LIVER FUNCTION TESTS IN PATIENTS ON ORAL PROGESTOGENS

by

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Contraception with oral progestogens containing a small dose of oestrogen has been widely practised during the last ten years in the West, but it was only two years ago that Eisalo *et al* reported raised S.G.O.T. and S.G.P.T. levels in post menopausal women receiving these drugs, the transaminase values being usually elevated within 20 days of starting treatment. Other reports have since then appeared corroborating this (Palva and Mustala 1964), but other investigators, like Swaab (1964), do not believe that these steroids cause liver damage. In view of these controversial reports it was deemed worth while to carry out a study in Indian women, for it was felt that in a population in which anaemia, malnutrition, and amoebic hepatitis are practically endemic, the effect of these drugs on liver function needs to be evaluated before they can be recommended for long term use as oral contraceptives. The only other report on Indian women is that of Shah (1966) in which he has reported elevation in transaminase levels and no effect on serum alkaline phosphatase after oral progestogens.

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Material & Methods

A total of 145 women have been included in this study which covers a period of 16 months from August 1965 to October 1966. The following two preparations were tested.

I. Gynovlar containing 3 mgm. norethisterone acetate + 0.05 mgm. ethinyl oestradiol (76 cases).

II. Noracyclin containing 5 mgm. Lynestrenol (19-nor-17-alpha-pregnenynol) + 0.15 mestranol (3-methyl ether ethinyl oestradiol). (69 cases).

Gynovlar was prescribed for oral contraception and Noracyclin was given for treatment of gynaecological disorders, such as functional uterine bleeding and dysmenorrhoea. Both drugs were given for 20 days each month from day 5 of the menstrual cycle.

Age variation in these cases was from 11 to 43 years and they were selected from the patients attending the family planning clinic and gynaecological out-patient-department of Queen Mary's Hospital or from patients admitted in the gynaecological wards.

In all 145 cases, after a careful history, general and pelvic examinations were done and urine examination and haemoglobin estimation were carried out.

The following four liver function tests were carried out in each case:

1. Serum bilirubin. 2. Serum alkaline phosphatase. 3. Cephalin cholesterol flocculation test and 4. Zinc sulphate turbidity test.

In addition in 123 cases S.G.O.T. and S.G.P.T. estimations were done by Colorimetric method of Reitman and Frankel (1957). These two investigations seem more sensitive than others (Eisalo, 1964).

All cases were studied on the basis of the period of follow-up and the diet taken.

The period of follow-up is shown in Tabel I.

I. Women taking high protein diet	55	Vegetarian	33
		Non-vegetarian	22
II. Women taking low protein diet	90	Vegetarian	48
		Non-vegetarian	42

This grouping was made on the basis of their daily diet, monthly income of the family and number of family members.

Results

1. *Serum Bilirubin:* This was found to be less than 0.5 mgm% in all groups of patients regardless of the diet even after the 7th course which was the longest period of follow up in this study.

II. *Serum alkaline phosphatase:* Mean value of serum alkaline phosphatase before starting the drug was 10.7 K.A. units, and after subsequent courses of the pills the mean values showed a steady rise, being 11.1 after the first course, 12.1 after the second course and ranging between 15.0 to 16.7 K.A. units after the third, fourth, fifth, sixth and seventh courses. After stopping the drug for 1 to 4 months the mean values almost reverted to pre-treatment levels. This is shown in Table II.

When these results were analysed on the basis of diet, it was found that

TABLE I

Period of follow-up	Gynovlar cases	Noracyclin cases
A. 2 cycles	76	69
B. 3 cycles	5 out of 76	18 out of 69
C. 4 cycles	2 out of 5	11 out of 18
D. 5 cycles	1 out of 2	6 out of 11
E. 6 cycles	1	4 out of 6
F. 7 cycles	1	2 our of 4
No. of cases who stopped therapy and returned after interval of 1 to 4 months	44	39

It can be seen that follow-up was better in the Noracyclin group as these were the patients who had some gynaecological complaint and were consequently benefited by these pills. It appears that in the women of Uttar Pradesh at any rate, acceptance of these pills as oral contraceptives over long periods of time may prove difficult.

