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EFFECTS OF ORAL CONTRACEPTION ON LIVER FUNCTION TESTS AND SERUM PROTEINS IN WOMEN WITH ACTIVE SCHISTOSOMIASIS

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ABSTRACT

Thirty-eight women with urinary or intestinal schistosomiasis but without clinical or laboratory evidences of hepatic involvement and 30 healthy control women were treated with an oral contraceptive containing 0.05mg ethinyl estradiol and 0.5mg levonorgestrel for six consecutive months. Liver function tests (serum bilirubin, SGOT, SGPT, serum alkaline phosphatase) and serum proteins (total, albumin, globulins, ceruloplasmin, haptoglobin and alpha-1 antitrypsin) were measured before beginning the treatment and after three and six months of use. Both group experienced significant increases in SGOT, SGPT and serum alkaline phosphatase during the first three months of treatment with tendencies to decrease during the subsequent 3 months. No change occurred in serum bilirubin. There was significant decreases in serum albumin and haptoglobin and increases in alpha-1 globulin, ceruloplasmin and alpha-1 antitrypsin. With the exception of serum level of alpha-1 globulin, there were no significant differences between schistosomiasis patients and the controls in terms of changes in any laboratory test as a result of the treatment, thus suggesting that patients with active schistosomiasis do not incur a higher risk of hepatic dysfunction while using oral contraception.

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INTRODUCTION

In 1972, it was estimated that women of the age group 15 to 39 years living in villages in southern Egypt had an incidence of schistosomal (Bilharzial) infestation varying between 20-37% (1). It is expected that the incidence has risen since then, and after changing the system of land irrigation following the building of the High Dam of Aswan, the prevalence of schistosomiasis is much higher in the northern parts of Egypt. Schistosoma haematobium, the species present in southern Egypt, is an important cause of chronic liver disease (2). Other species of schistosoma prevalent in other parts of Egypt and of the world are also known to affect the liver and to ultimately cause hepatic fibrosis.

Women with evident liver involvement are not given hormonal contraception but patients having urinary or intestinal schistosomiasis per se are not denied use of the pill. It is possible that these patients may have clinically undetected liver damage and that their liver functions may be adversely affected by the contraceptive steroids. The present work investigated, in a longitudinal study, the effect of the contraceptive pill on liver function tests (LFTs) and on the serum levels of proteins produced in the liver in women with visceral schistosomiasis as compared to normal women.

MATERIAL AND METHOD

The study was carried out on volunteers among the attendants of a family planning clinic in Beni Elias Village, Sedfa District, Assiut Governorate. They expressed desire to use oral contraception. Women were subjected to clinical examination and a battery of clinical laboratory tests including hemoglobin estimation, careful urine and stool examination for parasites, and measurement of serum levels of transaminases, alkaline phosphatase, total proteins, albumin, globulins, ceruloplasmin, haptoglobin, and alpha-1 antitrypsin. Methods used for these tests are listed in Table I. Patients with live schistosoma ova in their urine or stools were included in the study group and those without such infestation in the control group, provided that they had no clinical or laboratory evidence of liver disease and provided they met with qualifying prerequisites. Both groups were treated with an oral contraceptive containing 0.05mg ethinyl estradiol and 0.5mg levonorgestrel (Primovlar, Schering) for six consecutive months. The physical examination and the battery of laboratory tests were repeated after three and six months of treatment. Giving blood specimens was so objectionable with the patients that out of 104 women initially admitted to the study, 38 schistosomiasis patients and 30 controls completed their 6-month term. Only the data belonging to these patients will be presented. All the 38 patients had Schistosoma haematobium ova in their urine and

5 of them had the ova detected in the stools as well. The mean age of the schistosomiasis patients and the controls were 29.5 and 29.2 years and their mean parity was 4.9 and 5.4, respectively. Ninety-six per cent reported not having used any contraceptive before.

A repeated measures analysis of variance, with group (schistosomiasis versus control) and time of test (admission, 3-month follow-up, and 6-month follow-up) as main effects, was performed.

Table I. Methods Used for Clinical Laboratory Tests

Test	Reference for the method used
S. Bilirubin	Jendrassik, L., and Grof, P.: Biochem. Z, 297: 81, 1938.
SGOT and SGPT	Reitman, S. and Frankel, S.: Am. J. Clin. Path., 28: 56, 1957.
S. Alkaline Phosphatase	Bessey et al.: J. Biol. Chem., 164: 321, 1946.
S. Total Proteins	Miller, G.L.: Analyt. Chem., 31: 964, 1959.
S. Albumins and Globulins (electrophoresis on cellulose acetate strips)	Kohn, J. Chromatographic and Electrophoretic techniques, Vol. II. Ed. Smith, I. William Heinemann Medical Books, Ltd., London, P., 56, 1960.
S. Ceruloplasmin S. Haptoglobin S. Alpha-1 Antitrypsin	Single Radial Immunodiffusion Plates of Behringworke AG, Marburg, W. Germany.

