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Contraception with a Six-Monthly Injection of Progestogen

Part 1. Effects on Blood Pressure, Body Weight and Uterine Bleeding Pattern, Side-Effects, Efficacy, and Acceptability

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Summary: A clinical study of the use of medroxyprogesterone acetate as a method of contraception, administered as 6-monthly intramuscular injections of 300 mg., was carried out in 61 women. A total of 989 months of study were completed and 14 women received 4 injections or more.

There were no significant changes in the systolic and diastolic pressure or in the body weight during 18 months of observation as compared with the pre-treatment levels.

Disorganisation of the uterine bleeding pattern was encountered, particularly during the first 6 months. However, there was a progressive decrease in the duration of bleeding per month and increase in the proportion of women who had amenorrhoea with time.

Side-effects were varied but mild; depression and diminution in libido were comparatively common.

No pregnancy occurred during the period of study. Twenty of the 61 women discontinued treatment for reasons related to the drug, the important factor in 75% of the drop-outs was unacceptable bleeding.

In view of the problems associated with currently employed contraceptives, pure progestogens, either in oral or injectable form, have been the subject of recent investigation.

Preliminary clinical studies with long-acting progestational compounds given at intervals of 1 to 3 months have been promising (Zanartu et al., 1966; Zartman, 1966; Tyler, 1967; Mishell et al., 1968). By this means the woman is no longer encumbered with the chore of daily pill-taking, and one of the main causes of failure in unreliable or poorly motivated patients is avoided.

Experience with depo-medroxyprogesterone acetate, a 6 α-methyl 17 α-hydroxy-synthetic derivative of progesterone with potent progestational but little or no oestrogenic or androgenic activity (Greenblatt and Barfield, 1959) forms the basis of the present report. The therapeutic safety of this compound has previously been assessed in patients with endometriosis, dysfunctional uterine bleeding, threatened and habitual abortion, and malignancy of the uterine body. The development of improved suspension bases has provided a slower and more uniform release of the progestogen.

Clinical findings and laboratory tests were monitored before, during, and after treatment. The endocrine profile and endometrial reaction were evaluated in an endeavour to elucidate the mode of action of the drug. In the present paper, the effects on blood pressure, body weight, and uterine bleeding pattern are described, together with an assessment of side-effects, and the efficacy and acceptability of the method.

MATERIAL AND METHODS

Patients

The clinical study comprised 61 women of Caucasian origin who had demonstrated their fertility by having had at least 1 previous pregnancy; 55 were postpartum. The possibilities of prolonged amenorrhoea, irregular and unpredictable vaginal bleeding, and prolonged infertility during and after the treatment period were explained to the women and accepted by them before their inclusion in the study.

Drug

An intramuscular injection of medroxyprogesterone acetate, 300 mg., in a slow-release aqueous suspension (100 mg. per ml.) was given deeply into the gluteal region after ascertaining that the pre-treatment physical examination and the laboratory tests, in particular the bromsulphthalein excretion test for hepatocellular function, were normal. This injection was repeated at 6-monthly intervals in those women who desired to continue the treatment.

The majority of women (90%) commenced the treatment between the fourth and sixth postpartum week; by that time, only one woman was still lactating. Of the 3 women who were postabortal and 3 who were not recently pregnant, treatment was given on the fifth day of the menstrual period.

Clinical Method

Before commencement of treatment, a complete history and general physical examination, including breast palpation, pelvic examination and cervical cytological smear were performed in each woman to ensure absence of any serious pre-existing disease. This examination was repeated at intervals of 2 months, and the cervical smear at intervals of 6 months.

In addition, each patient was interviewed each month and enquiry was particularly directed to the presence of side-effects and the menstrual bleeding pattern during the preceding 30-day period. This information was recorded daily by the patient on a menstrual data card, with (O) for no bleeding, (S) for spotting and (X) for bleeding — the number of (S) or (X) denoting the number of pads used.

Blood pressure and body weight were measured before treatment and at each monthly follow-up visit.

If the woman decided to discontinue treatment, the reason for the drop-out was elicited. Poor attenders were contacted to ensure adequate follow-up. In 7 women, particularly in the initial 3-4 months of treatment, in whom the bleeding was unacceptable because of heavy or continuous loss, oral ethinyl oestradiol in doses of 0.01 to 0.03 mg. daily was given for 3 weeks in the month.

Laboratory Procedures

The bromsulphthalein excretion test (Mater et al., 1942) was carried out before treatment was started and repeated at 24 months.

