THE EFFECT OF MENOPAUSAL STATUS AND OESTROGEN AND PROGESTERONE ON SERUM BIOCHEMICAL PROFILES

by

T. R. VARMA

SUMMARY

Serum biochemical profiles were studied in 390 postmenopausal women before, during and after treatment using Premarin (conjugated equine oestrogens, Ayerst), Harmogen (piperazine oestrone sulphate, Abbott) and Progynova (oestradiol valerate, Schering) alone and combined with progestational agents. Postmenopausal women in general had slightly elevated serum sodium, urea, calcium, alkaline phosphatase, glucose and lipids, which showed a reduction while they received oestrogen replacement therapy. There was no evidence of impairment of hepatic and renal function, serum blood glucose and lipid levels.

Introduction

Possible benefits and drawbacks of hormone replacement therapy for postmenopausal women have been widely debated. In recent years a better understanding of the changes of the climacteric has led to the widespread use of oestrogen therapy. The possible adverse effects of long-term oestrogen therapy need careful evaluation before such recommendations can be widely accepted. There are fewer reports of the effect of oestrogen replacement therapy in postmenopausal women who are in a high-risk age group.

The aim of the study was to observe the effect of ovarian failure at the climacteric and oestrogen replacement therapy on serum biochemical profiles.

From: St. George's Hospital Medical School, Cranmer Terrace, London.

Accepted for publication on 18-5-83.

Material and Methods

We studied a group of 390 patients attending our special menopause clinic for 5 years for treatment of climacteric symptoms. The ages of patients ranged from 35 to 70 years (mean 52.3) and the time that had elapsed since the menopause ranged from 1 to 25 years (mean 6.4). The main climacteric symptoms were hot flushes, night sweats, insomnia and dyspareunia. Serum levels of pituitary gonadotrophins and oestradiol were measured to confirm the climacteric state. The patients were asked to take no other medications. Patients with proven cardiovascular, hepatic, renal and thrombo-embolic disorders were excluded from the study.

Group I Consisted of 150 patients who received Premarin (conjugated equine oestrogen) alone and combined with the progestational agents such as 'Neogest' (Norgestrel, Schering) 0.5 mg for 7 days

(Prempak), 'Duphaston' (dydrogesterone, Duphar) 5 mg for 10 days and Primolut N (norethisterone, Schering) 5 mg for 10 days for a total period of 5 years. The dosage of Premarin was 0.625 and 1.25 mg.

Group II consisted of 105 patients who received Harmogen (piperazine oestrone sulphate, Abbott) in two different dosages 0.75 and 1.5 mg alone and combined with 'Duphaston' (dydrogesterone) 5 mg for 10 days and 'Primolut N' (norethisterone) 5 mg for 10 days for a total period of 5 years.

Group III consisted of 135 patients who received Progynova (oestradiol valerate, Schering) in two different dosages 1 and 2 mg alone and in combination with 'Norgeston' (Levonorgestrel, Schering) 0.25 mg for 10 days (cycloprogynova, 1 mg), 'Neogest' (norgestrel, Schering) 0.5 mg for 10 days (cycloprogynova, 2 mg), 'Duphaston' (dydrogesterone) 5 mg for 10 days and 'Primolut N' (norethisterone) 5 mg for 10 days for a total period of 5 years.

Serum biochemical tests were carried out on all patients after an overnight fast and the assays were carried out within four hours. The assays were carried out before treatment was given and they were repeated at every 3 monthly visits to clinic and 6 weeks after the cessation of treatment. On all patients electrolytes and urea, liver function tests, calcium and phosphate, and blood lipids and sugar were measured at each visit.

Results

Table I shows that the mean age, mean duration after menopause, mean weight and mean levels of systolic and diastolic blood pressure were comparable for the three groups.

Table II shows the mean values with two standard deviations for each chemical measurement in Group 1 (Premarin).

One hundred and fifty patients were receiving Premarin alone and in combination with progestational agents; each regimen lasting for 6 months, for 5 years. All the values during the whole treatment period Were taken together and the mean and standard deviations were calculated. Table II shows that the mean levels of sodium, urea, calcium, albumin, alkaline phosphatase, glucose, cholesterol and triglyceride were lower during the treatment period as compared with the pre-treatment values and the difference was significant (Student 't' test $P < 0.05$). The levels remained low 6 weeks after the cessation compared to the pre-treatment levels.

The difference remained significant when the above values were analysed during each treatment regimen, whether the Premarin was used alone or combined with progestational agents and whether the dosage of Premarin was 0.625 mg and 1.25 mg.

TABLE I

Details of the Patients in the Three Groups (I, II and III).

