EFFECT OF 50 μG ETHINYL ESTRADIOL ON LIPID FACTORS AND LIVER FUNCTION TESTS

by

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Introduction

It is generally believed that the adverse effects of oral contraceptives on lipid metabolism are due to its estrogen content. It has been observed in earlier studies that combined pill containing estrogen had more pronounced effects on lipid factors as compared to mini pill containing progestogen only (Shahani and Patel. 1974, 1977).

In the present study an attempt was made to elucidate and confirm the effects of ethinyl estradiol (EE) only on lipid factors and liver function tests in a group of women from a similar socio-economic starata and during active reproductive phase.

Material and Methods

A group of healthy female subjects in the age group of 15-35 years with irregular menstrual periods or amenorrhea were selected for this study. The average weight of these women was 35.4 ± 9.1 kg. Most of these were used to a low protein vegetarian diet. None of them gave a history of intake of alcohol or smoking.

Ethinyl Estradiol (EE) 50 μg was administered daily for 20 days in a month starting on day five of a cycle to regularise the menstruation in these subjects.

Fasting blood samples were collected from these subjects before commencement of treatment and following the completion of third cycle on this therapeutic schedule.

The biochemical investigations and the references of methodologies used on these serum samples are as follows:

Lipid Studies

1. Total cholesterol (Zurkowski, 1964).
2. Triglycerides (Van Handel and Zilversmit, 1957).
3. Esterified fatty acids (Stern and Shapiro, 1953).
4. Free fatty acids (Dole, 1956).

Liver Function Tests

1. S.G.O.T. and S.G.P.T. (Reitman and Frenkel, 1957).
2. Alkaline phosphatase (Bodansky, 1965).
3. Total Protein. Albumin and Globulin (Reinhold *et al*, 1965).

Basal levels were available in 44 subjects and post-therapy levels in 39 sub-

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jects. In 20 subjects both basal as well as post-therapy levels were available.

The significance of the difference between the mean values was calculated by Student's 't' test.

Results

Table I shows the basal and post-therapy levels of total cholesterol, triglycerides (TG), esterified fatty acids (EFA) and free fatty acids (FFA).

The results indicate that TG, EFA and FFA are stignificantly increased (all $P < 0.001$) with intake of ethinyl estradiol. Total cholesterol also showed an increase, but it was not statistically significant.

Table II shows the basal and post-treatment levels of lipid factors in 20 subjects where they were their own controls. Cholesterol levels showed marginal increase. but TG, EFA and FFA showed significant increases.

Table III shows changes in various

TABLE I

Basal and Post Lipid Levels in Women Treated with 50 μg Ethinyl Estradiol

Parameters	Basal level Mean ± SD n = 44 mg/dl	Post level Mean ± SD n = 39 mg/dl	P
Total Cholesterol	219.1 ± 37.3	238.1 ± 48.7	NS*
Triglycerides	92.7 ± 33.2	146.0 ± 53.7	<0.001
Esterified Fatty Acids	312.0 ± 69.0	389.9 ± 85.9	<0.001
Free Fatty Acids	21.4 ± 4.6	26.7 ± 6.5	<0.001

* NS — Not significant.

TABLE II

Lipid Levels in 20 Women Treated with 50 μg EE Who Were Their Own Controls

Parameters	Basal level Mean ± SD mg/dl	Post level Mean ± SD mg/dl	P
Total Cholesterol	219.9 ± 37.9	225.7 ± 45.9	NS*
Triglycerides	97.1 ± 35.7	139.2 ± 63.6	<0.02
Esterified Fatty Acids	338.4 ± 58.3	386.4 ± 73.7	<0.05
Free Fatty Acids	20.5 ± 4.6	26.9 ± 4.9	<0.001

* NS — Not significant.

