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Relationship of Mastodynia with its Endocrine Environment and Treatment in a Double Blind Trial with Lynestrenol

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Zusammenfassung. Bei 33 Patienten mit Mastodynie und 20 Kontrollpatienten wurden Serumanalysen 7 Tage vor der Menstruation durchgeführt. Die Untersuchung hat ergeben, daß der Progesterongehalt häufig abnimmt; der Prolaktingehalt jedoch ansteigt verglichen mit Kontrollpersonen gleichen Alters.

In einem Doppelblindversuch zeigte die Verabfolgung von Lynestrenol (10 mg/Tag; 10.–24. Zyklustag) bei 47 Patienten eine signifikante Verminderung der Mastodynie in 80% der Fälle.

Die therapeutischen Versager können durch Abnormalitäten in der Prolaktinsekretion erklärt werden und können möglicherweise auch verursacht werden durch unterschiedliche Ansprechbarkeit.

Schlüsselwörter: Progestogen – Mastodynie – Thermographie.

Summary. Serum analysis carried out about 7 days before menstruation in 33 patients with mastodynia and 20 controls confirmed that progesterone is frequently decreased and prolactinaemia increased in the patients with mastodynia compared with controls of the same age.

In a double blind trial, administration of Lynestrenol to 47 patients with mastodynia (each of whom was given 10 mg per day from the 10th to the 24th day of the cycle) resulted in a significant improvement of this condition in 80% of the treated cases. The therapeutic failures may be explained by anomalies in the secretion of prolactin, and may possibly be linked to individual sensitivity factors.

Key words: Progestogen – Mastodynia – Thermography.

Mastodynia is characterised subjectively by transitory bilateral pain in the breasts during the premenstrual period and which may extend later on throughout the menstrual cycle.

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Clinically it is defined as the presence of at least one palpable area of glandular induration which is radio-opaque and associated with thermal changes in the skin (Colin, 1975). On histological examination, foci of microcystic dilatation and epithelial proliferation are seen alternating with areas of sclerosis and atrophy (Geschickter, 1945).

According to Bernard (1966), absolute or relative hyper-oestrogenism plays a large part in the pathogenesis of this condition. The preponderant oestrogenic influences increase capillary permeability and stimulate oedema of the connective tissue (Zeppa, 1969). They also stimulate epithelial proliferation of the lacteal ducts resulting in cystic dilatation (Pullinger, 1947; Meites, 1972).

Mauvais-Jarvis et al. (1975) have reported that progesterone levels are frequently lowered as mastodynia progresses. According to Dasgupta et al. (1970), the anti-oestrogenic activity of progesterone may reduce the oestrogenic effects on the permeability of the capillary walls, and according to Martin et al. (1973), it may limit the epithelial proliferation in the ducts.

More recently the role of prolactin in the development of mastodynia has been investigated (Schulz et al., 1975). A higher level of prolactinaemia has been observed in patients who presented with the premenstrual syndrome, as compared with a control group (Halbreich et al., 1976).

Before initiating an objective study of the therapeutic value of progestogens in the treatment of mastodynia, we also wished to investigate this condition within its hormonal context by means of the radioimmunological measurement of ovarian steroids and prolactin, in the premenstrual phase.

Material and Methods

Patients with a normal menstrual cycle according to their history and clinical examination but who presented with the radiological and thermal changes characteristic of mastodynia were selected. This study was carried out in two phases:

1. Radioimmunological analysis of serum progesterone, oestradiol (Abraham, 1969) and prolactin (Reuter et al., 1976) was carried out about 7 days before menstruation in 33 patients with mastodynia; this was compared with the results obtained in 20 controls of the same age, who had no mammary pathology.

2. A double blind trial was carried out in 50 patients who presented with mastodynia. This involved the administration of 2 tablets containing either 5 mg Lynestrenol or a placebo from the 10th to the 24th day of the menstrual cycle for a period of 3 months. The progestogen and the placebo were given under identical conditions, at random, both the patient and the investigator being unaware of the nature of the product. Variations in pain, clinical induration and thermal changes in the skin measured by infra-red thermography were compared before and after treatment in 47 patients (24 of whom were given Lynestrenol and 23 the placebo).