Details of Patients	Group I (Premarin) n = 150	Group II (Harmogen) n = 105	Group III (Progynova) n = 135
Mean age (years)	51.9	52.1	50.9
Mean duration after manopause (years)	5.95	5.88	5.79
Mean weight (Kg)	63.2	64.10	63.91
Mean systolic blood pressure (mm Hg)	132.5	129.8	130.8
Mean diastolic blood pressure (mm Hg)	84.6	81.9	82.8

TABLE II

Serum Biochemicals Levels (mean values ± 2SD)

Group I (Premarin)

	Pre-treatment	A	Treatment	Post-treatment
Sodium (in mol/L)	140.73 ± 1.29	S	138.82 ± 1.31	140.92 ± 1.62
Potassium (in mol/L)	4.12 ± 0.32	NS	4.05 ± 0.38	4.14 ± 1.62
Bicarbonate (m mol/L)	24.82 ± 1.52	NS	23.25 ± 1.25	25.26 ± 1.32
Urea (m mol/L)	5.92 ± 0.92	S	4.82 ± 1.02	4.92 ± 1.12
Bilibrubin (UMol/L)	8.86 ± 1.34	NS	8.02 ± 1.21	8.42 ± 1.32
Albumin (g/L)	43.82 ± 2.21	S	40.12 ± 2.16	40.62 ± 2.09
Alkaline phosphatase (IU/L)	76.89 ± 3.20	S	62.24 ± 3.12	61.12 ± 2.12
Alanine transaminase (IU/L)	16.92 ± 2.04	NS	15.94 ± 2.24	16.42 ± 2.12
Calcium (m mol/L)	2.42 ± 0.81	S	2.21 ± 0.91	2.28 ± 0.86
Phosphate (m mol/L)	0.92 ± 0.09	NS	0.91 ± 0.08	0.89 ± 0.09
Glucose (m mol/L)	4.76 ± 0.68	S	4.22 ± 0.73	4.28 ± 0.65
Cholesterol (m mol/L)	5.68 ± 0.89	S	5.08 ± 0.96	5.12 ± 0.86
Triglyceride (m mol/L)	1.58 ± 0.09	S	1.32 ± 0.11	1.30 ± 0.09

Paired data 't' tests—A = Difference between pre-treatment and treatment value.
S = Significant ($p < 0.05$).
NS = Not significant.

Table III shows the mean values and the two standard deviations for each biochemical measurement in Group II (Harmogen).

Table III shows 105 patients, while receiving Harmogen alone and combined with progestational agents, had a lower mean value of sodium, urea, calcium, albumin, alkaline phosphatase, glucose, cholesterol and triglyceride as compared with levels prior to treatment ($P < 0.05$). The levels remained slightly lower 6 weeks after the cessation of treatment compared to the pre-treatment levels.

The difference remained significant when the values were analysed during each regimen of treatment when Harmogen was used alone and combined with progestational agents.

Table IV shows the mean values and the two standard deviations for each biochemical measurement in Group III (Progynova).

TABLE III

Serum Biochemical Levels (Mean values ± 2 SD)

Group II (Harmogen)

	Pre-treatment	A	Treatment	Post-treatment
Sodium (in mol/L)	141.83 ± 1.31	S	137.78 ± 1.48	140.12 ± 1.52
Potassium (in mol/L)	4.29 ± 0.31	NS	4.18 ± 0.36	4.11 ± 0.28
Bicarbonate (m mol/L)	25.96 ± 0.1.92	NS	24.78 ± 1.98	24.68 ± 1.86
Urea (m mol/L)	5.75 ± 0.86	S	4.38 ± 0.92	4.32 ± 0.96
Bilibrubin (UMol/L)	8.84 ± 1|92	NS	8.21 ± 1.86	8.69 ± 1.92
Albumin (g/L)	43.86 ± 2.32	S	40.09 ± 2.18	41.24 ± 2.11
Alkaline phosphatase (IU/L)	74.92 + 3.19	S	68.92 + 3.02	69.24 ± 3.10
Alanine transaminase (IU/L)	15.88 + 2.12	NS	15.01 + 2.16	15.35 + 2.17
Calcium (m mol/L)	2.48 + 0.81	S	2.14 + 0.91	2.21 + 0.86
Phosphate (m mol/L)	0.92 + 0.09	NS	0.89 + 0.08	0.84 + 0.09
Glucose (m mol/L)	4.68 ± 0.80	S	4.28 ± 0.86	4.30 ± 0.91
Cholesterol (m mol/L)	5.72 ± 0.98	S	5.18 ± 0.89	5.22 ± 0.96
Triglyceride (m mol/L)	1.60 ± 0.11	S	1.22 ± 0.09	1.31 ± 0.08

Paired data 't' tests—A = Difference between pre-treatment and treatment values.
S = Significant ($p < 0.05$).
NS = Not significant.