RESULTS

There was no difference between the two group in menstrual symptoms related to pill use except for the duration of menstrual flow. The control group experienced a significant decrease in the duration of flow during the study which was not evident in the schistosomiasis patients. This was confirmed by a group X time of test interaction ($F(2,130)=18.69$, $p<.001$). There were no differences in other relevant symptoms or physical signs between the two groups, or as a result of the treatment. At the time of admission to the study, there was no difference between the mean hemoglobin concentration of the schistosomiasis patients and that of the controls (10.8 ± 1.6gm% (S.D.) and 10.7 ± 1.3gm%, respectively) and there was no change in these means along its course.

The mean values for each liver function test done at admission, 3 months and 6 months are shown in Table II. At admission the schistosomiasis and control groups were

Table II. Liver Function Tests for Schistosomiasis and Control Groups at Admission, 3-Month and 6-Month Follow-ups

	Controls (n = 30)			Schistosomiasis (n = 38)		
	Adm	3-Mos	6-Mos	Adm	3-Mos	6-Mos
Serum Bilirubin						
Total (mg/100ml)	.39	.44	.43	.37	.42	.37
Conjugated	.17	.19	.17	.17	.18	.16
Unconjugated	.22	.25	.26	.20	.23	.22
Transaminases						
SGOT (U/L)	14.67	23.27	22.20	23.87	34.10	33.50
SGPT (U/L)	6.83	8.33	7.33	7.60	10.71	9.00
Alkaline Phosphatase (U/L)	23.50	25.33	27.40	25.21	29.47	29.29
Serum Proteins (gm/100ml)						
Total	6.76	6.50	6.16	6.69	6.48	6.16
Albumin	3.50	3.24	3.00	3.35	3.07	2.84
Globulin (Electrophoresis)	3.25	3.25	3.16	3.34	3.41	3.31
Alpha-1 Globulin	.33	.40	.40	.40	.44	.43
Alpha-2 Globulin	.70	.72	.65	.77	.73	.75
Beta Globulin	.91	.88	.87	.87	.93	.89
Gamma Globulin	1.32	1.26	1.25	1.28	1.30	1.24
Serum Ceruloplasmin (mg/100ml)	29.67	51.27	63.93	27.74	45.24	60.68
Serum Haptoglobin (mg/100ml)	156.37	127.33	107.73	156.10	121.87	102.53
Serum Alpha-1 Antitrypsin (mg/100ml)	223.33	279.43	298.43	226.68	301.32	327.10

equivalent on all tests except SGOT which was significantly higher in the former group ($F(1,66) = 12.16$, $p < .001$). Table III depicts the percent changes from admission to each follow-up in the two groups. With the exception of alpha-1 globulin, no significant differences were found between schistosomiasis patients and the control women in the incidence or degree of change of the variables. No group X time of test interaction was observed. Several significant trends were observed for the following tests over the 6-month study period:

Table III. Percent Change, by Group, in Liver-Function Tests between Admission and 3-month Follow-up and Admission and 6-month Follow-up

	Controls		Schistosomiasis	
	Adm-3mos	Adm-6mos	Adm-3mos	Adm-6mos
	%	%	%	%
Serum Bilirubin				
Total	+13	+10	+14	0
Conjugated	+12	0	+ 6	- 6
Unconjugated	+14	+18	+15	+10
Transaminases				
SGOT	+59	+51	+43	+40
SGPT	+20	+ 6	+41	+18
Alkaline Phosphatase	+ 8	+17	+17	+16
Serum Proteins				
Total	- 4	- 9	- 3	- 8
Albumin	- 7	-14	- 8	-15
Globulins	0	- 3	+ 2	- 1
Alpha-1 Globulin	+21	+21	+10	+ 8
Alpha-2 Globulin	+ 3	- 7	- 5	- 3
Beta Globulin	- 3	- 4	+ 7	+ 2
Gamma Globulin	- 5	- 5	+ 2	- 3
Serum Ceruloplasmin	+73	+115	+63	+119
Serum Haptoglobin	-19	-31	-22	-34
Serum Alpha-1 Antitrypsin	+25	+34	+33	+44

1. SGOT: Table III notes a large increase in SGOT levels during the first three months in both groups followed by a slight drop during months 4 through 6. The repeated-measures analysis of variance confirmed that this trend was significant ($F(2,132) = 17.02$, $p < .001$). SGOT was the only variable in which the two groups differed at admission. This difference was maintained throughout the study.