Estimation of serum progesterone was carried out about 7 days before menstruation occurred during the cycle before treatment, and evaluation of the prolactin levels was performed before and after treatment in 25 of these patients (11 on Lynestrenol and 14 on the placebo).

Statistical Analysis

The significance of mean statistical differences between groups was calculated according to Student's t-test for non-paired data. The probability values were taken from two-tail tables and only values of $P < 0.05$ were considered significant.

χ^2 analysis according to Pearson was also used for comparing progesterone levels and progestogen activity in the control and treated groups.

Results

1. Hormonal Study

The mean values of serum progesterone (Table 1) were significantly lower ($t = 3.38$ with $P < 0.005$) in the patients with mastodynia compared with the controls of the same age. The mean levels of oestradiol were at the lower limits of normal and those of prolactin at the upper limits, but the statistical difference between both groups of women was not significant. Furthermore, the results were widely dispersed and no significant relation between the values for oestradiol, progesterone or prolactin was found.

No clearly pathological value for prolactin, i.e. more than 1200 μU/ml (Franchimont et al., 1976), was found in this series.

Serum progesterone levels of less than 5 ng/ml, typical of progesterone deficiency (Abraham et al., 1974), were more frequent ($\chi^2 = 6.1$ with $P < 0.02$) in the mastodynia patients than in the control group (Table 2).

Although it was not observed in all cases, a greater number of menstrual cycles characterized by progesterone deficiency and prolactin levels at the upper limit of normal were found among the mastodynia patients than among the controls.

2. Double Blind Trial

The results were classified into three categories, depending on variations in clinical and thermographic criteria. The first group was characterized by the disappearance of the painful nodules and the focus of hyperthermia (Fig. 1). Improvement according to one of the two examinations, clinical or thermographic, represents the second

Table 1. Analysis of oestradiol (E_2), progesterone (P) and serum prolactin (PRL) in controls and in patients with mastodynia. Mean values and standard deviation

	Age	E_2 pg/ml	P ng/ml	PRL μU/ml
Controls (n = 20)	26.6 ± 4.4	130 ± 52	8.6 ± 4.6	260 ± 104
Mastodynia patients (n = 33)	31.9 ± 8.5	91 ± 80	4.7 ± 4.3	368 ± 220

Table 2. Distribution of controls and mastodynia cases according to serum progesterone at about 7 days before menstruation (normal lower limit 5 ng/ml)

Serum progesterone levels	Controls 20 (100%)	Cases of mastodynia 33 (100%)
< 5 ng/ml	4 (20%)	18 (55%)
≥ 5 ng/ml	16 (80%)	15 (45%)

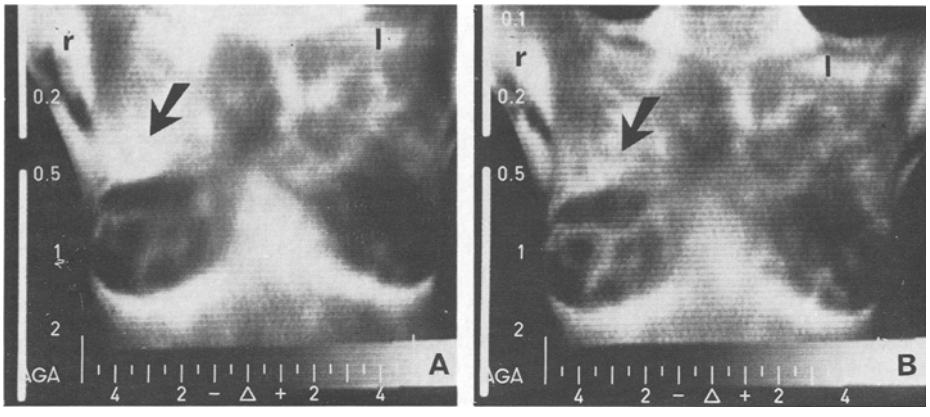


Fig. 1. Mastodynia, 28 years old patient (No. 20500). Infrared thermography (AGA Thermograph). (A): Perceptible right supra-median glandular area, 2 cm × 3 cm, with focus of hyperthermia (+2° C) (arrow). (B): 3 months after progestogen treatment; induration has disappeared and the right supra-median focus of hyperthermia has regressed (+1° C)

category, while the third comprises the cases in which no progress was observed.

