USE OF ANOVLAR* IN GYNAECOLOGICAL DISORDERS AND CONTRACEPTION**

by

SHANTI M. SHAHANI, M.D., D.G.O. and ALKA CHIKLIKAR, M.B.B.S.

The 19 nor-progestins have stimulated a lot of interest in recent years not only because they have proved to be effective contraceptive agents but also because they are very potent progestational agents and hence have an important place in various gynaecologic disorders.

The purpose of this study was to evaluate the effects of Anovlar as an oral contraceptive and in various gynaecological disorders.

Materials and Methods

The cases selected were from Endocrine Clinic, B. Y. L. Nair Hospital, Bombay. The drug was administered to 101 patients for 318 cycles, but follow up was possible in only 90 patients for 304 cycles. Their ages ranged from 18 to 42 years, average 26.7 years.

The types of patients are summarized symptom-wise as follows:—

TABLE I

1.	Infertility with regular periods	21
2.	Infertility with irregular periods	22
3.	Amenorrhoea	16
4.	Dysfunctional bleeding ..	13
5.	Dysmenorrhea	3
6.	Contraception	26

The patients were investigated by the following methods: Cervical mucus for spinbarkeit test, vaginal cytology, endometrial biopsy, basal body temperature and urinary 17-ketosteroids. Skull and chest x-rays were carried out when required, before the patient was selected for clinical trials.

Dosage employed

The drug was administered orally from the fifth day of a normal or induced cycle for the next 20 days. In most cases, 1 tablet was given daily but in some cases (16 cycles) 2 tablets or even 3 tablets were administered daily for the same period. This higher dosage was given in some cases of sterility to bring about a greater suppression of hypothalamic pituitary gonadal axis. No untoward effects were noted as a result of higher dosage.

In cases of infertility with proved ovulatory cycles, Anovlar was administered to inhibit ovulation for some time. This temporary suppres-

---

Anovlar tablets were supplied by courtesy of Schering Asia.

** *From the Dept. of Endocrinology, T. N. Medical College and Y. L. Nair Charitable Hospital, Bombay 8.*

Paper read at the 14th All India Obstetrics and Gynaecological Congress held at Nagpur on 26th November 1967.

Received for publication on 20-1-68.

nature of their patient population. Three-fourths of all the pregnancies of the women studied were delivered by the F.N.S. whose nurse-midwives subsequently inserted the IUCD. Thus repeated evaluations of the pelvis had been made by the nurse midwives before the time came for the IUCD insertion. From the Sixth Progress Report we do not know how prolonged a contact the inserting physician had had with the patient before an IUCD was offered and accepted by the patient.

Conclusion

These data are consistent with those of the preliminary report and are of greater value as they include only nurse-midwife insertions. The conclusion is again offered that graduate nurse-midwives can be equipped by carefully supervised training for the insertions of IUCD's in areas where control of population growth must be undertaken without adequate supply of local physicians.

Summary

It has been demonstrated that continuing oral contraception is significantly correlated with patients who have close association with the nurse-midwives as the chief resource for medical care.

A modest but significant series of IUCD insertions is reported. Graduate nurse-midwives prepared the patients for these insertions and the insertions were done by graduate nurse-midwives, who subsequently did careful nursing follow up to reassure the patient and manage the minor complications. The cumulative retention rate at 12 months (73.4%) compares favourably with that of those cases managed by physicians alone (67.7%).

In rural areas where medical manpower is numerically inadequate, skilled paramedical personnel can make a significant contribution to an oral contraceptive programme and can achieve retention rates with IUCD's comparable to rates attained by physicians. This study suggests that successful rural family planning depends more on specific training of and supervision of available personnel (Graduate nurse-midwife) and the close relationship of patient to the staff rather than on any particular contraceptive technique or the availability of physicians.

References

1. Beasley, W. B. R.: Am. J. Obst. & Gynec. **98**: 2, p. 201, 1967.
2. Beasley, W. B. R.: Midwives Chronicle, **79**: p. 52, 1966.
3. Teitze, Christopher. *Comparative Statistical Programme for the Evaluation of Intra-Uterine Devices.* The Sixth Progress Report, Part I, 1965, National Committee on Maternal Health, New York.

sion of hypothalamic hypohyseal gonadal axis was attempted with the object of inducing the Rock's Rebound Phenomenon (Pincus, Rock, Garcia 1958).

The patients with anovulation with or without amenorrhoea were given the drug to induce regular menstruation and temporary inhibition of the pituitary thereby hoping to restore the menstrual dysfunction to normality after the therapy was over.

