Review

USE OF PROGESTATIONAL COMPOUNDS IN GYNAECOLOGY AND OBSTETRICS

(A Review)

by

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This review mostly covers the literature published during the last 5 years, which in the author's opinion have contributed significantly to the field of gynaecology and obstetrics. A definite bias may be seen in selection of papers of the Indian workers as it is felt that this review is primarily written to acquaint the readers with the work done on this subject in India. By no means, this review is intended to be a complete summary of the literature and so the author assumes full responsibility both for the particular selections and for any omissions.

Interest in this subject has continued to grow ever since the first report on the synthesis of potent orally active 19-norsteroids was published in 1952 (Djerassi *et al*) and the effects of these compounds on mammalian reproductive processes were studied in 1953 by Pincus and Chang. Other orally active progestational compounds, some of which are more potent than the original compounds, have been developed. Some of these have the added advantage that when administered parenterally they provide a prolonged effect. Each of these compounds is a potent steroid and although they are not the panacea for all gynaecological disorders, they will give, if used intelligently for specific conditions, the desired results in most patients.

Perhaps the most dramatic and important effect of these compounds, if given in proper regimen, has been their unfailing ability to suppress ovulation in women. It may be of interest to know that as early as 1893 it was postulated by Beard that the corpus luteum of the ovary was responsible for the inhibition of ovulation during pregnancy and this concept was supported by various studies performed on the corpus luteum during the ensuing twenty years. Following the isolation of progesterone in 1934, Makepeace *et al* reported in 1937 that the administration of this steroid inhibits ovulation in the rabbit. However, the new era in the history of contraception began with the report of Pincus at the Fifth International Conference on Planned Parenthood in Tokyo 1955, which stated that ovulation could be inhibited in women by taking synthetic progestogens orally. Since then, no

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medical development in recent years has aroused more controversy, even in medical circle, as the oral "Pill". A number of excellent reviews have appeared during the past 5 years on the use of these new progestogens for the control of fertility in the human females (MacLeod and Tietze, 1964, Pincus, 1965, Mears, 1965, Drill, 1966, Goldzieher and Rice-Wray, 1966, W.H.O. Report, 1968).

Chemistry

The structural formula of the basic steroid nucleus is shown in Fig. 1.

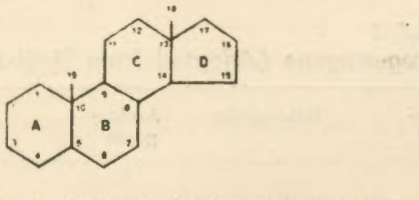

Fig. 1

The structural formula of the basic steroid nucleus. It is composed of a fully hydrogenated phenanthrene nucleus, (A, B and C rings) and a cyclopentane ring (D). The position of the different carbon atoms are conventionally numbered as indicated over here.

The chemical structures of new synthetic progestational compounds are shown in Figs. 2 & 3, in comparison with testosterone and progesterone. Considered chemically, orally active synthetic progestogens are essentially variants of testosterone (19-nor testosterone) which is made progestogenic by the addition of an ethinyl radical in the 17 position. The other group is characterised by modification of the basic progesterone structure with varying types of radicals to form the so called "substituted" progestogens. Biologically speaking, 19-nor testosterone derivatives are partly metabolised to oestrogens and hence are called oestrogenic progestogens. They can (i) readily inhibit

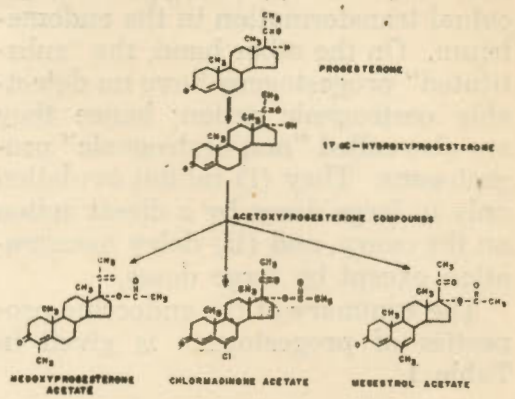

Fig. 2

Structural formulae of "19-nortestosterone" synthetic progestogens. Removal of the methyl group from position 19, increased the potency of these compounds. Additional potency is obtained by the addition of an acetate group at position 3 and 17 (ethynodiol diacetate) or of cyclopentylenol ether at 3 position (quingestanol acetate).