Every 2 months the following studies were undertaken: lateral wall vaginal smear for maturation index, endometrial biopsy, and quantity of mucus in the cervical canal (measured with a tuberculin syringe).

The women were instructed in the collection of 24-hour urine samples—these were obtained at intervals of 1 to 3 months for the estimation of ketosteroids/17-hydroxycorticosteroids, gonadotrophins, oestrogens, and pregnanediol.

RESULTS

The distribution of age and parity of the women and their duration of treatment are shown in table 1. A total of 989 months of study were completed; 14 women had received 4 injections or more. Only 3 (5%) of the women were nulliparous; 53 (87%) had had 2 or more children.

Blood Pressure

The mean and standard deviation of the systolic and diastolic blood pressures before treatment and after each 6-month period of study are shown in table 2. There were no significant differences in mean systolic and diastolic levels at these stages of the treatment period.

In an attempt to test the randomness of the change in individual blood pressure levels, the incidence of an increase or decrease in blood pressure of at least 10 mm.Hg. during and at the end of each 6-month period of treatment was examined (table 3). No significant change

Table 1. Distribution of Age, Parity and Duration of Treatment Completed

		Age (years)					
		20	20-24	25-29	30-34	35-39	>39
No. of patients		4	15	11	14	8	9
		Parity					
		0	1	2	3	4	5	>5
No. of patients	Live births	3	5	6	16	16	2	13
	Abortion	36	15	7	0	1	1	1
	Ectopic	57	3	1	—	—	—	—
		Duration of treatment (months)					
		1-6	7-12	13-18	19-24	25-30	
No. of patients		1	8	38	12	2	

Table 2. Mean Systolic and Diastolic Blood Pressure and Standard Deviation During Treatment

Blood pressure (mm. Hg.)		Before treatment	End of 6 months	End of 12 months	End of 18 months
Systolic	Mean	129.9	132.7	132.5	134.0
	Standard deviation	19.5	17.9	20.8	15.6
Diastolic	Mean	80.1	81.3	82.2	81.0
	Standard deviation	13.4	12.1	12.1	19.1

Table 3. Incidence of Change of Blood Pressure with Treatment

	Change in blood pressure	First injection		Second injection		Third injection	
		During first 6 months	6th month	During second 6 months	12th month	During third 6 months	18th month
Systolic blood pressure	a = Increase*	101	20	70	12	28	3
	o = No change	69	14	52	10	28	3
	b = Decrease*	92	16	72	13	32	3
Diastolic blood pressure	a = Increase*	86	18	61	9	22	2
	o = No change	101	19	74	16	42	4
	b = Decrease*	75	13	59	10	24	3

*Increase or decrease in blood pressure of 10 mm.Hg. or more.
Distribution not significant at any stage of treatment.

Table 4. Mean Body Weight (and Standard Deviation) in Relation to Period of Treatment

		Before treatment	End of 6 months	End of 12 months	End of 18 months
Body weight (lb.)	Mean	134.3	138.8	145.2	141.3
	Standard deviation	26.1	34.5	37.1	22.4

Table 5. Changes in Body Weight in Relation to Period of Treatment

		Months of treatment																		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Change in body weight (lb. per month)	Mean	0.35	0.87	3.07	0.30	0.26	0.08	−0.78	0.26	0.75	0.33	0.24	−0.74	0.91	0.32	−1.18	0	−1.6	0.6	2.80
	Standard deviation	3.13	3.16	8.01	3.83	3.01	4.33	4.87	3.92	2.20	2.94	4.20	2.52	3.24	3.11	3.39	2.30	3.46	2.76	3.24

Table 6. Duration of Bleeding and Spotting per Month (Mean and Standard Deviation) with Treatment

		Before treatment	Month of treatment: First injection						Second injection						Third injection						Fourth injection	
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Days of bleeding	Mean	4.9	5.9	6.1	6.7	6.8	5.1	5.1	2.3	3.1	4.8	2.5	2.7	3.0	4.0	1.3	2.1	1.4	1.9	0.6	0.5	
	Standard deviation	1.5	6.8	8.5	8.8	9.5	8.1	7.0	4.4	5.1	9.2	4.3	5.2	5.6	6.8	2.3	4.3	3.5	2.5	1.0	1.1	
Days of spotting	Mean	0	4.4	5.2	5.9	4.7	3.3	2.8	1.6	3.0	3.1	2.9	1.7	1.6	0.9	3.0	3.6	2.0	2.4	0.5	0	
	Standard deviation	—	6.9	7.7	8.2	7.9	6.2	5.6	4.8	5.4	6.0	5.1	3.3	3.8	1.6	5.5	5.0	3.7	4.5	0.9	—	

