The effect of inaccuracies in assessing gestational age alone in terms of final management may be estimated. With 60% concordance nearly 2% of all women may be subjected to amniocentesis when they do not really need it while in 2% the test may be omitted when it is actually required. Even with 90% concordance (unattainable in practice at present) the false-positive and false-negative rates are still over 1%. Expressing this differently, with an amniocentesis rate of 5%—that is, all mothers with serum AFP concentrations over the 95th centile—and 70% accuracy of gestational dating to ± 1 week, 32% of mothers referred for amniocentesis may not actually need it and only 68% of those who need it will actually have it. The present study was carried out in optimal clinical circumstances and the levels of precision obtained are likely to underestimate rather than overestimate the true extent of the problem.

Clearly, if acceptable results are to be achieved with serum AFP screening, precise gestational dating is required and in a large proportion of cases reliable ultrasound examination will be necessary to supplement clinical findings. This must be taken into account when planning a screening programme for neural tube defects. In some areas it may be more convenient or appropriate for the primary-care physician rather than the hospital clinic to take the blood sample for AFP estimation at the appropriate time, but if he is to be responsible for interpreting results he will require access to ultrasound facilities at least for those of his patients who have uncertain dates or an irregular cycle.

We are grateful to the obstetricians who participated in this study and to the Department of Health and Social Security for giving financial support to the South Wales Anencephaly and Spina Bifida Screening Project, of which this study forms a part.

References

1 UK Collaborative Study on Alpha-fetoprotein in Relation to Neural-Tube Defects, *Lancet*, 1977, **1**, 1323.
2 Chamberlain, R, *et al*, *British Births* 1970, vol 1. London, Heinemann, 1970.
3 Beazley, J M, and Underhill, R A, *Nursing Times*, 1971, **67**, 1414.
4 Dubowitz, L M S, Dubowitz, V, and Goldberg, C, *Journal of Pediatrics*, 1970, **77**, 1.
5 Campbell, S, and Newman, G B, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1971, **78**, 513.
6 Ferguson Smith, M A, *et al*, *Lancet*, 1978, **1**, 1330.
7 Bennett, M J, *et al*, *Lancet*, 1978, **2**, 1296.

(*Accepted 28 February 1979*)

Relation between plasma hormone profiles, symptoms, and response to oestrogen treatment in women approaching the menopause

S CHAKRAVARTI, W P COLLINS, M H THOM, J W W STUDD

British Medical Journal, 1979, **1**, 983-985

Summary and conclusions

Out of a consecutive series of 300 patients seen at a menopause clinic, 82 complained of symptoms generally associated with the climacteric, although they were still menstruating. Vasomotor disturbances were absent in 42 of these patients (group 1) and present in 40 (group 2). Headaches, insomnia, and dyspareunia were the most common complaints among the women with vasomotor symptoms, whereas loss of libido and depression predominated in those without. Conjugated equine oestrogens (Premarin) 1·25 mg daily given for three weeks out of four relieved nearly all symptoms in group 2, but in group 1 the response was disappointing.

The mean plasma oestradiol concentration in women with vasomotor symptoms was significantly lower than that observed during days 1-10 of the menstrual cycle, but plasma testosterone values were not significantly different from those observed in younger women. Plasma follicle-stimulating hormone (FSH) and luteinising hormone (LH) concentrations were similar to those seen after the menopause. Concentrations of these hormones in the women without vasomotor symptoms were similar to those in the younger, regularly menstruating women. After six months of oestrogen treatment patients in group 2 had a 2·1-fold increase in mean plasma oestradiol concentration, and plasma FSH and LH concentrations were reduced to 39% and 66% of their pretreatment values respectively; in group 1, however, no such pronounced changes occurred.

High concentrations of FSH were present in patients with oestrogen-responsive symptoms, 15 U/l being the diagnostic cut-off point. This measurement in the presence of characteristic symptoms therefore constitutes the best method of selecting patients for oestrogen-replacement therapy.

