Hormonal profiles after the menopause

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Summary

The endocrinological changes of the climacteric have been defined by studying the concentrations of follicle-stimulating hormone (FSH), luteinising hormone (LH), androstenedione, testosterone, oestrone, and oestradiol in 60 normal postmenopausal women of different menopausal ages. The women were studied in six groups, according to the number of years since their menopause.

One year after the menopause androstenedione, oestrone, and oestradiol concentrations were reduced to about 20% of the values recorded during the early proliferative phase of the menstrual cycle. At the same time the mean concentration of FSH had risen by a factor of 13·4 and that of LH by a factor of 3·0. Concentrations of both gonadotrophins reached a peak of 18·4 and 3·4 times the proliferative phase value respectively after two to three years, and then gradually declined in the next three decades to values that were 40-50% of these maximal levels. Testosterone concentrations remained mostly in the normal range for premenopausal women but were depressed to 60% of these levels two to five years after the menopause, and the mean androstenedione levels showed a significant increase in the same group of women. The concentrations of both oestrone and oestradiol remained consistently low for 10 years after the menopause, but oestradiol concentrations inexplicably increased in the last two decades, with levels at the lower end of normal range for reproductive women in six patients.

The LH:FSH ratio was found to have no value in diagnosing the climacteric, but a single FSH assay, which can be performed in most hospitals, was valuable.

Introduction

During the latter stages of reproductive life ovarian activity gradually declines and menstruation eventually stops. This period is known as the climacteric and it may be associated with physical or mental symptoms of varying intensity and duration. Some of the hormonal and morphological changes have been discussed.[1-4].

Other studies have tried to ascertain gonadal activity after the menopause. Ovarian venous plasma,[5] and peripheral venous plasma taken after stimulation and suppression tests[6] have been analysed. The results have confirmed the refractory state of the senescent ovary.[7] Thus oestradiol and progesterone concentrations in the circulation seem to decrease rather abruptly,[2 5 6] whereas concentrations of the androgens androstenedione and testosterone fall more gradually.[5 6] These primary defects probably disturb the negative feedback mechanism between the ovaries and the hypothalamic-pituitary complex. Increased levels of follicle-stimulating hormone (FSH) and luteinising hormone (LH) have been found in peripheral venous plasma, probably because of increased secretion, as the metabolic clearance rates of both hormones remain virtually unchanged.[1] Often, however, the concentration of both gonadotrophins starts to rise a year or more before the last menstrual period, when the oestradiol concentration in peripheral venous plasma is still within the normal range for younger women. Furthermore, this phenomenon may be associated with an increased response, particularly by FSH, to the administration of gonadotrophin-hormone releasing hormone.[8 9]

Some evidence also shows that hypothalamic-pituitary function changes with increasing age.[4 10] So far, however, there has been no systematic study on the interrelationship between the activity of the gonads and the activity of the pituitary gland at different biological ages. Our aim was to clarify the endocrinology of the climacteric by measuring the concentrations of FSH, LH, androstenedione, testosterone, oestrone, and oestradiol in the same samples of peripheral venous plasma from well-defined groups of women at progressive intervals after the menopause. We made no attempt to correlate the symptoms of the climacteric with the hormonal status as this forms the basis of further communications.

Methods

Sixty apparently healthy women were selected from hospital staff, geriatric inpatients, or new patients attending a menopause clinic at Dulwich Hospital. Their ages ranged from 49 to 91 years. None had ever received oestrogen replacement treatment, and all were free from current medical or surgical conditions. They were divided into six groups according to their menopausal age (table I).

TABLE I—*Age groups according to time elapsed since menopause*

Group:	1	2	3	4	5	6
Mean No of years after menopause (and range)	8·4 months (3·13 months)	2·7 (2-3)	5·2 (4-5)	10·6 (9-11)	20·8 (18-23)	31·4 (27-34)

Peripheral venous plasma (20 ml) was removed from every woman, and a second sample was taken a week later. All specimens were removed between 10 am and 2 pm. They were analysed in a random order.