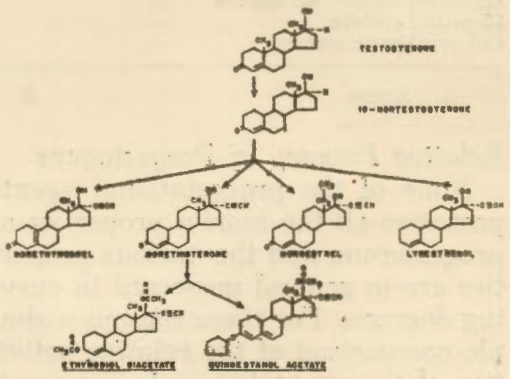

Fig. 3

Structural formulae of "substituted" synthetic progestogens. By addition of the methyl group at 6 position in an acetate ester of 17 α-hydroxyprogesterone, progestational potency is markedly enhanced as in medroxyprogesterone acetate. Chlormadinone acetate and megestrol acetate are similar compounds but by removal of 2 hydrogen atoms in the B ring and addition of chlorine or methyl at 6 position, the potency is increased.

ovulation, (ii) delay menstruation and in adequate doses produce endometrial haemostasis, (iii) produce decidual transformation in the endometrium. On the other hand, the "substituted" progestogens have no detectably oestrogenic action; hence they are also called "non-oestrogenic" progestogens. They (i) inhibit ovulation only in large doses by a direct action on the ovary, and (ii) delay menstruation except by large doses.

The summary of the endocrine properties of progestogens is given in Table 1.

(b) The production of mid or late secretory endometrium after a 10-day course of progestogen.

Both the aforementioned tests can be carried out on castrated women. Before performing the test the endometrium has to be sensitized with two courses of oestrogen and progestogen and during the cycle used for the test the endometrium has to be primed with oestrogen.

(c) Withdrawal bleeding following a 5-day course of progestogen in women with secondary amenorrhoea.

(d) Postponement of menstruation

TABLE I

Summary of endocrine properties of progestogens (Adapted from Drill-1966)

	Pituitary inhibition	Proges-tational	Estrogenic	Andro-genic	Anabolic
Norethynodrel	+	+	+	0	0
Norethindrone	+	+	0	+	+
Norethindrone acetate	+	+	0	+	+
Lynestrenol	+	+	+	+	+
Ethynodiol diacetate	+	+	+	+	0
Medroxyprogesterone acetate	+	+	0		
Megestrol acetate	+	+	0	0	0
Chlormadinone acetate	+	+	0		

\+ Active. 0 Inactive.

Relative Potency of Progestogens

None of the progestational agents possesses all the known properties of progesterone and the various properties are in general possessed in varying degrees. For these reasons a simple comparison of the relative activities of the progestogens is not possible. The results obtained will depend on the type of test used.

The following criteria can be employed in the clinical assessment of progestational agents:

(a) The production of sub-nuclear vacuolation in the epithelium of the endometrial glands following a 5-day course of progestogen.

in normal regularly ovulatory women given a 20-day course of progestogen from the twentieth day of the cycle. This ability to delay onset of menses for an arbitrarily chosen period of 2 weeks, has been employed as a simple, practical and critical test for the efficacy of progestational compounds (Table II). The usefulness of this test has been attested by Swyer and Little (1962) who feel that the test is an objective one which serves to quantitate results in testing progestogenic activity for statistical evaluation. If a standard dose of oestrogen equivalent to 0.1-0.2 mg of ethinyl oestradiol was added to the pro-

gestational compound to be tested and administered from day 20 to day 40 to regularly ovulatory females it was found that very large doses are required for some progestational compounds and very small amounts for the other progestogens. Some information on the relationship of structure to the efficacy of certain progestational compounds by this test can be gathered from Table II; of the "substituted" progestogens, chlormadinone has proved the most potent while of the 19-norsteroids, ethynodiol diacetate has proved to be the most effective of all progestogens so far tested in human females.

(e) Depression of the pyknotic index in the vaginal smear.

(f) Inhibition of oestrogen-induced changes, such as fern crystallization in the cervical mucus of castrated women given oestrogens.

(g) Inhibition of ovulation, determined by the failure of the urinary pregnanediol level to rise after the fourteenth day when the progestogen is given from the fifth to the twenty-fifth day of the cycle.

TABLE II

Structure	Daily dose required for delay of menses
Progesterone	1000 mg
Medroxyprogesterone	30 mg
Megestrol	10 mg
Chlormadinone	4 mg
Norethynodrel	13.8 mg
Norethisterone	10.0 mg
Norethisterone acetate	7.5 mg.
Ethynodiol diacetate	1.0 mg

Clinical Applications

These can be grouped into: (i) Proved and (ii) Proposed indications.

Proved Indications

Dysfunctional uterine bleeding: Normal menstrual cycles are characterised by the proper balance in the secretions between the hypothalamic-hypophyseal system and the ovary. Dysfunctional uterine bleeding probably results from an imbalance of these hormones rather than a deficiency of the pituitary gonadotropins or ovarian hormones. At any rate, this term is employed to describe abnormal uterine bleeding which cannot be accounted for by organic lesions of the uterus or any systemic disease. The highest incidence of this disturbance is found in the postmenarchal and premenopausal period, viz. during the initiation and the decline of ovarian function. The menstrual pattern lacks any rhythm, the type most commonly seen in so-called "anovulatory bleeding", which occurs as a result of rises and falls in estrogen levels without the differentiating effect of progesterone. The endometrial growth pattern in this entity often reveals a deficiency of progesterone effect and usually shows a proliferative hyperplasia of occasionally anaplastic pattern. Attempts should be made, therefore, to find the cause of bleeding and correct it; but regulation of cycles and prevention of excessive bleeding may be accomplished even if the exact etiological factors are not discovered. Thus, to be effective endocrine therapy must be based on an accurate diagnosis of the hormonal defects, and in practically all instances, vaginal cytological studies and examination of endometrial tissue obtained at the proper time is helpful (Shah and Dave 1959). If the patient is seen during an episode of profuse bleeding, any of the potent 19-nor compounds in adequate dose is quite efficient. (Das and Popli 1964). The ingestion of Norethyno-

