Human Fertility Control

Theory and practice

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Preface

In the last decade, family practitioners have come to realise that their patients' family planning needs involve more than a prescription for 'the pill' or the occasional referral for consideration of a legal abortion. At the same time, specialist obstetricians and gynaecologists have taken an increasing interest in fertility control procedures and realised that family planning has come to be a major part of their practice. Once it is understood by these groups of practitioners that there is no 'best' contraceptive, only the most appropriate procedure for a given patient, much background knowledge is required to individualise effectively.

Most of the books on fertility control which have been published in recent years are either instruction manuals for the tyro or volumes dealing with either one or many specialised topics. We feel that the needs of the most potent groups currently involved in clinical fertility control practice, the family practitioners with a special interest and the obstetricians and gynaecologists, have been neglected. The present volume is intended as a textbook for both of these groups, which will enable them to tailor their counselling and practice to the needs of their patients as individuals. We have dealt with practical clinical procedures in some detail, and also discussed the basis of the methods at a depth which should be appropriate for the specialist. It is our intention to present both reasoned evaluations and firm opinions on controversial topics, so that these conclusions may assist medical and postgraduate students, and nurses and midwives concerned with family planning, as well as enable specialists in training to assess the evidence. This book is not a 'recent advances' volume, and we have tried to emphasize points of view which will survive in future years. One partial exception to this is that we have given a full account of the use of intra-amniotic hypertonic saline instillation for legal abortion, as it is still employed in some centres in the United States of America.

We have provided numerous references to the literature, both to deal with matters which need 'chapter and verse' for substantiation and to enable readers to pursue authoritative individual sources.

It was a pleasure to invite Mr Jack Parsons to write an epilogue for us. Doctors find it expedient to pay lip service to the sermons of population experts and economists, but they weary of being asked to implement programmes which have little respect for the intellectual ability of the doctor or the needs and rights of the individual patient. Clinical practice is based on a doctor's assessment of each situation as it presents and the welfare of the patient is paramount. Mr Parsons is one of the few in his field who have appreciated the need of those in the health professions to have some understanding of the demographic

principles of fertility control at a level which is meaningful with respect to the individual. We are also grateful to one of his former pupils, Miss Zara Whitlock, for writing the chapter on motivation, which is based in part on the extensive behavioural studies she has conducted with the aid of patients at the Hammersmith Hospital family planning clinic.

We are greatly indebted to the late Professor J C McClure Browne for his encouragement both of our work in this field and of the production of this book. Mr J Duncan Murdoch had started the fitting of intra-uterine devices at Hammersmith Hospital in 1961 and in 1968 Professor Browne gave one of us the remit of developing this nucleus into a comprehensive clinic in which the training of doctors could take place and clinical trials could flourish in close relation to laboratory studies. Much of our knowledge of these aspects developed in relation to the Hammersmith Hospital clinic.

We are grateful to Miss Nancy Philcox for typing the manuscripts, the staff of the publishers, Butterworths, and, not least, to our wives for their tolerance over the last six years.

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Part I
Hormonal Contraception

1 Introduction

In 1937 Makepeace *et al.* discovered that progesterone inhibited ovulation in rabbits. Three years later Sturgis and Albright (1940) found that oestrogens used in the treatment of dysmenorrhoea also inhibited ovulation. In the early 1950s research was carried out to develop orally-active progestational steroids to be used to suppress ovulation. Norethynodrel was the first such compound to be synthesised in 1952, followed by norethisterone in 1954. Norethynodrel is the progestational component of the first oral contraceptive, Enavid (Enovid), which was shown to inhibit ovulation in the rabbit by Pincus *et al.* (1956) and in the human by Rock *et al.* (1958). The first clinical trials with Enavid were carried out on Puerto Rican women during 1956 and were followed by more extensive studies (Pincus *et al.*, 1958).

Enavid was marketed for the treatment of menstrual disorders in 1957 and as an oral contraceptive in 1960. The initial dose of norethynodrel was 10 mg, but with the introduction of more effective progestational agents and the realisation that an oestrogen component is the main factor in suppressing ovulation the hormone content of oral contraceptives has been considerably reduced. Most combined oral contraceptive pills now contain 0.5–2.0 mg of progestagen; some contain as little as 0.15 mg of norgestrel.

