[*Probe* (1978): (XVII), 2, 115-122]

Effect of an Indigenous (Herbal) Drug Liv.52 on the Hepatic Damage caused by Oral Contraceptives–A Biochemical (Enzymatic) Approach

Khuteta, K.P., *B.Sc., M.B.,B.S., M.Sc. (Med.), M.A.M.S.,*
Professor of Physiology, Upgraded Dept. of Physiology & Biochemistry,
S.M.S. Medical College, Jaipur-4 (Rajasthan)

(Paper presented at Sixth International Congress of Pharmacology,
Helsinki, Finland, July 20-25, 1975.)

Lehfeldt (1973) in a comprehensive monograph *Current Status of Oral Contraceptives* says that steroidal hormones are taken orally for contraceptive purposes by more than 20,000,000 women, largely in North America, Western Europe and increasingly in Latin America. Reports from the Republic of China indicate that since 1958, a 22nd day pill developed in China is increasingly replacing the IUD and other devices, with no figures available. In India oral contraception is used by a small portion of the vast population. In USSR, the oral method of contraception has been viewed with extreme scepticism until recently. He further stresses that based on his personal experience gained in private practice as well as the Family Planning Clinic of Bellevue Hospital, the pill is still the method most often selected by patients and physicians.

Only a few sporadic attempts have been made so far to study the effect of oral contraceptives on some enzymes chiefly related to hepatic metabolism. What's more, there is a great paucity of studies in human subjects further accentuated by a lack of knowledge about the repairs of hepatic damage caused by the continuous use of oral contraceptives.

There are over a dozen recent Indian studies including long-term reports on oral contraceptives or the “pill”. Research on the toxicity and side-effects of oral contraceptives in human beings seems to be quite difficult in our country. At least with whatever little work we have done and are doing, we are confronted with a good many problems. For a start, women do not want to take the ‘pill’ regularly - they actually miss the timings or even days because of their manifold household responsibilities; they are not prepared to give the blood/urine samples, except for a few educated subjects; they actually avoid doing so despite strong motivation and temptations such as giving them tonics, samples and drugs for their family. Ladies have even thrown the oral contraceptives on the table with anger and gone away when asked for blood samples during *consecutive* menstrual cycles.

The ‘pill’ is being used by millions of women around the world. It is taken by women around the world as regularly and as automatically as putting on their clothes or brushing their teeth. It has been established that the ‘pill’ leads to imbalance of hormones and metabolism. Hess (1962) has claimed that the function of steroid hormones in an organism would depend on their regulatory effect on enzymatic reaction. In tissues, many enzymes have been found to be under the hormonal control, but less is known about the relationship between hormones and enzymes in the serum.

Fenton Schaffer (1966) and Briggs *et al.* (1970) reported that these hormones cause different degrees of hepatocellular damage which can be demonstrated both morphologically (with Light and Electron Microscope) and functionally by the elevation of serum isocitric dehydrogenase (ICD) activity and other enzymes. There may be liver cell enlargement, hyperplasia of Kupffer cells or biliary hyperplasia. Martti *et al.* (1967) reported decrease of serum lactic dehydrogenase (LDH) and alkaline phosphatase (Alk. phos.) and elevation of ICD. Larson-Cohn *et al.* (1966) observed a rise of SGOT and SGPT, while Brohult *et al.* (1965) observed rise of serum carbamyl tranferase and

LDH and Alkaline phosphatase was reported normal. Khuteta *et al.* (1974) reported a significant rise of ICD and aldolase, while the effect on LDH was variable.

Since very little work has been done on the preventive and prophylactic aspect of disturbed hepatic activity caused by the continued use of oral contraceptives, this study has been undertaken to investigate the effect of a well known drug Liv.52 (The Himalaya Drug Co.), which has been reported to increase the functional efficiency of the liver–using serum isocitric dehydrogenase, alkaline phosphatase, lactic dehydrogenase and blood total sulfhydryl groups as an index of hepatic metabolism.

MATERIAL

Seventy female subjects (35 for each type of 'pill') of all classes between the conceptual age, attending the Family Planning Clinics of State Zenana Hospital, S.M.S. Highway Maternity Centre and normal cases attending Female Outdoors were selected for this study. Each subject was clinically examined to exclude any cardiovascular, gastrointestinal, hepato-renal and endocrinal disease.