The parameters of the study were

1. Effect of menstruation
2. Cervical mucus test (spinbarkeit & Fern test)
3. Vaginal cytology to assess the karyopyknotic index
4. Basal body temperature charts
5. Endometrial biopsy
6. Clinical side-effects
7. Amelioration of presenting complaints.

Effect on Menstruation

Withdrawal Bleeding: Majority of the cases bled after stopping the tablets, 3-4 days. However, two cases had withdrawal bleeding when the last one or two tablets were still to be taken.

There were three patients with amenorrhoea who did not have withdrawal bleeding. Two of the patients did not bleed till about 10 days after the tablets were over, but no further follow up was available. The third case was found to have a non-responsive endometrium.

Results are given in Table II.

Amount of Flow: On the whole it was noted that the patients on Anovlar bleed less than usual. The results are shown in Table III.

TABLE II

Occurrence of withdrawal period

Withdrawal day	% of cycles
1	9.6
2	17.4
3	31.3
4	26.5
5	9.63
6	1.7
7	1.2
10	1.2
During Tablet	1.2

TABLE III

Effect on amount of flow

Amount	% of cycles
Scanty	36%
Moderate	59%
Excess	2.3%
No bleeding	1.7%

Cervical mucus tests

These were carried out during therapy every week to evaluate the oestrogenic status. Spinbarkeit test and the fern reaction were noted. A positive reaction indicated good oestrogenic index whereas a negative reaction denoted a low oestrogenic and a progestational influence. In majority of the cycles a positive reaction was maximum after the second week of therapy indicating high oestrogenic index whereas by the end of the third week of therapy the results were negative or equivocal.

Vaginal cytology

These were carried out to evaluate cytohormonal effects of the drug. The smears were taken in the first, second and the third weeks of therapy. Smears were collected from

the lateral fornices with a pipette and stained by Papanicolaou's method. There was a constant differential pattern noticed during the 1st week of therapy in all the patients which was maintained throughout the cycle.

The majority of the cells were intermediate and precornified with a small number of cornified cells (Moyer Dean *et al* 1964). Typical progestational changes were not seen although the cells had a tendency to grouping and the cell borders showed folding. In many cases grouping of the cells had a mosaic appearance (Fig. 1, 2.).

Endometrial biopsy

Ninety biopsies were taken on different days of therapy.

Effect on endometrium: Subnuclear vacuolation, the earliest sign of secretory activity appeared by Pill D_3 of treatment cycle and became well marked by Pill D_5 (Fig. 3, 4). The appearance of supranuclear vacuoles occurred around Pill D_6 and could be seen till Pill D_{10}. Secretion in the gland lumen was noted between Pill D_5 to D_{17} in some samples. Marked tortuosity of the glands was found for first 5 days of therapy. Hardly any mitosis was noticed at any time. Stromal oedema in varying degree was found in the initial stages but became more pronounced in the latter half of therapy. The stromal cells exhibited a moderate increase in cytoplasmic volume by Pill D_{13} which increased progressively towards the end of cycle. Pseudodecidual reaction was seen towards the end of therapy cycle. Stroma showed marked fibrillar network, increased vascularity and dilated sinusoids towards the end of the therapy. In contrast to the stroma the glandular development was dampened beyond Pill D_{13}. The glands became fewer in number and diminished in size. The epithelium changed from columnar in early days to low columnar or cuboidal in the later stages. Thus towards the end of cyclic therapy there was marked glandular regression in a well developed stroma. The atrophy of glandular elements was marked in cases of cystic glandular hyperplasia (Fig. 5, 6).

Basal body temperature

85.7% of the cycles showed increase in BBT thus proving the thermogenic effect of the drug. The rise in the temperature was by 0.4° to 1.4° F. It was evident from the day after the ingestion of the drug and was maintained as long as the patient was on therapy.

Clinical side-effects

The occurrence of side-effects or their severity had no specific relation to the dosage of the drug. They were noted mostly in the first cycle though a few of them continued to complain during the subsequent cycles. There was a very small group of women who developed side-effects only in the later cycles. The results are given in Table IV.