After Inman *et al.* (1970) suggested that the thrombo-embolic side-effects of the combined pill depended on the oestrogen dose, this was generally reduced from 200 to 100 to 50 μg of ethinyloestradiol or mestranol. Some oral contraceptives now contain as little as 20 μg of synthetic oestrogen.

The realisation that oestrogens were responsible for many of the major metabolic side-effects of the combined pill caused a return of interest in the study of products containing only progestational steroids. The first such preparation was chlormadinone acetate which became available during the mid 1960s. Tablets containing only norethisterone (norethindrone), ethynodiol diacetate, lynoestrenol, quingestanol acetate, norgestrel or clogestone have subsequently been tried or marketed with varying degrees of success. They are not widely prescribed but are useful for the woman who desires oral contraception and is advised against the use of the combined pill for medical reasons or is reluctant to accept any small risks that might be associated with synthetic oestrogens.

TYPES OF ORAL CONTRACEPTIVE

The Combined Pill

The combined pill contains an oestrogen and a progestagen. One tablet is taken daily for 21 days, though with a few preparations 20 or 22 days are advised. The tablets are stopped for seven days and consumption continued cyclically.

Oestrogens presently used in combined oral contraceptive tablets are ethinyloestradiol or its 3-methyl ether derivative, mestranol. The latter may be partly converted to ethinyloestradiol in the body. Most preparations now available contain 50 μg or 30 μg of one of these oestrogens.

The progestagens used belong to two groups, the 19-nortestosterone and the 17α-hydroxyprogesterone derivatives. The former group includes norethynodrel, norethisterone, lynoestrenol, ethynodiol diacetate and norgestrel. The latter group includes chlormadinone and megestrol. The doses of progestagens used vary from approximate equivalents of 0.5–4 mg of norethisterone. The absolute amount of each progestagen used is supposed to be related to its progestational potency.

A list of some of the combined pills available is given in *Table 3.1*, p. 50.

The Sequential Pill

Sequential pills were marketed for several years. All the 21 pills for a cycle contained an oestrogen, but usually only the last seven or eight contained progestagen. This sequence was an attempt to mimic the hormone pattern of the normal menstrual cycle. During the seven pill-free days some manufacturers included a placebo so that a pill was in fact taken every day. Poorly motivated patients found this confusing. A placebo tablet might be taken in error for an active pill at the mid cycle with the possibility of pregnancy resulting. The amounts of oestrogen and progestagen in the sequential preparations were similar to those in the combined pills. These preparations went out of favour despite the better menstrual cycle control provided. The failure rate was higher and it was also suggested that the sequential pills predisposed to the development of carcinoma of the endometrium.

Long-acting Oral Contraceptive Pills

These contain relatively large doses of a potent long-acting oestrogen and a progestagen. They were developed to provide a contraceptive which can be taken as a single oral dose once a month. This method best suits two classes of patients, highly motivated women with good memories who do not want the bother of taking a daily pill, and poorly motivated patients who can ingest the pill monthly supervised by a visiting nurse. The problems of the method are predictable – the metabolic and other side-effects of a high dose of oestrogen and the consequences on menstruation of initially high hormone levels falling throughout the month.

Low-dose Progestagen Pills

These preparations contain only a progestagen such as ethynodiol diacetate, 0.5 mg, norethisterone, 0.35 mg, or *dl*-norgestrel, 0.075 mg, and are taken daily with no break during menstruation. Their virtue lies in the very low dose of progestagen and the freedom from exogenous oestrogen therapy. The major problem they present – finding a drug whose dose is small enough not to cause menstrual irregularity and yet large enough to prevent pregnancy consistently – has not yet been entirely resolved.

The Postcoital Pill

The search for a pill which can be taken after intercourse and still prevent pregnancy has been pursued despite criticisms that such an agent essentially provides very early abortion on demand and contributes to promiscuity.

Effective regimens of oestrogen therapy have been developed to be initiated within 72 hours after a single episode of coitus. The object is to prevent pregnancy in rape victims and in women who subsequently regret their participation in unprotected intercourse.

Attempts have also been made to develop progestagen postcoital oral contraceptives for regular use – a pill to be taken after each episode of coitus. The concept is sound and involves using small doses of relatively harmless steroids at the most appropriate time. Some would also argue that motivation is strongest after intercourse. Unfortunately some of the early trials included women who undertook coitus several times a day. This resulted in an intake of progestagen sufficient to cause major disturbances of menstruation.

