

## TREATMENT OF FIBROCYSTIC DISEASE OF THE BREAST WITH GESTRINONE, A NEW TRIENIC SYNTHETIC STEROID WITH ANTI-ESTROGEN, ANTI-PROGESTERONE PROPERTIES

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### Abstract

Coutinho EM (Maternidade Climerio de Oliveira, Department of Maternal Health, Federal University of Bahia, School of Medicine, Salvador, Bahia, Brazil), Azadian-Boulanger G (Roussel-Uclaf, Paris, France). Treatment of fibrocystic disease of the breast with Gestrinone, a new trienic synthetic steroid with anti-estrogen, anti-progesterone properties.

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Twenty-eight patients with radiologically diagnosed fibrocystic disease were given twice weekly 5 mg tablets of Gestrinone, a synthetic contraceptive steroid with potent anti-estrogen, anti-progesterone properties, for periods ranging from 3 to 9 months. Treatment was discontinued when the nodularity disappeared and the patient became asymptomatic. Twelve patients had palpable nodules or masses in both breasts, while the remaining 16 had a single nodule or lump. In 12 patients, all with small nodules or lumps, complete elimination of nodularity occurred at the end of the first 3 months of treatment. In a further eight patients, five of whom had small nodules and three of whom had large ones, an additional 3 months of therapy were required to achieve complete elimination of nodularity. In two subjects, nodularity was eliminated at the end of 9 months of therapy, and in the remaining six subjects, although a reduction in nodularity greater than 50% occurred,

masses remained palpable at the end of 9 months. Pain and tenderness were eliminated during the first 2 weeks of therapy in most cases. The most common complaints were acne and seborrhea (70% of patients) and a weight gain of between 2 and 5 kg in patients treated for 9 months. Main side effects encountered were acne and seborrhea.

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**Keywords:** Gestrinone; Fibrocystic disease; Nodularity; Steroid; Mammography.

### Introduction

Pincus et al. reported 25 years ago diminution of diffuse indurations in the mammary glands of women with fibrocystic mastopathy receiving Enovid for contraception [8]. The protective effect of oral contraceptives on benign breast disease was later confirmed in large retrospective studies [3,9], and Vessey and Doll reported that in women taking the "pill" for 2 years or longer, the need for biopsies of mammary nodules dropped by 75% [10].

Oral contraceptives appear to act by inhibiting endogenous estrogen production, while their progestational component decreases the concentration of estrogen receptors in abnormal mammary tissue, therefore reducing the stimulatory effect of estrogens. Recently Danazol, a potent inhibitor of the pituitary gonadal axis with weak androgenic potential,

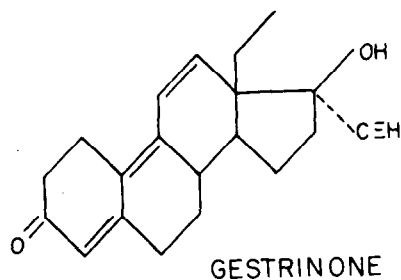


Fig. 1. Structural formula of Gestrinone (13-ethyl-17-alpha-ethynyl-17-hydroxy-gona-4,9,11-trien-3-one). Note the three alternated double bonds.

has been reported to reduce benign nodularity and suppress breast pain, but the doses required to achieve a high degree of effectiveness are too large for long-term or repeated use [1,2].

For the last 10 years, we have conducted clinical trials with Gestrinone (13-ethyl-17-alpha-ethynyl-17-hydroxy-gona-4,9,11-trien-3-one), a 19-norsteroid with three conjugated double bonds obtained by total synthesis in France (Roussel-Uclaf, Paris) (Fig. 1). The compound is a potent anti-estrogen, anti-progesterone which has been used as a weekly contraceptive and in long-acting subdermal implants for long-term contraception [4,7].

