REVIEW ARTICLE

A Review of Mastalgia in Patients with Fibrocystic Breast Changes and the Non-Surgical Treatment Options

Khalid Rida Murshid FRCS(C), FACS

Department of Surgery, College of Medicine, Taibah University,
Al Madinah Al Munawwarah, Kingdom of Saudi Arabia

Abstract

Objectives

The objectives of this study are to review fibrocystic changes of the breast, their causal and associated factors and their correlation to mastalgia, and then to review the available treatment options for mastalgia (caused by fibrocystic changes) short of surgery.

Methods

The author reviews all the articles obtained from a PubMed research on mastalgia and fibrocystic changes of the breast, published in English over the last 14 years.

Results

Fibrocystic changes of the breast are common and can be considered as a normal phase of breast development. These changes are sometimes asymptomatic; however, when painful, patients would seek medical advice. Lifestyle changes and the avoidance of certain dietary elements as well as the use of some non-pharmacological agents have shown some beneficiary effects. In severe cases, stronger pharmacological and hormonal agents are resorted to being more effective but are associated with greater side effects.

Conclusion

Fibrocystic changes of the breast are common and should not be considered a disease. When painful, reassurance and non-pharmacological measures should be used first as a treatment. Stronger pharmacological and hormonal agents hold more serious side effects. Some of these remedies are supported by good clinical evidence, while others are not. The ideal treatment for mastalgia caused by fibrocystic changes is to be identified by sound recent randomized controlled clinical studies on simple remedies before being performed on stronger ones. Treatment should start with simple lifestyle changes and advance with a stepwise fashion to stronger remedies only in those where other means fail.

Key words: Fibrocystic breast disease, Fibrocystic breast changes, Fibrocystic breast condition, Mastalgia, Mastodynia.

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Correspondence to:
Dr. Khalid Rida Murshid
Associate Professor of Surgery
Department of Surgery, College of Medicine
Taibah University, ✉ 30001 Al Madinah Al Munawwarah
Kingdom of Saudi Arabia
☎+966 4 8460006
🖷 +966 4 8461407
🖰 kmurshid@yahoo.com

Introduction

Fibrocystic breast changes as well as mastalgia are common conditions that women suffer from. They may occur separately or in combination. The nature of these changes as well as the associated factors responsible for their development are not fully understood by many who treat patients suffering from breast pain. Unfortunately, mastalgia caused by fibrocystic breast changes is treated by breast specialists as well as by those not specialized in breast diseases. This results in patients receiving inappropriately strong medication with severe side effects, where simpler remedies could have done the job more efficiently.

Breast histology

The life cycle of the breast consists of three main periods: development, mature reproductive life, and involution. The breast is identical in males and females until puberty. After the breast has developed, it undergoes regular changes in relation to the menstrual cycle that results in an increased rate of cell proliferation during the luteal phase leading to an increase in breast size[1]. Pregnancy results in a progressive increase in breast weight till term, and the breast involutes following pregnancy. Breast involution begins at some time after the age of 30 in nulliparous women. During involution the breast stroma is replaced by fat, so that the breast becomes less radiodense, softer, and ptotic (droopy). Changes in the glandular tissue include the development of areas of fibrosis, the formation of small cysts (microcysts), and an increase in the number of glandular elements (adenosis)[1]. This leads to a spectrum ranging from normal histologic features to features that mainly exhibit patterns of fibrous change and cyst formation, formerly called fibrocystic disease of the breast. Since this histologic pattern may be evident in up to 50 or even 60 percent of women without breast disease, it led Love et al to suggest that fibrocystic "disease" does not exist[2]. The currently accepted term for this condition is 'fibrocystic change', an emphasis that has been evolving in the literature[3].

Classification and Synonyms

In the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, (the ICD-10), fibrocystic disease or fibrocystic changes also known as chronic cystic mastitis and fibrocystic mastopathy is classified under 'benign mammary dysplasia' category N60, and in case of 'diffuse cystic mastopathy' sub-category N60.1. If there is epithelial proliferation, it is classified under 'fibrosclerosis of the breast' category N60.3. 'Mastodynia' is classified under N64.4[4].

Eponyms

This entity (fibrocystic disease of the breast) has historically been termed as Bloodgood's disease, Cooper's disease (after Sir Astley Paston Cooper), Phocas' disease, Reclus' disease, Reclus' syndrome (after Paul Reclus), Reclus-Schimmelbusch disease, Schimmelbusch disease and Tillaux-Phocas disease[5].