drel* in 10 mgm doses twice a day or Norethisterone acetate, 8-12 mg per day, or Ethynodiol diacetate* in the daily dose of 4 mg for a few days will stop bleeding. All these contain added oestrogen in the commercially available preparations. In order to avoid withdrawal bleeding after cessation of the medication, the author advocates that as the bleeding stops, the medication is to be continued in reduced dosage to be employed for another 10-15 days. Following stoppage of this schedule, within 2-4 days withdrawal bleeding will occur but this period will be scanty and would last for a few days. Beginning on the fifth day of the withdrawal cycle, cyclic therapy can then be instituted as shown in Fig. 4.

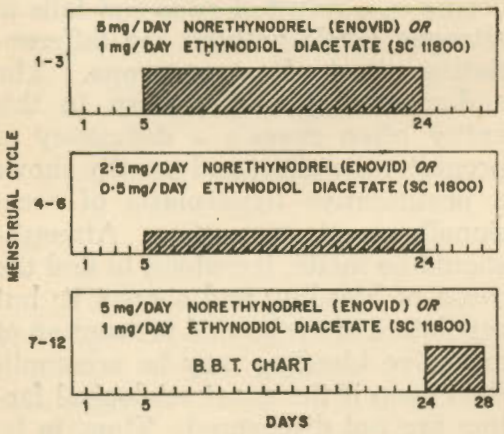

Fig. 4

In the author's experience, if the pretreatment biopsy has shown simple proliferative endometrium, the aforementioned artificial cycle should be continued for at least three months and this treatment may have to be repeated as the need arises. If the biopsy has shown hyperplasia, the artificial cycles are maintained for 9-12 months on a decreasing dose schedule and then depending upon the patient, an endometrial biopsy is performed or B.B.T. charts are maintained to see if ovulatory cycles are established (Shah, 1964).

The progestogens along with oestrogen have also been utilised where loss of blood is dangerous or when such a patient is waiting for surgery. These combined preparations can be used to produce amenorrhoea for several months. A successful dosage is 5 mg of lynestrenol plus 150 ug of mestranol or 2 mg of ethynodiol diacetate plus 100 μg of mestranol daily.

Menorrhagia: When excessive or prolonged menstrual flow is accompanied with normal cycles, in the presence of histologically normal secretory endometrium and in absence of organic lesion, the etiology of menorrhagia becomes theoretical and is ascribed to "unstable endometrial vasculature". At any rate, the incidence of such dysfunctional bleeding is not uncommon after the age of 35 years and relief from this distressing problem can be obtained by using preferably one of the aforementioned 19-nor derivatives or the "substituted" progestogens. (Pathak and Shah 1968). More often than not, the administration of these compounds during the last 10 days of a menstrual cycle sufficies to bring about a satisfactory flow for 4-5 days. If the patient does not respond to this treatment, careful search for other causes of excessive bleeding should be assiduously undertaken. Fibromyomata, abnormal pregnancy, polyps, adenomyosis or endometriosis or endometritis may be missed at the first examination, but re-evaluation

will frequently lead to their discovery.

Hypomenorrhoea: Although not a frequent problem, most women dislike scanty periods especially when they were used to heavy or normal flow before. If obesity or any organic lesion, such as tuberculous infection, is excluded (specific therapy for such entities should be instituted) and if the histological pattern is of "inadequate secretory endometrium", such women may be treated with 19-nor derivatives from the 15th to 25th day for three successive cycles. If the pattern is of the hypoplastic inadequate proliferative type, oestrogen should be also added in the early part of the cycle. The author has observed a number of pregnancies following 3-6 months' treatment with the sequential (10/10) schedule suggested in the text.

Amenorrhoea: This is always a symptom and a careful search must be made for its etiology. Amenorrhoea resulting from a systemic disease, ovarian failure, or pituitary tumours cannot be corrected by substitution therapy with ovarian-like hormones. Primary amenorrhoea is practically never corrected by the use of progestational agents, but while diagnostic procedures are being performed, therapy may be instituted since the response may be most informative. For example, if bleeding occurs following the administration of progesterone, one may conclude that: (1) endogenous estrogen is being produced; (2) a responsive endometrium is present; (3) pituitary gonadotropic activity is present; and (4) the amenorrhoea is not due to pregnancy. Progestogens containing estrogen are therefore not ideal for this test. If bleeding does not occur after progesterone alone, it is necessary to find the ability of the endometrium to response by a preliminary estrogen priming. In a country like India where tuberculous endometritis is not uncommon, it is frequently difficult and occasionaly impossible to obtain endometrial tissue by biopsy or curettage which shows the characteristic histological picture sufficient to make an unqualified diagnosis of tuberculous endometritis. The author has had several occasion where the typical tuberculous processes in the endometrium became evident only after the administration of adequate amount of progestogens, especially the "substituted" derivatives. In all such cases, prior to progestogen administration, priming of the endometrium was done with oestrogen given orally or intracervically (Shah *et al* 1961).

