Inadequate Corpus Luteal Function in Women with Benign Breast Diseases

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ABSTRACT. The corpus luteum function of 109 patients with benign breast disease was appreciated by way of plasma progesterone and estradiol determinations during the luteal phase. These patients had ovulatory cycles according to a biphasic basal body temperature curve; blood samples for plasma progesterone and estradiol estimation were collected between the first and the last day of the thermal plateau following the thermal nadir. Results obtained were compared to those observed in 50 normal ovulatory women.

In the patients' group, the mean daily levels for progesterone ranged from 3.5 ± 0.4 (SE) ng/ml to 8.1 ± 3.8 (SE) ng/ml according to day of blood collection. These values are significantly different from the corresponding daily values observed in normal women.

No significant difference was observed concerning plasma estradiol between patients and normal women. These findings indicate that women with benign breast disease have an inadequate corpus luteum function which may be secondary to an ovulation disorder. Pathophysiological implications resulting from this observation are discussed. (*J Clin Endocrinol Metab* **44:** 771, 1977)

ONE RECENT work has shown that certain oligomenorrheic women with reduced fertility present, in a presumed luteal phase, hormonal symptoms reflecting inadequate corpus lutem, characterized by abnormally low progesterone concentrations contrasting with normal estradiol values (1). A disequilibrium between estrogens and progesterone of a similar nature was reported by Backstrom and Cartensen in the premenstrual syndrome (2). These clinical data leave the possibility that such an ovarian dysfunction may be responsible for the development of benign mammary diseases. It was therefore interesting to explore in the same experimental conditions the luteal function of women having diverse mastopathies.

Materials and Methods

One hundred and nine women between 18 and 40 years of age suffering from benign mastopathies were studied. They included 47 cases of severe incapacitating mastodynia which did not demonstrate a mass either clinically or by mammography; 28 cases of cystic mastitis authenticated by mammography followed by aspiration and finally 34 cases of fibroadenomas demonstrated by mammography with negative aspirations. All of them were suffering from mastodynia for all or part of the cycle.

All of these patients presented a presumably ovulatory cycle. This presumption was based on basal body temperature measurements showing a nadir, followed by a luteal plateau lasting for eight to twelve days. The length of cycles studied varied between 24 and 40 days.

One blood sample for progesterone and estradiol was collected in each of the 109 patients between the first and the last day of their thermal plateau. The same determinations were carried out in 50 normal women of similar age with regular 28–30 day cycles with a 14 day thermal plateau. In these normal women, one or two blood samples were collected between day 1 and day 13 of the thermal plateau in order to have 5 to 9 progesterone and estradiol values for each day of the luteal phase.

Plasma progesterone was assayed by radioimmunoassay using ^{3}H-progesterone (NEN 100 Ci/mM) as tracer and an antiprogesterone-11-hemisuccinate-BSA antibody (A 79540 Institut Pasteur Paris). The assay was similar to that described by Abraham *et al.* (3) with slight modifications: 0.2 ml of plasma were extracted with 10 volumes of hexane/ethyl acetate 1/1; due to the specificity of the antibody, the chromatographic step was omitted; the dry extract was dissolved in phosphate buffered saline containing 1% gelatine and triplicate 0.1 ml aliquots were incubated 30 min at room temperature and 15 min at 0 C; the free steroid was adsorbed on dextran-coated charcoal and after centrifugation the supernatant was transfered into counting vials and counted in a Packard Tricarb 3330 scintillation spectrometer with 25% efficiency. The specificity of the assay rests mainly on the antibody which cross-reacts only 0.02% with 17α-hydroxyprogesterone, 0.01% with cortisol, 0.03% with testosterone, the highest cross-reactivity being with 5α-pregnan-3,20 dione: 1.7%. Furthermore, 6 samples were assayed after chromatography on celite microcolumn (3); the results were similar to those obtained with the routine assay. In addition increasing dilutions (1/2; 1/5; 1/10) of plasma obtained from women

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during the luteal phase yielded similar results. The lowest concentration which can be detected on the standard curve is 5 pg (9.4 ± 2.4% inhibition of tracer binding); since the assay is performed on 1/10 of the initial 0.2 ml plasma sample, the lowest concentration which can be detected in these conditions is 0.25 ng/ml of plasma. The reproducibility and precision are checked by including duplicate samples of a pooled plasma stock in each assay. The intra-assay coefficient of variation is 14% and the inter-assay 13.5%. The blank was less than the sensitivity of the assay.