Are fibrocystic changes and Mastalgia synonymous?

Fibrocystic changes of the breast involve various histological findings in both asymptomatic and symptomatic women, and are common in both groups. Fibrocystic changes and mastalgia are two different things although they commonly occur together. They can also occur separately, making the association between breast pain and fibrocystic histology inconsistent[6].

Mastalgia (Breast Pain)

Mastalgia (breast pain) was described in the medical literature as early as 1829[7] and is a common complaint amongst women. Most of them describe premenstrual mild cyclic mastalgia (CM) that lasts for 1 to 4 days as "normal"[8]. Recent population based[9], and breast clinic-based[10,11] studies suggest that up to 70% of women under 55 experience breast pain. Although 45% of them report minimal to mild symptoms, about 25% report moderate-to-severe mastalgia lasting for more than 5 days.

Etiology

What causes fibrocystic breast condition to cause mastalgia?

Researchers have found no clear hormonal or specific pathological processes that explain cyclical breast pain[12]. However, certain associations and factors cannot be ignored **(Table 1)**.

Table 1: Factors with possible relation to the development of Fibrocystic Changes of the breast.

Factors possibly related to Fibrocystic Breast Changes	
1	Age
2	Hormones
3	Premenstrual syndrome
4	Duct ectasia
5	Stress
6	Smoking
7	Caffeine

Age

Breast pain is most common amongst women aged 30–50 years[10].

Hormones

1. ***hormonal associations***

The fact that mastalgia in patients with fibrocystic changes is related to hormonal events, such as the menstrual cycle, pregnancy, menopause and hormone therapy suggests a relationship between the two.

2. ***hormone therapy***

In one study 16% of women reported breast pain as a side effect of estrogen therapy and 32% reported the same in cases of combined hormonal therapies[13]. Other researchers have also identified increased breast density during hormonal therapy[14]. On the other hand, hormonal contraceptive was found to be associated with significantly less mastalgia and premenstrual syndrome (PMS)[9].

3. ***relationship to other premenstrual symptoms***

Most agree that CM and tenderness are part of the PMS[12,15]. Luteal-phase symptoms, including water retention, negative affect, impaired concentration and behavior change were significantly greater in women with severe CM compared to women without breast symptoms. Also, women with severe CM experienced more breast symptoms and negative affects in the follicular phase of the menstrual cycle[16]. A study of 30 subjects showed that most women whose symptoms met the criteria for CM had experienced other premenstrual and somatic symptoms[17]. However, others have found that although premenstrual symptoms were common in women with CM, only 16% of women in one study[18], and 22.5 % in another study[9] had sufficient symptoms that met the criteria for both CM and PMS.

Duct ectasia

Ultrasonographic measurement of the maximum mean width of the milk ducts was 1.8 mm in asymptomatic women, 2.34 mm in women with CM, and 3.89 mm in women with non-CM ($P<0.001$). Ductal width correlated with pain intensity[19].

Other Risk Factors and High Risk Groups

Stress appears to be a factor as women with severe breast pain seem to have had greater incidence of significant life events than women without severe breast pain[9]. *Smoking* as well as *caffeine* intake also seems to be risk factors[9].

Clinical Features

Fibrocystic breasts are lumpy or nodular and although the breast changes categorized as "fibrocystic" are normal; they can cause breast pain and tenderness that is usually related to the period[12]. This glandular texture may be finely granular, nodular, or even grossly lumpy. Breast pain and palpable mass are the symptoms most frequently described by women presenting to general practitioners or breast clinics[20, 21].

CM accounts for approximately 2/3 of breast pain in specialty clinics, whereas non-CM accounts for the remaining 1/3[22]. CM typically presents during the third or the fourth decade of life and the symptoms tend to persist with a relapsing course[22]. It usually starts during the luteal phase of the menstrual cycle and increases in intensity until the onset of menses, when it dissipates[6]. Mastalgia may be severe enough to influence usual daily activities[11]. In spite of that, mastalgia generally is underreported. Remission often occurs with hormonal events such as pregnancy or menopause. Only 14% of women with CM experience spontaneous resolution; however, 42% experience resolution at menopause[22]. The outcome can be successful in most patients with reassurance, non-pharmacological measures and in some instances one of several effective medications[23].