Primary Dysmenorrhoea: This common disorder of young women is associated with ovulatory menstrual cycles, since relief may be obtained in almost all patients by suppression of ovulation. The physiopathology of primary dysmenorrhoea is unknown but is believed to be associated with tissue anoxia, sloughing of endometrium, and uterine muscle hypermotility. It has been common knowledge that if the 19-nortestosterone derivatives are given in doses adequate to suppress ovulation, menstrual cramps are alleviated in about 80 to 90 per cent of cases. Further, numerous patients using the estrogen-progestin combination as an oral contraceptive have noted marked improvement in the usual degree of uterine cramps accompanying their periods. This is an unusual finding

since, in the past, the addition of progesterone in the last half of an estrogen-induced artificial cycle usually resulted in severe dysmenorrhea. Administration of the newer progestogens throughout the cycle may affect the sloughing process and improve myometrial contractility.

Where dysmenorrhoea is encountered in married women, particularly when associated with infertility, the relatively new preparation available in our country, called Duphaston-a retroprogesterone, when given from day 5 to 24 day of each cycle produces a painless period without suppressing ovulation.

TABLE III

Dosage schedules of progestogens for treatment of endometriosis

Norethynodrel with Mestranol	2.5 mg daily for 1 week 5.0 mg daily for 1 week. 10.0 mg daily for 2 weeks 15 mg daily for 2 weeks 20 mg daily for 34-46 weeks
Medroxyprogesterone Acetate	2 ml (100 mg) inj. every 2 weeks for 4 doses ; than 4 ml every 4 weeks. Add oral estrogen if breakthrough bleeding occurs or 1000 mg inj. (10 ml of 100 mg/ml in one Site) add oral estrogen or 30 mg. estradiol valerate for breakthrough bleeding.
Norethisterone Acetate (4.0 mg) with ethynyl oestradiol (0.05 mg) Megestrol Acetate (5.0 mg) with mestranol (0.1 mg) Ethynodiol Diacetate (2.0 mg) with mestranol (0.1 mg) Chlormadinone Acetate (2.0 mg) with mestranol (0.08 mg)	One tablet daily (starting from the 5th day of the cycle) until breakthrough bleeding occurs. Increase by one tablet for recurrent bleeding.

Endometriosis: This disease is frequently seen in women who have long intervals of uninterrupted ovulatory menstruation. It is frequently associated with infertility. When conception occurs the disorder improves and this is believed to be due to the formation of a decidual reaction in areas of endometriosis brought about by the placental oestrogen and progesterone. It has been suggested that repeated pregnancies actually prevent or delay the development of the disease. In lieu of pregnancy, in the unmarried or the infertile patient, one of the regimens suggested by Kistner (1968) may be utilized to secure a pseudopregnancy for periods of time varying from nine to twelve months (Table III). It should be noted that the progestogens are administered continuously and not cyclically. However, equally good results are claimed by Grant (1964) by cyclic treatment using 19-nortestosterone derivatives in patients with endometriosis. Besides cyclic bleeding, the added advantage is in the cost of the treatment which with the continuous method suggested by Kistner (1968) is at least 5 times that of the interrupted regime.

These progestogens have also been utilized for softening tissue planes in the pelvis prior to conservative laparotomy for extensive endometriosis. The dissection in the region of the cul-de-sac, especially when the rectum is adherent to the

posterior aspect of the uterus and cervix, is simplified by this procedure. Medication should be given from six weeks to three months prior to operation depending upon the extensiveness of the endometriosis.

In the initial phases of treatment with large doses of progestogen in continuous schedule about 15 per cent of the patients complain of nausea. This generally disappears within four or five days and is followed by a sense of well being and increased appetite. When the nausea is severe, it may be obviated to some extent by beginning with a smaller dosage and then gradually increasing doses to a maintenance of 20 mg. Also, the use of antiemetics and tranquilizers is of some value. If salt and water retention is bothersome, restriction of sodium in the diet and chlorthiazide can be prescribed. Growth of leiomyomas has been noted in patients receiving estrogen-progestin combinations and is probably due to estrogen stimulation. For these patients one of the "substituted" progestogens such as medroxyprogesterone acetate may be substituted. Treatment should last for a minimum of six months and in certain patients with recurrent endometriosis following operation, should be continued for 12 to 24 months.

