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Letter to the Editor

Progesterone Levels in Breast Duct Fluid*

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SHERMAN and Korenman [1] have postulated that inadequate corpus luteum function is a risk factor for breast cancer because it permits excessive estrogen activity which results from a lack of the normal modulating action of progesterone (PRG). It is also recognized that a history of biopsy-defined benign breast disease is associated with an increased breast cancer risk, and that this relationship applies specifically to the more hyperplastic forms with atypia [2–5]. Reports that serum PRG levels are low during the luteal phase of the menstrual cycles of some women with benign breast disease [6–8], while consistent with the inadequate luteal phase hypothesis of breast cancer risk, have not been confirmed by other investigators [9–11]. Similarly, while a recent report described low serum PRG in premenopausal breast cancer patients [8], this abnormality was not detected in previous studies [9, 10].

One difficulty in interpreting such results is that the studies are usually performed on single serum samples, with the assumption that the PRG levels found reflect the situation in the breast tissue. A better choice might be the breast duct fluid obtained by nipple aspiration, the constituents of which are believed to reflect the biochemical environment of the mammary ducto-alveolar system [12–15]. Also, a practical advantage of performing assays on duct fluid may be that preliminary cellular binding and subsequent passage through the breast tissue diminishes, or even eliminates, the hour-to-hour episodic fluctuations which occur in serum steroid [16] and protein hormone [17, 18] levels.

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As far as we are aware, there are no published reports describing PRG levels in breast duct fluid. The purpose of the preliminary work reported here was to demonstrate the presence of PRG in breast duct fluid, determine the levels to be expected relative to those in serum and examine the influence of stage of the menstrual cycle. Breast duct fluid (10–100 μl) was obtained using the device developed by Sartorius *et al.* [19] and PRG determined by radioimmunoassay as described by Abraham *et al.* [20], using reagents purchased from Radioassay Systems, Inc., Carson, CA. The sensitivity of the assay in our laboratory is 0.1 ng/ml, with an intra-assay coefficient of variation of 7.8% and an inter-assay coefficient of variation of 11.7%.

We followed the changes in PRG levels through a menstrual cycle in a healthy 32-yr-old volunteer. Figure 1 shows the increase in both serum and breast duct fluid PRG which occurred during the luteal phase of the cycle, and the relatively higher concentration of the steroid in duct fluid.

Thirty women were studied once in the follicular phase (days 2–10) of their menstrual cycles, 11 of whom had been diagnosed clinically as having fibrocystic disease; the other 19 had no evidence of breast abnormality. Another 30 women had serum and breast duct fluid samples collected in the luteal phase (days 18–26), of whom 18 were considered to have fibrocystic disease of the breast. Table 1 shows that, as expected, the serum PRG levels were higher in the women sampled during the luteal phase of the menstrual cycle, although two of the normal women and four of those with fibrocystic disease had luteal values of less than 3 ng/ml. In addition, the levels of PRG in breast fluid were considerably higher than those in serum at both stages of the cycle. Both the serum and breast fluid PRG levels were closer to a logarithmic–normal than a normal distribution, but even after logarith-

Table 1. Follicular and luteal phase serum and breast duct fluid progesterone levels (mean ± S.D.)

Group	Serum (ng/ml) Follicular	Serum (ng/ml) Luteal	Breast fluid (ng/ml) Follicular	Breast fluid (ng/ml) Luteal
Normal	0.49 ± 0.34 (n = 19)	13.35 ± 9.64 (n = 12)	48 ± 45 (n = 19)	185 ± 172 (n = 12)
Fibrocystic disease	0.88 ± 1.02 (n = 11)	17.28 ± 14.50 (n = 18)	103 ±75 (n = 11)	162 ± 121 (n = 18)

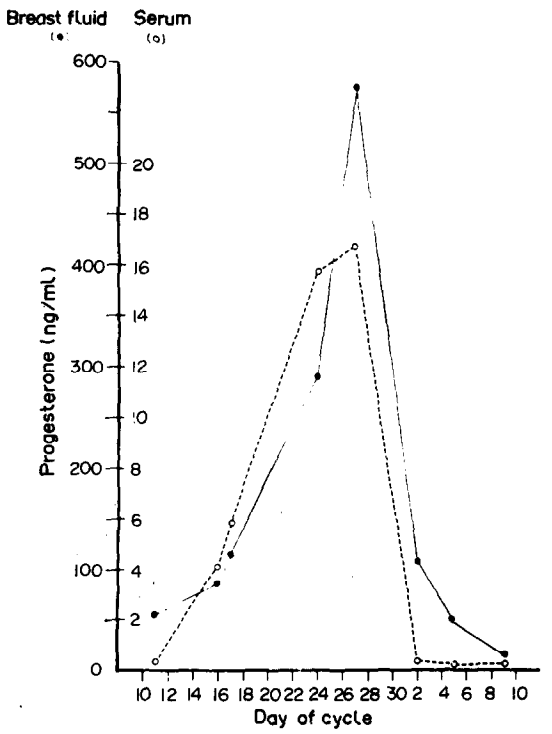

Fig. 1. Changes in serum and breast duct fluid PRG levels during a normal menstrual cycle.

mic conversion of the data there was no significant difference in the results for the two groups of women. The results were examined statistically for correlations between the serum and duct fluid PRG levels, but there were no such relationships for samples collected at either phase of the menstrual cycle. This is, perhaps, not unexpected given the various factors which may influence the passage of a steroid from the circulation, through the breast epithelium, and its ultimate appearance in duct fluid.

Estrogens [13], androgens [14, 15] and prolactin [13] have all been found in breast duct fluids at higher concentrations than occur in serum, suggesting that assays of this material may provide an indirect means of assessing the exposure of mammary tissue to hormonal action. Future studies of breast duct fluid should include both PRG and estrogen assays of the same samples, so that the ratio of the two steroid concentrations can be calculated. When this was done using plasma values, Sitruk-Ware *et al.* [7] found benign breast disease patients to have reduced PRG/estradiol ratios, an abnormality which was particularly pronounced in women with mastodynia but no evidence of fibrocystic disease.

We found no difference in the serum or breast duct fluid PRG levels in our two groups of women. However, the cases of fibrocystic disease had been diagnosed largely by physical examination, and may well have included women whose breast nodularity was within normal limits. Love *et al.* [21] have stressed the poorly defined nature of a diagnosis of fibrocystic disease, and a recent histopathological study [5] confirmed previous work showing that most benign breast disease is non-proliferative in character. In future studies we will include only patients with a histopathological diagnosis of benign breast disease, so that they may be classified into those with or without hyperplasia and atypia.

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