INJECTABLE HORMONES AND IMPLANTS

Depot steroid preparations have been developed to cater both for a small sophisticated group of women who do not wish to be bothered with personal involvement with contraceptive methods and for underdeveloped populations where it is necessary for professional personnel to participate actively in contraception programmes. These products contain relatively large doses of steroids and are injected or implanted at intervals of one, three or even six months.

Monthly injections of oestrogen–progesterone preparations have no advantage over monthly pills and carry the same risks. Injections of progestagens in doses which produce an effect lasting for several months have been used in selected groups of patients. Whether they carry any risk of an increased incidence of breast or other cancer has yet to be evaluated.

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2 The Clinical Pharmacology of Oestrogens and Progestagens

Oestrogens

Oestrogens are the principal functional hormones produced by the ovarian follicles. They are trophic hormones which play a part in growth and development of the non-pregnant woman, having a specific function in promoting the development of the female genitalia and secondary sexual characteristics. Cyclical increases in oestrogen production by the ovary are involved in the processes of ovulation and of the menstrual cycle. A massive addition to oestrogen production occurs in the feto-placental unit during pregnancy.

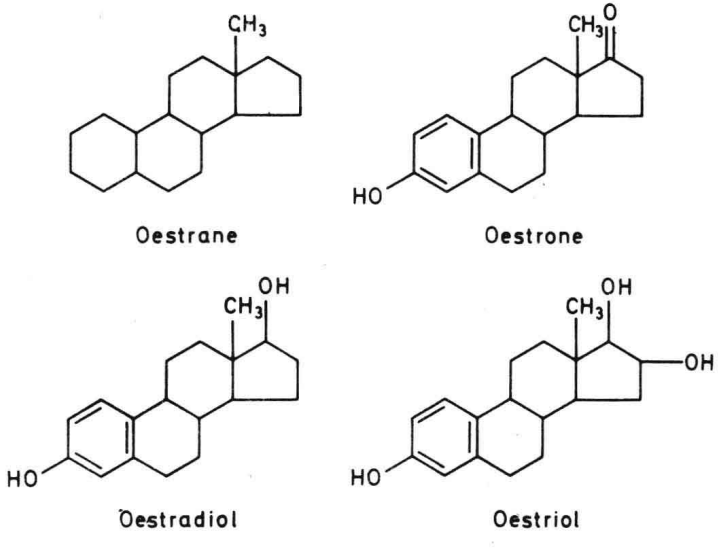
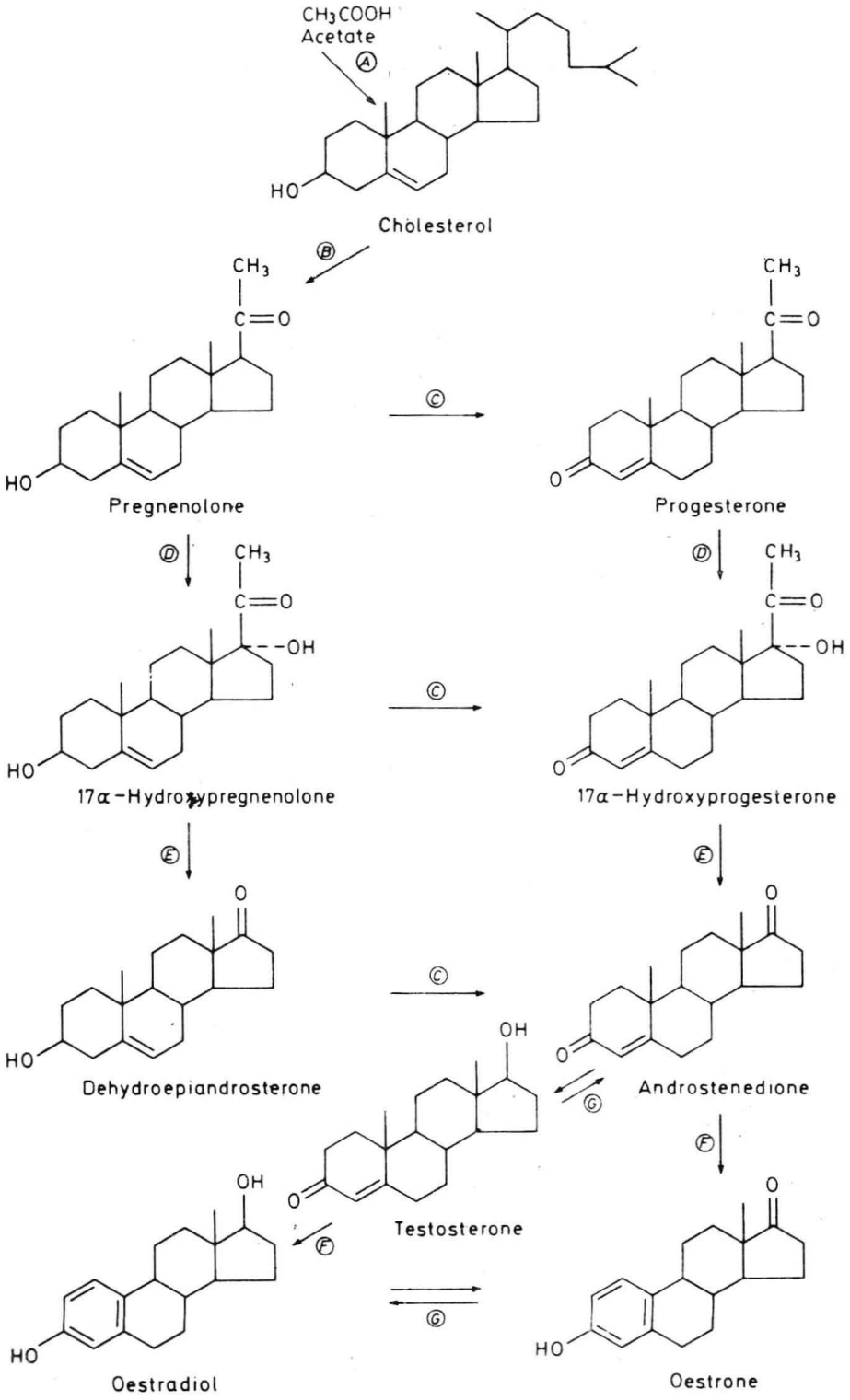