All compounds were measured by methods based on the principles of radioimmunoassay. The antisera to FSH and LH were a gift from Professor Leif Wide (Department of Clinical Chemistry, University Hospital and Institute of Biochemistry, Uppsala, Sweden), and were prepared from highly purified pituitary extract.[4] Preparations of FSH (MRC 71/333) and LH (NIH LER 960) were labelled with iodine-125 using chloramine T.[11] Antibody-bound protein was separated with a donkey anti-rabbit precipitating serum (RD 17, Wellcome Reagents Ltd, Beckenham, Kent). The amount of FSH was calculated relative to MRC Standard 68/39 (designated 32·8 units per ampoule) and LH to MRC standard 68/40 (designated 77·1 units per ampoule) Androstenedione and testosterone were separated on a column of Sephadex LH20 and determined in liquid-phase systems comprising tritiated antigens and antisera to androstenedione-11α-succinyl-bovine serum albumin or testosterone-3-carboxymethyl oxime-bovine

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TABLE II—*Arithmetic mean concentrations (and range) of FSH and LH in peripheral venous plasma from postmenopausal women*

Years after menopause:	≤1	2–3	5	10	20	30
FSH (U/l)	48·2 (15·4-81·2)	66·1 (15·4-94·0)	55·0 (21·6-105·0)	42·1 (25·5-79·0)	27·3 (0·7-60·0)	24·2 (0·7-40·7)
LH (U/l)	53·8 (21·5-80·2)	60·7 (37·2-87·4)	48·3 (26·0-71·9)	55·3 (32·3-63·8)	29·4 (1·3-63·4)	30·3 (1·8-58·4)

thyroglobulin respectively.[12 13] Oestrone and oestradiol were separated on a similar column and determined in assay systems containing the appropriate tritiated antigen and an antiserum to either oestrone or oestradiol-6-carboxymethyl oxime-bovine serum albumin.[14 15]

Results

The frequency with which the concentration of every compound appeared in each group was studied, and we concluded that in general the distribution pattern of both gonadotrophins was best described by the arithmetic mean and range, while that of the steroids was best defined by the geometric mean and range. The degree of significance between concentrations in the various groups was assessed with Student's *t* test on the normal and logarithmic data.

FSH and LH—The mean percentage difference between the two samples from each patient was 20% for FSH and 15% for LH. The concentrations of both gonadotrophins are shown in table II. The corresponding values for samples removed from healthy women during days 1-10 of the menstrual cycle were 3·6 U/l (range 1·5-7·0) for FSH (see figure) and 17·8 U/l (range 4·1-41·7) for LH. The mean incremental increases from these premenopausal values are shown in table III. Two to three years after the menopause the concentrations of FSH and LH were significantly higher ($P < 0.0005$) than during the period of follicular development in premenopausal women. Subsequently, the concentration of FSH gradually decreased, and in 30% of the women who were 20 to 30 years past the menopause the mean concentrations of LH and FSH were lower than those observed during reproductive life. The pattern of FSH levels is illustrated in the figure.

Androstenedione and testosterone—The mean percentage difference between the two samples from each patient was 25% for androstenedione and 15% for testosterone. The corresponding values for samples removed during days 1-10 of the menstrual cycle were 5·05 nmol/l (145 ng/100 ml) (range 1·11-10·14 nmol/l (32-290 ng/100 ml)) for androstenedione, and 1·42 nmol/l (41·0 ng/100 ml) (range 0·60-2·24 nmol/l (17·3-64·6 ng/100 ml)) for testosterone (table IV). The percentage changes in these mean values are shown in table V. One year after the menopause there was a significant reduction ($P < 0.0005$) in the concentration of androstenedione and five years later a significant decrease ($P < 0.005$) in the amount of testosterone.

Oestrone and oestradiol—The concentrations of both phenolic steroids are shown in table IV. The values during days 1-10 of the menstrual cycle were 439·1 pmol/l (11·9 ng/100 ml) (range 158·7-664·2 pmol/l) (4·3-18·0 ng/100 ml)) for oestrone and 250·3 pmol/l (6·8 ng/100 ml) (range 90·4-600·8 pmol/l (2·5-16·4 ng/100 ml)) for oestradiol. The percentage changes in the concentrations from premenopausal values are shown in table V. All groups had significantly lower values ($P < 0.0005$) than those observed during days 1-10 of the menstrual cycle, but levels of oestradiol in the lower end of the normal range in the reproductive phase were found in six patients in the last two age groups.