King's College Hospital, London SE5 9RS
S CHAKRAVARTI, FRCS, MRCOG, senior registrar
W P COLLINS, DSC, reader in clinical endocrinology
M H THOM, MRCOG, research senior registrar
J W W STUDD, MD, MRCOG, consultant obstetrician and gynaecologist

Introduction

The transition from reproductive life to the postmenopausal years is often protracted and commonly associated with oestrogen-deficiency symptoms which may be confused with commonplace life stresses. Symptoms due to oestrogen deficiency in premenopausal women are easily overlooked,[1] and Jaszmann,[2] in an epidemiological study, found that vasomotor symptoms and depression and irritability not only could precede the disappearance of periods by several years but were often at their most severe before the menopause. An essential feature of any treatment is accurate diagnosis, since otherwise the indications for oestrogen replacement may be extended incorrectly to patients with domestic and personality problems. We have therefore sought a means to distinguish true symptoms of

oestrogen deficiency from those that are not oestrogen-responsive.

We have reported the plasma hormone profiles in the 30 years after a natural menopause and after bilateral oophorectomy.[3 4] Furthermore, Utian[5] and Campbell and Whitehead[6] have conducted careful and convincing placebo cross-over trials to establish the true symptoms of the endocrinopathy after ovarian failure. We now examine the symptoms and endocrine changes in women approaching the menopause and attempt to define the type of criteria needed for diagnosis and correlate the occurrence of various climacteric symptoms with hormonal state.

Patients and methods

Out of a consecutive series of 300 patients seen in the menopause clinic at Dulwich Hospital from October 1974 to December 1976, 82 were still having periods although they complained of symptoms generally associated with the climacteric. A patient was considered to be postmenopausal if one year had elapsed since the last menstrual period. All patients in the study were menstruating cyclically, those whose last menstrual period had occurred more than three months before admission to the clinic being excluded. At the first attendance a detailed history was taken, symptoms were recorded, and a thorough clinical examination was performed. A peripheral venous blood sample (20 ml) was obtained between 10 am and 12 noon, the plasma being separated immediately and stored at −15°C.

All patients were prescribed conjugated equine oestrogens (Premarin) 1·25 mg a day, cyclically three weeks out of four. They were seen after three months and again at six months. Their symptomatic response to treatment was recorded at each visit and a sample of peripheral venous blood (20 ml) taken and stored as before.

Concentrations of follicle-stimulating hormone (FSH), luteinising hormone (LH), testosterone, and oestradiol were measured in all samples by radioimmunoassay techniques.[3 4] The distribution patterns of FSH and LH concentrations were described by the arithmetic mean and range, while that of steroid values was best defined by the geometric mean and range. The significance of difference between concentrations of various hormones in groups of patients with and without vasomotor symptoms was assessed with Student's *t* test applied to normal and logarithmic data.

Results

Table I gives the age distribution of the 82 women studied, and table II lists the symptoms recorded at the time of the first visit to the clinic. The patients were assigned to one of two groups depending on the absence (group 1, n=42) or presence (group 2, n=40) of vasomotor symptoms. Headaches, insomnia, and dyspareunia were the most common complaints among women who were experiencing these vasomotor disturbances, whereas loss of libido and depression were more prevalent in women who were not complaining of hot flushes. Other symptoms were evenly distributed between the two groups.

Three patients stopped oestrogen treatment because of nausea and breast discomfort, and four were lost to follow-up. Of the 38 patients in group 2 who completed six months of treatment, all except four obtained relief in the frequency and intensity of symptoms (table II). There was pronounced relief of nearly all symptoms in this group, whereas in group 1 the response was disappointing.

