A CLINICAL TRIAL WITH INJECTABLE LONG ACTING PROGESTOGEN (D.M.P.A.) FOR CONTRACEPTION

by

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Following on the widespread acceptance of oral progestogens as contraceptive agents in the western world, studies were initiated by the Indian Council of Medical Research at various centres in this country to find out the acceptability of this form of contraception amongst Indian women, and the contraceptive Clinic attachced to the K. G. Medical College, Lucknow, was one of the centres selected for this purpose.

Our study was started with great enthusiasm but it was soon apparent that the participants lacked the motivation necessary for sustained pill taking and out of 255 women who accepted this method 110 dropped out within 1-2 months (at present only 7 women are on the pill). When, therefore, an injectable progestogen, Medroxyprogesterone Acetate (D.M.P.A.), became available it was felt that as the drug would be given parenterally, the factor of lack of sustained motivation would be obviated and better results obtained.

Material and Method

One hundred and forty-six women attending the Family Planning Clinic of Queen Mary's Hospital, Lucknow, were registered and followed over a period of 2½ years from November, 1967 to May, 1970.

Sixty-eight of the women had previously worn I.U.C.D.s which had been removed on account of bleeding, while the remaining 78 opted for the method in preference to oral contraceptives and I.U.C.D.s

The ages of the women varied between 16-40 years and they had a parity of 0-14 with the majority in the age group 25-29 and parity of 2-4.

A complete physical examination including a pelvic examination was done in every case. The size of the uterus and the condition of the cervix was noted, and Papanicolaou smears taken whenever indicated. Haemoglobin estimation and urine examination for albumin and sugar were done and weight and blood pressure recorded.

The compound used was "Depo Provera" marketed by the Upjoin Co., and containing 50 mg. of Medroxyprogesterone Acetate per c.c. The dosage advocated was an intramuscular injection of 150 mg. 3 monthly. However, since very little data was available about the effect of such a heavy dose of progestogen and particularly since there were no means of controlling undesirable side-effects, should any be found to occur, the trial was started with certain reservations and injections of only 50 mg.

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of the drug were given every month, instead of 150 mg. 3 monthly as advocated.

Ninety-four women received the injections monthly. The first injection was given on the 5th day of menstruation and the subsequent ones were given on the same date each month irrespective of the date of the menstrual period.

In 33 women the injection was given shortly after an abortion, but as 13 of them continued to bleed, it became difficult to differentiate between postabortal bleeding due to retained products of conception and bleeding due to the drug. This procedure was therefore, abandoned, and injections were not given to postabortal cases unless at least one normal period had occurred.

As the trial progressed the women complained that it was difficult for them to come at monthly intervals for the injections, and as no serious side effects had been noted after giving 50 mg. monthly, the dose was increased to 100 mg. 2 monthly (22 cases) and finally to 150 mg 3 monthly.

Seventy-one women received the 150 mg. injections 3 monthly and this report deals with the results seen in these 71 cases.

Six women did not return for follow up after the first 150 mg. injection and were excluded from the study. The remaining 65 women were followed for varying periods, the maximum being 24 months. The number of 3 monthly 150 mg. injections received by these 65 women were as follows:

Only	1 injection	32 women.
	2 injections	14 women.
	3 injections	7 women.
	4 injections	5 women.
	5 injections	3 women.
	6 injections	3 women.
	8 injections	1 women.

Observations.

No pregnancies occurred during the 2½ years of the trial but various side effects were encountered, and the drop-out rate was high on this account.

Side-effects: The principal side effects were menstrual disorders (which ranged from amenorrhoea to menorrhagia) and gain in weight. Nausea was conspicuous by its absence, but headache and dizziness were complained of by several women on the day of injection. No discontinuations, however, occurred on this account. Complete suppression of lactation occurred in only one of the 10 lactating women who received the injections and one woman complained of breast discomfort. No alteration in the blood pressure occurred in any of the cases. Allergy, with itching all over the body followed the injection in 3 cases but was completely relieved with administration of Avil tablets.

Menstrual Abnormalities. The commonest menstrual abnormalities noted were scanty and/or delayed periods. Next in frequency was amenorrhoea, then came break through bleeding (BTB) and heavy or prolonged periods. It should be pointed out, however, that there was no set pattern in the type of menstrual disorder encountered, and a woman who developed amenorrhoea in one cycle would develop either scanty or profuse periods or have BTB in the next cycle. Each of the menstrual abnormalities will now be discussed separately.

Delayed and Scanty Periods: This occurred off and on in 77% cases (50 out of 65).

In 23 (35.3%) the flow was reduced to mere spotting and this was followed by amenorrhoea in 13.

Amenorrhoea: Episodes of amenorrhoea occurred in 60% of the women (39

out of 65) and their duration varied from 2-12 months.

The patients were perturbed by amenorrhoea and feared that they had conceived, but once they were examined and reassured that they were not pregnant, they were willing to continue the injections.

Complete atrophy of the endometrium was a constant feature of the endometrial biopsies done in these amenorrhoic women and the uterus was also found to be reduced in size.

B.T.B.: Break through bleeding occurred in 33.8% (22 out of 65) women. Sixteen women had continuous bleeding for 2-3 months which persisted in 6, even after discontinuation of the drug. These cases were therefore subjected to dilatation and curettage. Bleeding was checked immediately in 2 women while 3 continued to bleed and one woman did not return for follow up. The curettings obtained were very scanty in 4 cases and no histopathological report could be obtained, while in 2 cases the endometrium was reported as nonsecretory. In 6 other cases of B.T.B. who were subjected to endometrial biopsy, no tissue could be obtained in 2, while 4 showed scanty nonsecretory endometrium.

Heavy or Prolonged Periods: were complained of by 30% women (20 out of 65).