Metastatic endometrial carcinoma: A dramatic response to the use of the synthetic progestogens has been noted in patients with disseminated endometrial carcinoma. Although the exact mode of action is unknown, it is presumed to be due to a direct effect of the hormone on the tumor cell. The effects of medroxyprogesterone acetate, hydroxyprogesterone caproate and ethynodiol diacetate administered into the cavity of the uterus of patients with endometrial carcinoma suggest that well-differentiated cancer cells are affected by direct contact. Similarly, tissue cultures of endometrial cancer cells have been noted to grow in the presence of estrogenic substances but not when progesterone is added.

Objective remissions have been obtained in approximately 35 per cent of patients and subjective remissions in 70 per cent. Pulmonary metastases have responded more frequently than pelvic metastases, and well-differentiated tumours more than anaplastic ones. Side effects associated with the administration of these agents have been minimal, especially when compared with the serious, and occasionally fatal, reactions seen subsequent to the use of alkylating agents (Kelly and Baker, 1961; Kennedy, 1963; Cox and Kirkland, 1964; Steiner *et al*, 1965).

The dose should be adequate and early "loading" is important. The optimum dose of 17-alpha-hydroxyprogesterone caproate is between 3 to 5 gm given intramuscularly, weekly, for a minimum of 6 weeks. The optimum dosage of medoxyprogesterone acetate is a minimum of 3 gm during the first 5 to 6 weeks and a maintenance of 400 mg, each month for an indefinite period. Recommended doses of the various progestational agents are outlined in Table IV. (Kistner 1968).

Certain patients who have had a remission from one progestational agent and then subsequently have developed a recurrence may respond to the administration of another progestational agents or an alkylating agent with a progestogen. Progesta-

TABLE IV

Dosage schedules for progestogens for the treatment of metastatic endometrial carcinoma

17—Hydroxyprogesterone caproate	3 to 5 G (parenterally) for at least 6 weeks. If a remission is obtained, therapy should be continued indefinitely.
Medroxyprogesterone acetate	400 mg (parentaerally) daily for 5 days ; then 400 mg 3 times weekly for 3 weeks ; then 400 mg twice weekly for 2 weeks. If a remission is obtained after 6 weeks, therapy should be continued in a dose of 400 mg monthly.
Ethynodiol diacetate	100 mg daily for 5 days ; then 100 mg 3 times weekly for 5 weeks. If a remission is obtained after 6 weeks, therapy should be continued in a dose of 100 mg weekly.

tional agents may be administered as adjuvant therapy to surgical and radiation treatment. The salvage rate eventually may be shown to be improved by such combination of therapies.

Contraception: The strikingly successful results of the use of Norethynodrel as an oral contraceptive in the experiments conducted by Pincus and his colleagues (1955) in Puerto Rico women are now well known. According to the survey in 1967, the oral "Pill" is effectively used by well over 13 million women all over the world. Of these only 22 per cent were found to be living in the developing countries (Jones and Parker 1967). As far as India is concerned, over the last two and a half years the consumption of the oral pill has grown much more rapidly, though actual figures are, as yet, not available.

This is not a place to have a resume on the voluminous literature on oral contraceptives on various aspects. However, several basic facts should be kept in mind before the present status and recent developments of the oral pill are discussed. First, all the preparations currently in use consist of a synthetic progestogen in combination with an oestrogen called "combined" pill or a "sequential" pill where oestrogen alone is given for 15-16 days and then the remaining 5 days progestogen is given in addition to oestrogen. Secondly, it is important to emphasize that in spite of the need to consume a tablet daily for 20 or 21 days during each cycle, the use acceptability and use effectiveness are remarkably high in poorly educated women of low socio-economic level in different parts of the world (Pincus *et al*, 1958; Rice-Wray *et al*, 1965; Chinnatamby, 1963; Upadhyay and Rohtagi, 1965; Shah, 1965; 1968; 1969, ii; Mehra, 1969). Again, the regularity of bleeding following medication appears to be rather strictly regulated by the regimen. These artificial cycles give an assurance to the user of "normal genital function".

The various compositions of the pills used in India and elsewhere, their dosage and the method of administration are given in Table V. The author has felt that the dosage employed for contraception was too large for the small statured, low body weight Indian women, and since 1963 he has not only evolved low-dosage pills using these compounds, but has

TABLE V

Currently marketed oral contraceptives

A. Combined Formulations

Progestogen (mg)	Oestrogen (mg)	Trade Name*
Ethynodiol diacetate	mestranol	
1.0	0.1	Ovulen
Lynestrenol	mestranol	
5.0	0.15	
2.5	0.075	Lyndiol 22, Noracycline 22
Medroxyprogesterone acetate	ethinylestradiol	
10.0	0.5	
5.0	0.5	
5.0	0.075	
Megestrol acetate	ethiylestradiol	
4.0	0.05	Voldys 21
2.0	0.1	Volidan V
Megestrol acetate	mestranol	
5.0	0.1	
Norethisterone	mestranol	
10.0	0.6	
5.0	0.075	
2.0	0.1	
1.0	0.05	Orthonovum
Norethisterone acetate	ethinylestradiol	
4.0	0.05	Anovlar
3.0	0.05	Gynovlar
2.5	0.05	Norlestrin
1.0	0.05	Minovlar E. D
Norethynodrel	mestranol	
10.0	0.15	
5.0	0.075	
2.5	0.1	Enavid E
Norgestrel	ethinylestradiol	
0.5	0.5	Ovral
Norgestrienone	ethinylestradiol	
2.0	0.05	

*Only those available commercially at present in India.