Table III gives the mean plasma hormone concentrations in the two groups before treatment. The plasma oestradiol concentration in women with vasomotor symptoms was significantly lower ($P < 0.005$) than the values observed during days 1-10 of the menstrual cycle (mean 250·3 pmol/l (68·2 pg/ml), range 90·4-600·8 pmol/l (24·6-164·0 pg/ml)), even though they were still menstruating. The concentration of testosterone, however, did not differ significantly from that in the younger women (mean 1·4 nmol/l (0·4 ng/ml), range 0·6-2·2 nmol/l (0·17-0·63 ng/ml)). These premenopausal women experiencing hot flushes had plasma FSH and LH concentrations comparable to those seen after the menopause (LH: mean 53·8 U/l, range 21·5-80·2 U/l; FSH: mean 48·2 U/l, range 11·2-81·2 U/l).

TABLE I—*Age distribution of the 82 patients studied*

Age in years	≤39	40-45	46-50	≥51
No (%) of patients	16 (19·5)	20 (24·4)	28 (34·1)	18 (22·0)

TABLE II—*Presenting symptoms and proportions of patients in each group relieved of symptoms after six months' treatment with cyclical conjugated oestrogens 1·25 mg daily for three weeks out of four*

Symptoms	Group 1				Group 2			
	Patients with symptoms before treatment (n=42)		Patients relieved by oestrogen treatment (n=37/42)		Patients with symptoms before treatment (n=40)		Patients relieved by oestrogen treatment (n=38/40)	
	No	%	No	%	No	%	No	%
Hot flushes					40	100·0	34	85·0
Headaches	6	14·3	1	16·7	28	70·0	22	78·6
Insomnia	6	14·3	0		31	77·5	22	71·0
Dyspareunia	4	9·5	0		10	25·0	9	90·0
Depression	36	85·7	15	41·7	15	37·5	9	60·0
Loss of libido	19	45·2	6	31·6	9	22·5	3	33·3
Loss of concentration	24	57·1	8	33·3	21	52·5	14	66·7
Irritability	24	57·1	8	33·3	24	60·0	21	87·5
Aches and pains	8	19·0	2	25·0	20	50·0	10	50·0

TABLE III—*Mean plasma FSH, LH, oestradiol, and testosterone concentrations before treatment in the two groups of women (ranges in parentheses)*

	Group 1 (n=42)	Group 2 (n=40)	Significance of difference
FSH (U/l)	5·4 (0·8-16·3)	37·9 (14·6-84·6)	P<0·0005
LH (U/l)	15·8 (0·8-42·5)	40·7 (17·9-63·7)	P<0·01
Oestradiol (pmol/l)	200·8 (82·4-400·8)	76·6 (38·7-140·3)	P<0·005
Testosterone (nmol/l)	1·5 (1·1-2·1)	1·6 (0·5-2·3)	NS

NS = Not significant.
Conversion: SI to traditional units—Oestradiol: 1 pmol/l ≈ 0·27 pg/ml. Testosterone: 1 nmol/l ≈ 0·29 ng/ml.

The concentrations of these hormones in women who did not complain of vasomotor symptoms were similar to those found in younger, regularly menstruating women. Plasma oestradiol and testosterone values were also found to be in the normal range of values as obtained during days 1-10 of the menstrual cycle in younger women. These symptomatic, premenopausal women who had never experienced vasomotor symptoms but requested medical attention had plasma hormone concentrations indistinguishable from those of younger women.

After six months' treatment with oestrogens women with hot flushes showed a 2·1-fold increase in the mean plasma concentration of oestradiol and a 1·9-fold increase in the concentration of testosterone (table IV). Plasma FSH and LH concentrations in these patients were reduced to 39% and 66% of the pretreatment values respectively, although the values remained higher than those found in younger, normally menstruating women. On the other hand, no pronounced changes occurred in the plasma concentrations of FSH, LH, and oestradiol in the women who did not have hot flushes, but there was a 2·2-fold increase in mean plasma total testosterone concentration (table IV). The figure shows the distribution of plasma FSH and LH concentrations before and after treatment in the two groups. High FSH concentrations were recorded in women with oestrogen-responsive symptoms, 15 U/l being a valuable diagnostic cut-off point.