After decoding the data of the 47 patients submitted to this investigation, we found (Table 3) that 15 out of 24 patients (62.5%) showed clinical and thermographic improvement after Lynestrenol, whereas 6 out of 23 (26.1%) only, were improved after placebo. Partial therapeutic success concern four patients (three with clinical and one with thermographic improvement) out of 24 (16.7%) after Lynestrenol and eight (six with clinical and two with thermographic) out of 23 (34.8%) after placebo administration. No clinical or thermographic changes were observed in 5 out of 24 (20.8%) mastodynia patients who were on progestogens, and in 9 out of 23 (39.1%) on placebo.

Complete or partial success was significantly more frequent on Lynestrenol ($\chi^2_{(df:2)} = 6.31$ with $P < 0.05$). Treatment with progestogen thus seemed objectively effective when the patients were assessed by clinical *and* thermographic examinations. However, when taking solely clinical examination into account, we found an improvement in 18 cases out of 24 after Lynestrenol and in 12 cases out of 23 after placebo ($\chi^2 = 2.6$), which is not statistically significant.

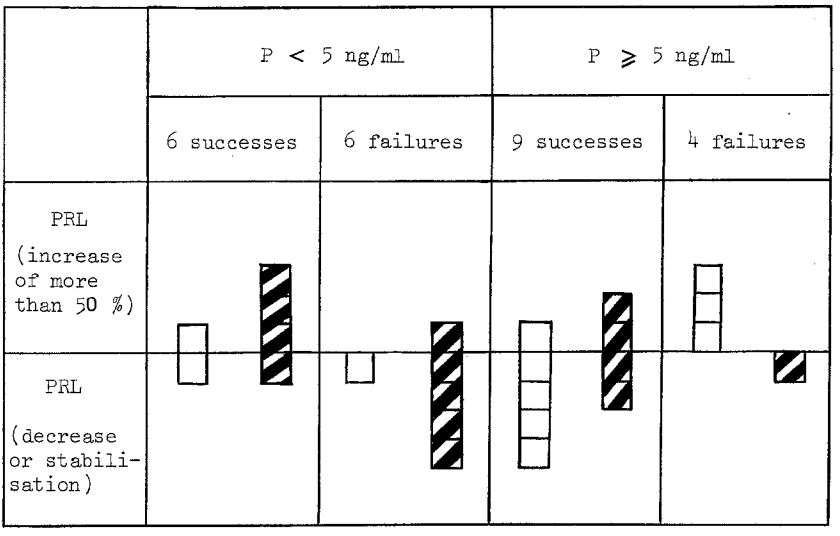
Nausea and breakthrough bleeding were the only side-effects which were recorded: three patients presented with these symptoms after Lynestrenol, versus five after placebo. Four patients withdrew from treatment: three of these were on placebo (two of them gave up because their symptoms had worsened, and one because of breakthrough bleeding), while only one was on Lynestrenol. In the latter case, progesterone levels were normal (8 ng/ml before treatment and 5.3 ng/ml 1 month after treatment), while prolactinaemia increased from 250 to 1 120 μU/ml during this period.

The complete or partial successes and the therapeutic failures with Lynestrenol and placebo could be confronted in most cases with the initial serum levels of progesterone and the levels of prolactin obtained during treatment (Table 4).

