# NORETHYNODREL IN DYSFUNCTIONAL UTERINE BLEEDING

## (A Preliminary Report)

by

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The discovery of 19-norsteriods of which one is 'Enovid' with a chemical formula of 17 $\alpha$ ethinyl $^{5,10}$ -19 nortestosterone, has revolutionised the treatment of several diseases, the most well-known of which is endometriosis. The marked success in inhibiting ovulation by these drugs has given them wide publicity as oral contraceptives. There have, however, not been many reports of the effect of these progestogens in the treatment of dysfunctional uterine bleeding. Until recently the only progestational agents available were progesterone and ethisterone. The disadvantage of progesterone is that it can only be given parenterally and is very expensive, whereas ethisterone, though effective orally is a week progestational compound. On the other hand Enovid, the synthetic progestogen is comparatively cheaper, easily administered and has a powerful progestational activity. Drill et al. studied the effect of its administration on animals in 1957 and found that it has three main properties — namely progestational action, inherent oestrogenic effect and thirdly inhibition of the pituitry gland. Working on oestrogen-primed ovariectomised rabbits Saunders (1957) came to the conclusion that the oral administration of norethynodrel produces a maximal progestational response which is far more intense than that obtained by progesterone. By injection this activity is much reduced. Southam (1957) reported the effect of this drug in 15 cases of abnormal uterine bleeding and was struck by the dramatic haemostatic effect. Weinberg (1958) treated 12 cases of functional uterine bleeding with Enovid and claimed a successful response in 11 cases. Dockerty et. al. (1959) reported on the increased activity of fibromyomata after administration of Enovid. He presented a 71 years old patient who got red degeneration in fibromyoma after Enovid therapy.

Kistner (1958) reported the effects of Enovid on the endometrium. The stroma showed pronounced intracellular oedema, simulating marked predecidual reaction, with glandular arrest.

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Sweyer (1960) observed the effect of Enovid in normal menstruating women and with a daily dose of 10-20 mgm., secretory changes could be observed in the endometrim after 5 days of administration. Later the glands showed exhaustion atrophy. Twenty per cent women, in his series showed intolerance in the form of nausea, vomiting, headache and breast discomfort.

Out of a total of 117 cases of dysfunctional uterine bleeding studied in detail where no obvious cause for bleeding could be discovered, 35 cases were selected for treatment with Enovid. The drug was available in three strengths:

Norethynodrel 2.5 mg. containing 0.15 mg. ethinyloestradiol 3 methyl ether.

Norethynodrel 5 mgm. containing 0.075 mgm. ethinyloestradiol 3 methyl ether.

Norethynodrel 10 mgm. containing 0.15 mgm. ethinyloestradiol 3 methyl ether.

Only those cases were selected for treatment where conservative measures had failed; 27 of the patients had one dilatation and curettage whereas 3 had more than one. Most of these patients were not old enough to be considered for hysterectomy, or refused it. Two patients were above 40 years and in one of them the drug was used purely as a haemostatic agent in order to prepare her for surgery. The haemoglobin was 1.5 gms. and even dilatation and curettage could not be undertaken as she was very poor in general health and also suffered from hypertension. The other patient was an unmarried woman aged 43 years where dilatation and curettage had been done twice without relief. Enovid 5 mgms. from 5-25th day was given for two months with complete relief.

This treatment had three aims:

(a) For haemostasis and improvement of the patient till surgery or cyclic therapy could be undertaken,

(b) To assess the curative value of the drug with regard to the abnormal uterine bleeding,

(c) The study of side-effects.

*Age:* Table I shows the distribution of cases according to age.

TABLE I

*Showing Distribution of Cases According to Age*

| Age | No. of patients | Percentage |
|---|---|---|
| 10-20 years .. .. | 9 | 25.7 |
| 21-30 years .. .. | 10 | 28.5 |
| 31-40 years .. .. | 14 | 40.0 |
| Above 40 years .. | 2 | 5.7 |

The age of the patients ranged between 12-40 years. Only two patients were above 40 years. The maximum age incidence of patients with dysfunctional uterine bleeding on the other hand, was 41-50 years, which tallies with the findings of Sutherland and MacGregor et al. It shows that Enovid is of use in patients 10 years younger to the other patients; 25.7% of the patients are below 20 years, this indicated that dysfunctional uterine bleeding in India is seen at a much earlier age. Sutherland reported 3% of his patients below 20 years.