Discussion

Endocrine function in normally menstruating women early in their reproductive life has been well documented.[7] Similarly, endocrine changes after the menopause and after castration have been reported,[3 4] but there is a lack of comparable data on women at a later stage of reproductive life and especially as they approach the menopause. This is odd, since cycles for many years before the menopause may be anovulatory[8] and be associated with distressing symptoms.[6 9] Our patients were all premenopausal and menstruating cyclically and had a wide age distribution, one-fifth being under 40 and one-fifth over 50.

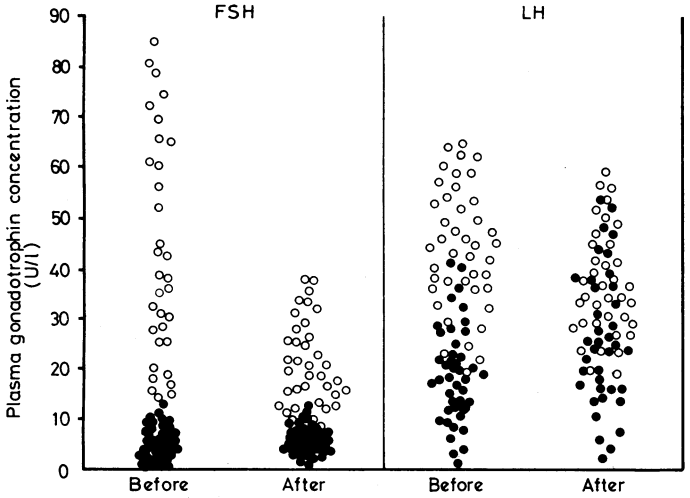
Before attempting to interpret the symptomatology we must

emphasise that the data consist of self-reported symptoms that cannot be independently verified. The design of the study did not allow us to test the reliability of reporting or any placebo response. There was also a problem of suggestion—namely, that an affirmative response might have been given to a listed symptom which, had it not been suggested, might not have been mentioned. This would be likely to lead to overreporting of symptoms. Thus, we do not emphasise the prevalence of symptoms but have attempted to correlate groups of symptoms to hormonal state in order to identify women who would benefit most from oestrogen-replacement therapy.

TABLE IV—*Mean plasma FSH, LH, oestradiol, and testosterone concentrations after six months' oestrogen treatment in the two groups of women (ranges in parentheses)*

	Group 1 (n = 37)	Group 2 (n = 38)
FSH (U/l)	4·4 (2·1-14·2)	14·8 (8·1-38·7)
LH (U/l)	20·1 (1·2-52·4)	30·4 (18·2-59·2)
Oestradiol (pmol/l)	210·5 (89·4-495·6)	157·2 (54·1-364·0)
Testosterone (nmol/l)	3·4 (2·0-5·6)	3·3 (1·5-4·8)

Conversion: SI to traditional units—Oestradiol: 1 pmol/l ≈ 0·27 pg/ml. Testosterone: 1 nmol/l ≈ 0·29 ng/ml.



Plasma FSH and LH concentrations before and after treatment in women with (○) and without (●) hot flushes.

Climacteric symptoms in premenopausal women may not be easy to diagnose. A particular problem is in differentiating true oestrogen-deficiency symptoms from those due to other factors. In a prospective placebo study, Utian[5] concluded that only hot flushes, sweats, atrophic vaginitis, and depression responded convincingly to oestrogen-replacement therapy. Other workers reported a large placebo effect on all of the alleged symptoms of the climacteric,[6 10] but a definite benefit of oestrogen treatment was shown in the studies over and above the placebo response. A contemporary danger in difficult cases is the risk of extending the proper indications for oestrogen therapy to patients with affective disorders and personality or domestic problems in a desperate attempt to find treatment. This is particularly a problem in premenopausal patients, in whom the precise diagnosis of oestrogen-deficiency symptoms may not be straightforward.