Table 3. Distribution of mastodynia according to clinical *and/or* thermographic improvement after administration of Lynestrenol or Placebo

Criteria of the double blind trial	Lynestrenol 24 (100%)	Placebo 23 (100%)
Clinical *and* thermographic improvement	15 (62.5%)	6 (26.1%)
Clinical *or* thermographic improvement	4 (16.7%)	8 (34.8%)
No improvement	5 (20.8%)	9 (39.1%)

Table 4. Complete or partial successes and therapeutic failures on Lynestrenol □ or placebo ▨ in relation to progesterone level (P) before treatment, and to the variations of prolactinaemia (PRL) after treatment



A large proportion of patients on Lynestrenol in whom therapy was a success had progesterone levels of more than 5 ng/ml and did not experience any increase in prolactinaemia at the end of the treatment. Among the failures, most presented with normal progesterone levels but showed an increase of more than 50% in the prolactin levels after treatment, although levels of 1200 μU/ml were not exceeded in any individual.

The therapeutic successes on placebo seemed independent of the initial progesterone levels but were often associated with an increase of more than 50% in prolactin levels after treatment. Progesterone levels of less than 5 ng/ml associated with low prolactin levels, were on the other hand, more frequent in the failure group on placebo.

Discussion

The hormonal studies enabled us to confirm the frequent deficiency of progesterone in mastodynia (Mauvais-Jarvis et al., 1975). The double blind thermographic study combined with the clinical examination also enabled us to show that an oral progestogen, Lynestrenol, is effective in the treatment of this condition.

Even though it was difficult to assess the results over such a brief period of time, we found that in almost 80% of the patients treated, there was complete (62.5%) or partial (16.7%) remission of the symptoms. A dose of 10 mg Lynestrenol per day thus seemed to be sufficient and well tolerated when administered from the 10th day of the cycle onwards.

It is noteworthy that thermographic examination allowed to correct clinical examination. The latter one appeared to be in some instances falsely indicative of remission, particularly in patients on placebo. In that prospect, thermographic *plus* clinical examination allowed us to more precisely delineate the cases objectively improved from those who were not. This enabled us to outline a statistically significant improvement in the treated versus placebo patients, contrarily to Dargent (Personal communication, 1977) who could not see any difference between both groups on the basis of clinical criteria alone.

We also noted that most of the failures of the progestogen treatment occurred in patients who developed a prolactinaemia of more than 50% above starting levels during the course of therapy (Table 4). However these values never reached or exceeded the normal limits at 1200 μU/ml (Franchimont et al., 1976).

These results agree with those of Schulz et al. (1975), who found an improvement in mastodynia after administration of a substance inhibiting the release of prolactin (Bromocriptine, Sandoz, Basle), even though prolactin levels were in the normal range before treatment. Therapeutic failures were however reported by these authors despite a significant decrease of prolactin levels. It is most probable that in such cases an associated progesterone deficiency is present, which is suggested by the numerous failures on placebo that were recorded in our study.

Retrospectively, we can see that the difficulty in interpreting our results stems from the fact that, owing to randomization hazards, progestogens were administered to women who were not presenting with marked progesterone deficiency, if any. The successes recorded in this group seem to be allied to the fall in prolactin value although the doses of Lynestrenol used could, by themselves, enhance the secretion of prolactin by means of hypothalamic inhibition (L'Hermite et al., 1972). When this did occur, failures were generally observed. The beneficial effect of placebo was manifest independently of the variations in serum levels of prolactin, while failures were more often evident in the presence of progesterone deficiency.

In view of these results, it seems that there is, in the development of mastodynia, at least one functional lesion at two levels: progesterone deficiency is the most common, but excessive prolactin secretion is also involved though less frequently, in our study.

The true sequence of these disorders still lies in the realm of speculation. Cases do exist however, in which neither progesterone deficiency nor excessive prolactin can be found to cause mastodynia. This situation was found in particular in our group where there was unexpectedly therapeutic success on placebo, despite initial

deficient luteal function and an increase of more than 50% in prolactin levels after treatment.

In the present state of our knowledge, we may consider that mastodynia is probably due to a number of factors, in which progesterone deficiency predominates and where individual sensitivity plays an essential part.

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