#### Patients and methods

Twenty-eight patients aged 18–40 years with mammary nodules were selected for the study. All patients had had well-individualized nodules or lumps for at least 3 months. Pre-treatment mammography was carried out in every case in order to establish the nature and size of the lesions and to rule out malignancy. A second mammogram was done only in a few selected cases where tumors remained palpable at the end of the treatment. Only those cases diagnosed radiologically as fibrocystic disease were accepted. Patients with a diagnosis of fibroadenoma or suspected of malignant tumors were not accepted. Also included were those having large cysts. In 12 patients, nodules or masses were palpable in both breasts. In the remaining 16 subjects, a single nodule or lump consisting of numerous microcysts was present. Treatment con-

sisted of the administration of 5 mg tablets of Gestrinone twice weekly for 3–9 months. Treatment was discontinued before 9 months whenever the nodularity disappeared and the patient became asymptomatic. Clinical evaluation consisting of assessment of changes in breast pain, tenderness and size of nodules was made monthly. Side effects associated with the anti-estrogenic action of Gestrinone, such as acne, seborrhea, hoarseness and hirsutism, were carefully checked.

#### Results

In 12 patients, complete elimination of nodularity occurred at the end of the first 3 months of treatment. All patients in this group had small nodules or lumps measuring 1–2 cm in diameter. In eight patients, although significant reduction in size and consistency of the nodules was detectable at the end of the first 3 months, an additional 3 months of therapy were required to eliminate the nodularity and render the patient asymptomatic. In five patients of this group, the nodules were smaller (1–2 cm) than in the remaining three patients. In two subjects, nodularity was eliminated at the end of 9 months of therapy. In the remaining six subjects, although a reduction in nodularity greater than 50% occurred, masses remained palpable at the end of 9 months. In these latter cases, a significant diminution in fibrotic tissue and microcystic masses could be documented by mammography, as shown in Fig. 2. Pain and tenderness were eliminated during the first 2 weeks of therapy in most cases. Acne and seborrhea were the most common complaints, occurring in 70% of patients. Most subjects gained weight. In those treated for 9 months, weight gain was between 2 and 5 kg. Although both acne and seborrhea were fully reversible, concern of some patients about this condition required reassurance of prompt reversibility in order for them to remain in the study. Breast size was fully restored following discontinuation of therapy and as a result of resumption of ovarian function.