The commonest side-effect noted was nausea though actual vomiting was rare. Antihistaminics given to severe cases were found to be effective. The other common side-effects were giddiness and loss of appetite. Oral glucose tolerance tests were carried out in 14 cases of giddiness. The sugar curve was found to be

TABLE IV

Side-effects with a Anovlar

	No. of Cycles						% of cycles
	1st	2nd	3rd	4th	5th	6th	
Nausea	19	11	3	1	1	—	17.5
Loss of appetite	11	4	1	—	—	1	8.5
Giddness	12	3	2	—	—	1	9.0
Breast enlargement	3	2	—	—	—	—	2.5
Leucorrhea	2	3	1	—	—	—	3.0
Other G.I. symptoms	7	6	3	—	—	—	8.0
Other nervous symptoms	2	3	1	—	—	—	3.0
Aches & pains	6	6	3	1	3	1	10.0
Increased libido	4	—	1	—	—	—	2.5
Decreased libido	1	1	—	—	—	—	1.0

within normal limits before and after therapy. Other gastro-intestinal symptoms like distension and heaviness, were negligible. So were other nervous symptoms like headache, sleeplessness, and aches and pains in the body. No allergic reaction to the drug were noted in any of the cases.

Weight changes

Table V shows the changes in body weight during the therapy. There seems to be a slightly increased tendency for gaining weight, more so during the 3rd week of therapy.

TABLE V

Weight Changes

Increased wt.	Decreased wt.	No change
48.5%	37.1%	14.4%

Break-through bleeding: Twelve cases had break-through bleeding and out of these 10 had it during the 1st cycle and the rest in the 2nd and 3rd cycle. Bleeding was successfully controlled in all cases within 36-48 hours by doubling the dose.

Glucose tolerance test was done in 15 women before and after taking this drug. The results indicated no significant change from the nomal limits. Actually the sugar values seemed to be somewhat lower in cases taking Anovlar.

Amelioration of presenting complaints

Infertility: Though not many of the patients conceived, Anovlar definitely regulated menstrual disturbances in these patients if any. The results are as follows:—

Infertility with irregular periods: Out of 21 patients:

Conceived	Failed to conceive	Other drugs tried	Failed to attend
3	12	1	5

Infertility with irregular periods: Out of 22 patients:

Conceived but aborted	Regular cycles	Failed	Other drugs	No long term follow-up
2	7	3	1	9

Amenorrhoea

Sixteen patients with primary and secondary amenorrhoea were treated with 3 to 6 months course of Anovlar. Cases with any known organic lesion were excluded from study.

Most of the patients had a withdrawal bleeding with this drug even though they had failed to bleed with oestrogen-progesterone injections. After the stoppage of therapy none of the patients started spontaneous menses. Long term follow up was not possible.

Dysfunctional bleeding: The use of progestine to arrest dysfunctional bleeding is well established (Southam). In all the patients bleeding was arrested within 24-28 hours. Thereafter, all of them had moderate and regular bleeding while on therapy. In these cases drugs had to be administered on the first or second day of the menstruation according to the severity of bleeding. No long term follow up was possible to ascertain whether subsequent periods became regular.

Dysmenorrhoea

There were 8 patients in whom dysmenorrhoea was the predominant complaint. The pain was relieved during the treatment in all cases. Four of them continued to be free from symptoms on subsequent follow up. In the remaining patients long term follow up was not available. In one patient with endometriosis the drug was continuously given for 7-8 months. For first 1 or 2 periods the symptoms were relieved but they recurred later on.

Contraception: For 80 cycles.

Anovlar was found to be very effective as an oral contraceptive. None of the patients conceived while on therapy.

On follow up it was found that few of the patients who had left using the tablets had full-term normal deliveries thus proving that the drug has no ill effect on subsequent pregnancies.

Conclusions

1. The results indicate that these progestational drugs besides acting as effective contraceptive agents also have a place in the treatment of other menstrual dysfunctions.

2. The side-effects are negligible and in most cases disappeared after 1-2 cycles.

3. The drug has a special therapeutic use in cases of dysfunctional bleeding where satisfactory control of bleeding can be achieved in a very short period.

4. Its action on the genital tract, especially the endometrium, probably produces an out of phase change

which will not facilitate the process of nidation.

Acknowledgements

The authors gratefully acknowledge the stimulating interest taken by Dean T. H. Rindani. They are also grateful to Prof. E. DeSouza for taking the microphotographs.

This study was supported by a grant from the Ford Foundation.

References

1. Moyer, Dean, Tyler, E. T., Olson, H. J., Zoeldis, L. J.: Fertie. Sterie. **15:** 164, 1964.
2. Pincus, C., Rock, J. & Garcia, C. R.: Am. J. Obst. & Gynec. **75:** 82, 1958.
3. Shahani, S. M. & Chiklikar, A. R.: J. Reprod. & Fertil. **14:** 1, 1967.
4. Southam, A. L.: Ann. N. Y. Academy Sciences. **71:** 666, 1958.

Figs. on Art Paper IV