*Type of bleeding:* The bleeding was acyclic in 21 cases, while profuse cyclic bleeding was found in 14 cases giving incidence of 60% and 40% respectively. The various clinical

patterns of bleeding are indicated in Table II.

TABLE II
*Showing the Bleeding Patterns in Patients*

| Type of bleeding | No. of patients | Percentage |
|---|---|---|
| A. Acyclic bleeding .. | 21 | 60.0 |
| (i) Following amenorrhoea .. | 10 | 28.5 |
| (ii) Following normal period .. | 8 | 22.8 |
| (iii) Following menorrhagia .. | 3 | 8.5 |
| B. Cyclic bleeding .. | 14 | 40.0 |

The acylic bleeding is more common than the cyclic one and of the types of acyclic bleeding, the one following amenorrhoea is the most common constituting 28.5%.

*Type of endometrium:* Endometrial study was carried out in 28 out of 35 patients. The patterns are indicated in the Table III.

TABLE III
*Showing the Type of Endometrium*

| Type of endometrium | No. of cases | Percentage |
|---|---|---|
| Secretory endometrium | 10 | 35.8 |
| Proliferative endometrium .. .. | 6 | 28.5 |
| Cystic glandular hyperplasia .. .. | 10 | 28.5 |
| Irregular shedding .. | 2 | 7.1 |

Secretory endomerium was the most common and formed 35.8%. The only point which was brought out in the stndy was that secretory endometrium is least responsive to conservative measures.

*Relationship of age to different endometrial patterns:* Anovular bleeding was commoner in age groups below 20 years and above 30 years, while ovulatory pattern was maximum in age group 21-30 years, as shown in Table IV.

*Endometrial pattern as related to the type of bleeding:* The bleeding pattern met with in these cases were:

A — Irregular bleeding.

B — Continous bleeding of more than two weeks, duration starting as normal menstruation.

C — Bout of bleeding following a period of amenorrhoea.

D — Polymenorrhoea or menorrhagia — In this group the bleeding is cyclic. The relationship of the endometrial patterns to the type of bleeding is shown in Table V.

Though any pattern of endometrium may be encountered in any type of bleeding, proliferative phase was commoner in the irregular or acylic bleeding pattern, while proliferative cystic hyperplasia was mainly met with in those patients who complained of bleeding follow-

TABLE IV
*Showing Relation of Age to Different Endometrial Patterns*

| Age grorps | Ovulatory | | Anovulatory | |
|---|---|---|---|---|
| | Secretory | Irregular shedding | Proliferative | Cystic glandular hyperplasia |
| 10-20 years .. | 0 | — | 2 | 1 |
| 21-30 years .. | 7 | — | 1 | 1 |
| 31-40 years .. | 3 | 2 | 2 | 7 |
| Above 40 years .. | — | — | 1 | 1 |

TABLE V

*Showing Relation of Endometrial Pattern to the Type of Bleeding*

| Endometrial pattern | A | B | C | D |
|---|---|---|---|---|
| Secretory .. .. | 0 | 1 | 1 | 8 |
| Proliferative .. .. | 4 | 1 | 1 | — |
| Cystic glandular hyperplasia .. .. | 2 | 1 | 5 | 2 |
| Irregular shedding .. | — | — | — | 2 |

ing a period of amenorrhoea. Menorrhagia was usually associated with ovulatory pattern.

*Treatment*

(a) *Haemostatic:* when an already anaemic woman is bleeding profusely, the question of stoppage of bleeding becomes very important. Jacob et al. (1957) used stilboestrol for stoppage of bleeding and found it to be effective in 83% of the cases.