Our analysis of symptoms shows that the patients who suffered from hot flushes more often complained of headaches, dyspareunia, pains in the muscles and joints, and insomnia, possibly due to night sweats. These complaints may be regarded as related to the climacteric since they noticeably improved with oestrogen treatment and were oestrogen-responsive in Campbell and Whitehead's double-blind placebo study.[6] Patients with so-called "menopausal symptoms" but not hot flushes complained of a multiplicity of symptoms, loss of libido and depression predominating, and did not have such a beneficial response to oestrogen. The fourth and fifth decades in a woman's life are often accompanied by distressing psychological changes,[11 12] and the variability in therapeutic response in depressive illness suggests multiple aetiological factors in these cases.

The plasma FSH concentrations in our patients complaining of hot flushes were significantly higher than those observed in the reproductive age group. Our results support the view of Moore *et al*,[12] who suggested that 15 U/l was the upper limit of normal and served as a useful cut-off value in distinguishing true symptoms of oestrogen deficiency in the climacteric. This was not true of plasma LH concentrations, which, although significantly raised in patients with hot flushes responding to oestrogen treatment, never reached the high values of the preovulatory surge in the younger, fertile woman.

Plasma oestradiol concentrations were significantly ($P < 0.005$) lower in the premenopausal women with hot flushes than in those without; with oestrogen treatment values increased to normal. Plasma testosterone concentrations remained in the normal premenopausal range in both groups of patients. Oral oestrogen treatment for six months resulted in a two-fold increase in concentrations in both groups. This was probably consequent on an increase in sex-hormone-binding globulin with oestrogen treatment, which results in a higher proportion of bound testosterone in the plasma and is of no biological importance.

FSH and LH concentrations in the plasma declined with oestrogen therapy, but even after six months of continuous treatment the values remained higher than those observed in the proliferative phase of the ovarian cycle.

About a quarter of the women referred to the menopause clinic are premenopausal with symptoms that may respond to oestrogen treatment. Characteristic symptoms, which must include vasomotor disturbances, and the finding of a high plasma FSH concentration are the best criteria on which to select patients for oestrogen-replacement therapy. Some of the remaining patients may respond to oestrogen treatment, but a prospective, double-blind placebo trial is needed to clarify this. Clearly, however, many such patients would benefit from specific psychiatric counselling rather than oestrogen-replacement therapy.

We are grateful for the financial help given by Ayerst Laboratories Ltd, Organon Laboratories Ltd, Schering Chemicals Ltd, and Syntex Pharmaceuticals Ltd.

Requests for reprints should be addressed to: Mr John Studd, King's College Hospital, Denmark Hill, London SE5 9RS.

References

1 Studd, J W W, in *Current Diagnosis, 5*, ed H F Conn and R B Kahn, p 1068. London, Saunders, 1977.
2 Jaszmann, L J B, in *Epidemiology of Climacteric and Post Climacteric Complaints*, ed P A van Keep and C Lauritzen, p 22. Basle, Karger, 1973.
3 Chakravarti, S, *et al*, *British Medical Journal*, 1976, **2**, 784.
4 Chakravarti, S, *et al*, *British Journal of Obstetrics and Gynaecology*, 1977, **84**, 769.
5 Utian, W H, *South African Medical Journal*, 1972, **46**, 732.
6 Campbell, S, and Whitehead, M, in *The Climacteric*, ed R B Greenblatt and J W W Studd, p 30. London, Saunders, 1977.
7 Adamopoulos, D A, Loraine, J A, and Dive, G A, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1971, **78**, 62.
8 Studd, J W W, Chakravarti, S, and Oram, D H, in *The Menopause*, ed R B Greenblatt and J W W Studd, p 1. London, Saunders, 1977.
9 McKinley, S, Jeffreys, M, and Thompson, B, *Journal of Biosocial Science*, 1973, **4**, 161.
10 Coope, J, Thomsom, J M, and Poller, L, *British Medical Journal*, 1975, **4**, 139.
11 Ballinger, C B, *British Medical Journal*, 1976, **1**, 1183.
12 Moore, B, Gustafson, R, and Studd, J W W, *Current Medical Research and Opinion*, 1975, **3**, 42.

(*Accepted 9 February 1979*)