Endometrial biopsy done in 3 of these revealed nonsecretory endometrium in 2, while very scanty tissue was obtained in the 3rd and no report was possible.

Change in Weight: Weight gain of 1-4 Kg. was noted in most of the women but 3 women gained as much as 10, 12 and 17 Kg. over a period of 15-17 months. Loss in weight of 1-2 Kg. was seen in 4 women. Excessive weight gain has also been reported by Douglas *et al*, (1970), while Lee reporting from Mayo Clinic (1969) did not find any significant change in weight in his series.

Drop Outs: Fifty women (75.9%) discontinued the use of the method mainly due to side effects. B.T.B. was the main reason for discontinuation and of the 22 women who developed this complaint, 20 discontinued the injections (40%). Powell and Seymour (1970) have reported a discontinuation rate as high as 60% on account of B.T.B., but in Douglas and Newton's series (1970) discontinuation on this account was only 13.5%.

Amenorrhoea was the next common reason for discontinuation and was responsible for 34% (17 out of 50) of the drop outs. In Douglas and Newton's series (1970) only 2.8% discontinued on this account.

Scanty periods were responsible for discontinuation in 3 women (6%) and heavy and prolonged periods in another 3 (6%).

Other Reasons: Suppression of lactation was the reason for discontinuation in 1 case (2%) and one woman who had gained 17 Kg. in weight did not wish to continue with the injections. One other woman discontinued as she desired another baby. In the remaining 4 cases (8%) the reasons for discontinuance could not be ascertained as the women were not traceable. Only 15 women (23%) were continuing with the injections at the time of termination of the study in May, 1970. Thirteen of these had amenorrhoea, but were still willing to continue.

Effects of administration of concomitant Oestrogen (Stillboestrol) on B.T.B. and Menstrual Disorders: After a report by Soichet (1969, 1970) that bleeding following Medroxyprogesterone Acetate injection could be easily controlled by the

concomitant administration of oestrogen, it was decided to give this procedure a trial, and 24 women were given one tablet of 0.5 mg. stilboestrol daily for 7 days starting from the day of injection and repeated monthly on the same dates. Sixteen out of the 24 women (66.6%) did not develop any bleeding complications, while 33.4% did have B.T.B. or heavy periods. In 41 women who were not given concomitant stilboestrol, bleeding ocurred in 31 (75.6%). Concomitant administration of stilboestrol, therefore, does seem to lower the incidence of bleeding to some extent.

Habashy *et al*, (1970) tried continuous daily administration of 1 mg. stilboestrol for 3 months following the injection, but failed to diminish the incidence of B.T.B.

Histopathological Studies of the Endometrium: Endometrial biopsies were done in 45 women. Very scanty tissue or none at all was obtained in most of the cases and absence of ovulation was seen in all the biopsies studied.

Lee from Mayo Clinic (1969) reported cystic dilatation of the glands after two injections of 150 mg. of Depo-Provera given 3 monthly in 6 out of 14 women. In our series too, cystic dilatation of the glands was seen in 3 biopsies, which were done 2, 4 and 5 months after discontinuing the injections.

Eighteen of the remaining 42 endometrial biopsies were done in women complaining of amenorrhoea and 12 were in women with B.T.B., while in 12 cases biopsies were taken at intervals varying from 16-105 days after the administration of a 150 mg. injection to see the response of the endometrium to the drug and to find out how long the effect of a single injection persisted.

Of the 18 biopsies done during amenorrhoea no tissue was obtained in 15, while 3 showed nonsecretory endometrium with marked glandular atrophy (Fig. 1).

In the 12 biopsies done in women complaining of B.T.B., nonsecretory endometrium was seen in 6, while in the remaining 6 the tissue was too scanty for any opinion to be given.

Scanty nonsecretory endometrium was found in all the 12 biopsies done at intervals ranging from 16-105 days of receiving the injection. It will thus be seen that the effect of the injection persisted beyond the 3 month limit prescribed by the manufacturers.

The finding of cystic dilatation of the glands in the biopsies done after discontinuation of the injections is an interesting finding (Fig. 2) and it seems likely that before full secretory activity is restored in the endometrium, the glandular elements pass through a phase of cystic dilatation.

The marked endometrial atrophy and the high percentage of women developing amenorrhoea after injections of Medroxyprogesterone Acetate was commented upon by several investigators at the 4th Asian Congress of Obst. & Gynaecology, held at Singapore in November, 1968 and the consensus of opinion was that this method of contraception should, therefore, only be advocated in women who desired family limitation and not family spacing.

The time of resumption of menstruation in the women who developed amenorrhoea and the subsequent fertility of all the 146 women who received Medroxyprogesterone Acetate injections in our clinic, is the subject of a separate publication.

Comments

Injections of long acting progestogen proved to be an effective method of con-

traception, which, however, was not free from undesirable side-effects. The high percentage of menstrual abnormalities which followed in the wake of the injections resulted in a drop out rate as high as 76.9% showing that the method, though effective, was not universally acceptable.

References

1. Douglas, F., Scutchfield, F. and Newton, W. L.: Obst. & Gynec. Survey. Vol. 25; No. 9; Sept. 1970.
2. Habashy El, M. A., Mishell Jr., R. and Moyer, D. L.: Obst. & Gynec. 1970; 35 (1); 51-4 (Biol. Abstr.); 1970; 51 (9) 4807.
3. Lee, R. A.: Am. J. Obst. & Gynec. 104: 130, 1969.
4. Powell, L. C. Jr. and Seymour, R. J.: Am. J. of Obst. & Gynec. 110: 36, 1970.
5. Soichet, S.: Int. J. Fertil. 1969, 14; 33, (Biol. Abstr.; 51 (2); 879); 1970.

See Figs. on Art Paper I