TABLE III—*Incremental changes from premenopausal values in concentrations of FSH and LH in peripheral venous plasma from postmenopausal women*

Years after menopause:	≤	2-3	5	10	20	30
Mean incremental increase in:						
FSH	13·4	18·4	15·3	11·7	7·6	6·7
LH	3·0	3·4	2·7	3·1	1·7	1·7

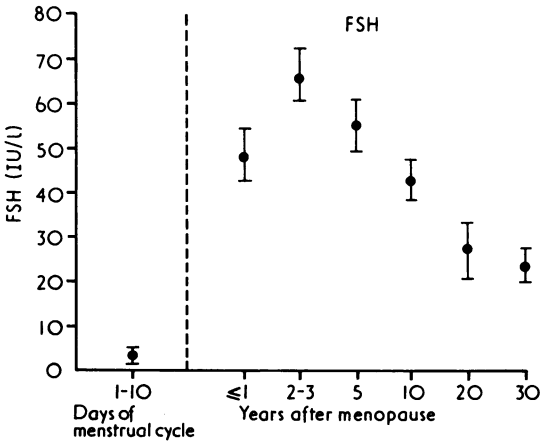

FIG 1—Concentration of FSH (mean ± SE) in peripheral venous plasma from groups of women in defined age groups after the menopause compared with concentration in first 10 days of menstrual cycle.

TABLE V—*Percentage mean change from premenopausal values in andostenedione, testosterone, oestrone, and oestradiol concentrations in peripheral venous plasma from postmenopausal women*

Years after menopause:	≤1	2-3	5	10	20	30
Percentage changes in:						
Androstenedione	−75	−77	−59	−68	−71	−75
Testosterone	+29	−4	−34	+5	+30	+42
Oestrone	−80	−85	−85	−92	−92	−91
Oestradiol	−79	−80	−80	−83	−69	−74

Discussion

Our results show that the concentrations of androstenedione, oestrone, and oestradiol all fall to about 20% of their premenopausal values within a year after the menopause. After

TABLE IV—*Geometric mean concentrations (and range) of various steroids in peripheral venous plasma from postmenopausal women*

Years after menopause:	≤1	2-3	5	10	20	30
Androstenedione (nmol/l)	1·24 (0·62-3·02)	1·15 (0·45-2·46)	2·08 (1·05-4·46)	1·64 (0·98-4·39)	1·48 (0·75-3·88)	1·27 (0·35-5·60)
Testosterone (nmol/l)	1·83 (0·79-3·38)	1·36 (0·67-2·70)	0·94 (0·55-2·18)	1·49 (0·59-2·98)	1·85 (1·19-2·47)	2·01 (1·45-2·62)
Oestrone (pmol/l)	88·9 (36·9-147·6)	64·6 (36·9-92·9)	67·9 (36·9-156·8)	34·3 (9·2-101·4)	34·3 (9·2-119·3)	41·7 (27·7-73·8)
Oestradiol (pmol/l)	51·8 (27·6-147·1)	50·7 (27·6-119·5)	49·4 (27·6-183·8)	43·4 (18·4-91·9)	76·5 (27·6-294·1)	65·1 (27·6-229·8)

Conversion: SI to traditional units—Androstenedione: 1 nmol/l ≈ 28·6 ng/100 ml. Testosterone: 1 nmol/l ≈ 28·8 ng/100 ml. Oestrone: 1 pmol/l ≈ 0·0270 ng/100 ml. Oestradiol: 1 pmol/l ≈ 0·272 ng/100 ml.

five years, however, the amount of androstenedione has increased and during this period the testosterone concentration falls significantly. In the next three decades the pattern is reversed: the amount of androstenedione tends to decrease, with a corresponding increase in the testosterone concentration. The values for oestrone and oestradiol were not significantly different between the samples removed during the first 10 years after the menopause. There was, however, a significant reduction in the amount of oestrone and a corresponding increase in the concentration of oestradiol 10 to 20 years later. Enzymes for converting androstenedione into testosterone or oestrone and both of these steroids into oestradiol are located in many peripheral and growth-responsive tissues. The inverse relations in the concentration of androstenedione to testosterone and of oestrone to oestradiol are therefore of interest.

