Depot Medroxyprogesterone Acetate (Depo-Provera) as a Contraceptive Preparation*

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SUMMARY

Experience with depot medroxyprogesterone acetate as a contraceptive preparation in 7 335 patients for a total of 38 714 months over a 3-year period is described. The discontinuation rate was 18·3% and the failure rate 0·35 per 100 women-years of use. This compares very well with all other methods of contraception.

The only troublesome side-effect was breakthrough bleeding which diminished with continued use. The aetiology of this menstrual disruption and methods of prevention and treatment are discussed. The role of this preparation in present-day contraceptive practice is outlined.

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The search for the so-called 'universal' or 'perfect' contraceptive preparation continues. It was inevitable that, following the successful use of hormonal agents taken orally for the control of ovulation, efforts to avoid a daily dosage schedule—and the accompanying risk of a pregnancy due to forgotten pills—should be initiated and pursued. One avenue that clearly held promise was the use of long-acting or depot injectable steroid hormones; and combinations of long-acting oestrogens and progestogens have been tried with varying degrees of success. More recently, long acting progestogens alone have been tried, and this article deals with experience with the latter, using 17 alpha-hydroxy-6 alpha methylprogesterone acetate, better known as medroxyprogesterone acetate (DMPA) or Depo-Provera.†

Depo-Provera has been extensively used in the treatment of threatened and habitual abortion and endometriosis, and recently it has been found to be of use in endometrial, renal and breast carcinoma.

As a progestational agent, DMPA is 20 - 30 times more effective than progesterone in the inhibition of ovulation in rabbits.[1] It is also 10·5 times as active as progesterone when checked by the Clauberg assay for endometrial stimulation in immature rabbits.[2]

Mode of Action

Prevention of contraception is thought to be due to a number of complementary actions:

1. Inhibition of the secretion of gonadotrophic hormones, particularly luteinizing hormone, and thereby preventing ovulation.[3-5] There is no influence on the secretion of growth or thyrotrophic hormones.[6]
2. Alteration of endometrial histology which, in turn, prevents nidation.[7-9] It would also appear from studies on lower animals that myometrial activity is significantly reduced in the presence of DMPA.[10]
3. Increase in the viscosity and alteration of the pH of the cervical mucosa, thereby forming a spermicidal barrier.

MATERIALS AND METHODS

All patients were examined fully before commencement of treatment, and the examination was repeated annually. A Papanicolaou smear was done as a routine whenever this was possible. Only those patients considered clinically free from gynaecological and endocrine disorders were given the DMPA and only patients of proven fertility were included in the study. An aqueous suspension of DMPA 50 mg/ml was used. The dosage was 150 mg (3 ml), given every 90 days.

The programme has continued over the past 3 years and at present involves 5 991 patients. Table I sets out our experience of this method for a total of 7 335 patients who have used DMPA over a total of 38 714 woman-months.

Discontinuation Rates

It will be seen that the number of patients who have discontinued the use of this method is 1 344. The reasons for discontinuation are as follows:

	No.	%
Change requested by patient	171	2·3
Change for medical reasons	64	0·87
Planned pregnancy	28	0·38
Unplanned pregnancy	11	0·15
Moved away from clinic	35	0·48
Reason unknown	1 035	14·1

The dropout or discontinuation rate is thus 18·3%, which compares well with the figures reported by other investigators listed in Table II.

*Date received: 19 October 1970.
†Upjohn, Johannesburg.

TABLE I. DEPO-PROVERA SURVEY

Clinics	Number of patients: (a) Currently in attendance	(b) Attendance discontinued: Change requested by patient	Changed by doctor	Planned pregnancy	Unplanned pregnancy	Moved away from clinic	Unknown reason for default	Total defaulters	Gross total patients (a) + (b)	Total months of use	Greatest number of months of use	Number given oestrogen
Europeans:												
Oasim	123	5	10	1	1	1	31	49	172	1 176	39	28
Others	1 222	16	1	5	7	15	310	354	1 576	7 761	30	180
Non-Europeans:												
Empilweni ...	1 712	75	39	9	0	7	228	358	2 070	12 624	18	140
Others	2 934	75	14	13	3	12	466	583	3 517	17 153	30	168
Total:	5 991	171	64	28	11	35	1 035	1 344	7 335	38 714		516
% of gross total:	81·7	2·3	·87	·38	·15	·48	14·1	18·3	100			7