Figure 2.1 Formulae of the steroid nucleus, oestrane, and the three naturally occurring oestrogens

In the human female the three major oestrogens are oestrone, oestradiol and oestriol. Oestradiol is the most biologically active of the three, oestriol the least active. They are C-18 steroids, that is, derived from oestrane, which has 18 carbon atoms. The formulae of the steroid nucleus and the three naturally occurring oestrogens are shown in *Figure 2.1.*


CH3COOH
Acetate
A
HO
Cholesterol
B
CH3
C=O
HO
Pregnenolone
C
O
Progesterone
D
OH
17α-Hydroxypregnenolone
17α-Hydroxyprogesterone
E
Dehydroepiandrosterone
Androstenedione
OH
Testosterone
F
G
Oestradiol
Oestrone

Metabolism

Oestrogen is secreted by the theca interna cells of the Graafian follicle, and in addition it is synthesised in the adrenal cortex and produced peripherally. The principal metabolic pathways in the ovary are shown in *Figure 2.2.*

During pregnancy precursors produced by the placenta are sulphated in the fetus and then converted to oestrogens in the placenta. Large amounts of oestriol, oestrone and oestradiol then pass into the maternal circulation and are conjugated and excreted by the mother.

Physiological Role

Oestrogens have an anabolic action, favouring retention of nitrogen, calcium and phosphorus. They promote skeletal growth and epiphyseal closure. They act on the kidney to cause retention of water, sodium and chloride. In connective tissue, water content is increased and the mucopolysaccharides binding collagen are altered, rendering the tissue more supple. There is some evidence that oestrogens increase the blood volume and are involved in the consequent vasodilation by a direct action on the smooth muscle of vessel walls. Whether or not oestrogens have a generalised action on the process of ageing is not clear but they tend to prevent osteoporosis and, in the case of the natural oestrogens, atherosclerosis.

The tissues of the female reproductive tract have a much greater ability to incorporate and retain oestradiol than other tissues (Jensen and Jacobson, 1962) and this may account for its specific actions on the development of the genitalia. This binding capacity is due to a specific receptor protein for 17β-oestradiol within the genital tract epithelium. There are 4000–5000 such receptor molecules in each target cell. These receptors take up oestradiol from the blood as they have an affinity about 100 000 times greater than the binding carrier proteins in the blood. Oestradiol is then transferred from the cell cytoplasm to the nucleus where it is bound to a new receptor; progesterone may impair this transfer (Taylor, 1974).