Breast Pain Assessment

Quantifying breast pain may be difficult because of its variability[23,24]. Before starting any therapy for breast pain, patients should be asked to document the frequency and severity of their pain on daily basis for at least one menstrual cycle using a visual analog scale. The pain scale is also helpful in assessing treatment response in mastalgia, which is characterized by the waxing and waning of symptoms and a high spontaneous remission rate[24]. In one study, the total breast pain score was found to be most efficiently estimated by a combination of a visual analog scale, present pain index, and quality-of life questions[25]. These measures are particularly important for CM as the diagnosis based on recall of symptoms is only 65% sensitive, and the diagnosis based on the prospective breast pain diary is 69% specific[17]. Research criteria for the diagnosis of CM are (1) pain severity greater than 4.0 cm measured on a 10.0-cm visual analog scale and (2) pain duration of at least 7 days per month[11].

Relationship to Breast Cancer

Mastalgia is rarely considered as a presenting symptom of breast cancer[6]. In one study, the relative risk of Breast Cancer developing ranged between 0.3 and 0.7 in patients with breast pain and was significantly higher (1.9-3.0) only in patients aged > 40 years with breast lumps. They concluded that in symptomatic patients Breast Cancer risk is strictly related to age and independent of the referred symptoms[26]. Conversely, in a review of 1532 women with breast pain (when women with breast pain as a sole complaint were excluded) the risk of breast cancer was lower in women having pain incidental to another presenting complaint[27]. In a recent case-control study of women referred for diagnostic breast imaging to evaluate pain, there were no differences between the mammographic findings and frequency of malignancy in women with pain compared with a matched control group undergoing routine screening[28]. However, because of the increased awareness of breast cancer, more women are seeking professional advice than ever before[23, 29,30,31,32]. Classically, breast pain associated with cancer is unilateral, constant and intense[8].

Treatments (Table 2)

General

A wide variety of therapies are used, but danazol is the most commonly used by 75% of surgeons. Breast specialists tend initially to use methods that are associated with fewer side-effects and reserve stronger treatments such as danazol and bromocriptine for more difficult cases. Hormonally active medications are more effective for patients with CM and are prescribed only for patients with severe prolonged symptoms[33,34].

Nonpharmacological Interventions

Education and reassurance

Education and reassurance are integral parts of the management of mastalgia and should be the first-line of treatment[35].

Table 2: Treatment options for mastalgia of the breast.

Remedy	Evidence For	Evidence Against	Other Remarks
Non-Pharmacological, Non-Nutritional Recommendations			
Education and reassurance	35		
Relaxation Training	36		
Wearing A Bra	35,38		
Nutritional Recommendations			
Dietary Fat Reduction	39,40	41,42,43	
Dietary Fiber		43	
Methylxanthine Restriction	31		
Nutritional Supplements and Herbal Agents			
Vitamin E	46,47,48	35	
Soy	54,55		
Fish oil		56	
Evening Primrose Oil	12,24,33,48, 57, 58	31,35,41,56,60	Not to be used in patients on anticonvulsant therapy. Its safety during pregnancy or lactation has not been established.
Flax Seed Oil	35	62	
Chasteberry	44,63		
Pharmacological Interventions			
Non-Hormonal Medications			
Simple Analgesics	35,65,66,67	23	
Hormonally Active Medications			
Oral Contraceptives	69,70,71	68,70,71	
Progesterone, Progestogens + Progestins	72		
Antigonadotropins			
Danazol	46,79,80		To reduce side effects reduce the dose once a response is achieved and/or luteal-phase administration. It is contraindicated in women with H/O thromboembolic disease and potentially teratogenic.
Dopamine Agonists			
1-Bromocriptine	84	86	Side effects less if the drug is taken with meals. Strokes, seizures and death have been reported after its use to inhibit lactation, and the US FDA has withdrawn its licence for this indication.
2-Lisuride	87		
3-Quinagolide	88		
Selective Estrogen Receptor Modulators (S.E.R.M.)			
1-Tamoxifen	80,91,92	8,93	Tamoxifen has a risk of potentially serious adverse effects and is contraindicated in pregnancy because of potential teratogenicity.
2-Toremifene	94		
Gonadotropin-Releasing Hormone Agonists:			Adverse effects related to the hypoestrogenic state produced by these medications are frequent and often severe
Buserelin		96	High decline in trabecular bone mineral density.

