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## Hormonal Investigation in Benign Breast Disease

D. Marchesoni, M. Gangemi, B. Mozzanega, G.B. Nardelli,  
T. Maggino, and M. Velasco

*Department of Obstetrics and Gynecology, University of Padua, 35100 Padova, Italy*

The hormone-responsiveness of breast tissue and the hormone-dependence of its morphostructural modifications and functional potentialities are generally acknowledged. A chronologically and quantitatively precise ratio between the two hormones that condition its development, estradiol and progesterone, is necessary to assure breast eutrophy. Estradiol-induced cell proliferation in galactophorous ducts and edema formation in periductal stroma are followed by progesterone-induced growth inhibition and acinar differentiation toward secretion.

When the equilibrium found in normal menstrual cycles is broken, with an even partial loss of progesterone modulation, structural changes may occur in breast tissue. These changes are clinically grouped in the mastosis syndrome: their origin is neither phlogistic nor neoplastic, but, much more likely, seems dysendocrinic.

This etiopathogenetic hypothesis is supported by epidemiological observations indicating that the disease is more frequent in women in the reproductive age who are nulliparous, or never breast-fed, or show evidence of neurovegetative lability, or are obese, or who experienced anovulatory cycles. Physiological menopause is often associated with a disappearance of symptoms. Also, low progesterone levels have been noted in the luteal phase of women who, though ovulating, were affected with this syndrome.

This chapter investigates estradiol and progesterone plasma levels in normally menstruating women affected with mastosis, and offers a rationale for endocrine therapy of this disease.

### MATERIALS AND METHODS

Of 22 normally menstruating outpatients studied 10 were breast disease-free controls, and 12 complained of mastodynia, mostly affecting their premenstrual phase. A mono- or bilateral breast micronodularity was also present in the affected patients, which was clinically evident and diagnostically confirmed by the use of plate thermography, transillumination, echography, and, when necessary, mammography. The affected patients' mean age was  $27 \pm 7$  years; the average length of their menstrual cycles was  $29 \pm 4$  days; their basal body temperature curves were biphasic; and none had galactorrhoea.

All patients underwent blood drawings from the cubital vein taken between 8 and 10 a.m. on the third, sixth, and ninth days of the thermal plateau, for radioimmunoassay (RIA) of plasma estradiol and progesterone levels (Serono-Biodata Kit, sensitivity = 10 pg/tube and 15 ng/ml, respectively).

### RESULTS

The significance of the differences between the averages of the two hormones was calculated in the two groups by the Student's *t*-test. The luteal phase ratio P/E<sub>2</sub> was then calculated in both groups, according to the formula (6):

$$PEL = \frac{P \text{ (pg/ml)}}{E_2 \text{ (pg/ml)}} \times 0.01$$

Table 1 illustrates the average levels of estradiol and progesterone in both groups, and the results of the statistical analysis. The PEL ratio was 0.52 in the affected patients and 1.13 in the controls.

### DISCUSSION

The results of our research clearly point out that progesterone plasma levels are diminished in the luteal phase of patients affected with benign breast disease compared with controls.

Our data agree with the almost (3) unanimous (2,4-6,8,9) findings in the literature that benign breast disease, associated or not with mastodynia, can be due to a luteal deficit as occurs in the short or inadequate luteal phase. The presence in the affected patients of luteal estradiol levels that are the same as in the controls makes the hormonal balance shift toward hyperestrinism, which is the common base of the different ways through which mastosis can arise.

The prevalence in target tissues of estrogen stimulation can be associated with anovulatory syndromes (obesity, ovarian polycystosis) in which estradiol secretion and action are unopposed; or with the missed occurrence of physiological conditions (pregnancy, breast feeding) which protect the target tissues from estrogen-dependent risks; or with other situations that cannot be clinically diagnosed unless we resort to plasma progesterone radioimmunoassay (short or inadequate luteal phase).

TABLE 1. *Estradiol and progesterone levels in the luteal phase of the affected and control patients*

|               | Estradiol (pg/ml) <sup>a</sup> | Progesterone (ng/ml) <sup>b</sup> |
|---------------|--------------------------------|-----------------------------------|
| Controls (10) | 203.9 ± 11.4(SE)               | 23.4 ± 1.5(SE)                    |
| Affected (12) | 194.3 ± 16.8(SE)               | 10.9 ± 0.7(SE)                    |

Student's *t*-test used.

