceptive effectiveness was not as good as with the combined tablet.

CONTINUOUS DAILY PROGESTAGEN

In 1965 Rudel and his colleagues reported that the continuous daily administration of a progestagen, chlormadinone acetate, at a dose of 0·5 mg, was an effective contraceptive even though ovulation was not inhibited in most cycles. Subsequent trials in several countries showed that pregnancy did occur occasionally, but that the pregnancy rate, although greater than with the sequential preparations, was lower than that occurring with conventional barrier or spermicide techniques. The method can produce unpredictable and variable episodes of endometrial bleeding, but is attractive because the small amount of progestagen and the absence of oestrogen may produce less side-effects, such as those connected with blood coagulation.

Chlormadinone acetate became available in 1968 as Normenon and Verton. However, these products were withdrawn in 1970 because, when given in large amounts, chlormadinone acetate had been found to cause the development of nodules in the mammary glands of beagle bitches (see page 46). Other progestagens, such as megestrol acetate, norethisterone, norethisterone acetate, norgestrel, ethynodiol diacetate, and lynoestrenol, are now being evaluated for general use in continuous dosage or are already being marketed in several countries (see page 63).

INJECTIONS AND IMPLANTS

Contraceptive steroids can also be given by intermittent injection. The

compounds used orally usually have too brief an effect when given by injection, but when esterified with certain organic acids their effect can be prolonged. In the early 1960s A. I. Csapo found that an injection of from 1 to 4 g of medroxyprogesterone acetate given to women in premature labour resulted in sterility for 12–21 months postpartum.

The first study published on the contraceptive use of medroxyprogesterone acetate by injection was by Zañartu, Rice-Wray and Goldzieher, who used up to 1,000 mg once a year. Lower doses at shorter intervals are now in common use (see page 64).

A different way of using progestagens was introduced by Dziuk *et al.* when they reported in 1966 that steroids would diffuse slowly through silicone-rubber (polymer silastic). Research in animals has shown that steroids contained in silastic capsules implanted beneath the skin can affect the reproductive cycle. In women research has been cautious and on a small scale, but silastic capsules and devices have been tested by being implanted under the skin. Intrauterine devices and vaginal rings impregnated with progesterone, medroxyprogesterone acetate and other steroids are currently being investigated as potential locally acting contraceptive agents.

Research

Research into steroidal contraception is continuing. To be effective a steroidal contraceptive must have properties similar to those of the natural sex steroids, but should avoid disturbing normal physiology, apart from the control of conception. Ideally, such a steroid should only act locally. Perhaps steroids will never fulfil these aims, but great progress has been made since Haberlandt suggested that 'hormonal sterilization' should be possible in women.

PHYSIOLOGY OF THE MENSTRUAL CYCLE AND CONCEPTION

Neuro-endocrinology

There is evidence that the central nervous system is directly concerned with the menstrual cycle. Environmental influences, such as emotion and stress, affect the cycle. Anatomically, it seems likely that extrahypothalamic regions of the central nervous system, such as the amygdaloid nucleus and the limbic system, are among the centres most clearly involved. The concept of a biological clock system has been proposed.

The existence of a portal system serving as a method of communication between hypothalamic neurones and the hormone-secreting cells of the adenohypophysis has been demonstrated. The concept of a neurohumoral control of anterior pituitary function which is mediated by means of this vascular system was developed by Harris and his group in Oxford. There is now abundant evidence that the release of the pituitary hormones is controlled by varying concentrations of relatively specific humoral agents called releasing hormones (or releasing factors) which are liberated into the primary plexuses of this portal system in the median eminence. The releasing hormones are carried by these portal vessels to perfuse the pituitary gland and regulate the secretion of the anterior pituitary hormones (see Fig. 1).

RELEASING HORMONES

The releasing hormones are present in minute amounts in the hypothalamus and median eminence, where their concentration is far greater than in the systemic circulation. Direct neuronal involvement in the release of gonadotrophins is suggested by the observation that there are brief 'spurts' of luteinizing hormone (LH) release followed by periods of little or no hormone secretion. The current view is that the releasing hormones are probably small basic polypeptides (about 10 amino-acid units), that their molecular weight is less than 2,000 or even 1,000, that they are not species-specific, and that they have a brief half-life. In fact, small peptides capable of influencing the release of pituitary hormones have been synthesized. Whether there is a separate releasing hormone for each of the gonadotrophins or a single gonadotrophin releasing hormone responsible for the release of both LH and follicle-stimulating hormone (FSH) from specific gonadotrophin cells in the pituitary is uncertain.