Psychological Associations and Relaxation Training

The potential psychological origin of breast pain has been explored throughout the medical literature. As far back as 1829, Sir Astley Cooper wrote that women seeking advice for breast pain usually had "a nervous and irritable temperament."[7]. More recently, anxiety and other psychological disorders have been found by others to be more frequent among women with mastalgia compared with asymptomatic women[36]. In another study, women with breast pain had, in addition, increased somatization, and history of emotional abuse compared with women with breast lumps alone[37]. This led some to explore the effect of relaxation on breast pain. H.Fox et al found that approximately 61% of women who listened to relaxation audiocassettes daily for 4 weeks experienced substantial or complete relief of breast pain compared to 25% of controls ($P < 0.05$). The subjects also had substantially more pain-free days and less anxiety than controls[36].

Stop Smoking

Patients with mastalgia should stop, or at least reduce the number of cigarettes taken daily, based on a study that identified smoking as being a factor associated with mastalgia[9].

Wearing A Bra

B.R. Mason et al have hypothesized that breast pain is mainly associated with the movement of breast tissue, and have shown that wearing an external breast support reduced absolute vertical movement and maximum downward deceleration force on the breast. Breast support also reduced perceived pain. Of the three garments examined in this study, the fitted sports bra provided superior support resulting in pain reduction[38]. V. Rosolowich et al also agree that the use of a well-fitting bra that provides good support should be considered for the relief of mastalgia[35].

Nutritional Recommendations

Dietary Change

The effectiveness of dietary interventions to reduce breast pain are continually undergoing investigations. The following have recently been studied.

Dietary Fat

Lower dietary fat intake has been associated with less severe mastalgia symptoms[39]. By reducing dietary fat, other parameters that may be related to mastalgia are altered, including mammographic breast density[40]. However some claim that the effect of decreased dietary fat intake on other fibrocystic changes of the breast is limited and also claim that in order to derive benefit from this approach, women must decrease fat intake to less than 20% of total daily caloric intake[41]. This reduction in fat intake, in addition to being difficult to sustain, may not be optimal in some cases[42].

Fruits,Vegetables,andDietaryFiber

The results of T.E. Rohan et al suggest that a modest reduction in fat intake and an increase in fruit, vegetable, and grain intake does not alter the risk of benign proliferative breast disease[43].

Methylxanthine (Caffeine) Restriction

Caffeine reduction or elimination is recommended by many specialists to alleviate breast pain, and although many women reported that it alleviates their breast pain, clinical studies have not shown consistent findings[6]. Since caffeine is present in coffee, tea, chocolate and cola, this makes it difficult to completely eliminate from the diet; even in clinical trials. It also puts a big question mark on studies performed using total elimination of methylxanthines from the diet for long periods. In addition, some recommend that women with breast pain should not be advised to reduce caffeine intake[35]. An association between methylxanthines (caffeine or theophylline) and breast symptoms of pain, tenderness, nodularity, has been reported by other investigators[9]. In an uncontrolled study, 61% of women with breast pain who substantially decreased caffeine intake for 1 year had decreased pain or complete relief[31].

Many of us will continue to advise patients to practice some restriction in their caffeine intake on the basis of clinical experience and the few studies with breast pain as a discrete outcome, especially in women with problematic breast pain who have moderate to heavy caffeine consumption[9].

Nutritional Supplements and Herbal Agents

Interest is growing in herbal agents, nutritional supplements and alternative strategies for treatment of breast pain[6]. Patients frequently use herbs and dietary supplements to treat chronic conditions that are poorly responsive to prescription drugs, or when prescription drugs carry a high side effect burden[44]. Physicians must be cognizant that herbal agents and nutritional supplements are not standardized or monitored for adulteration[45]. Potential interaction with medications and other herbal medicinal also must be considered.

Vitamins

Vitamin E (a-tocopherol)

Vitamin E is by far the most commonly used and most commonly studied vitamin to use as a treatment for breast pain. While some go as far as stating that vitamin E should not be used for the treatment of mastalgia[35], when comparing vitamin E to danazol, Khanna et al found that the treatment with vitamin E showed a 41% response rate with minimal side-effects, while treatment with danazol showed a 72.1% response rate but was associated with side-effects in one third of the patients[46]. More recently, a study concluded that a 2-month prescription of vitamin E has positive therapeutic effects on cyclic mastalgia. Given its lack of significant side effects, vitamin E can be considered a safe alternative to hormonal therapies currently used in the treatment of cyclic mastalgia[47]. Also, Pruthi et al concluded that daily doses of 1,200 IU vitamin E, 3,000 mg Evening Primrose Oil (EPO), or vitamin E and EPO in combination at these same dosages taken for six months may decrease the severity of CM mastalgia[48].