Table 7. Distribution of the Uterine Bleeding Pattern

Zone and score*	Classification of pattern	Before treatment	Months of treatment: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1 (0)	Amenorrhoea	—	12	11	13	16	19	19	27	19	20	22	22	20	12	15	8	12	6	7	5	—
2 (1-15)	Acceptable	45	18	17	15	13	14	10	8	10	10	9	9	8	8	8	9	8	5	4	1	1
3 (16-30)	Marginally acceptable	15	12	15	8	12	9	13	8	7	3	2	4	6	2	3	5	—	3	1	—	—
4 (> 30)	Unacceptable	—	18	16	21	15	12	11	3	7	9	7	4	4	6	2	1	—	—	—	—	—
% Patients with amenorrhoea		—	20	19	23	29	35	36	59	44	48	55	56	53	43	54	35	60	43	58	83	—
% Patients with unacceptable bleeding		—	30	27	37	27	22	21	7	16	21	18	10	11	21	7	4	—	—	—	—	—

*Key to scoring: bleeding per day = 3 points; spotting per day = 1 point.

in systolic or diastolic pressure in either direction was found at any stage of the study.

Body Weight

The mean and standard deviation of body weight before treatment and after each 6-month period of study is shown in table 4. There was a slight increase in mean body weight from 134.3 lb. (60.8 kg.) before treatment to 145.2 lb. (65.7 kg.) after 12 months and 141.3 lb. (63.9 kg.) after 18 months of study. However, the differences did not reach statistical significance.

The mean change in weight (and standard deviation) after each month of treatment is shown in table 5. There appeared to be a gradual increase in weight in the first 3 months, reaching a maximum mean change of 3.1 lb. (1.4 kg.) in the 3rd month. This value, however, was not statistically significant. Thereafter, the change was erratic and not significant.

Uterine Bleeding

The mean duration of bleeding and spotting and standard deviation before treatment and after each month of treatment is shown in table 6. Disorganisation of the menstrual bleeding pattern during treatment was more evident on viewing the menstrual data cards: irregular periods of amenorrhoea, bleeding and spotting were experienced. Despite the irregularity of bleeding, the mean duration of bleeding per month only increased by approximately 2 days, reaching a maximum at the fourth month; there was, however, a more marked increase in the standard deviation. In 12 of the patients the loss was increased to a troublesome degree. After the first 6 months there was a progressive decrease in the duration of bleeding per month, with a reduction to 3.0 ($\pm$ 5.6) days at the end of the 12th month and 0.6 ($\pm$ 1.0) days at the end of the 18th month. A similar but less marked decrease in the amount of spotting was also observed.

The pattern of uterine bleeding was classified according to a score system which awarded 3 points to each day of bleeding and 1 point to each day of spotting. By this method the women were distributed into 4 groups before treatment and after each month of treatment as shown in table 7. The proportion of women who had amenorrhoea showed a progressive increase with treatment, being 36% after 6 months, 53% after 12 months and 83% after 19 months. The proportion of women who had an unacceptable amount of bleeding progressively decreased with treatment, and there was no woman who had unacceptable bleeding after 15 months of treatment. However, the relatively high proportion of women with this complaint during the first 6 months resulted in drop-outs and need for oestrogen therapy.

It is interesting to note that the mean duration of bleeding and spotting reached a peak 3-4 months after each injection (table 6). This trend was similarly reflected in the percentage of women who had unacceptable bleeding.

Side-Effects

The incidence of side-effects occurring in each month of treatment is shown in table 8. Depression and diminution in libido were comparatively common. In 4 patients, the depressive state was troublesome enough to require treatment with oral diazepam which was effective in alleviating the mood disorder; in one woman, psychiatric consultation was requested because of her previous psychiatric history. The complaint of diminution in libido was most frequently made 3 months after the first and second injections.

It was observed after close interrogation of the women who complained of depression, anxiety, headaches and irritability, that there was a coincidental disturbance in their domestic environment at the time of complaint. This made the assessment of drug effect difficult.

The symptoms of nausea, malaise, dizziness, headache, mastalgia and backache were mild and required no treatment.

One woman who was a known sufferer of migraine and who required treatment with ergotamine during attacks found the migrainous headaches aggravated on the 3rd and 18th month of treatment. However, the intervening period of treatment was relatively free of headaches.