Table IV shows 135 patients, while receiving Progynova alone or combined with progestational agents, had a lower mean value of sodium, urea, calcium, albumin, alkaline phosphatase, blood glucose and lipids compared with pre-treatment levels ($P < 0.05$). The difference remained, but slightly less, 6 weeks after the cessation of treatment. The difference remained significant when values were analysed at the end of each regimen of treatment.

Discussion

More *et al* (1981) reported that postmenopausal women had slightly higher serum sodium levels and showed a reduction while they received Mestranol and Norethisterone. We also noted similar changes in serum sodium levels in postmenopausal women. Factors influencing sodium and water metabolism in women have been studied by a number of workers

TABLE IV
Serum Biochemical Levels (Mean Values ± 2 SD)
Group III (Progynova)

	Pre-treatment	A	Treatment	Post-treatment
Sodium (m mol/L)	142.12 ± 1.42	S	137.91 ± 1.52	139.42 ± 1.92
Potassium (m mol/L)	4.22 ± 0.32	NS	4.01 ± 0.41	4.04 ± 0.28
Bicarbonate (m mol/L)	25.22 ± 1.86	NS	24.68 ± 1.91	24.86 ± 2.21
Urea (m mol/L)	5.86 ± 0.96	S	4.82 ± 0.86	4.74 ± 0.91
Bilibrubin (UMol/L)	8.86 ± 1.30	NS	8.12 ± 1.22	8.25 ± 1.40
Albumin (g/L)	42.92 ± 2.42	S	39.12 ± 1.92	39.13 ± 1.90
Alkaline phosphatase (IU/L)	72.92 ± 3.45	S	65.82 ± 2.82	66.91 ± 2.11
Alanine transaminase (IU/L)	15.24 ± 2.11	NS	14.89 ± 2.16	15.20 ± 1.98
Calcium (m mol/L)	2.59 ± 0.78	S	2.18 ± 0.82	2.20 ± 0.78
Phosphate (m mol/L)	0.92 ± 0.09	NS	0.86 ± 0.09	0.89 ± 0.08
Glucose (m mol/L)	4.74 ± 0.95	S	4.09 ± 0.82	4.10 ± 0.78
Cholesterol (m mol/L)	5.70 ± 0.92	S	5.08 ± 0.88	5.28 ± 0.94
Triglyceride (m mol/L)	1.58 ± 0.10	S	1.28 ± 0.09	1.38 ± 0.08

Paired data 't' tests—
A = Difference between pre-treatment and treatment values.
S = Significant ($p<0.05$).
NS = Not significant.

including Klein and Carey (1975) who recorded no change in total body sodium during the menstrual cycle despite premenstrual fluid retention and Newman (1957) who noted that fluid retention in pregnancy was accompanied by hyponatraemia. Aitkin *et al* (1974) stated that serum sodium concentrations were lower and the extra cellular fluid volume higher after mestranol therapy in a group of middle-aged women. The effect of ovarian failure at the menopause may be due to reduced extra-cellular fluid volume, and haemoconcentration may be the reason for the generally higher serum levels which were found among the postmenopausal women.

We also found a reduction in serum urea level in postmenopausal women during treatment with oestrogen as compared with the pre-treatment level. Urea concentration in women has been shown to increase with age (O'Kell and Elliott, 1970) although these studies did not take menopausal status into account. Moore *et al*

(1981) stated that postmenopausal women had a higher serum urea level and it showed a significant reduction following oestrogen treatment.

The mean calcium, albumin and alkaline phosphatase concentrations were all higher in the postmenopausal women and the levels of all three factors reduced following oestrogen treatment. This was consistent with the findings of Moore *et al* (1981). Calcium and alkaline phosphatase levels in middle-aged women have been investigated by many workers in view of their relevance to osteoporotic changes. Wilding *et al* (1972) noted marked increases in the concentrations of both calcium and alkaline phosphatase in women in the fifth and sixth decades of life. Gallagher *et al* (1972) reported that serm calcium levels increased following bilaterial oopherectomy. Van Passen (1976) noted higher levels of calcium and alkaline phosphatase after the menopause. Since the other parameters of liver function have not shown any change the raised alkaline phosphatase levels in the postmenopausal women should originate from both and together with raised serum calcium levels suggested increased metabolic activity of bone. Previous studies have suggested that hormone therapy at the climacteric adversely affects liver function (Eisalo, *et al* 1968; Palva and Mustala, 1964 and Stoll, *et al* 1966). *However,* these studies involved different treatment regimens and higher dosages than those used in the present work.