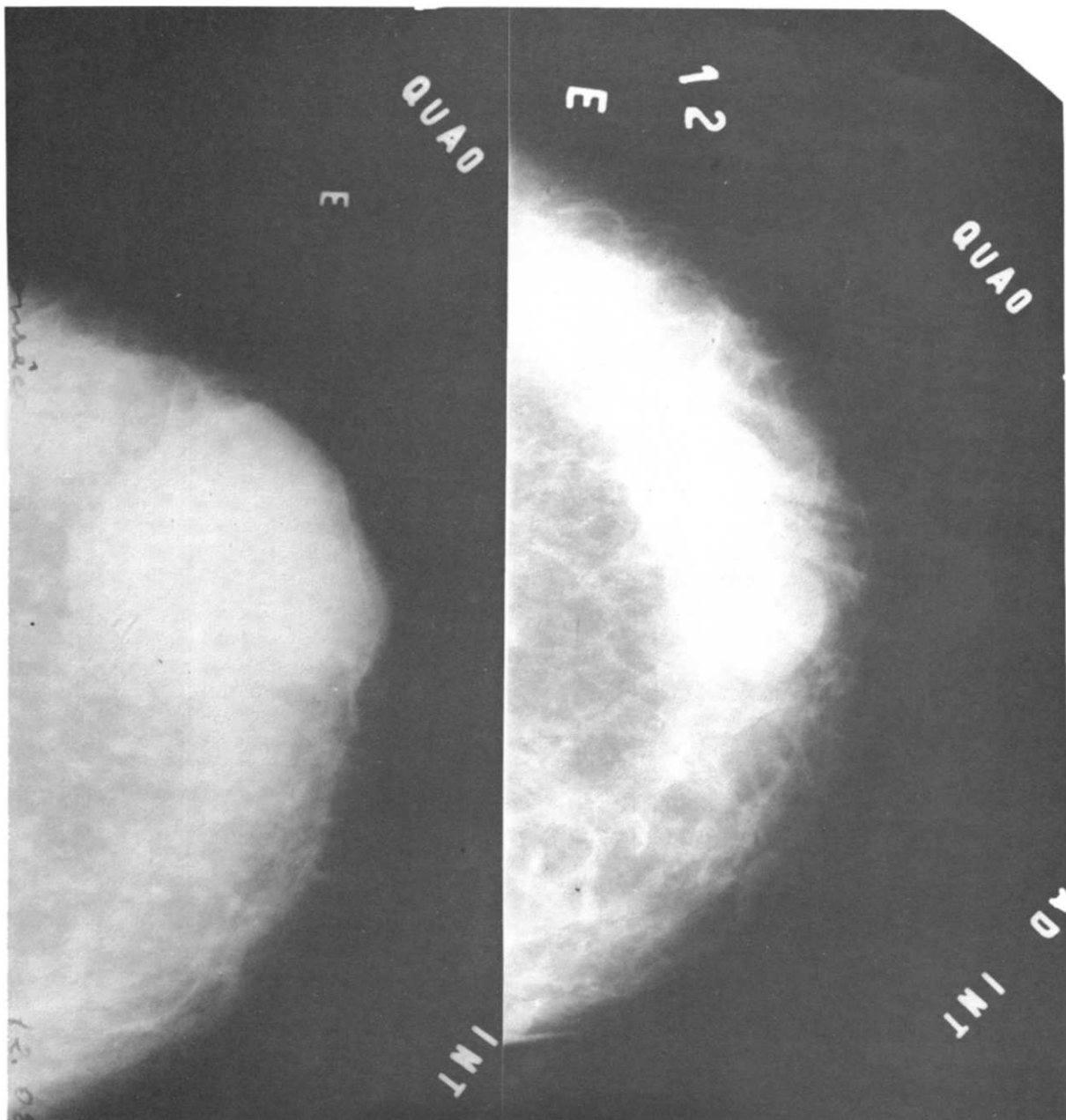


Fig 2. Mammography before (left) and after (right) 9 months of treatment with Gestrinone 5 mg twice weekly. Note reduction in the large masses and fibrotic tissues.

Follow-up at 6 months of 20 patients in whom complete elimination of nodularity occurred following therapy revealed only three recurrences requiring an additional course of Gestrinone.

#### Discussion

Fibrocystic disease is the most common disorder of the human female breast. It is estimated that 30% of the women between

the ages of 35 and 50 years develop some form of the disease. The importance of fibrocystic disease cannot be over-emphasized, since it is calculated that malignant tumors are three times more common in a breast affected by this condition.

Although the exact cause of the mastopathy is not known, the detrimental influence of estrogen is widely recognized. The disease develops during the estrogen-producing years of life and tends to regress and disappear with the onset of the menopause. Estrogen therapy tends to provoke an increase in the incidence, aggravate the pain and stimulate growth of pre-existing lumps, whereas progestogens apparently reduce the occurrence and prevent the growth of existing fibrocystic tissue.

Regression of nodularity associated with fibrocystic tissue was achieved with the anti-gonadotropin Danazol, but the doses used were in the range of 200–400 mg daily [1,2]. These doses may be too high for prolonged or repeated use, which is often necessary to treat recurrences. On the other hand, the use of a potent, anti-estrogenic substance such as Gestrinone in the conservative treatment of fibrocystic disease appears to hold great promise in view of the promptness of the clinical response with relatively low doses. Elimination of small nodules in which microscopic cysts are surrounded by fibrotic tissue occurs in less than 3 months, sometimes in 3–5 weeks.

In the present series, lumps existing for 1 year or longer were the most resistant to therapy. However, a reduction in lump size was achieved in every case, and complete elimination occurred in all but the very large (>5 cm in diameter) masses. Since Gestrinone was tolerated well in the study, its use for longer periods could be recommended for the treatment of larger nodules or for the treatment of recurrences.

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