The postmenopausal ovary continued to secrete significant amounts of androgenic hormones, even though cyclic activity is lost during the climacteric.[16] Thus analysis of ovarian venous plasma has shown that the postmenopausal ovary secretes testosterone.[17] Moreover, bilateral oophorectomy in women of this age results in a fall in androstenedione and testosterone levels in peripheral venous plasma.[6] Vermeulen has also reported the results of human chorionic gonadotrophin stimulation and dexamethasone suppression tests on postmenopausal women, which strongly suggest that the gonads contribute to about 50% of the testosterone and 30% of the androstenedione in peripheral plasma.[6] Barberia and Thorneycroft[18] have deduced a similar contribution from the ovaries to the concentration of circulating testosterone, but other workers[19] did not find similar changes after oophorectomy. The low levels of testosterone in peripheral venous plasma that have been reported[6 20] probably reflect the different biological ages of the donors. The significant increase in the level of testosterone 20-30 years after the menopause probably indicates an increased conversion of androstenedione, which would agree with previous findings.[21]

Ovarian secretion of oestradiol during reproductive life proceeds in a series of cycles.[22] The production of oestrone, however, depends less on ovarian activity, and the level in peripheral plasma is more constant.[23] During the climacteric oestradiol secretion is reduced, and after the menopause the contribution from the ovaries is thought to be negligible.[24 25] In contrast, it has been reported that oestrone concentrations in peripheral plasma remain almost unchanged.[26 27]

In the light of the work by Longcope[2] and Siiteri *et al*[28] the conversion of androstenedione in peripheral tissues is now considered to be the major source of oestrone. Furthermore, recent studies by Vermeulen,[6] Barlow *et al*,[29] and Saez *et al*[30] have shown that plasma oestrone values are similar in postmenopausal women who have undergone oophorectomy and those who have not. MacDonald *et al*[31] have suggested that the amount of androstenedione converted to oestrone is positively correlated with the weight of the individual. More recently adipose tissue has been shown to play an important part in this conversion.[32] Our results showed that the levels of androstenedione and oestrone in peripheral venous plasma at different times did not seem to be related in a simple manner, which suggest that many factors must contribute to the circulating levels of these steroids. In addition, our findings are consistent with those of studies on ovarian tissue removed after the menopause that have shown only relatively small amounts of the enzymes necessary for steroidogenesis—that is, Δ^5-3β-ol dehydrogenase and 17β-reductase.[33] It is impossible to discriminate between ovarian, adrenal, and extraglandular origin of the sex steroid hormones studied, but a similar age-matched analysis of women who had undergone oophorectomy by Studd *et al*[34] showed higher pituitary gonadotrophin and lower oestrone and oestradiol levels, suggesting a continued ovarian contribution, at least in the first 10 years after the end of menstruation.

With regard to hypothalamic-pituitary function our results have shown that the levels of both gonadotrophins in the circulation reach a maximum two to three years after the menopause and that the increase is substantially greater for FSH. Work by Adamopoulos *et al*[24] on the urinary excretion of gonadotrophins showed an earlier and disproportionate rise in the concentration of LH in samples from postmenopausal women. Thus the mean level of LH was seven times higher than in healthy women during the follicular phase of the ovarian cycle, whereas the mean level of FSH had only increased threefold. They hoped that this difference might serve as a diagnostic index for women approaching the menopause. Lauritzen[10] studied the ratio of LH to FSH in peripheral venous plasma from women before and after bilateral oophorectomy and showed that the value changed from >1 to 0·7 four days after castration. They suggested that the altered ratio might be a useful index, providing a more exact and scientific diagnosis of the climacteric, but we found that the ratio of LH to FSH varied from 0·6 to 2·3. This suggests that this index has no additional diagnostic value during the postmenopausal period. Nevertheless, the increase in FSH levels after the menopause to values substantially higher than those we found in the reproductive phase enable the climacteric to be diagnosed by this assay, which is nowadays standard in most hospitals. Moore *et al*[35] used 15 U/l as the upper limit of normal, and Studd *et al*[36] have shown that this level is a useful cut-off value in distinguishing true symptoms of oestrogen deficiency in premenopausal women. The same is not true of LH values because the highest postmenopausal levels are exceeded by the preovulatory surge in younger fertile women.