TABLE II. DISCONTINUATION RATES

	No.	%
McDaniel[11]	346 out of 1 730	20
Zanartu[12]	316 out of 1 580	20
Zartman[13]	96 out of 480	25
Mishell et al.[14]	57 out of 100	57
Tyler[15]	28 out of 148	19
Karstadt[16]	239 out of 1 685	14·4
Present series	1 344 out of 7 335	18·3

These figures must, however, be compared with the discontinuation rates of other commonly used methods of contraception. As will be seen from Table III, the figure is substantially lower.

TABLE III. DISCONTINUATION RATES

Oral contraceptives	30 - 65%	at 2 years
Intra-uterine devices	30 - 60%	at 2 years
Injectable contraceptives (present series)	18·3%	

Failure Rate

The unplanned pregnancy or failure rate in this series is 0·35 per 100 woman-years of use. Again, this must be assessed in the light of figures reported by other investigators (Table IV).

The reported failure rates vary between 0·00 and 2·72 per 100 woman-years of use, and, to be of statistical value, this failure rate must be seen in its true light, i.e. by comparison with the other commonly used and effective methods of contraception. These are tabulated in Table V.

TABLE V. FAILURE RATES

Method	Pregnancy rate (per 100 woman-years' use)
DMPA	0·35 - 2·72
Oral contraceptive tablets	0·4 - 2·7
Intra-uterine devices	1·8 - 7·2

TABLE IV. FAILURE RATES

Author	Dose	No. of patients	Total woman-months of use	Unplanned pregnancy rate per 100 woman-years
McDaniel[11]	150 mg/3 months	1 730	15 584	0·40
Zanartu[12]	300 mg/6 months	1 580	30 900	2·72
Zartman[13]	150 mg/3 months	480	4 528	0·00
Soichet[17]	150 mg/3 months	298	3 010	0·00
Mishell[14]	150 mg/3 months (postpartum)	100	975	0·00
Tyler[15]	150 mg/3 months	148	1 285	0·00
Present series	150 mg/3 months	7 335	38 714	0·35

TABLE VI. SIDE-EFFECTS

	Breakthrough bleeding	Weight gain (av. 2 - 5 lb)	Headaches	Nervousness	Loss of libido	Nausea	Dizziness	Vaginal discharge	Breast problems	Skin rashes
	%		%	%	%	%	%	%	%	%
From 4 series (Upjohn) ...	8·8 (discont.)	1·0	14·8	8·1	4·4	3·5	3·5	2·7	2·1	
Tyler	2·1 to 29·0	1·4	2 2	7·2	0·7	4·3	1·4	0·7	0·7	
Karstadt ...	12·9		1·2							1·0
McDaniel ...	1·1 routine oestrogen									
Zartman ...	4·2									
Soichet ...	9·3									
Mishell ...	12·1	10·0								
Present series ...	Over-all 7·0 Oasim 16·2									

Side-Effects

The common side-effects are given in Table VI. The commonest and most troublesome side-effect will be seen to be disruption of the menstrual pattern with bleeding problems (breakthrough bleeding). The other problems which arise are usually relatively minor ones, and include weight gain, headaches, nervousness, loss of libido, nausea, dizziness, vaginal discharge, breast problems and skin rashes. It has been observed that the incidence of bleeding problems gradually decreases with the continuation of treatment. This is illustrated in the following table:

TABLE VII. BLEEDING PROBLEMS

	% days with breakthrough bleeding	
Injection No.*	Tyler[15]	Zartman[13]
1	29·0	27·5
2	21·1	20·4
3	17·3	15·4
4	13·2	12·2
5	7·0	10·7
6	10·5	8·8
7	0·1	8·6
8	0	7·4
9	0	6·6

* Injection period 90 days.

Treatment of Bleeding Problems

The treatment of side-effects for practical purposes involves only the management of bleeding problems. It is most important, before attributing all menstrual problems to the use of the drug, to be absolutely certain that no coexistent pathology exists. This applies particularly to pelvic infection, cervicitis, moniliasis, trichomoniasis and gynaecological malignancies. These conditions, if suspected clinically, should be diagnosed and treated by the appropriate methods and with the usual drugs before assuming that the DMPA is causing the menstrual disorganization. Only in this way will the best results be obtained from this method of contraception, and in addition, no serious coexistent disease will be missed.