Seven patients complained of vague lower abdominal pain which lasted between 1 to 3 days. Despite careful examination, no obvious

Table 8. Incidence of Side-effects in Relation to Period of Treatment

Side-effects	Months of treatment						
	3	6	9	12	15	18	21
Depression	7	5	2	5	3	1	—
Decrease in libido	8	3	9	4	—	—	—
Anxiety (*acute fear)	3	3	2(*1)	2	1	—	—
Nausea	4	2	2	—	—	—	—
Headaches (*migraine)	3(*1)	1	—	—	1	—(1*)	—
Malaise	—	2	—	1	—	—	—
Irritability	3	1	1	2	1	1	—
Abdominal pain	1	2	—	2	2	—	—
Dizziness	1	—	2	—	—	—	—
Breast symptoms (soreness)	1	1	—	—	—	—	—
Backache	1	3	—	1	1	—	—
Skin rash	—	—	1	—	3	—	—
Shortness of breath	—	—	1	—	—	—	—

abnormality was found in any of them and the symptom underwent spontaneous remission.

A mild, transient macular skin rash occurred in 3 women, in one, it recurred twice. The appearance of the rash on the thorax and abdomen was not associated with other symptoms and no other cause was elicited. Interestingly, the rash appeared within 3-5 days after the second injection (1 occasion) and third injection (3 occasions).

Efficacy and Acceptability as a Contraceptive Agent

No pregnancy occurred in the study during the 989 completed months of treatment.

A decision to discontinue treatment was made by 12 of the 61 women after the first injection and a further 15 after the second injection. Subsequent to this, no further dropouts occurred. Discontinuance was related to the therapy in 20 of the 27 patients (table 9).

A high degree of acceptability was expressed by those patients remaining in the study.

The reasons given for discontinuing treatment are shown in table 10. The most important factor was disturbance of the menstrual pattern. Curettage was necessary in 1 of the 8 patients with heavy bleeding. Oral ethinyl oestradiol was given to 7 of the women who complained of heavy or continuous bleeding without, however, satisfactory control.

It is interesting that 2 of the 3 women who complained of diminution in libido also complained of dyspareunia related to "dryness in the vagina". In the follow-up period, these women observed an improvement in sexual

Table 10. Reasons for Discontinued Treatment

Main reasons (*additional reasons)	After first injection	After second injection
Heavy bleeding	6 (1*)	2
Irregular bleeding	3	2
Induced amenorrhoea	1	1 (1*)
Depression	1	0
Anxiety	0	1
Decreased libido	0	3 (1*)
No further need for contraception	1	4
Desire for further pregnancy	0	2
Total	12	15

Table 9. Efficacy and Acceptability as a Contraceptive Agent

	No. of injections administered				
	1	2	3	4	5
No. of patients	61	49	21	9	5
No. of pregnancies	0	0	0	0	0
No. discontinuing treatment	12 (20%)	15 (25%)	0	0	0
No. discontinuing treatment for unrelated reasons	1 (2%)	6 (10%)	0	0	0

relationships by the 8th month after the last injection.

DISCUSSION

At present, over 20 million women are considered to be using steroidal contraceptives (Kleinman, 1970). Although the wealth of data is confusing, there appears to be risks associated with usage — morbidity and mortality rates of 3.9 and 1.5 per 100,000 users respectively have been reported from thromboembolism (Kleinman, 1970), and about 50 adverse metabolic changes have been described (Salhanick et al., 1969). Most of these effects appear to be related to the oestrogen component. For this reason, a new concept in steroidal contraception has been introduced with the use of the long-acting progestogens. In the present study, the number of injections has been reduced to 2 per year. The efficacy of this method has been demonstrated previously by clinical trials with 150 mg. of depomedroxyprogesterone given at 3-monthly intervals (Zartman, 1966; Mishell et. al., 1968; Gardner and Mishell, 1970). In a large collative study of 2,926 women and 35,049 patient-months of experience, a very low pregnancy rate of 0.506 per 100 woman-years was reported (Upjohn, 1968). This compared favourably with the reported pregnancy rates of 0.4 - 2.7 per 100 woman-years with the oral oestrogen-progestogen combination and 1.8 - 7.5 per 100 woman-years with the intrauterine device (Calderone, 1964; Committee on Human Reproduction, 1965). The present study has shown the equal efficacy of a 6-monthly injection of progestogen; no pregnancies occurred during 989 patient-months.