B. Sequential Schedules

Composition	Days	Trade Name
Chlormadinone acetate and mestranol :		
mestranol 0.08 mg	15	
mestranol 0.08 + chlormadinone acetate 2 mg	5	
Dimethisterone and ethinylestradiol :		
ethinylestradiol 0.1 mg	16	
ethinylestradiol 0.1 mg + dimethisterone 2.5 mg	5	
Megestrol acetate and ethinylestradiol :		
ethinylestradiol 0.1 mg	16	
ethinylestradiol 0.1 mg + megestrol acetate	5	Serial 28
1 mg inert tablets	7	
Norethynodrel and mestranol :		
mestranol 0.1 mg (days 5–19)	15	
mestranol 0.075 mg + norethynodrel 5 mg (days 20-24)	5	

also modified the sequential schedule to mimic the physiological hormonal interplay that would produce normal withdrawal bleeding. This 10/10 sequential schedule using minimal progestogen, on extensive trial, is virtually 100% effective and has been associated with a gratifying drop

in the side effects (Shah, 1966 i; 1967; 1969 i) (Fig. 5 Table VI).

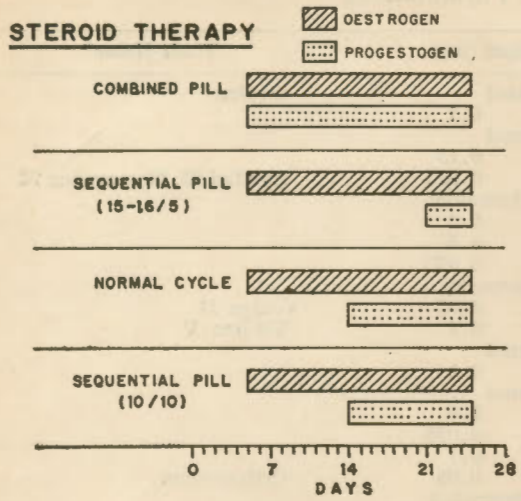

Fig. 5

not exist, a single dose of progestogen given as slow-release injection early in cycle would provide antifertility effect. The recent development in low-dosage continuous progestogen is the silicone plastic time capsule (small enough to be introduced through a needle into the tissues) wherein absorption of low-dosage is continuously maintained for one, two, three or 20 years. Such encapsulated progestogen could be tailored to suit the individual need and, if found practical in women, would really be a boon for developing countries (Segal, 1967).

It is perhaps doubtful if in its ultimately perfected form the pill will be a progestogen alone. Preliminary clinical trials indicate that monthly injections of a long-acting progestogen-oestrogen compound is another safe and effective method of birth control (Rizkallah and Taymor, 1966; Plesner, 1969). This progesterone derivative (dihydroxyprogesterone acetophenide) combined with

TABLE VI

Contraceptive efficiency of the sequential preparations available for contraception

Oestrogen in Mg	No. of days	Progestogen in mg	No. of days	Trade Name	Pregnancy Rate/ 100 women years
Ethinyl Oestradiol	16	Megestrol Acetate (5.0)	5	Ovisec (BDH)	1.2 (2056)*
Mestranol (0.1)	15	Norethynodrel (5.0)	5	Feminor (L.R.I.)	
Mestranol (0.08)	15	Chlormadinone Acetate (2.0)	5	Sequens (Lilly)	1.28 (25000)
Ethinyl Oestradiol (0.1)	16	Dimethisterone (25.0)	5	Oracon (Made Johnson)	3.4 (9195)
Mestranol (0.1)	10	Ethynodiol Diacetate (0.5 mg)	10	Present study	0.22 (5924)
Mestranol (0.1)	10	Ethynodiol Diacetate	10	Present study	0.50 (5121)

*Figures in brackets show number of cycles of medication.

Another low-dosage oral pill, containing a small daily oral dose of progestogen alone, given throughout the 365 days has shown a high antifertility effect (Manautou *et al*, 1966). Ovulation, however, is not suppressed by this schedule (Gutierrz-Najar *et al*, 1968). Where motivation does

estradiol enanthate (Deladroxate) has been tested in at least six United States' institutions in more than 500 women. A combination of 150 mg of the progesterone derivative and 10 mg of the estrogen, injected on the 8th day of the cycle, fairly consistently inhibits ovulation in most patients. Furthermore, this results in reasonably consistent cycles which average 27.2 days, with 80 to 90 per cent of the cycles falling within a plus or minus 3-day range. Only occasionally is the flow excessive and undesirable effects are minimal. After discontinuation of this medication, normal ovulatory cycles return within 6 to 13 weeks. Similarly, human trials with "one pill a month" (administered on the first day of the cycle) containing both oestrogen and progesterone are under way and, if found acceptable, would indeed be a great advance in oral contraception.