On the basis of diet and nutrition these 145 cases were classified as follows:

TABLE II

Mean value of serum alkaline phosphatase (in K. A. Units)

	In relation to course of drug	No. of patients			Mean value	Range
		Total	Gynovlar	Nora-cyclin		
I	Before drug	145	76	69	10.7	4.0 to 14.4
II	After 1st course	145	76	69	11.1	5.0 to 16.0
III	After 2nd course	145	76	69	12.1	6.4 to 18.4
IV	After 3rd course	23	5	18	16.0	14.0 to 20.0
V	After 4th course	13	2	11	15.0	14.0 to 20.4
VI	After 5th course	7	1	6	16.3	12.6 to 20.6
VII	After 6th course	5	1	4	16.7	13.5 to 20.6
VIII	After 7th course	3	1	2	16.2	14.8 to 20.2
IX	After gap of 1 to 4 months	83	44	39	11.2	4.6 to 27.8

statistically significant changes in serum alkaline phosphatase occurred in cases taking a low protein diet and these were particularly marked in the low protein vegetarian group, 10 cases of which registered a highly significant rise in serum A.P. values (results are taken to be statistically significant if the calculated value of 't' is more than the tabulated value of 't'). Highly significant results were thus obtained in 10 out of the total 145 cases. Five of these were taking Gynovlar and 5 Noracyclin. Table III.

III. *Zinc sulphate turbidity test (in Int. units):* Mean value of this test before starting the drugs was 4.1 Int. units; after the 1st course it rose to 5.3, after 2nd course to 5.6 and after the 3rd course the values ranged between 9.0 to 13.0 Int. units. When the drugs were stopped for 1 to 4 months the mean values reverted to 4.6 I.U. This is shown in Table IV.

Statistical analysis of the results of this test on the basis of nutrition also revealed a significant rise in 11 cases in the low protein group. This rise occurred after the 2nd and 3rd courses of therapy irrespective of whether the diet was vegetarian or non-vegetarian. Six of these cases were taking Gynovlar and 5 Noracyclin, and 6 of the 11 cases had also registered a highly significant rise in alkaline phosphatase values after the 2nd course.

Eleven out of the total of 145 cases (7%) thus showed highly significant changes in Zinc Turbidity values.

This is shown in Table V.

IV. *Cephalin Cholesterol Flocculation Test:* Out of the total 145 cases only 23 came for follow-up after the 3rd course, and only one out of these 23 cases who were taking Noracyclin showed flocculation up to 3 + after the 3rd and 4th courses. This case, too, belonged to the low protein non-vegetarian group and also showed significant rise in serum alkaline phosphatase and zinc sulphate turbidity after 2 courses of therapy. Clinically, she complained of only mild nausea and there was no jaundice, and bile salts and pigments were absent in the urine. After the 4th course she refused to give blood and so no pills were given and when she agreed to give blood after an interval of 3 months all the values were back to normal. Again after one course she did not turn up.

TABLE III

Serum alkaline phosphatase:—Calculated and tabulated value of "t" in different groups of cases according to diet and nutrition after each course of 20 pills and then after interval of 1 to 4 months.

	GYNOVLAR CASES (76)				NORACYCLIN CASES (69)		
	Value of " t " after				Value of " t " after		
Type of Diet	1st course	2nd Course	Gap of 1 to 4 months	Type of diet	1st course	2nd course	Gap of 1-4 months
I. High protein	Ct — 1.500	Ct — 1.004	Ct — 0.536	I. High protein	Ct — 0.594	Ct — 2.087	Ct — 0.507
(a) vegetarian	Tt — 2.052	Tt — 2.064	Tt — 2.040	(a) Vegetarian	Tt — 2.042	Tt — 2.042	Tt — 2.110
(17 Cases)				(16 cases)			
(b) Non-veg.	Ct — 1.013	Ct — 0.985	Ct — 0.936	(b) Non-Veg.	Ct — 0.322	Ct — 0.473	Ct — 1.010
(12 Cases)	Tt — 2.014	Tt — 2.074	Tt — 2.120	(10 cases)	Tt — 2.101	Tt — 2.101	Tt — 2.160
II. Low protein	Ct — 1.811	Ct — 2.768*	Ct — 0.054	II. Low Protein	Ct — 0.884	Ct — 2.111*	Ct — 0.234
(a) vegetarian	Tt — 2.014	Tt — 2.088	Tt — 2.021	(a) Vegetarian	Tt — 2.072	Tt — 2.012	Tt — 2.036
(26 cases)				(22 cases)			
(b) Non-veg.	Ct — 1.033	Ct — 2.071*	Ct — 0.0351	(b) Non-veg.	Ct — 0.820	Ct — 2.263*	Ct — 0.702
(21 cases)	Tt — 2.025	Tt — 2.021	Tt — 2.045	(21 cases)	Tt — 2.021	Tt — 2.021	Tt — 2—030

Note— Ct — Calculated value of " t "
Tt — Tabulated value of " t "
*donates statistically significant results.