Soy

Soy is a rich source of the isoflavones genistein and daidzen, which exert their effect by binding to estrogen receptors[49]. In premenopausal women, this increases the duration of the follicular phase of the menstrual cycle and delays menstruation. In addition, it may decrease midcycle surges of luteinizing and follicle-stimulating hormones[43] and decrease estradiol levels[50]. Others have found that flavonoids exhibit significant steroid hormone activity[51]. Some studies of soy on breast epithelium revealed markers of increased proliferation[52], whereas others did not[53]. R.M. Fleming conducted a study to examine the effect of daily soy protein consumption which showed both objective and subjective reduction in both breast tenderness and fibrocystic disease[54]. In another study, the reduction of pain was significantly better than placebo[55].

Fishoil

J. Blommers et al studied the effect of both EPO and fish oil on breast pain and concluded that neither EPO nor fish oil offered clear benefit over control oils in the treatment of mastalgia[56].

Evening Primrose Oil (EPO)

There is some evidence suggesting that women with mastalgia have increased levels of saturated fatty acids and reduced proportions of essential fatty acids, especially of gamma-linolenic acid (GLA).
These abnormal fatty acid profiles may cause hypersensitivity of the breast epithelium to circulating hormones. GLA is believed to restore the saturated/unsaturated fatty acid balance and decrease sensitivity to steroidal hormones[41]. Also, low levels of the GLA metabolite, dihomogamma-linolenic acid may affect breast sensitivity to prolactin via prostaglandins[41]. EPO is rich in Omega-6 Fatty Acids. GLA is an omega-6 fatty acid found primarily in vegetable oils including EPO. EPO typically contains 9% GLA by

weight[57]. For women with CM who elect treatment, EPO has been advocated by many as an initial option[12,24,33,58], and several have reported efficacy in the treatment of breast pain with low adverse effect rates[48,57]. One randomized controlled trial found that most adverse effects were gastrointestinal. However, there were no significant differences in rates between the EPO plus multivitamins and the placebo plus multivitamins group[59]. Proponents of its usefulness suggest the dosage for breast pain to be 3000 mg/d (in divided doses), and claim that patients may continue to improve after 3 months of treatment and therefore recommend assessing response to therapy after at least 6 months[57]. GLA however, may affect the seizure threshold; for this reason, some researchers advise against its use in patients requiring anticonvulsant therapy[45]. In addition, the safety of EPO during pregnancy or lactation has not been established. Its benefits have been found in some studies to be only modestly better than placebo, and some question its therapeutic value for breast pain[31,35,41,56,60].

Borage Seed Oil

Although borage is the highest known plant-based source of gamma-linolenic acid (GLA), the seed oil content being between 26-38% and the oil is often marketed as "starflower oil" or "borage oil" for uses as a GLA supplement[61], I have not come across any recent studies on its use in mastalgia.

Flax Seed Oil

Although V. Rosolowich et al claimed that flaxseed should be considered as a first-line treatment for CM[35], E. Basch et al performed an extensive electronic search in an attempt to evaluate the scientific evidence on flaxseed. They found that most of the available evidence investigates the efficacy of alpha-linoleic acid found in flaxseed compared with fish oil, and state that almost all of the available studies are poor quality that do not support recommendations for any condition at this time[62].

Chasteberry (Vitex agnus-castus)

Theoretical mechanisms of the actions of Vitex agnus-castus are that it binds to opioid, histamine, and estrogen receptors[63], or acts via dopaminergic and prolactin-suppressant effects[64]. In a study of the fruit extract of Vitex agnus-castus (chaste tree berry) in 1634 subjects for 3 menstrual cycles, 93% of the subjects reported improvement in symptoms related to premenstrual syndrome and 81% of subjects rated their status after treatment as much better or very much better. Few adverse effects were identified[63].