This definition of the hormonal status of normal postmenopausal women is an initial report of a study of the climacteric in patients attending the menopause research clinic at Dulwich Hospital. Subsequently hormone profiles in women who have undergone oophorectomy and the relation between symptoms and response to treatment will be reported.

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Observations on electrocardiogram and plasma catecholamines during dental procedures: the forgotten vagus

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Summary

Emotional stress is conventionally considered to be associated with tachycardia and enhanced sympathetic activity. The electrocardiogram and plasma catecholamine and lipid concentrations were observed in 21 young healthy women undergoing dental procedures. Ten of these received premedication with the beta-blocking agent oxprenolol and 11 with a placebo, administered on a double-blind randomised basis. Mild tachycardia occurred in the placebo group a few minutes before and a few minutes after dentistry, but there was a reduction in heart rate immediately before and during the procedure. The pattern was similar in the group who received oxprenolol, though the heart rates at each stage were lower. Plasma adrenaline concentrations were much higher in the samples taken during the procedure than in those taken shortly before and after it. Plasma noradrenaline and lipid concentrations remained unchanged.

A decrease in heart rate in the face of intense emotional arousal and an increased plasma adrenaline concentration suggest that the expectation or experience of pain may be associated with parasympathetic dominance despite greatly enhanced sympathetic activity.

Introduction

Emotional stress is conventionally considered to be associated with enhanced sympathetic activity and a tachycardia. Tachycardia associated with increased plasma concentrations of adrenaline or noradrenaline, or both, has been shown to occur at times in response to emotional stress.[1-4]

Nevertheless, among the increasing number of reports implicating the autonomic system as the mediator of physiological effects induced by emotion[5] little mention has been made of the parasympathetic system. We have become increasingly aware that certain emotions, particularly those during the witness, expectation, or actual experience of pain, may be associated with a bradycardia, or at least an absence of tachycardia, despite obviously intense behavioural evidence of arousal and increased circulating catecholamines.[6] This would suggest parasympathetic dominance despite greatly enhanced sympathetic activity.

We report here a study designed to test this theory since we believe that if correct it may have important application to the management of people with coronary heart disease.

Subjects and methods

The electrocardiograms (ECGs) and plasma catecholamine and lipid concentrations were observed in a group of young women undergoing routine dental procedures after receiving either a placebo or the beta-blocking agent oxprenolol. This was selected as representing a common experience in which the fear of pain constituted the emotional challenge.

Twenty-two members of the nursing staff of the Middlesex Hospital volunteered to participate in the study and were allocated to one of two groups. The subjects were matched for age, and although one was later excluded from analysis owing to a technical failure of ECG recording, the ages of each group remained comparable. The mean age (±SD) was 27±6·3 years in the 11 patients in the placebo group and 27±5·8 years in the 11 patients in the oxprenolol group. All had apparently normal hearts, and none had any obvious psychiatric reason to disqualify them from participating in the study. Nurses were chosen because previous observations had suggested that young women may show a more labile emotional response and because they were a homogeneous group.

Medication—Each subject was given either a placebo or a single oral dose of 40 mg oxprenolol, administered on a double-blind randomised basis, 45 minutes before entering the surgery.

ECGs were recorded[7] using the miniaturised Recard system (Kimal Scientific Products Ltd, Hillingdon, Middlesex). Two chest electrodes were connected to the subject to approximate to a V5 position.

Blood samples were taken by venepuncture a few minutes before the start of the procedure, during the procedure, and about 10 minutes after completion. Samples were collected, preserved, and analysed for catecholamines according to methods described.[8] Lithium sequestrine samples were similarly preserved for lipid estimations.

Dental procedure—All subjects had been patients of the dentist (PDG). The dental work carried out consisted of routine restorative procedures performed with both high-speed air-turbine equipment and low-speed handpieces. The local anaesthetic used was Citanest

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