With dilatation and curettage immediate relief of symptoms was present in 72.7% of our cases.

Weinberg (1958) tried acetoxyprogesterone and found a successful response in 6 out of 9 patients. Beacham (1954) secured complete haemostasis in 88% of the cases with delalutein. Shah (1963) found 100% response in 7 cases of menometerorrhagia with Enovid. In the present series 10-20 mgms. daily were employed in 17 patients, of whom 11 patients had acyclic bleeding and 6 patients had profuse cyclic periods. Of these 17, 3 patients had severe nausea with the drug and it had to be stopped in these cases. In all the above cases the haemoglobin ranged from 1-6 gms%. In 6 patients 10 mgms. daily controlled the bleeding in 24 hours with success rate of 66.6%. In the remaining 8 cases 20 mgms. per day controlled the haemorrhage within 72 hours — that is a 100% success. In two of the above patients surgery could only be carried out after continued administration of the drug. In one case where break through bleeding occurred with 20 mgms, the dose was increased to 30 mgms. This proves the superiority of Enovid over all the other therapies as a haemostatic agent. This shows that 20 mgms. daily acts better for haemostasis than 10 mgms. a day.

(b) *Curative Value:* On account of increased side-effects with higher doses, the minimum effective dose for withdrawal bleeding was studied; 2.5 mgms. were given from 5-25th day of the cycle in 10 cases. However, 71% of the patients had breakthrough bleeding and each time the dose was doubled. In the remaining 21 cases 5 mgms. daily were given in cyclic fashion for 20 days. Withdrawal bleeding occurred after 1-4 days in all the cases and lasted for 2-7 days. Bleeding was not profuse in any case and in some cases it was even scanty. Endometrium was studied at the end of the first cycle by endometrial biopsy. It showed typical changes of oedematous stroma, prominent blood vessels and glandular exhaustion. Periodic Acid Schiff staining showed absence of glycogen granules and glycoprotein. In one case receiving 2.5 mgm. daily

the endometrium still showed early secretory phase with hardly any oedema of the stroma. It is possible that this was due to the small amount of the drug administered. The endometrial changes did not follow a set pattern and in most of the cases with anovulatory pattern the endometrial histology remained the same after withdrawal of the drug. In 16 cases with anovulatory endometrium, 10 cases showed cystic glandular hyperplasia whereas 6 cases showed proliferative phase of the endometrium. In 6 cases with cystic glandular hyperplasia the endometrium changed to proliferative hyperplasia but on further follow up, two cases showed reversion to the original pattern Figs. 1, 2, 3. In only one case was the secretory pattern observed. Shah (1963), on the other hand, showed a change from anovulatory to the ovulatory pattern after therapy and two of these became pregnant.