It seems likely that the oestrogen-progestogen combinations act in several ways that reinforce each other to produce high contraceptive efficiency. Ovulation is blocked because the ovulatory burst of urinary luteinizing hormone (LH) appears to be damped which may be related to the observation that small doses of oestrogen suppress LH more easily than the follicle stimulating hormone (FSH) (Stevens *et al*, 1965), Ovarian quiescence and focal cortical condensation of stroma, which appear to be reversible, have been found in about half of the biopsies of the ovaries of women who have had the medication for more than one year (Taymor and Rizkallah, 1965). That these compounds may have a direct effect on the ovary that blocks responsiveness to gonadotropin is suggested by Ryan *et al* (1964) based on the biopsy studies of the ovary and on the lack of response to exogenous gonadotropin in women who have had medication for more than one year. Hostility of the cervical secretion probably prevents the sperms from penetrating (Zanartu, 1964). The endometrium is profoundly altered with endometrial thinning developing after several months of treatment (Rice-Wray *et al*, 1963). Some of these have adequate control of the endometrial blood vessels, thus menstruation appears somewhat lighter. This ability of the drug to reduce the menstrual flow has led to its therapeutic use in many conditions involving excessive menstrual flow, as already mentioned under dysfunctional uterine bleeding. Since the pattern of endometrial maturation more nearly mimics the normal ovulatory cycle when "sequential" pills are used, some investigators have favoured this method of contraception (Shah, 1965; Durkin *et al*, 1965). There is, however, no evidence in the human of the antiblastocyst effect and the inhibition of nidation.

The undesirable effects of the 'pill' are the subject of considerable discussion. It is, however, generally recognised that these progestational compounds do not represent a serious threat. Fluid retention and weight gain are definite problems in some patients but this is usually self limiting and in most patients the weight at the end of one year is similar to that before treatment. The protein anabolic properties of some of the compounds may be a contributory factor to producing an increased appetite and deposition of muscle mass.

As a matter of fact, Indian women of low average weight welcome this gain and feel better while on the oral 'pill' (Shah, 1966 ii).

Regarding the serious adverse effects, it is unfortunate, in view of the great importance of this virtually 100% effective method for control of fertility, that well controlled studies of some of the problems, e.g. abnormalities of glucose metabolism or of uterine cervical changes, are not available at present. Wherever there is definite evidence about the increased frequency of the serious adverse effects, such as thrombo-embolic disease in women taking pills as compared to non-users, one has to weigh the advantages accrued in such cases by not becoming pregnant against the disadvantages of this undesirable effect (Schartz *et al,* 1962; Vessey and Doll, 1968; Vessey and Weatherall, 1968). At any rate for any such hazard one should also consider its incidence in the various ethnic normal populations since venous thrombosis and embolism for reasons unknown are rare, even after trauma, operation or childbirth in Indian women, unlike their counterparts in the West (Purandare, Personal Communication).

On the other hand, the increased risk of liver damage in 'pill' users has not been confirmed. In developing countries where malnutrition is rampant and infective hepatitis or amoebic infection are not uncommon, one would naturally be concerned about its adverse effect in women belonging to the low socio-economical strata. The published reports from various parts of India have so far not shown any deleterious effects on the liver function tests carried out in pill users belonging to the low socio-economic level (Shah *et al,* 1965; Shah, 1966 i; Purandare *et al,* 1965; Sheth *et al,* 1967; Engineer *et al,* 1968). It is, therefore, felt that there is no justification to restrict the use of oral pill on the basis of its hepatotoxicity. As an extra precautionary measure, however, the consensus is that the pill should not be given to women with hereditary defects in hepatic excretory function.

As far as the reproductive potential and function are concerned, there is also no statistically valid evidence that the oral contraceptives either accelerate or delay the onset of the menopause. Even when patients with endometriosis after recurrent operations are treated with massive doses for two or three years, following treatment a marked delay in the ovulatory menstrual cycle is not reported. Many of these patients indeed have become pregnant during the first two or three ovulatory cycles, further emphasizing the integrity of the total endocrine system. The suggestion that prolonged therapy with oral contraceptive agents might predispose to ovulation and pregnancy beyond the age of 50 seems to be more fancy than fact. Such a supposition completely disregards the natural aging process of the ovary and the natural diminution in fertility even in the woman who ovulates regularly beyond the age of 40. Pregnancy after the age of 56 has not been recorded even in grand multiparas who have ovulated only 15 or 16 times during their lifetime. It should be remembered that the eggs are not simply stored in the ovary during the period of anovulation, but undergo a process of follicular development and

atresia in a fashion similar to that noted during pregnancy.

There is no evidence available at present to suggest that the incidence of genetic abnormalities is higher in the offspring of women previously treated with oral contraceptive agents than in untreated patient of similar age groups. Similarly, the incidence of spontaneous abortions is not increased in patients who become pregnant subsequent to discontinuance of oral contraceptives. The extensive follow-up has also failed to prove any significant irreversible effect on the ovary, pituitary, thyroid or adrenocortical glands (Garcia and David, 1968; Schartz *et al*, 1968; Daly *et al*, 1968).

