Other theoretical reasons for continuing breast feeding during diarrhoea also need to be considered. Short term deprivation of nutrients by withholding breast feeding during the early acute phase of diarrhoea is serious as a fasting child loses an estimated 1-2% of his or her body weight daily even in the absence of fluid losses due to diarrhoea.[9] Breast fed children with diarrhoea have been shown to average a total energy intake 35% greater and a protein intake 250% greater than children who are completely weaned.[10] Thus breast feeding not only confers protection against infections including diarrhoea and provides a low cost, highly nutritious source of uncontaminated food but also minimises the reduction in energy and protein consumption during diarrhoea and, as found in this study, exerts a beneficial effect on the clinical course and outcome of acute diarrhoea by reducing the number (and volume) of diarrhoeal stools.

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Effect of long term hormone replacement on plasma prolactin concentrations in women after oophorectomy

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Abstract

Plasma prolactin concentrations were studied in 88 oophorectomised women who had been receiving mestranol or placebo for three to 11 years. Thirty one of them were also studied under basal conditions and by tests with thyrotrophin releasing hormone. Under basal conditions the mean prolactin concentration was higher in the oestrogen treated group but under non-rested, clinic conditions the difference was lost because of a rise in prolactin value in the placebo group only. Hence the groups showed a different prolactin response to the mild stress of clinic attendance but the same proportionate responsiveness to thyrotrophin releasing hormone.

The data suggest that long term hormone replacement has no significant effect on circulating prolactin concentrations under non-rested, everyday conditions and that the prolactin stimulating effects of minor stress and oestrogen may share a similar mechanism.

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Introduction

A large number of women now receive oestrogen preparations on a long term basis. Oestrogen stimulates prolactin release in normal[1] and hypogonadal women,[2] probably by both hypothalamic dopamine suppression and direct action on the lactotroph.[3 4] There has been concern whether women receiving oestrogen preparations long term are at increased risk of developing prolactinoma or breast cancer. In relation to prolactinoma current evidence favours no increased risk in users of oral contraceptives,[5 6] though some workers have mooted such a risk.[7 8]

The question of a relation between use of oral contraceptives and breast cancer has been examined recently.[9] Published work on postmenopausal use of oestrogen and the risk of breast cancer is contradictory, but current data do not suggest a significant increased risk.[10 11] There is a potential for oestrogen treatment to stimulate breast tissue by direct action and by virtue of a chronic increase in circulating prolactin concentrations. The role of prolactin in the induction of breast cancer remains ill defined,[12 13] but there is evidence that prolactin promotes the development and growth of mammary tumours in rodents.[14]

There is limited information on the effect on plasma prolactin of menopausal oestrogen replacement therapy as used in clinical practice.[15 16] This study examines the effect of long term, low dose mestranol on plasma prolactin concentrations and responses to thyrotrophin releasing hormone in a large placebo controlled series originally set up to study oestrogen prophylaxis against postoophorectomy oesteoporosis.[17]

Patients and methods

All patients in the study had undergone hysterectomy and bilateral oophorectomy three months, three years, or six years before entry to the series. Allocation to treatment was randomised and patients took continuous oral mestranol 24 μg daily (17-ethinyloestradiol-3-

methyl ether) or placebo on a double blind basis. Patients gave informed consent to the study, which was approved by the ethical committee. Long term follow up to assess bone density was at yearly intervals. All patients remaining in the osteoporosis study were sampled at their yearly visit. They attended fasting for venous blood sampling without a tourniquet between 0830 and 0930. Concomitant drug treatment was noted.

The original randomised series consisted of 68 women given mestranol and 66 given placebo.[17] The duration of treatment at the time of sampling ranged from three to 11 years, and since some patients had stopped treatment in those years the numbers tested were 51 taking mestranol (oestrogen group) and 37 taking placebo (control group). There had been a greater loss of patients from the placebo group. Table I lists the characteristics of the two groups studied.

Seventeen of the mestranol treated patients and 14 controls volunteered for a thyrotrophin releasing hormone test. Table II gives the characteristics of these groups. A baseline blood sample was taken after 30 minutes' recumbency, then 200 μg thyrotrophin releasing hormone was given intravenously and subsequent blood samples taken after a further 30 and 60 minutes. Blood was sampled through an indwelling cannula to minimise stress. All blood samples were centrifuged, the plasma being separated and stored frozen until assayed by radioimmunoassay for prolactin, luteinising hormone, and follicle stimulating hormone concentrations.

Prolactin was measured by a specific, sensitive, and precise radioimmunoassay using MRC prolactin preparation 75/504 (650 mU ampoule) as standard. The detection limit of the assay was 30 mU/l and mean intra-assay precision 5% and interassay precision 10%.[18] The radioimmunoassay methods for luteinising hormone and follicle stimulating hormone are detailed elsewhere.[19] Statistical analysis was by t test for paired or unpaired data, as appropriate. Since the data exhibited a skewed distribution logarithmic transformation was employed. This produced a normalisation of the data, and the t tests were performed on the log transformed data.