If, however, the bleeding problems are found to be due to the drug, treatment is based on the assumption that the bleeding is caused by the drug's potent anti-oestrogenic effect which so lowers ovarian oestrogen secretion that endometrial disruption follows. Treatment has been with oestrogens, usually by the oral route, and the recommended dosage is stilboestrol 1 - 3 mg daily, ethinyloestradiol 0·05 - 0·1 mg daily, or Premarin 1·25 - 2·5 mg daily, usually given for from 5 to 10 days.

It is important to warn patients of this possibility before starting treatment, to emphasize that these problems almost invariably improve with the passage of time and continuation of treatment, and to reassure them while these problems are troublesome.

Re-establishment of Fertility

This can only be judged by the criteria commonly employed for determining the occurrence of ovulation. These criteria include the return of natural menstruation, vaginal smear patterns, monthly endometrial biopsies, cervical mucous testing, pregnanediol estimations and also subjective findings.

Using the above criteria (of which at least 3 must be positive) it has been estimated[15] that 33% of patients ovulated within 6 months of their last injection; that 99% of patients ovulated within one year of their last injection; that ovulation was not always consistent and in some cases

was sporadic for up to 18 months; and that the interval for re-establishment of fertility appeared unrelated to dosage.[12]

Effect on Lactation

In a recent comparative study[18] the conclusion arrived at was that DMPA had given the most satisfactory results in relation to milk yields, infant growth curves and lactose and protein content of milk. There was a drop in the lipid content. It was concluded that this type of contraception was ideal in the postpartum period, as bleeding problems were expected to some extent and thus did not cause concern to these women.

The Problem of Thrombo-embolism

To date, there has been only one report[17] of a thrombosis of the subclavian vein. In view of the large number of women who have had this preparation at various times, for various reasons and in varying doses, and also because of the fact that no oestrogen is being administered, it seems unlikely that thrombosis will be a major problem.

Breast Tumours

The occurrence of breast tumours in beagle bitches after continuous administration of chlormadinone acetate (Normenon) in doses of 0·5 mg daily, naturally poses this question in regard to DMPA.

The findings at present are that mammary nodules have been observed to occur after 18 months of treatment in beagle bitches known to be prone to their occurrence, but not in monkeys. These dogs differ from humans in their metabolism of DMPA and also in their propensity to develop hypertrophic endometriosis, and these results therefore cannot be extrapolated to humans. Furthermore, breast nodules have not been reported in humans after 10 years of use for various indications, for periods extending up to 60 months.

However, it would seem to be necessary to impress upon patients the advisability of the periodic breast examinations which are recommended with any hormonal contraceptive regime.

Advocated Use at Present

At present, because of the uncertainty in regard to restoration of fertility, this method should not be used for family spacing. Ideally, it should be confined to patients who should not conceive for a long period of time, or have any more children. This general category would include the following large groups of patients:

1. Failure with or an inability to use other forms of contraceptives.
2. Chronic illness where no further pregnancies are desirable, e.g. TB, chronic renal disease.
3. 'Problem' patients with 'problem' families who will not, or cannot, use other methods of contraception reliably. Motivation is usually lacking or very poor in these cases.
4. Patients where clinic attendance is a problem, due to distance.

THOUGHTS FOR THE FUTURE

As the major problem with this preparation is a disorganization of the menstrual cycle, with the most troublesome side-effect being breakthrough bleeding, this would appear to be the most urgent problem for investigation.

All findings suggest a lowering or absence of oestrogenic effect on the target organs, particularly the endometrium and vagina. To determine whether this effect is due to an inhibition of endogenous oestrogen production by DMPA, or due to the drug's effect overwhelming the end-organ action of normal levels of circulating oestrogen, is important; if the endogenous oestrogen level is low, perhaps additional oestrogen should be given to prevent the possible early development of oesteoporosis or arteriosclerosis.

This should be fairly easy to determine and is a priority on a study set up in our series recently, and which we hope to report on in the future.

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