Pharmacological Interventions

Simple Analgesics

It is very likely that patients would have already used simple mild over the counter analgesics before seeing their doctor to prescribe. In one study, topical application of the nonsteroidal anti-inflammatory agents diclofenac and piroxicam yielded satisfactory relief in 81% of 26 women with severe cyclic, noncyclic, and surgical scar–related breast pain[65]. In another study, Rosolowich et al recommend that topical non-steroidal anti-inflammatory gel, such as diclofenac 2% in pluronic lethicin organogel, be considered for pain control for localized treatment of mastalgia[35]. S. Qureshi and N. Sultan found topical non-steroidal anti-inflamatory drugs (NSAIDs) to be a safe, effective, rapid and acceptable mode of treatment for CM and non-CM in addition to being superior to EPO in all aspects[66]. A prospective, randomized, blinded, placebo-controlled study of topical diclofenac showed significant pain reduction in patients with CM as well as those with non-CM compared with placebo. No adverse effects occurred[67]. Conversely, another study of topical ibuprofen used in clinical practice determined no beneficial effect on breast pain[23].

Hormonally Active Medications

Most researchers favor less aggressive measures before hormonal agents are embarked upon. However when these measures fail, danazol, bromocriptine, or

tamoxifen are the most widely resorted to, while focusing on a balance between relief of pain and side effects of these hormonal agents. Many oral contraceptives list breast pain and tenderness as potential adverse effects. Eliminating or decreasing the dose of estrogen in an oral contraceptive or hormone regimen is often effective in clinical practice, particularly if the onset of symptoms is temporally related to the initiation or change of medication[6].

Oral Contraceptives (OCs), Estrogen, and Progesterone

While some studies of low-dose OCs (20 µg ethinyl estradiol) have found no increased breast symptoms compared with placebo[68]. Others have shown that many women reported a reduction in severity and duration of cyclic breast discomfort and PMS while taking OCs[9]. A multicenter case-control study was performed on women receiving medroxyprogesterone acetate (Depo-Provera) for contraception compared with age matched controls. Frequent breast pain and medication use for breast pain were noted in 9% and 5%, respectively, of women using Depo-Provera compared with 21% and 9% of women in the control group[69]. TE Rohan and AB Miller investigated the association between OC use and the risk of benign breast disease (BBD), overall and by histological subtypes, within the 56,537 women in the Canadian National Breast Screening Study (NBSS). There was an inverse association between the use of OCs and the risk of all types of BBD combined. The risk of BPED with atypia was increased somewhat in association with OC use for the use of more than 7 years, but not in a dose-dependent manner[70]. In a follow up study on the 17,032 women in the Oxford-Family Planning Association study using different methods of contraception, M Vessey and D Yeates found that low-dose combined OCs containing <50 mcg estrogen appear to reduce the risk of hospitalization for fibroadenoma and chronic cystic disease as well as older preparations containing higher doses of estrogen. The apparent protective effect was not present for women using progestogen-only OCs[71].

Hormonal Supplements

Progesterone, Progestogens and Progestins

A progestin is a synthetic progestogen that has progestinic effects similar to progesterone. The two most common uses of progestins are for hormonal contraception (either alone or with an estrogen) and to prevent endometrial hyperplasia from unopposed estrogen in hormone replacement therapy[61]. In a controlled, randomized, double-blind, parallel-group study by UH Winkler et al, 31 women with mastopathy/mastodynia were treated with the progestins medrogestone or dydrogesterone (10 mg/day) from day 14 to day 25 for six cycles. They concluded that cyclic administration of these low-dose progestins proved to be an effective and safe treatment of mastodynia and mastopathy, evidenced by improvement in objective parameters in more than 50% of patients. Improvement was particularly marked in women with low progesterone levels in the second half of the cycle. After six treatment cycles, 75% of the patients treated with dydrogesterone and 86% of the patients treated with medrogestone were completely pain-free[72].