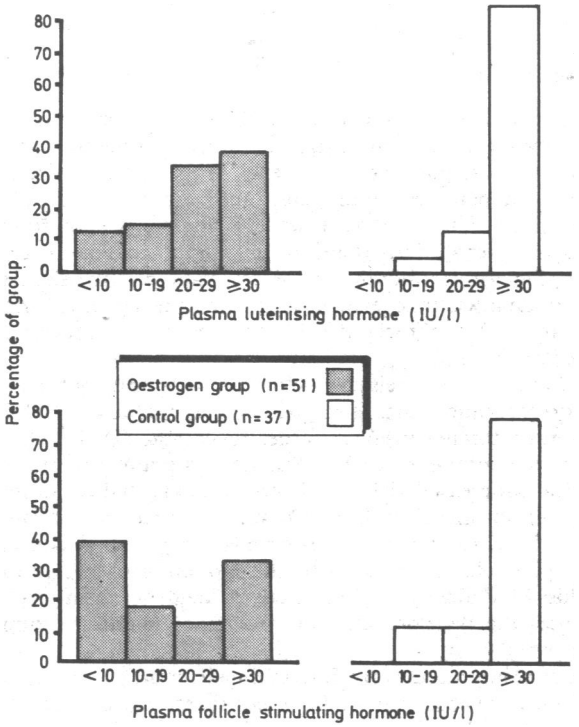

FIG 1—Plasma gonadotrophin concentrations in oestrogen treated and control groups.

Results

Total population—Figure 1 shows the distribution of plasma follicle stimulating hormone and luteinising hormone concentrations in the two groups. In the oestrogen group 35 patients (69%) had a plasma follicle stimulating hormone concentration below 30 IU/l compared with 8 (22%) of the controls. Similarly, 32 (63%) of the oestrogen group had a plasma luteinising hormone concentration below 30 IU/l compared with 6 (16%) of the controls. Figure 2 shows the distribution of plasma prolactin concentrations in the two groups, and table III gives the ranges and median and mean values. Mean prolactin concentrations were 242·3 (SD 118·7) mU/l in the oestrogen group and 232·6 (124·6) mU/l in the control group. These values were not significantly different.

Thyrotrophin releasing hormone tests—After 30 minutes' rest to achieve a basal state the mean plasma prolactin concentrations were 216·1 (SD 140·1) mU/l in the oestrogen group (n = 17) and 103·6 (36·1) mU/l in the controls (n = 14) (table IV). These values were

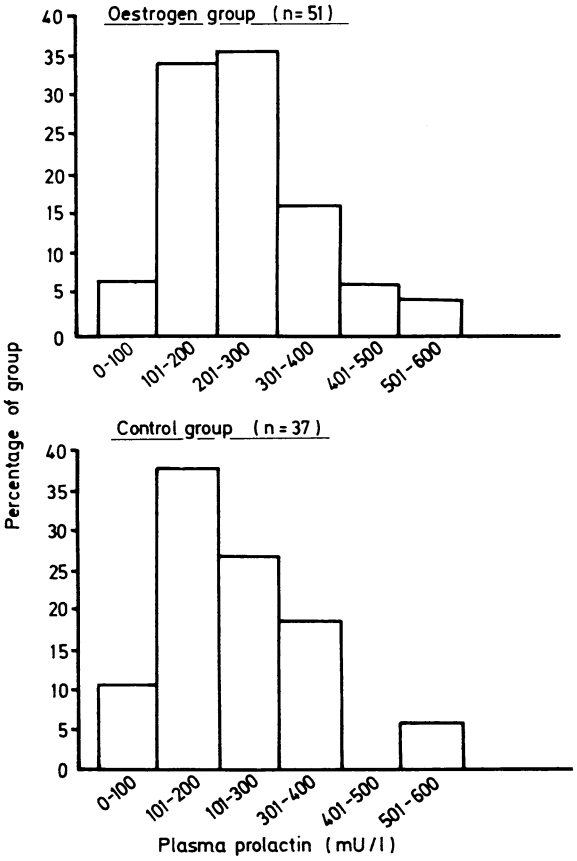

FIG 2—Distribution of plasma prolactin concentrations in oestrogen treated patients and patients taking placebo (control group).

TABLE I—*Characteristics of patients in population studied at time of sampling*

		Oestrogen group (n = 51)	Control group (n = 37)
Age (years)	Mean (SD)	56·6 (4·3)	57·7 (4·7)
	Range	45-64	46-66
Time since hysterectomy (years)	Mean (SD)	11·3 (3·5)	11·4 (3·7)
	Range	4-17	4-17
Duration of treatment at time of sampling (years)	Mean (SD)	8·1 (2·4)	8·5 (2·4)
	Range	4-11	3-11
No (%) who began treatment at stated times after hysterectomy	3 months	7 (13·7)	8 (21·6)
	3 years	35 (68·6)	23 (62·2)
	6 years	9 (17·6)	6 (16·2)
No (%) who had been receiving treatment for the times stated	3-5 years	10 (19·6)	6 (16·2)
	6-8 years	14 (27·5)	10 (27·0)
	9-11 years	27 (52·9)	21 (56·8)