2. SGPT: Women in both groups experienced increases in SGPT levels during the first three months of the study and decreases, approaching admission levels, during the last three months. Collapsed across groups, the main effect for time of test proved to be significant ($F(2,132) = 9.19$, $p < .001$).

3. Alkaline phosphatase: A time of test main effect (F (2,132) = 5.83, $p < .01$) confirms the significant increase noted for alkaline phosphatase levels for both groups, particutarly during the first three months.

4. Serum proteins: Serum albumin tended to decrease ($p < .001$) and alpha-1 globulin to increase ($p < .01$). Collapsed across tests, schistosomiasis patients had significantly higher alpha-1 globulin levels than control patients.

5. Serum ceruloplasmin: Dramatic (100%) increases in ceruloplasmin were noted for both group (F (2,132) = 313.78, $p < .001$). The change was maintained throughout the study period.

6. Serum haptoglobin: Haptoglobin levels for subjects in both groups decreased significantly during the 6-month study period (F (2,132) = 140.23, $p < .001$).

7. Serum alpha-1 antitrypsin: Alpha-1 antitrypsin levels increased for both groups over the entire study period, although resutls presented in Table III suggest that most of this increase occurred during the first three months. The main effect for time of test was significant (F (2,132) = 216.35, $p < .001$), and although the group X time of test interaction just failed to reach significance ($p < .02$), data suggest that a more rapid increase in alpha-1 antitrypsin was experienced by schistosomiasis patients.

Table IV. Correlation* Between Percentage Changes in Ceruloplasmin, Haptoglobin and Alpha-1 Antitrypsin and Changes in LFT's After 6-Months of Pill Use

	Ceruloplasmin	Haptoglobin	Alpha-1 antitrypsin
Bilirubin	-0.1144 (0.177)	0.2474 (0.021)	0.0602 (0.313)
Total Proteins	-0.0649 (0.300)	-0.0711 (0.282)	-0.1255 (0.154)
Albumin	-0.1278 (0.149)	-0.1334 (0.139)	-0.3341 (0.003)
Alkaline Phosphatase	0.0433 (0.363)	0.0865 (0.241)	0.0374 (0.381)
SGOT	-0.1941 (0.056)	-0.0647 (0.300)	-0.0736 (0.275)
SGPT	0.0347 (0.389)	0.1079 (0.191)	0.3181 (0.004)

* Correlation coefficients; significance in parentheses.

Table IV depicts the degree of correlation between the percent changes that occurred after 6-month treatment in serum ceruloplasmin, haptoglobin and alpha-1 antitrypsin and the percent changes in LFTs. The only significant correlations were between changes in alpha-1 antitrypsin and changes in SGPT and serum albumin.

DISCUSSION AND CONCLUSIONS

With the exception of serum level of alpha-1 globulin, there were no significant differences between patients with schistosomiasis and the healthy controls in terms of changes in the conventional LFTs or in the serum levels of the proteins examined as a result of treatment with the contraceptive pill. The schistosomiasis patients had higher SGOT from the time of admission, a difference which was maintained throughout the study. There were no significant group X time of test interactions for any of the variables. It can be concluded that patients with active urinary or intestinal schistosomiasis do not incur a higher risk of liver dysfunction on taking the pill. This is very assuring since a major sector of potential pill users in the rural parts of Egypt are having this infestation. Studies of the histopathology of hepatic schistosomal affection (2,3) support these findings. They have demonstrated minimal liver cell necrosis and preservation of lobular architecture till very late in the disease. Women with advanced schistosomiasis will have clinically evident hepatic involvement and will identify themselves as having an obvious contraindication for pill use. Indeed, advanced cases are already infertile due to profound alterations in steroid metabolism (4).

Both the schistosomiasis group and the controls equally showed changes in the LFTs during the first three months of oral contraceptive treatment with tendency of the changes to halt or revert towards the admission values during the subsequent three months. This may represent an adaptation of hepatic cell to the action of the contraceptive steroids.

The two groups studied showed decreases in serum albumin and haptoglobin and increases in ceruloplasmin and alpha-1 antitrypsin during pill use. These trends continued throughout the 6 months of the study. Changes in ceruloplasmin, haptoglobin and alpha-1 antitrypsin did not correlate with changes in most of the conventional liver function tests. The causes of the changes in these proteins are still not clear. The final judgment concerning the significance of changes in these proteins with the use of contraceptive pills awaits the aquisition of additional knowledge about the basic action of ovarian steroids.

Based on these findings, clinical practice policy should continue with the prescription of oral contraceptives for women with active schistosomiasis. However, additional laboratory tests should be performed at regular intervals to closely monitor any changes in liver function among those with active infection.

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