Variations in serum copper and ceruloplasmin activity following a long term intake of combined oral contraceptives in Iranian women

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ABSTRACT. Serum copper level and ceruloplasmin activity were measured in 104 middle class Iranian women from 17 to 49 years of age, using combined oral contraceptives from 3 to 108 months, and results were compared with those obtained from 24 normal individuals (21-45 years of age) from the same social class. Significant increases were observed in 100% of test subjects in serum copper level and ceruloplasmin activity (p < 0.005), which tend to decline following 48 months of intake, when liver probably adapts itself, and ceruloplasmin synthesis is not aggravated significantly any more. The variations observed in this study were higher than those obtained in Nigerian women and were comparable with those found in women from other countries.

INTRODUCTION
Significant increases in serum copper level and ceruloplasmin activity have been reported, following administration of oral contraceptives, in several different populations (1-10). However, much smaller increases were reported in serum copper level following the intake of two oral contraceptives in Nigerian women (11). The aim of the present study was to evaluate if changes in serum copper and ceruloplasmin following the intake of combined oral contraceptives (COC) were different in Iranian women.

MATERIALS AND METHODS
All reagents were from Merck or BDH. Serum copper was measured by either the cuprizone method (12) or atomic absorption spectrophotometry (AAS), in which serum was diluted with equal volume of 8% trichloroacetic acid, supernatant was submitted to an M4QIII Zeiss atomic absorption spectrophotometer, and values were recorded and compared with freshly prepared standards of copper sulphate, containing 25, 50, 100, 200, 400, and 800 μg of copper / 100 ml. Ceruloplasmin activity was measured by the use of O-dianisidine dihydrochloride method (13). Glassware was acid-washed and deionized water was used throughout the experiments. Blood samples were collected between 09:00 and 11:00 during the second half of the menstrual cycle, and sera were separated as soon as the clot was formed. Subjects were healthy middle class individuals, with no past history of severe illness, attending a family planning clinic.

RESULTS
Serum copper level and ceruloplasmin activity were measured in 104 subjects from 17 to 49 years of age, using COC 1 (ethinyl estradiol 0.05 mg, norgestrel 0.5 mg) and COC 2 (mestranol 0.15 mg, lynestrenol 2.5 mg) for 3 to 108 months. Results were compared with those obtained from 27 normal individuals (21-45 years of age) from the same social class, who had never taken oral contraceptives. Figures 1 and 2 illustrate the changes observed in serum copper level, during various intervals of the intake of COC 1 and 2, compared with control subjects. The increase was observed in 100% of the individuals and was equivalent to 11-175% of mean control (p<0.005). Figure 3 shows the changes observed in ceruloplasmin activity, during various intervals of the intake of COC 1 and 2, compared with control subjects. The increase was observed in 100% of the test subjects and was equivalent to 12-217% of mean control (p<0.05).

DISCUSSION
We have previously shown a significant increase in serum α2-globulin, of which ceruloplasmin is a fraction, following the intake of COC in Iranian women (14). This
increase in the activity of ceruloplasmin is most probably aggravated by: i) cholestasis and ii) the liver undergoing a physiological stress. The rise in serum copper level is undoubtedly secondary to the increase in ceruloplasmin synthesis. The increases in serum copper level and ceruloplasmin activity observed in our study do not confirm the report on serum copper level following the intake of oral contraceptives by Nigerian women, where comparatively smaller increases have been reported (11). Our observations are comparable with the previous findings from other countries. Variations in serum copper level and ceruloplasmin activity were observed in 100% of the individuals and were similar in the case of intake of COC 1 and COC 2 and were not dose-dependent. Moreover, there appeared to be a tendency for the observed increases to decline after 48 months of intake of COC, and that is probably when liver adapts itself to the physiological stress, caused by the intake of COC. The copper levels obtained by chemical method were higher than those obtained by AAS (Figs. 1 and 2).

REFERENCES