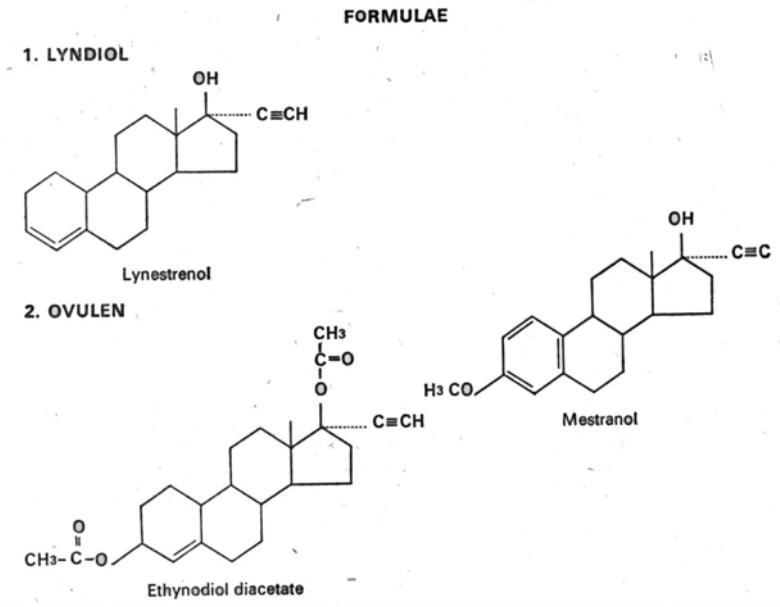
METHODS

Lyndiol (Lynestrenol 2.5 mg – Mestranol 0.075 mg) and Ovulen Ethynodiol diacetate 1.0 mg– Mestranol 0.1 mg) tablets were taken in single oral dose for 22 and 21 consecutive days respectively in each menstrual cycle, commencing on the fifth day after the onset of the menstrual cycle. This was done for five consecutive cycles and blood samples were taken before administering the 'pill', after the first cycle, third cycle, fifth cycle and after the sixth cycle in which the subject was given two Liv.52 tablets, three times a day along with the oral contraceptives.

Oral Contraceptives used in the Present Work

The following drugs were used:

	Name	Progestogen	Oestrogen
1.	Lyndiol	Lynestrenol	2.5 mg + Mestranol 0.075 mg
2.	Ovulen	Ethynodiol diacetate	1.0 mg + Mestranol 0.100 mg



Following instructions were given to the individual patient:

(i) To count the first day of her next period as Day 1st.

(ii) To take the first tablet of her cycle on Day 5th, whether or not her menstrual cycle had ceased.

(iii) To take one tablet daily in the evening until the packet was completed.

(iv) In case she had missed taking the tablet, she was instructed to take it next morning, so that the routine tablet could be taken in the evening as usual.

(v) At the end of the course, she was instructed to wait 6 days (Lyndiol) and 7 days (Ovulen) and to begin the next packet regardless of the time of onset of menstruation.

As far as possible, with the exception of a few cases, fasting blood samples were taken for the study and analysed by the same technical staff, often in duplicate, to avoid personal error.

The following estimations were undertaken:

(i) Serum Isocitric dehydrogenase (by the method of Bell and Baron, 1960).

(ii) Serum Alkaline Phosphatase (King, 1951).

(iii) Blood total sulfhydryl groups (by the method of Ellmen, 1959).

(iv) Serum Lactic dehydrogenase (by the method of Wrobleski and La Due, 1955).

COLLECTION OF BLOOD SAMPLES

10 ml of venous blood was drawn from the anticubital vein, by a sterilised, clean and dry syringe. The blood was then transferred to a clean, dry and sterilised stoppered vial. Then serum was allowed to be separated without any delay by keeping in an incubator at 37°C for 15 to 20 minutes and was finally taken out by a dry clean teat pipette. Every precaution was taken to avoid haemolysis. Estimations were not carried out in haemolysed samples.

RESULTS AND DISCUSSION

In this study the disturbance in the function of the liver caused by the administration of *Combined Pills*–Lyndiol (2.5 mg) and Ovulen (1.0 mg) for *five* consecutive menstrual cycles, has been studied by analysing the important, less studied serum enzymes after the 1st, 3rd and 5th cycles.

