INFLUENCE OF LOW DOSE OESTROGEN
ON CIRCULATING PROLACTIN, LH AND FSH LEVELS
IN POST-MENOPAUSAL WOMEN

By

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ABSTRACT

The effect on serum prolactin, LH and FSH levels of 25 µg ethinyl-oestradiol administered daily per os during 27 consecutive days was investigated in 5 post-menopausal women aged 52–78. Blood samples were collected before, during and after treatment. The hormones were assayed in serum by radioimmunological methods. Both LH and FSH decreased progressively and significantly from 120 and 115 mIU/ml before treatment to 52 and 51 mIU/ml, respectively after three weeks of oestrogen administration. Two weeks after interruption of treatment, LH (90 mIU/ml) and FSH (112 mIU/ml) were significantly higher than during the last week of treatment.

Mean prolactin level increased from 127 µU/ml before treatment to 237 µU/ml after 10 days of oestrogen administration (P < 0.001). This increase was significant after 4 to 8 days and the levels remained about twice as high as the control values for the rest of the treatment period. Two weeks after interruption of treatment, serum prolactin had fallen (136 µU/ml) to the pre-treatment levels. Such results raise the question of possible effects of elevated levels of this hormone during long term oestrogen medication in post-menopausal women on the development of breast cancer.

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In women with regular menstrual cycles prolactin secretion is stimulated by exogenous oestrogens but at relatively high doses: 200 $\mu$g of ethinyloestrodiol or more (Robyn et al. 1975).

The purpose of the present study was to investigate the effects of very low dose exogenous oestrogens on the secretion of pituitary prolactin in post-menopausal women.

**MATERIAL AND METHODS**

A daily dose of 25 $\mu$g ethinyloestradiol was administered orally during 28 days to 5 post-menopausal women aged 52 to 78.

The time elapsed from surgical or spontaneous menopause varied from 2 to 28 years. Blood samples were collected every second day at 10 a.m., before (one week), during (four weeks) and after (three weeks) treatment.

Serum prolactin, LH and FSH were measured by radioimmunoassay methods using the double antibody technique as described elsewhere for prolactin (Sinha et al. 1973; Badawi et al. 1974), LH (Robyn et al. 1971) and FSH (Odell & Hescox 1972).

Serum prolactin was measured by an homologous human assay method. The human pituitary prolactin (HPR VLS-1 = 1) used as tracer and an anti-human prolactin serum (Aubert et al. 1974; Badawi et al. 1974) were obtained from the National Institute of Arthritis, Metabolism and Digestive Diseases, USA. The assay results for this hormone were expressed in micro-units ($\mu$U) of a research standard (MRC 71/222) of human pituitary prolactin distributed by the National Institute for Biological Standards and Control, Medical Research Council, London (Cotes 1973).

For LH and FSH, the assay results were expressed in milli-international units (mIU) of the Second International Reference Preparation of Human Menopausal Gonadotrophins (International Laboratory for Biological Standards, National Institute for Medical Research, London, Great Britain).

**RESULTS**

As shown in Fig. 1 both mean serum LH and FSH levels decreased progressively and significantly ($P < 0.001$) from 120 and 115 mIU/ml before treatment to 52 and 51 mIU/ml, respectively, after 21 days of daily administration of 25 $\mu$g ethinyloestradiol. Two weeks after termination of treatment, LH (90 mIU/ml) and FSH (112 mIU/ml) were significantly higher ($P < 0.001$) than during the last week of treatment (52 and 51 mIU/ml, respectively).

As shown in Fig. 2, mean serum prolactin concentration increased from 127 $\mu$U/ml before treatment to 237 $\mu$U/ml after 10 days of oestrogen administration ($P < 0.001$). Two weeks after termination of treatment, serum prolactin level (136 $\mu$U/ml) had fallen and was no longer different from the mean control level found prior to steroid administration ($P > 0.05$).
Mean serum LH and FSH concentrations (mIU/ml) before, during and after daily oral administration of 25 μg ethinyloestradiol to five post-menopausal women. Vertical bars represent the standard error of the means. The open rectangle indicates the period of oestrogen administration.
**DISCUSSION**

In animals, it has been shown that endogenous oestrogens are controlling prolactin secretion (Neill et al. 1971; Meites 1972). It appears from accumulating clinical and experimental data that circulating oestrogens, also in women, control the release of prolactin: a parallelism in serum prolactin levels and serum oestrogens levels was reported during menstrual cycles (Delvoye et al. 1973; Robyn et al. 1973), pregnancy (L'Hermite & Robyn 1972; Robyn et al. 1973), and in cases of amenorrhoea without galactorrhoea (Robyn et al. 1973). Serum prolactin decreases with age in women (Robyn & Vekemans, in press) and this fall is parallel to that reported for circulating oestrogens (Longcope 1971) and for urinary oestrogens (Pincus et al. 1954; Furuhjelm 1966). Thus oestrogens can be regarded as an important physiological factor in the control of prolactin secretion both in animals and men.
It has also been found that in hypogonadal women a daily dose of 1 \( \mu g/kg \) body weight of ethinyloestradiol induces a significant rise in serum prolactin (Yen et al. 1974).

In post-menopausal women, very low doses of ethinyloestradiol such as 25 \( \mu g \) daily, are effective in stimulating prolactin secretion within few days of treatment. However, such doses of ethinyloestradiol have been reported to be ineffective in increasing serum prolactin levels in women with regular menstrual cycles (Robyn et al. 1976, in press). This difference could be due to the fact that in women of reproduction age endogenous oestrogens stimulate prolactin secretion to such an extent that moderate doses of ethinyloestradiol would not have further stimulatory effect. An alternative explanation might be the altered sensitivity of the prolactin releasing mechanism to oestrogen in women after the menopause.

It would be important to know whether or not elevated prolactin levels are maintained in post-menopausal women treated with oestrogens for periods of time much longer than in the present study.

In animals, elevated circulating prolactin is known to promote development and growth of mammary tumours (Meites 1972, 1973). It has been reported that women treated for prolonged periods of time with drugs known to release prolactin such as reserpine show an increased incidence of breast cancer (Eltigi et al. 1973; Armstrong et al. 1974; Heinonen et al. 1974). Therefore, it should be considered that elevated prolactin levels resulting from chronic treatment with oestrogens might increase the risk of breast cancer in post-menopausal women.

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