<sup>a</sup>*p* = N.S.

<sup>b</sup>*p* < 0.01.

In any of these cases, the androgen-induced progesterone induces in target tissues an increased synthesis of 17-beta-dehydroprogesterone. Its absence renders estradiol stimulation of ductal stroma, causing mastodynia in galactophorous ducts. Therefore, mastodynia can be hypothesized (1).

A critical examination of our results allows an etiological diagnosis of mastodynia in normally menstruated women and their controls. However, the normal occurrence of mastodynia was satisfactory, both in intensity and duration, without a corpus luteum dysfunction.

Progesterone values in the affected patients are lower than controls (10.9 ± 0.7 SE ng/ml and 23.4 ± 1.5 SE ng/ml). If we consider that progesterone levels are able to raise the thermal curve, this phylogenetic inhibiting of the luteal function (8) may be a manifestation of the thermal curve abnormalities in mastodynia pathologies. As our patients' thermal curves do not agnosc an inadequate luteal phase.

Finally, the affected patients' progesterone levels are critical to allow mastodynia to appear.

The assay of progesterone plasma levels during therapy. Progesterone supply in mastodynia, might induce a regression of mastodynia and breast micronodularity (7).

A further investigation of the progesterone levels suggest for progesterone luteal support toward breast malignancies.

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In any of these cases, the antiestrogenic action of progesterone is inadequate; progesterone induces in target tissues a drop in the levels of E<sub>2</sub>-receptors and an increased synthesis of 17-beta-dehydrogenase which converts estradiol to estrone. Its absence renders estradiol stimulation persistent, with edema induction in periductal stroma, causing mastodynia, fibrosis, and, eventually increased cellularity in galactophorous ducts. Therefore, the succession hyperplasia-dysplasia-cancer can be hypothesized (1).

A critical examination of our cases points out the impossibility of achieving an etiological diagnosis of mastodynia based solely on clinical findings. All our patients menstruated normally and their basal body temperature followed biphasic curves. However, the normal occurrence of ovulation does not mean their luteal function was satisfactory, both in intensity and in length. Only progesterone RIA can rule out a corpus luteum dysfunction.

Progesterone values in the affected patients were statistically lower than in the controls ( $10.9 \pm 0.7$  SE ng/ml and  $23.4 \pm 1.5$  SE ng/ml, respectively;  $p < 0.01$ ). If we consider that progesterone levels of 3 ng/ml are the minimum required to raise the thermal curve, this physical index appears unsuitable for a correct monitoring of the luteal function (8), even if, after progesterone RIA, a careful examination of the thermal curve may help in distinguishing between the luteal pathologies. As our patients' thermal plateaus were never shortened, we can diagnose an inadequate luteal phase.

Finally, the affected patients' progesterone levels were the same as levels believed critical to allow mastodynia to appear clinically.

The assay of progesterone plasma levels, then, seems to be important for proper therapy. Progesterone supply in the luteal phase, besides reducing or suppressing mastodynia, might induce a regression in breast objectivity, as recently reported in breast micronodularity (7).

A further investigation of the connection between dysplasia and cancer might suggest for progesterone luteal supply yet another effect: the possible prophylaxis toward breast malignancies.

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## Relationship of Breast Cysts Bre

\*Darrow E. Haag

\*Department of Surgery  
Bos

The pathological process of these cysts from metaplastic breast apocrine epithelium to the histiocarcinoma have been debated with opinions on this subject have been published by Campbell, 1934 (5), Higginson (1964 (53). The initial observation of apocrine epithelium and some features (31). Krompecher also recognized these cysts closely resembled the normal

In 1945 Lendrum (34) observed the presence of apocrine epithelium of the breast axillary apocrine epithelium. The histological patterns identified histochemically. Recent ultrastructural study of breast cysts (1) confirms on a subcellular level the similarity to normal axillary apocrine tissue. The study on the secretory glycoprotein synthesis in metaplastic breast apocrine epithelium along with the relationship of these cysts with apocrine features.

There are two phases of breast cystic disease pathologically divided into microcystic and macrocystic. The size delimitation being: cysts of the microcystic component is more discrete than any discrete discernible lesion of the macrocystic disease is discernible by palpation. Infrequently, gross cystic disease