Results (Mean Values)								
Cases	Lyndiol (2.5 mg) – 35 cases				Ovulen (1.0 mg) – 35 cases			
	ICD	Alk. Phos.	S.H. Gr.	LDH	ICD	Alk. Phos.	S.H. Gr.	LDH
Normal (70)	163	2.85	3.75	221	163	2.85	3.75	221
After first cycle	179	2.6	3.6	235	175	2.9	3.5	241
After third cycle	190	2.4	3.3	229	184	2.5	3.3	255
After fifth cycle	192	2.4	3.2	224	193	2.3	3.0	246
After sixth cycle with Liv.52	171.3	3.1	4.2	278	171	3.2	3.6	216
Units:	Serum Isocitric dehydrogenase activity (ICD) – Sigma units/ml. Serum Alkaline phosphatase (Alk. Phos.) – Klett units. Blood Total sulfhydryl groups (SH. Gr.) – m moles per litre. Serum Lactic dehydrogenase activity (LDH) – u mole/litre (I.U.)							

Further, Liv.52, a herbal indigenous drug was given orally; two tablets three times a day throughout the *Sixth* menstrual cycle along with the contraceptive and again the blood/serum was analysed.

Each Liv.52 tablet contains:

Capparis spinosa	65 mg
Cichorium intybus	65 mg
Solanum nigrum	32 mg
Cassia occidentalis	16 mg
Terminalia arjuna	32 mg
Achillea millefolium	16 mg
Tamarix gallica	16 mg
Mandur bhasma	33 mg

(Prepared in the juices and decoctions of various hepatic stimulants).

Alkaline Phosphatase–Fig. 1 shows a fall of this enzyme within normal limits. This is due to the hepatic insufficiency caused by these steroidal contraceptive agents during their metabolic degradation.

Isocitric Dehydrogenase Activity – As evident from Fig. 2 there is a significant rise, which is due to the steroids causing different degrees of hepatocellular damage from the oestrogens of the 'pill' (Stoll *et al.* 1965).

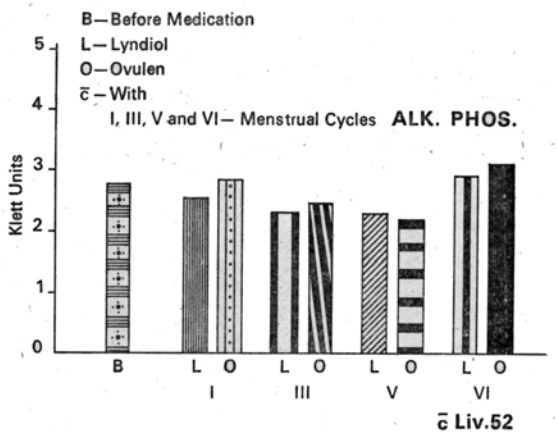


Fig. 1
Fall in Alk. Phos. due to oral contraceptives, returned to normal on Liv.52.

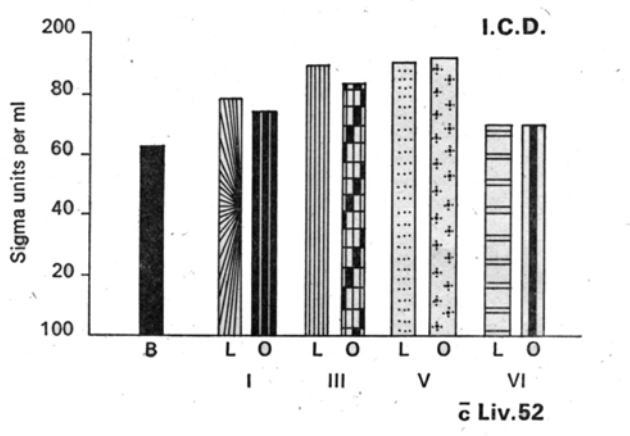


Fig. 2
Rise in Isocitric dehydrogenase due to oral contraceptives, returned to normal following Liv.52

Total Sulfhydryl Groups–as evident from Fig. 3 there is a fall of 'SH' groups after these combined 'pills'. This is due to their ('SH') partial utilisation in rapid breakdown of glycogen in the liver during inactivation of the steroid hormones and transient increased liberation of adrenaline by the continuous use of oral contraceptives.