The estradiol assay was similar but extraction was carried out on 2 ml of plasma. ^{3}H-estradiol (NEN 100 Ci/mM) was used as tracer and an anti-17β-estradiol-6 CMO-BSA (A/79520 Institut Pasteur Paris) as antibody. This antibody cross-reacts only 1% with estrone, 0.1% with estriol and 0.02% with testosterone, which allows the exclusion of a chromatographic step. Recovery of known amounts of estradiol added to a pool was 102% with a coefficient of correlation r = 0.98. The sensitivity of the assay is 10 pg/ml of plasma; the mean estradiol concentration in 10 menopausal women was 13.8 ± 4.05 pg/ml; the aqueous blank was less than the sensitivity of the method; the intraassay coefficient of variation is 9.2%, the inter-assay 8.5%.

Results

In Figs. 1 and 2 are represented the mean daily values ± SE for normal women and for the group of patients. While in normal women wide variations are observed in progesterone from one individual to another, particularly in the high values, no progesterone level lower than 10 ng/ml was observed between day 3 and 11 of the luteal phase. When daily values for patients plasma progesterone are compared with normal, it appears that except for day 1 of the thermal plateau, all patients levels are significantly lower ($P < 0.001$). On the contrary, no significant difference was noted between daily estradiol levels of patients and normal women ($P > 0.5$).

The 109 daily progesterone and estradiol determinations carried out in the group of patients were gathered according to clinical features: *i.e.*, the presence or not of breast mass (cystic mastatis of fibroadenomas) associated to mastodynia (Table 1). These two groups were compared to the mean of the 84 determinations performed in normal women. As above, plasma progesterone is significantly lower in each group of patients than in the group of normal women ($P < 0.001$), but there is no difference between the group of patients with breast mass and that with only mastodynia ($P > 0.5$). These results clearly indicate that in patients with breast disease (whatever its clinical expression), plasma progesterone levels are uniformly low during the luteal phase, whereas at the same period, plasma estradiol levels are within the normal range.

Discussion

Many recent studies have emphasized the importance of plasma progesterone to appreciate the corpus luteum function (4–6) as it did not seem possible to rely precisely on the basal body temperature curve and the level of urinary

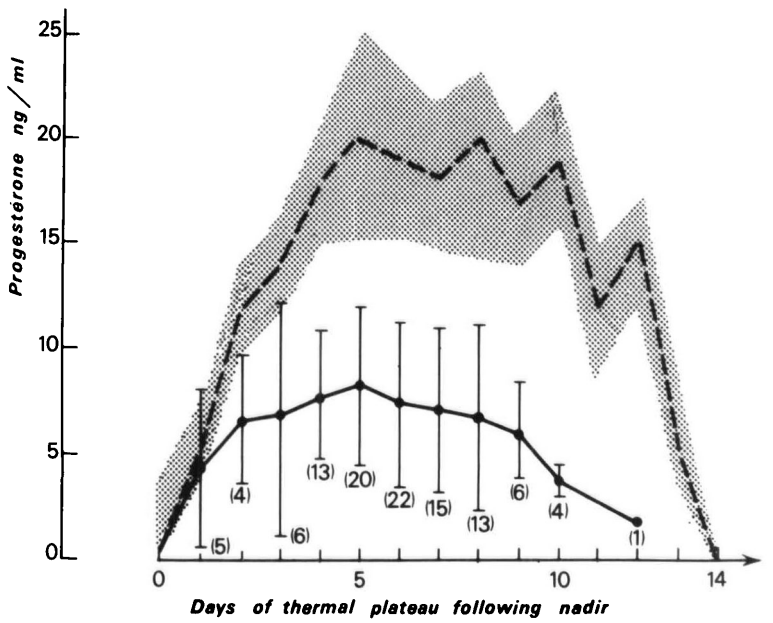

FIG. 1. Mean ± SE for plasma progesterone values in 109 patients with mastopathy studied from day 1 to day 12 of thermal plateau. In parentheses: number of determinations at each day. Shaded area: mean ± SE for plasma progesterone in 50 normal women studied at the same time of the menstrual cycle.