The relative effects of the various oral and injectable steroids on blood pressure and bodyweight are still uncertain. Oestrogens can cause fluid retention and progestogen has anabolic effects. Studies with 3-monthly injections of progestins have produced rather variable results. There appeared to be a slight decline in systolic and diastolic blood pressure as treatment continued (Upjohn, 1968). Only a slight increase in mean body weight (2.2 lb. (1 kg.) after 12 months of treatment) has been reported (Mishell et al., 1968). However, the mean weight was found to increase by 3.0 lb. at 6 months, 4.9 lb. at 12 months, and 7.3 lb. at 24 months (Upjohn, 1968). In our experience with the 6-monthly injection, effects on blood pressure and body weight were not at all remarkable. Such changes that did occur appeared to be random in nature.

There is general agreement that continued low dose progestogens tend to produce a disorganisation of the uterine bleeding pattern. The marked irregularity and prolonged bleeding episodes encountered in the first 6 months of our study have also been reported previously (Zartman, 1966; Mishell et al., 1968; Zanartu and Navarro, 1970). With the passage of time, this disturbance improves progressively. The incidence of amenorrhoea, which was well accepted by the majority of the women, also progressively increased with time. Amenorrhoea has been reported in 36.7 - 53.0% of women after 6 months, and 52.3 - 77.0% after 12 months with the use of the 3-monthly injection (Mishell et al., 1968; Upjohn, 1968). Similar findings were present in our present study with the 6-monthly injection; the rate of amenorrhoea was 36%, 53% and 83% after 6, 12 and 19 months, respectively. As found in the collative study (Upjohn, 1968), the problem of unacceptable bleeding became markedly less after 6 months. The mean duration of bleeding was reduced by more than half (from 5.1 to 2.3 days) and the proportion of women with unacceptable bleeding fell by a third (from 21% to 7%) in our series. This result was, however, influenced by drop-outs, 75% of whom had unacceptable bleeding.

Undesirable side-effects such as prolongation and irregularity of bleeding and diminution in libido showed an interesting peak incidence about 3 months after each injection. These manifestations probably reflected maximal absorption and effect of the drug at this stage of treatment. Oestrogen supplementation for 7 days in each calendar month has been suggested as an effective means of achieving a cyclic form of bleeding (Zanartu and Navarro, 1970). Such control of bleeding was not obtained in our study, although a too long period of supplementation may have been given. It has recently been reported that when oestrogen was incorporated into the injection, as with the injection of 50 mg.

medroxyprogesterone and 10 mg. oestradiol-17 β-cyclopentyl propionate, irregular bleeding occurred in 15% of the women (Scommegna et al., 1970).

The main advantage of this relatively simple contraceptive method is its freedom from serious adverse effects. The main disadvantage is irregular or heavy bleeding. However, these patients may be advised to cease this form of therapy or to persist, perhaps with supplementary oestrogen, until the menstrual loss becomes more acceptable with time. Diminution in libido was a relatively frequent complaint in the present study, but this symptom is difficult to assess, because of the relative roles of social, psychological and endocrine factors in human sexual activity. It is probably related in part to oestrogen deficiency in view of its virtual absence when an oestrogen-progestogen injection was used (Scommegna et al., 1970). As noted in previous studies (Tyler, 1967; Upjohn, 1968) symptoms of depression, anxiety, headaches and nausea also occurred, but again, objective and quantitative assessment is difficult.

The relative importance of socio-economic status and motivation has been emphasized in relation to the rate of discontinuation of treatment: where the women were predominantly Negroes and of low socio-economic class, the drop-out rate was extremely low (1.7% after 6 months) (Zartman, 1966), whereas where they were mainly Caucasian and of higher socio-economic class, it was high (57% after 12 months) (Mishell et al., 1968). The drop-out rate of 33% recorded in the present study was much higher than that obtained in the collated study using the 3-monthly injection (Upjohn, 1968). Most likely, this was associated with a difference in attitude towards bleeding and in motivation among the women concerned. Three-quarters of the patients who discontinued in the present study did so because of disturbance of bleeding pattern. It is probable that the acceptability of the method can further be improved.

Despite its limitations, this method of contraception appears to be ideal to many women in the community. It appeals to the woman who has had the desired number of children and who is intolerant of or does not wish to use other forms of contraception. To the woman who is predisposed to thromboembolism, this method offers a safer alternative. The simplicity of administration and efficacy of the method should recommend its more widespread use.

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