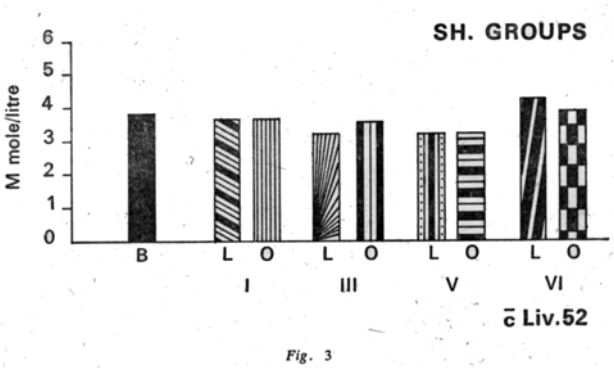


Fig. 3
Fall in Sulphydryl group due to oral contraceptives, rose to normal following Liv.52

Lactic Dehydrogenase Activity–Fig. 4 shows the effect of both Lyndiol and Ovulen. The results are quite variable in all cycles. Some cases showed a significant rise and some a fall. Similar controversial results have been reported by others also. This diversity of activity of this enzyme proves that the hormones in the 'pill' are metabolised,

inactivated and conjugated with glucornic acid in the liver at different rates, depending chiefly on the dosage and the type of 'progestins'.

All the aforesaid changes in the serum/blood levels of ICD, Alk. Phos., SH groups and LDH returned to normal or nearly normal after the administration of Liv.52 (a herbal drug) along with the 'pill' throughout the *Sixth* menstrual cycle.

This is positively due to the protection of the hepatic parenchyma against transient 'injury' caused by the hormones, acceleration of hepatic metabolic activity, promotion of regeneration of hepatic cells and thus increase in the functional efficiency of the liver by Liv.52.

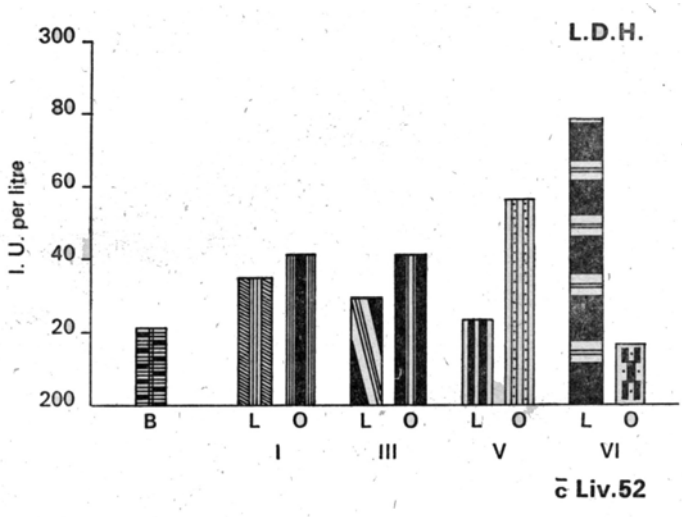


Fig. 4
Changes in Lactic dehydrogenase due to oral contraceptives.

CONCLUSION

The results of this study are very encouraging as they highlight that:

i. Liv.52 has shown promising results in simultaneous repair/protection of hepato-cellular architecture when administered along with oral contraceptives.

ii. Liv.52 must be prescribed prophylactically along with the 'pills' which cause predictable injury to the hepatic parenchyma.

ACKNOWLEDGEMENT

We are thankful to The Himalaya Drug Co., Bombay (India) for the generous supply of Liv.52 tablets.

REFERENCES

1. Brohult, J. and Westgren, A., *Lancet* (1965): 2, 1344.
2. Ellman, G.L., *Arch. Biochem. Biophys.* (1959): 82, 70.
3. Fenton Schaffer, *J. Am. med. Assoc.* (1966): 198, 1019.
4. Hess, B. (1962): Enzyme in Blutplasma, G. Thieme Stuttgart. Quoted in *Acta. Obs. & Gynec.* (1967): 46, 525.
5. Khuteta, K.P. and Rathore, V.S., *Proceed. Int. Union of Physiol. Sciences* (1974): Vol. XI, 325 (974).
6. Larsson-Cohn, U.L.F., *Acta. Obs. & Gyn.* (1966): 45: 196, 499.
7. Lahfeldt, *Obs. & Gyn. Annual* (1973): 261.
8. Martti, O. Pulkhinen and Willman Kalle, *Acta. Obs. & Gyn. Scan.* (1967): 46, 525.
9. Stoll, B.A., Andrews, J.T., Motteram, R. and Upfill, J., *Brit. med. J.* (1965): 1, 723.
10. Wrobleski, E., La Due, J.S., *Proc. Sooc. Expt. Biol.* (1955): 20, 210.