Similarly, several papers have appeared in the last two or three years describing the various fears and conflicts which can be triggered by oral contraceptives (Molinski, 1968). In short it may be said that the oral contraceptives themselves are not harmful but that they mobilise the fears which are already present in a psychically damaged personality.

Proposed Indications

Precocious puberty: Constitutional sexual precocity may be described as a premature initiation of the normal physiological and endocrinological processes characterised by breast development, appearance of pubic and axillary hair and menstruation. These signs are due to premature release of gonadotropins from the pituitary and the inciting factors are unknown. Kupperman and Epstein (1962), using medroxyprogesterone acetate parentally, suppressed the gonadotropins successfully in such cases. Based on this finding, by studying the changes in the vaginal cytology they claim to differentiate constitutional precocity from precocious puberty due to other organic lesions, say from granulosa cell ovarian tumour.

Increase in Linear Growth in Girls: In mammalian species including homo sapiens, it appears that an extremely important extragenital effect of oestrogen is retardation of the rate of linear growth by promotion of closure of the epiphyses. In these days of height consciousness, therapeutic approaches based on this principle can be envisaged. The author, for the ultimate aim to gain height in girls, particularly those whose parents are short for 'constitutional' reasons, has treated several cases with beneficial results and has not noticed any serious adverse effects during the follow-up period of two years when the treatment was discontinued. The therapeutic approach concerns the administration of adequate dose of medroxyprogesterone that would consistently inhibit the pituitary-ovarian axis so that premature closure of the epiphyses is prevented. The response of the treatment can be measured by estimation of the level of urinary gonadotropins, as well as from the changes in the vaginal cytology. Under this treatment, amenorrhoea follows if the subject had already started menstruation prior to treatment. Bone age of these subjects should be followed to determine the duration of therapy (Shah, Trivedi and Kothari, Unpublished data, 1969).

Timing of Menstruation: Various socio-religious obligations in these

days of highly complex organised life demand on occasions to delay or advance the occurrence of menstruation. Retiming of menstruation can be achieved by giving daily a high dosage "combined" pill from day 5 to 14 (menses advanced), by continuing this until the day 32 (delayed menses with inhibition of ovulation) or by giving a similar therapy from day 24-33 (delayed menses without inhibition of ovulation).

Hirsutism of Ovarian Origin: After the primary surgical treatment in the polycystic ovarian syndrome associated with hirsutism, viz. liberal wedge resection to reduce the tissue involved in the production of potent androgens, the author has maintained further inhibition of their production with Norethynodrel along with mestranol given for 18 cycles, (Shah, 1963). This treatment has indeed produced beneficial results in some cases as far as the superfluous hair growth is concerned. Recently Casey et al (1967) have shown that by using this compound, the synthesis of androgen in the ovary, as seen from the level of plasma testosterone, is successfully inhibited.

Idiopathic Infertility and Inadequate Luteal Phase: There is some evidence to suggest that the use of the 'combined' pill to produce a period of anovulatory cyclic bleeding results in an increased incidence of subsequent pregnancy in a group of functional infertility by a "pituitary-rebound" phenomenon. However, the reality of this "rebound" effect is still subject to wide divergence of opinion.

Inadequate luteal phase reflects a deficient state in the endometrium diagnosed by histological and histochemical characteristics of the endometrial tissue. Studies of the B.B.T., changes in the cytology of vaginal smear and pregnanediol excretion may corroborate the endometrial findings. The parenteral treatment using long acting "substituted" progestogens, viz. 17-hydroxyprogesterone caproate or medroxyprogesterone acetate, is given in such cases round about 18-20th day of the cycle. The results are variable.

Habitual abortion: Because of the multiplicity of uncontrolled factors entering into the maintenance of pregnancy in the human females and from the results of the recent double blind studies, it cannot be stated categorically that exogenous progesterone has improved the salvage rate in subjects classified as habitual aborters. If the clinician belongs to the group 19-nor derivatives or the "substitute," who believes in progesterone therapy, it is best started before conception and continued during pregnancy until foetal viability. Here again, long acting "substituted" progestogens are preferred to oral 19-nor derivatives. The treatment is started if the B.B.T. is elevated for 18 days and this is repeated at 7-10 days intervals till pregnancy is confirmed by an immunological or a biological pregnancy test. Along with this treatment, other measure including an ample amount of T.L.C. (tender loving care of both husband and the physician) cannot be overemphasised.

Metastastic Carcinoma of Breast: Although progesterone and synthetic progestogens have been given ade-

quate trials in the treatment of metastatic breast cancer, the results have not indicated that these agents are superior to, or even as good as, estrogen or testosterone. Recently, it is shown that a combination of estrogen-progestogen therapy gives beneficial response in postmenopausal women with advanced breast cancer. This response may be due either to a modification of in vivo metabolism of estrogens by the action of the progestogen or to specific synergistic action of the mixture (Kistner, 1968).

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