SERUM BILE ACIDS DURING BIPHASIC CONTRACEPTIVE TREATMENT WITH ETHINYL ESTRADIOL AND NORGESTREL

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ABSTRACT

Twenty-nine women were treated with biphasic combined oral contraceptive pills containg ethinyl estradiol 0.05 mg and levonorgestrel 0.050-0.125 mg. Serum primary bile acids (cholic acid and chenodeoxycholic acid) and one secondary bile acid (deoxycholic acid) were measured by radioimmunoassay. The serum samples were collected before the treatment and at one, three and twelve months during the treatment. No significant changes were found in these bile acid levels during the treatment. The ratio of cholic/chenodeoxycholic acid did not change either. No pathological values were found in the conventional liver function tests although serum alanine aminotransferase activity was significantly increased after twelve months treatment. It can, therefore be concluded that the present contraceptive pill does not cause any liver dysfunction detectable by bile acid measurements or other "classical" liver function tests.

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CONTRACEPTION

INTRODUCTION

Hepatic disorders may occur during oral contraceptive treatment (1,2) and transient changes in some liver function tests are sometimes seen during first cycles of oral contraceptive treatment. However, more sensitive tests are needed to reveal a possible subtle and early dysfunction during contraceptive treatment. During the last few years, it has been shown that serum bile acid determinations are very sensitive indicators for hepatic dysfunction (3).

Estrogens, anabolic steroids and some other drugs may cause intrahepatic cholestasis (4) which resembles the intrahepatic cholestasis occurring during pregnancy (5,6). In this disease, the primary bile acids are, in particular, indicators of early stages of cholestasis, and may be superior to any other conventional liver function tests (7). During the use of combined contraceptives,however,no changes in the serum concentrations of cholic acid conjugates have been found (8).

The purpose of the present study was to investigate the effect of one combined biphasic oral contraceptive pill on serum bile acid levels and on some of the usual conventional liver function tests and evaluate the sensitivity of these tests to detect possible liver dysfunction during the treatment.

PATIENTS AND METHODS

The series consisted of 29 women aged 24.9 $\pm$ 4.1 (mean $\pm$ S.D., range 17-33) years, who were treated with biphasic combined oral contraceptive pills for twelve months. Each tablet in each regimen of 21 pills (Sekvilar^{R}, Leiras, Finland) contained 0.05 mg of ethinyl estradiol and the first 11 tablets contained 0.05 mg while the subsequent 10 tablets had 0.125 mg of levonorgestrel.

The following laboratory tests were performed before and after one, three and twelve months' treatment: serum primary bile acids (cholic acid (CA)and chenodeoxycholic acid (CDCA)) and one secondary bile acid

(deoxycholic acid (DCA)) by radioimmunoassay (9) and serum aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), total bilirubin, gamma-glutamyltranspeptidase (G-GT) and alkaline phosphatase (AFOS) utilizing routine clinical-chemical techniques. The blood samples were collected in the morning after an overnight fasting period and stored at -20°C until assayed.

Statistical analyses of the results were performed with the random block design of variance analyses.

RESULTS

Serum cholic acid concentration before treatment was 0.59 ± 0.05 umol/l (mean ± SEM), chenodeoxycholic acid 0.79 ± 0.09 umol/l and deoxycholic acid 0.22 ± 0.03 umol/l. No significant changes were found in serum bile acid levels during the entire 12-month treatment periode (Table I). The ratio of CA/CDCA did not change either during the oral contraceptive treatment. In the conventional liver function tests (Table II), a significant change was found in the aminotransferase (ALAT) levels, which were higher after twelve months' treatment. Although the values were significantly increased, no values exceeding the upper reference limit (>40 U/l) were present.

DISCUSSION

In the studies of bile acid composition in human gallbladder bile, a decrease in the proportion of chenodeoxycholic acid has been reported to occur during the treatment with oral contraceptives (10) or with ethinyl estradiol alone (11). The latter synthetic estrogen has been extensively studied as a drug which causes bile secretory failure affecting bile salt independent of bile flow (12). However, no significant changes have been found in serum cholic acid levels from using combined contraceptive pills in either a preveious (8) or the present study. On the other hand, during treatment of climacteric symptoms with natural estrogen-progestin combinations (13), a decrease

Table I

Serum bile acid values (mean±SEM) before and during the contraceptive treatment

Bile acid (umol/l)	Before treatment	During treatment (months) 1	3	12
Cholic acid	0.59±0.05	0.52±0.06	0.51±0.06	0.68±0.08
Chenodeoxy-cholic acid	0.78±0.09	0.66±0.08	0.69±0.11	0.89±0.09
Deoxycholic acid	0.22±0.03	0.27±0.04	0.26±0.06	0.48±0.06
Ratio of CA/CDCA	1.10±0.18	0.96±0.14	1.15±0.22	1.03±0.22

Table II

Conventional liver function test values (mean±SEM) before and during the contraceptive treatment

	Before treatment	During treatment (months) 1	3	12
ALAT (U/l)	10.7±1.1	13.9±1.8	9.8±1.1	17.7±1.7*
ASAT (U/l)	15.0±1.2	16.1±1.1	14.4±1.0	17.6±1.0
Bilirubin (umol/l)	8.2±0.6	7.3±0.7	6.7±0.6	7.3±0.6
Gamma-GT (U/l)	13.1±1.5	13.8±1.4	12.8±1.2	15.7±1.9
Alkaline phosphatase (U/l)	141±7	130±9	115±6	132±7

Significance is given in comparison to the values before the treatment.

* =$p<0.01$

in serum chenodeoxycholic acid level was observed. This finding was suggested to be attributable to an inhibitory effect of the administered hormones on the bile acid synthesis (14). The climacteric patients studied by Ylöstalo et al. (13) were, on the average 23 years older than those in the present investigation, and also the pretreatment serum CDCA concentrations were higher than in the present study,the mean values being 1.5 and 0.8 umol/l, respectively.

In patients with intrahepatic cholestasis of pregnancy, we have previously shown that the increase in the primary bile acid concentrations and in the ratio of CA/CDCA over one are the first signs of cholestasis (7) and precedes alterations in conventional liver function tests. In the present series, there were no signs of intrahepatic cholestasis or other liver malfunctioning detected by the tests used. Also the ratio of CA/CDCA stayed unchanged. The changes in the conventional liver function tests were small and remained within the normal reference range. Although ALAT activity was significantly increased after twelve months' treatment, it remained within the normal reference range (<40 U/l).

Our findings allow us to conclude that, according to the laboratory tests utilized in this study, no liver dysfunction is associated with the use of this regimen.

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