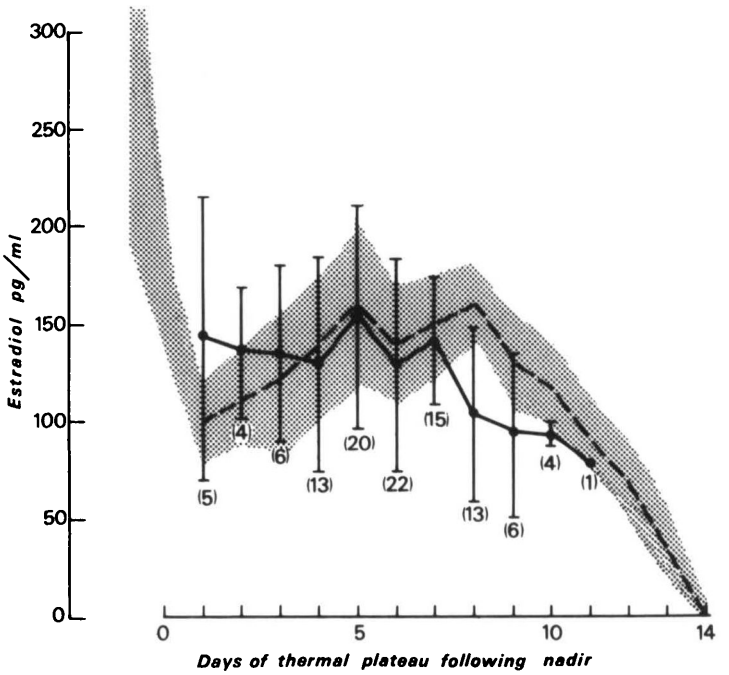

FIG. 2. Mean ± SE for plasma estradiol values in 109 patients with mastopathy studied from day 1 to day 12 of thermal plateau. In parentheses: number of determinations at each day. Shaded area: mean ± SE for plasma estradiol in 50 normal women studied at the same time of the menstrual cycle.

pregnandiol. A biphasic basal body temperature curve does not necessarily prove adequate corpus luteum function since a thermal plateau can be observed, even when the plasma concentration of progesterone reached only 3 ng/ml, a value incompatible with a good luteal function (5). With regard to urinary pregnandiol, its value is not necessarily related to the ovarian secretion of progesterone alone; in fact, the proportion of progesterone secreted which is metabolized and converted in the periphery varies in individuals between 15 and 77% and only 50% of these metabolites are found in the urine in the form of pregnandiol conjugates (7). The amount of urinary pregnandiol, therefore, depends not only on the secretion of progesterone, but also on the hepatic and renal functions (7).

Many studies have tried to evaluate plasma levels of progesterone compatible with normal luteal function. One can estimate that four days after the thermal nadir women presenting with a good functional corpus luteum have plasma values of progesterone equal to or greater than 10 ng/ml (1,4). By contrast, one experiences great variations in plasma estradiol values during the luteal phase of normal menstrual cycle, but usually they are greater than 90 pg/ml.

Considering these methodological data, it seems likely that women with benign breast disease have a corpus luteum which presents the same pathological secretory characteristics that were described by Sherman and Korenman under the name of "inadequate corpus luteum" (1). This corpus luteum is characterized by normal secretion of estradiol contrasting with an abnormally low secretion of progesterone. This progestational insufficiency in women presenting with apparently normal cycles is important, since many other women with the same mammary symptoms have a monophasic basal body temperature curve and an endometrial histology incompatible with ovulatory cycles (8).

TABLE 1. Plasma progesterone and estradiol (mean ± SE) evaluated during the luteal phase of 50 normal women and 109 patients with benign breast disease divided into 2 groups according to their clinical features

Subjects	Number of plasma determinations	Progesterone ng/ml	Estradiol pg/ml
Normal women	84	15.6 ± 3.2	131 ± 30
		$P < 0.001$	NS
Patients with only mastodynia	47	6.2 ± 2.7	155 ± 76
		NS	NS
Patients with mastodynia + breast mass	62	7.3 ± 4.2	141 ± 70

These women may have absolute progestational insufficiency. The frequency with which an inadequate corpus luteum is observed in women with benign mastopathy should warn the clinician not to be content with the simple appreciation of a biphasic basal body temperature curve for judging functional quality of the corpus luteum. Only the plasma progesterone level in the presumed luteal phase is capable of furnishing objective information on luteal function.

Under this pathophysiological scheme, the observation that women suffering from benign mammary diseases have an isolated defect of progesterone secretion by the ovary raises the question of the role of progesterone in proper mammary development and maintenance (9,10). It supports the hypothesis that the major mammary benign dystrophies have in common a hormonal component: the presence of a persistent estrogenic stimulation in the absence of sufficient cyclic progesterone secretion. Experimentally indeed, progesterone acts at the breast level in complementing and inhibiting estrogen both in the glandular and in the supporting perilobular tissue (11).

The present data point out the interest of a similar exploration of corpus luteum function in women with mammary carcinoma during the premenopausal stage and in women presenting one of the many high risk groups for breast carcinoma (8,12). If the hormonal conditions observed in premenopausal patients with breast cancer are the same as those associated with benign breast disease, a pathophysiological interpretation of human breast cancer epidemiology, in terms of luteal inadequacy, could be considered (12).

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