TABLE II—*Characteristics of patients having thyrotrophin releasing hormone tests*

		Oestrogen group (n = 17)	Control group (n = 14)
Age (years)	Mean (SD)	58·3 (4·4)	58·7 (4·5)
	Range	47-63	48-66
Time since hysterectomy (years)	Mean (SD)	11·8 (2·7)	11·4 (3·1)
	Range	7-14	5-15
Duration of treatment at time of sampling (years)	Mean (SD)	9·0 (1·5)	8·6 (1·5)
	Range	6-11	5-11

significantly different ($p < 0.001$). Comparison of these concentrations with those recorded in the same patients in the larger study showed no difference in the oestrogen group but a significant fall (paired t test; $p < 0.01$) in the controls (table IV). Mean prolactin concentration was significantly higher in the oestrogen group at 0, 30, and 60 minutes. The mean prolactin response, taken as the percentage increment over basal value, was not significantly different in the two groups.

TABLE III—*Plasma prolactin concentrations (mU/l) in total population*

	Range	Median	Mean	SD
Oestrogen group (n = 51)	77-598	224	242·3	118·7
Control group (n = 37)	68-548	218	232·6	124·6

TABLE IV—*Results of thyrotrophin releasing hormone (TRH) tests (prolactin mU/l). Values are means (SD in parentheses)*

		Oestrogen group (n = 17)	Control group (n = 14)	p value
Mean prolactin concentration for same patients from larger study		231·1 (99·4) *NS	203·0 (97·0) †p < 0·01	
Result of TRH test	Basal value	216·1 (140·1)	103·6 (36·1)	< 0·001
	30 minutes	1155·2 (582·1)	682·1 (291·4)	< 0·02
	60 minutes	792·8 (519·7)	415·5 (178·1)	< 0·02
Prolactin response to TRH (% increment over basal value)	30 minutes	536 (269)	659 (281)	NS
	60 minutes	367 (240)	401 (172)	NS

NS = Not significant.
*NS.
†$p < 0.01$.

Discussion

The plasma luteinising hormone and follicle stimulating hormone concentrations in the mestranol and placebo treated groups (fig 1) confirm the difference in oestrogenic activity, with a lowering of postoophorectomy gonadotrophin values in the oestrogen group. The gonadotrophin values of some mestranol treated patients remained in the postmenopausal range, but it is well recognised that gonadotrophin responses to oestrogen are variable and that oestrogen does not lower gonadotrophin concentrations into the premenopausal range in all women so treated.

The pattern of plasma prolactin concentrations seen at the clinic and in the rested basal state was different for the two groups of patients. In the rested state, minimising stress effects, the oestrogen treated women had higher mean circulating prolactin values than the control group. In the non-rested state, with the possible influences of minor stress, the difference between the groups was abolished because of a rise in mean prolactin concentration in the controls. There was no change in mean prolactin concentration in the oestrogen group.

Major surgical stress raises the plasma prolactin concentration,[20] but there are reports that in oestrogen treated women minor stress such as a clinic visit and venepuncture does not alter the concentration,[21 22] and our observations in the mestranol treated group confirm this. There is evidence that in the rested basal state there may be a difference in plasma prolactin concentrations between oestrogenised and non-oestrogenised women, as observed in this study, in that Cowden *et al* reported a higher mean basal prolactin concentration in women aged 30-50 than in those over 50.[18]

The observations suggest that the effect of minor stress in raising the plasma prolactin concentration may share a common mechanism with the oestrogen mediated effect on prolactin so that the two are not additive in effect in oestrogen treated women. Oestrogens influence neurotransmitter activity but the specific sex steroid-neurotransmitter interactions remain ill defined.

Results of the thyrotrophin releasing hormone tests show that the oestrogenic state of the women did not affect the proportionate lactotroph responsiveness of the two groups to the stimulus, although there was a difference in their response to minor stress.

This study has examined plasma prolactin concentrations in a sizable controlled series of women receiving mestranol at a dosage known to prevent osteoporosis.[17] An oestrogenic effect on prolactin release in controlled conditions is not disputed,[2] but the data indicate that in clinical use long term oestrogen replacement has no significant effect on circulating prolactin values, comparing mestranol and placebo in the non-rested state—that is, the state which applies most of the day. In the data of Lind *et al*[15] and Helgason[16] there was no change in mean prolactin values in smaller treatment groups for up to six months during treatment with "natural" oestrogens. In our study no patient had a prolactin concentration above 600 mU/l. It appears erroneous simply to attribute an abnormally high prolactin concentration to oestrogen replacement therapy, a clinical tendency which we have encountered on several occasions.

If prolactin plays a part in breast cancer it is unlikely to be a mechanism relevant to any relation between breast cancer and oestrogen replacement therapy. Indeed, in our experience of more than 2000 women years of treatment using mestranol or placebo breast cancer occurred in one patient taking mestranol and three receiving placebo; and in the recent report of Gambrell *et al* on more than 37 000 patient years of observation there was a reduction in the risk of breast cancer in postmenopausal women receiving oestrogen replacement therapy.

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