Oestrone passing into the cell is rapidly converted to oestradiol before it can combine with the nuclear receptors and exert an influence. Oestriol probably competes for the oestradiol receptors but is less potent.

Under oestrogen influence the pelvic blood supply increases, the uterus grows and the vessels, glands and connective tissue of the endometrium proliferate. As the cervix grows its glands develop, secreting mucus. The development of ovarian primordial follicles is stimulated. Superficial vaginal squamous cells cornify under the influence of oestrogen. Oestrogen is also involved in the development of the breasts, controlling growth of the ducts, proliferation of lobules and development of the areolae.

Figure 2.2 Metabolic pathways for the ovarian biogenesis of oestrogens. A, formation of the sterol nucleus; B, cleavage of the cholesterol side chain with formation of C-21 steroid; C, isomerase reaction with changing of double bond from Δ^5 to Δ^4 position and dehydrogenation at the 3 position by 3β-ol-dehydrogenases; D, 17α-hydroxylation; E, cleavage of side chain, converting C-21 to C-19 steroids; F, aromatisation, introducing double bonds into ring A and converting C-19 to C-18 steroids; G, 17β-ol-dehydrogenase reactions, reversibly converting hydroxy- to keto-radical (Smith and Ryan, 1962).

In response to follicle stimulating hormone (FSH) the thecal cells of the developing Graafian follicle secrete oestradiol, which produces a cyclical enhancement of the oestrogen effects on the reproductive organs, as well as regulating proliferation of the endometrium. Oestradiol also causes suppression of FSH production, a feedback mechanism which tends to give a self-regulating cycle, and at the mid cycle it stimulates a surge of production of luteinising hormone (LH) from the anterior pituitary gland with subsequent ovulation. The levels of prostaglandin $F_{2\alpha}$ in the follicular fluid rise during follicle development. Contraction of the smooth muscle fibres distributed through the ovary, in response to prostaglandin or catecholamines, may also be involved in rupture of the follicle. The regularity of the cycle is reinforced by ovulation and the production of progesterone from the corpus luteum.

The cyclical production of oestrogen under FSH influence affects the smooth muscle of the reproductive tract, tending to increase the conversion of myosin to actomyosin and also to increase high energy phosphate concentrations in parallel with an increase in the maximum working capacity of the myometrium. The intracellular water and sodium content of the muscle cells is increased disproportionately, raising the membrane potential. The muscle cells of the uterus and fallopian tubes then increase their tone and spontaneous electrical and mechanical activity and contract more readily in response to stimuli. Evidence is accumulating that myometrial prostaglandin metabolism is also facilitated. Under oestrogen influence the uterine sensitivity to stimulant drugs is increased, this response being accompanied by prostaglandin release and prevented by prostaglandin synthetase inhibitors.

The effects of oestrogen on the cervical mucus are to reduce its consistency and increase its volume. At mid cycle there is a copious flow of clear cervical mucus with a good spinnbarkeit, this being a measure of its elasticity. The reduced consistency of the mucus facilitates spermatozoal penetration by means of proteolytic enzymes in the spermatozoa heads. The spermatozoa are encouraged to move towards the uterus by the long, parallel, loosely bound glycoprotein molecules of the cervical mucus found at this time of the cycle.

In pregnancy the greatly increased production of oestrogen results in exaggeration of many oestrogen effects, though some are modified by the contemporaneous increase in progesterone influence. Oestrogen plays a part in the somatic, cardiovascular, fluid balance and metabolic changes of pregnancy. With progesterone it is involved in the suppression of ovulation and menstruation and in breast development. Increase in pelvic blood supply, softening of the pelvic connective tissue and uterine growth and increased functional capacity are oestrogen effects.

Synthetic Oestrogens

The synthetic oestrogens that have been used to any extent in clinical practice are stilboestrol, ethinyloestradiol and its 3-methyl ether, mestranol. These compounds are active when taken orally. Ethinyloestradiol is considerably more potent than stilboestrol, weight for weight, and probably a little more potent than mestranol. It is difficult to be dogmatic about the relative potency of ethinyloestradiol and mestranol, because the assessments have been carried out in terms of various animal functions, the relationship of which to the effects of