Our study showed that the serum glucose showed a reduction in level in the postmenopausal women during treatment as compared with pre-treatment levels. This was comparable with the findings of Moore *et al* (1981). Previous studies have shown mild impairment of glucose tolerance associated with mestranol and norethisterone treatment (Notelovitz, 1974; Sturdee, *et al* 1976 and Thom, *et al,* 1977). An impairment of glucose tolerance was found in 31 of 40 patients after 3 months of oestrogen therapy using ethinyl oestradiol and mestranol by Thom *et al* (1977). This effect was reported by Buchler and Warren (1966) and by Spellacy *et al* (1968) who reported a higher incidence of deterioration in glucose tolerance during oral contraceptive treatment in the older age group. However, Pi-Sunyer and Oster (1968) and Thom *et al* (1977) stated that there was no significant difference in fasting blood glucose level on oestrogen treatment. Thom *et al* (1977) stated that there was no abnormality in glucose tolerance while patients received conjugated equine oestrogen and oestradiol valerate. Sturdee *et al* (1976); Barrett-Connor *et al* (1979) and Moore *et al* (1981) recently reported that postmenopausal women showed a reduction in fasting blood sugar while they received mestranol and norethisterone for climacteric symptoms. We noted that postmenopausal women had a reduction in fasting blood sugar while they received Premarin, Harmogen and Progynova as compared with the pre-treatment level.

Our study showed that the presently available oestrogen preparations in small dosages, either alone or combined with the commonly used progestational agents, had no adverse effects on fasting serum cholesterol and triglyceride levels. In general, the lipid levels showed a reduction while the postmenopausal women were on oestrogen treatment. Our findings were consistent with that published by Royal College of Obstetricians and Gynaecologists Lind *et al* (1979). Our present work showed that postmenopausal women in general had slightly elevated serum sodium, urea, calcium, albumin alkaline phosphatase, glucose and lipids which showed a reduction

while they received oestrogen replacement therapy. There was no evidence of impairment of hepatic and renal functions and blood glucose and lipid levels while the postmenopausal women received replacement therapy.

Acknowledgement

I wish to express my thanks to my medical and nursing staff for their co-operation. My special gratitude to Professor J. Owen and his staff for their help in measuring all the biochemical profiles.

References

1. Aitken, J. H., Lindsay, R. and Hart, D. M.: Clin. Sci. **47: 179, 1974.**
2. Barrett-Connor, E., Brown, V. and Turner, J. **et al.:** J. Am. Med. Assoc. **241:** 2167, 1979.
3. Buchler, D. and Warren, J. C.: Am. J. Obstet. Gynec. **95: 479, 1966.**
4. Eisalo, A., Heino, A. and Rasanen, V.: Acta. Obstet. Gynec. Scand. **47: 58, 1968.**
5. Gallagher, J. C., Young, M. M. and Nordin, B. E. C.: Clin. Endocrinol. (Oxford), **1: 57, 1972.**
6. Klein, L. and Carey, J.: Am. Obstet. Gynec. **74: 956, 1975.**
7. Lind, T., Cameron, E. C. and Hunter, W. M. **et al.:** Brit. J. Obstet. Gynaec. **86:** Suppl. 3, 1979.
8. Moore, B., Paterson, M. E. L., Sturdee, D. W. and Whitehead, T. P.: Br. J. Obstet. Gynaec. **88: 853, 1981.**
9. Newman, R. L.: Obstet. Gynec. **10: 51,** 1957.
10. Notelovitz, M.: S. A. Med. J. **48: 2599,** 1974.
11. O'Kell, R. T. and Elliott, J. R.: Clin. Chem. **16: 161, 1970.**
12. Palva, I. P. and Mustala, O. O.: Brit. Med. J. **2: 688, 1964.**
13. Pi-Sunyer, F. X. and Oster, S.: Obstet. Gynec. **31: 482, 1968.**
14. Spellacy, W. N., Carlson, K. L., Birk, S. A. and Schade, S. L.: Metabolism. **17: 496, 1968.**
15. Stoll, B. A., Andrews, J. T. and Motteram, R.: Brit. Med. J. **I: 960, 1966.**
16. Sturdee, D., Gustafson, R. C. and Moore, B.: Post. Med. J. 52: Suppl **6: 52, 1976.**
17. Thom, M., Chakravarti, S., Oram, D. H. and Studd, J. W. W.: Brit. J. Obstet. Gynaec. **84: 776, 1977.**
18. Van-Paassen, H. C., Duursma, S. A. and Roelofs, J. M. M. **et al.:** In: Consensus on Menopause Research. Ed. Vankeep, R. B., Greenblatt, R. B. and Albeaux-Fernet, M. Lancaster: M.T.P. Press Ltd., P. 116-23, 1976.
19. Wilding, P., Rollason, J. G. and Robinson, D.: Clin. Chim. Acta. **41: 375,** 1972.