TABLE IV

Mean value of zinc sulphate turbidity test (in Int. Units)

In relation ot course of drug	No. of patients	Mean value	Range
I Before drug	145	4.1	1 to 10
II After 1st course	145	5.3	2 to 12
III After 2nd course	145	5.6	1 to 12
IV After 3rd course	23	9.0	4 to 10
V After 4th course	13	11.3	6 to 16
VI After 5th course	7	12.5	6 to 16
VII After 6th course	5	12.7	8 to 16
VIII After 7th course	3	13.0	8 to 16
IX After interval of 1 to 4 months	83	4.6	1 to 10

TABLE V

Zinc sulphate Turbidity test:—Calculated and tabulated of "t" in different groups of cases according to diet and nutrition after each course of 20 pills and then after interval of 1 to 4 months

	GYNOVLAR CASES (76)				NORACYCLIN (69)		
Type of diet	1st course	2nd course	Gap 1 to 4 months	Type of diet	1st course	2nd course	Gap of 1 to 4 months
I. High protein	Ct — 0.3846	Ct — 1.2945	Ct — 0.683	I. High protein	Ct — 1.408	Ct — 2.040	Ct — 2.046
(a) vegetarian	Tt — 2.052	Tt — 2.035	Tt — 2.064	(a) Vegetarian	Tt — 2.045	Tt — 2.042	Tt — 2.086
(17 cases)				(16 cases)			
(b) Non-veg.	Ct — 1.040	Ct — 0.8379	Ct — 0.2112	(b) Non-veg.	Ct — 0.0714	Ct — 0.780	Ct — 0.427
(12 cases)	Tt — 2,064	Tt — 2.074	Tt — 2.101	(10 cases)	Tt — 2.110	Tt — 2.101	Tt — 2.160
II. Low protein	Ct — 1.847	Ct — 2.567*	Ct — 0.927	II. Low protein	Ct — 1.560	Ct — 3.670*	Ct — 0.257
(a) vegetarian	Tt — 2.015	Tt — 2.010	Tt — 2.041	(a) Vegetarian	Tt — 2.019	Tt — 2.019	Tt — 2.049
(26 cases)				(22 cases)			
(b) Non-veg.	Ct — 1.790	Ct — 0.475*	Ct — 0.475	(b) Non-veg.	Ct — 1.470	Ct — 2.660*	Ct — 0.290
(21 cases)	Tt — 2.025	Tt — 2.021	Tt — 2.045	(21 cases)	Tt — 2.029	Tt — 2.029	Tt — 2.031

Note— Ct — Calculated value of " t ".
Tt — Tabulated value of " t ".
*Denotes statistically significant results.

V. *S.G.O.T. and S.G.P.T.* estimations have been done since February 1966 in 123 cases by the colorimetric method of Reitman and Frankal (1957). Seventy-nine of these were taking low protein diet and 44 were on high protein diet.

The mean vlaues and range of S.G.O.T. and S.G.P.T. are shown in table VI.

TABLE VI

Mean values and range (in I.U.) of S.G.O.T. & S.G.P.T.

Period of follow-up	No. of patients			S.G.O.T. (I.U.)		S.G.P.T. (I.U.)	
	Total	Gynovlar	Nora-cyclin	Mean	Range	Mean	Range
Before drug	123	70	53	15.6	7 to 20	10.5	3 to 17
After 15 days	83	36	47	22.1	9 to 41	15.7	9 to 30
After 1st course	107	60	47	20.0	11 to 35	15.4	10 to 26
After 2nd course	123	70	53	18.6	7 to 29	13.6	7 to 20
After 3rd course	19	1	18	15.9	9 to 23	13.0	8 to 19
After 4th course	2	1	1	22.0	19 to 25	14.5	14 to 15
After 5th course	2	1	1	20.0	19 to 21	15.0	14 to 16
After 6th course	2	1	1	18.0	17 to 19	13.5	12 to 15
After 7th course	2	1	1	17.0	18 to 19	13.0	12 to 14
After interval of 1 to 4 months	100	55	45	16.0	9 to 20	11.2	3 to 15

It will be seen that normal values of S.G.O.T. ranged from 7 to 20 I.U. and of S.G.P.T. from 3 to 19 I.U., with mean values of 15.0 and 11.5 respectively. These values are comparable with the values reported by Wroblewski (1956) and Reitman and Frankel (1957) by spectrophotometric methods.