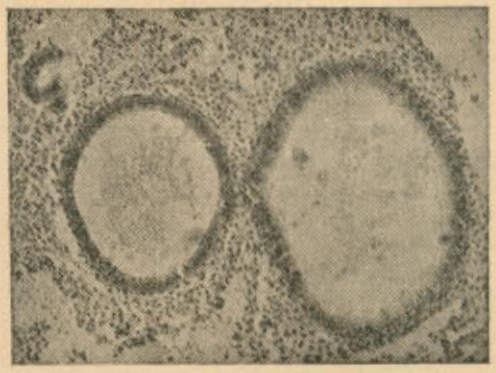

Fig. 1

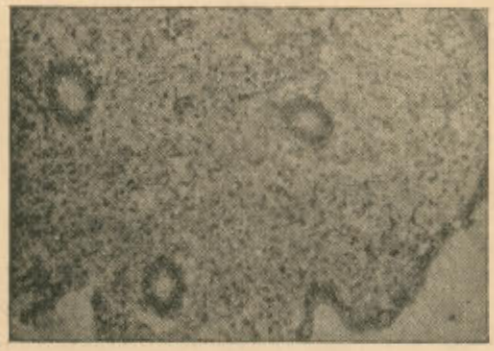

Fig. 2

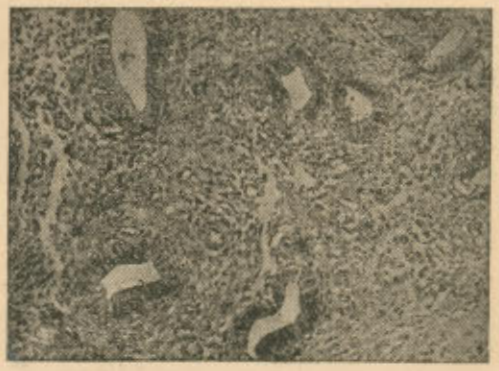

Fig. 3

In 10 cases with secretory endometrium and cyclic bleeding, who were treated for two or more cycles with Enovid therapy, endometrial biopsy after withdrawal of the drug continued to show ovulatory pattern. Of these 10 patients 4 had improved but 6 had reverted back to their original pattern of bleeding. One patient, however, came with twin pregnancy sometime after the stoppage of Enovid therapy. Multiple pregnancy after withdrawal of Enovid therapy had already been reported and is probably due to the withdrawal of the inhibitory effect of the drug on ovulation.

(c) *Side-effects:* The side-effects of Enovid are shown in Table VI. Excessive nausea was present in three patients and the drug had to be discontinued in all of them. Mild nausea was the main complaint in 18 out of the remaining 32 cases, which

TABLE VI

*Side-effects of Enovid Therapy*

| Side effects | No. of patients | Percentage |
|---|---|---|
| Excessive nausea necessitating stoppage of drug .. .. | 3 | — |
| Mild nausea .. .. | 18 | 56.2 |
| Breast discomfort .. | 4 | 12.5 |
| Menstrual cramping .. | 2 | 6.2 |
| Intermenstrual spotting | 7 | 21.8 |

gradually passed off and only three patients complained of it in the second cycle; 9 out of 38 women suffered from severe nausea in Shah's series (1963). Another 9 women in his series complained of mild nausea and vomiting which persisted in 4 cases in the second cycle as well. Breast discomfort was noticed in 4 patients in our series and that too in the first cycle only. Sixteen out of 38 women in Shah's series suffered from it. Menstrual cramping was complained of by two of our patients while it occured 8 times in Shah's group. Intermenstrual spotting was noticed by 7 patients taking Enovid. The spotting continued even after stoppage of the drug. The cause of spotting is unknown and has not been mentioned in any other paper.

*Summary*

The effects of Enovid in various gynaecologic conditions have been reviewed. In the present series, 35 patients out of a total of 117 cases of dysfunctional uterine bleeding were selected for Enovid treatment. The aim of the treatment was to study the haemostatic and curative value of the drug and also to study the side-effects. The haemostatic dose of the drug is 10-20 mgm. and the response for securing quick haemostasis is 100%.

As regards the curative value 5 mgm. were given from 5th to 25th day for 2-5 months. Withdrawal bleeding occurred after 1-4 days and was not excessive. Of the 16 cases with anovulatory endometrium, 10 showed cystic glandular hyperplasia and 6 showed proliferative phase. In the 6 cases with cystic hyperplasia, the endometrium changed to proliferative hyperplasia but on further follow-up two cases showed reversion to the original pattern. In 10 cases with secretory endometrium, endometrial biopsy continued to show ovulatory pattern. Of these 10, 4 had improved but 6 had reverted back to their original pattern of bleeding.

Side-effects were manifested in the form of severe nauses necessitating withdrawal in 3 patients. The other symptoms were mild nausea disappearing in the 2nd cycle, breast discomfort, menstrual cramping and intermenstrual spotting.

Conclusions from this small number of cases is that Enovid is very useful in cases of dysfunctional uterine bleeding when the disease manifests at a young age. It can also be used to build up the patient before surgery as a haemostatic. It is cent per cent successful when used in adequate doses i.e. 20 mgms. a day. There is, however, no lasting effect on the endometrium, the latter reverting to the original pattern on cessation of therapy.

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