TABLE III

Liver Function Tests in Women Treated with Ethinyl Estradiol

Parameters	Basal levels Mean ± SD n = 40	Post levels Mean ± SD n = 38	P
S.G.O.T. (K-units)	19.4 ± 5.8	20.0 ± 6.1	N.S*
S.G.P.T. (K-units)	14.5 ± 3.7	15.4 ± 4.6	N.S*
Alkaline Phosphatase (B-units)	2.3 ± 1.0	2.3 ± 0.9	N.S*
Total Proteins (gm/dl)	6.9 ± 0.5	6.8 ± 0.7	N.S*
Albumin (gm/dl)	4.0 ± 0.3	4.1 ± 0.4	N.S*
Globulin (gm/dl)	2.9 ± 0.4	2.6 ± 0.8	N.S*

* NS — Not significant.

parameters of liver function tests. The differences were not statistically significant in any of the parameters. Similar results were obtained even in 20 cases where both basal and post-therapy results were available in the same subjects.

Discussion

There are variable reports regarding the effect of estrogens on serum cholesterol. It was believed that estrogens lower the plasma cholesterol or that its effect is highly variable because of its divergent effect on cholesterol content in the alpha and beta lipoprotein fractions (Beck, 1973).

No effect on cholesterol levels has been reported with combined pills containing varying amount of EE (Roy *et al*, 1980; Nash *et al*, 1979; Hennekens *et al*, 1979). In the present study a non-significant increase was observed in serum cholesterol levels. In earlier studies a significant increase was reported with the combined pills. That could probably be explained by the duration of exposure to the therapy and the increased content of EE.

The triglycerides showed a significant increase following ethinyl estradiol administration. The hypertriglyceridemic effects of synthetic estrogen are considered to be dose dependant (Stokes and Wynn, 1971). It was observed in earlier studies that increase was more pronounced with combination pill containing 100 μg EE compared to that containing 50 μg EE. A significant decline ($P < 0.01$) in TG levels was observed in a group of women who were switched over to progestogen only pill (Shahani and Patel, 1974; 1977).

It is generally recognized that these contraceptive steroids decrease post-heparin lipoprotein (PHL) lipase activity, an enzyme considered to play an important role in the metabolic clearance of plasma TG (Hazzard *et al*, 1973). There is evidence that the combined pill may increase TG turnover (Hazzard *et al*, 1973; Kissebah *et al*. 1973). This complex mechanism may be due not only to increased formation of the TG in liver, but to decrease transport across the vascular eqithelium and decreased peripheral utilization (Fabian *et al*, 1971; White and Tullach, 1971). These metabolic effects may be due to the estrogen component of these compounds since the administration of progestogens either natural or synthetic when given alone, produced the opposite effects on PHL lipase activity and on TG turnover. Indeed progestogens given alone have been observed to lower plasma TG concentration.

Increase in EFA also seems to be dose related. It earlier studies, combined pill showed significant increase in proportion to the content of EE. Esterification of free fatty acids is an obligatory step in lipogenesis which is probably increased.

Free fatty acids also showed a significant increase in the study, though a decrease had been observed in our earlier studies, both with the combined pill as well as progestogen only pill (Shahani and Patel, 1974; 1977). It may be suggested that estrogens by itself tend to increase the FFA levels.

Estrogen-progestin analogues are known to have stimulatory and inhibitory effects on various enzymatic processes in the liver. However, our studies did not show any significant effect on liver function tests with EE probably due to short duration of estrogen intake.

In conclusion, this study shows that administration of 50 μg EE even for a short duration of three months is likely to affect the lipid factors in young women during active reproductive phase. Since the suggestive relationship between incrased TG

and premature coronary heart disease has become of major concern to the physician and patients at large, lowering the amount of estrogen further in a combined pill may lessen the coronary risk. However, this may also affect the cycle control. Further work on appropriate combination and safety are called for. The results of this study should caution the general physician against administering estrogen freely to premenopausal/menopausal women as a substitution therapy. Extra care may be required especially in women with obesity, hypertension, diabetes and a family history suggestive of coronary heart diseases.

Summary

A study was carried out in a group of young women from a low socio-economic strata to evaluate the effects of cyclic administration of 50 μg Ethinyl Estradiol (EE) for a period of 3 months on the various lipid factors and liver function tests. The results indicated that 50 μg of EE does affect the triglycerides, esterified fatty acids and free fatty acids to a significant level. No significant change was noted in cholesterol. No changes were detected in any of the parameters evaluated for liver function. The implication of raised lipid factors in relation to coronary heart diseases is discussed in women exposed to combination contraceptive pills or women taking estrogens during menopause.

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