The highest values of S.G.O.T. were obtained a fortnight after ingestion of the tablets. The figure thereafter gradually declined and reached practically pre-treatment levels at the end of the third month, as can be seen from Table VI. Only two cases continued therapy beyond three months and these registered a second rise in S.G.O.T. values in the fourth and fifth months. The reassuring feature, however, was that after discontinuance of the drug for periods varying from 1 to 4 months, the levels were the same as the pre-treatment ones in all the cases studied. When these results were analysed casewise, it was seen that 34 cases taking these drugs showed values above the normal range of 20 I.U. a fortnight after the commencement of therapy, 19 of these were in low protein group and 15 in high protein group, but statistically significant results were obtained only in 9 cases of the low protein group (7.3%).

S.G.P.T. It was seen that 36 cases showed values above the normal range of 17 I.U. a fortnight after ingestion of these pills. Twenty-two of these were in low protein group, and 14 in high protein group, but statistically significant results were obtained in only 11 cases in the low protein group (9%). Five of these 11 cases also showed raised alkaline phosphatase values and zinc sulphate turbidity, but the raised values in these two tests were only noted after two courses of therapy, showing that S.G.O.T. and S.G.P.T. estimations are

a far more sensitive index of liver dysfunction than the standard liver function tests. Cohn, in a recent study (1957), has also found raised transaminase values in women taking similar oral progestogens. It has been suggested that the abnormal values may be the result of the pseudopregnancy state induced by these drugs and not a measure of impaired liver function, and it is possible that the abnormal values revert to normal as the liver becomes adjusted to the altered "hormonal milieu".

In the present study, analysis of the data on the basis of diet has shown that protein deficiency in the diet potentiated the hepatotoxicity of both oral progestogens, as a statistically significant rise was found only in the low protein group. In this group too, the values returned to normal levels after stopping the drugs showing thereby that the liver damage, even in protein deficient subjects, was fortunately transient.

Conclusions

From this short study of 145 cases for evaluating the hepatotoxic effects of two oral progestogens, Gynovlar and Noracyclin, the following conclusions may be drawn:—

1. Both types of pills cause mixed type of hepatic dysfunction, i.e. hepatocellular as well as hepatocanalicular or cholestatic type. The impaired functions of the liver were, however, found reversible within the 4 months period of follow-up.

2. Significant changes in zinc sulphate turbidity and cephalin cholesterol flocculation tests indicate that these pills have a significant effect on protein metabolism, because significant changes in these tests denote qualitative and quantitative changes in serum albumin and gamma globulins.

3. Rise in serum concentration of S.G.O.T. and S.G.P.T. was demonstrated practically in all the cases studied after a fortnight of drug administration, but was significant only in patients on a low protein diet. In the majority of cases the increased values returned to control values or showed a tendency to do so following discontinuation of therapy for 1-4 months. Thus the increase in enzymatic level was both transitory and reversible.

4. The presence of significant results only in women taking low protein diet further shows that protein deficiency in diet potentiates the hepatotoxicity of these pills. This conclusion is very important for a country like ours where most of the women, to whom these pills will be given for oral contraception or for the hormonal treatment of gynaecological disorders, will be taking a low protein diet, either vegetarian or non-vegetarian, due to poverty. Even in this group impairment of liver function was found to be completely reversible within the 4 months' period of follow-up.

5. This short study further reveals that regular use of these pills for long periods of time is difficult in our country, due to lack of education. This is confirmed by the fact that follow-up was better in cases of functional uterine bleeding and dysmenorrhoea where the patients were benefitted for their illness by these tablets, rather than in those cases where Gynovlar pills were taken by

women otherwise "well" for oral contraception.

6. Oral contraceptives are highly effective if taken regularly, but our study high lights the difficulty in getting women to continue taking these pills regularly over long periods of time.

To summarise, it can be stated that these compounds influence the status of liver function and thereby alter protein metabolism. Both, hepatocellular as well as cholestatic liver damage are caused by these pills, but more so when the diet is deficient in proteins, particularly in vegetarian subjects.

It should, however, be pointed out that the progestogen content of the 2 compounds investigated was much higher than that present in tablets in current use as oral contraceptives, but the detection of alteration in liver function, transient though it was, raises the need for caution in large scale use of these drugs in protein poor population groups. A more prolonged follow-up with a larger series of cases is warranted in order to discover the pattern of hepatic dysfunction, yet unknown, which may appear by long term administration of these drugs.

Short term use for spacing of children using low dosage preparations appears to be safe in view of the transitory nature of the changes encountered. Long term use for family limitation does not appear justified for it would require their being taken for 15-20 years in view of the early age of marriage in this country, and some other form of contraception such as I.U.C.D. or sterilization of either partner should be advocated for this group.

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