Hormone Replacement Therapy (HRT)

Although HRT is not(in itself) a treatment for mastalgia or fibrocystic changes of the breast, it is mentioned here due to its strong causative relationship with breast changes. In an attempt to study the association between HRT use and the risk of benign proliferative epithelial disorders of the breast (BPED), TE Rohan and AB Miller found that in post-menopausal women, in whom most of the reported use occurred, there was a positive association between duration of HRT use and the risk of BPED[73]. LA Mattsson and T Sporrong reported a lower incidence of mastalgia during treatment with low dose regimen HRT compared to high doses. They suggested for cases requesting HRT to begin with low dose formulations since these doses are sufficient for the majority of women[74]. MC Yenen et al found that tibolone (a synthetic

steroid hormone acting as an agonist at all five of the Type I steroid hormone receptors[61]), was associated with a decrease in cyst dimensions which was statistically significant in benign cystic mastopathy patients compared to other hormone replacement therapy regimens[75]. A. Ozdemir et al when studying mammographic and ultrasonographic changes in the breast related to HRT showed that mammographic density changes related to HRT are dependent on the selected hormone regimen. The degree of density increase was evidently minimal in tibolone users compared to others. Formations of breast cysts or solid lesions did not seem to be related to HRT[76]. In a study by E.Lundström et al, HRT regimens were shown to have different effects on the normal breast. An increase in mammographic density was noted much more commonly among women taking continuous combined HRT (40%) compared to those using oral low-dose estrogen (6%) and transdermal (2%) treatment. They found the increase in density to be apparent as early as the first visit after starting HRT. During long-term follow-up, there was very little change in mammographic status[77]. M.D.Cahn et al stated that the use of HRT may promote lesions that predispose to cancer, and recommended that patients treated with HRT undergo vigilant surveillance by way of examination and mammography[78]. A change in dose, formulation, or scheduling should be considered for women on HRT, and HRT may be discontinued if appropriate[35]. Also, contraception is important during treatment and should be discussed with patients[6].

Powerful Drugs With Hormonal Effects

Antigonadotropins; Danazol

Danazol is a derivative of the synthetic steroid ethisterone, a modified testosterone. It was approved by the U.S. Food and Drug Administration (FDA) as the first drug to specifically treat endometriosis in the early 1970s[61]. It suppresses gonadotropin secretion, prevents luteinizing hormone surge, and inhibits ovarian steroid formation and is approved by the FDA for treatment of mastalgia[6]. While employing danazol in the management of cases with endometriosis, an unexpected voluntary comment patients frequently offered was that breast pain, nodularity and premenstrual engorgement were alleviated. This finding led some workers to the treatment of women with mammary dysplasia with danazol. Danazol subsequently was found, in controlled clinical trials, to considerably relieve breast pain and tenderness in the women treated[79]. In addition, comparative studies were conducted. In one such study, treatment with vitamin E showed 41% response rate with minimal side-effects while treatment with danazol showed 72.1% response rate but was associated with side-effects in one third of the patients[46]. Unfortunately, adverse effects occur with the use of danazol. They are dose related and primarily androgenic, including menstrual irregularity or amenorrhea, acne, hair loss, decrease in voice pitch, weight gain, headache, nausea, rash, anxiety and depression. Attempts at reducing side effects included reducing the dose once a response is achieved and/or luteal-phase administration of danazol (confining treatment to the 2 weeks preceding menstruation). These were shown to relieve premenstrual breast pain in women with PMS without increased adverse effects compared with placebo[80]. However, danazol is contraindicated in women with a history of thromboembolic disease, is potentially teratogenic and can interfere with oral contraception so that women who could become pregnant should use mechanical contraception[33,58,81].

Anti-Progestins

Gestrinone

Gestrinone is a synthetic steroid, reported to have androgenic, antioestrogenic, and antiprogestogenic properties in a way similar to danazol[82]. Gestrinone reduces ovarian hormone secretion, decreases follicular development and suppresses the midcycle surge of follicle-stimulating hormone and luteinizing hormone[83]. Adverse effects are primarily androgenic,

the most common complaints being acne, seborrhea and weight gain. However, I have not come across any recent study of value on its use in the treatment of mastalgia.

Dopamine Agonists

The rationale behind the use of dopamine agonists to treat breast pain is the increase in thyrotropin-induced prolactin secretion detected in women with mastalgia.

1. Bromocriptine

Bromocriptine is a dopamine agonist which was found to significantly decrease breast pain, heaviness, and tenderness[84]. Clinical improvement generally occurs in 47% to 88% of symptomatic women and is often sustained after cessation of the medication[6]. Some researchers advocate using the prolactin response to thyrotropin-releasing hormone (see below) to predict response for bromocriptine[84]. This was proved useful in a study using 2.5 mg b.i.d. of bromocriptine for 3-6 months, 73.6% of the subjects with an abnormal response experienced effective mastalgia treatment compared with 23.5% of subjects with a normal response, the difference was statistically significant[84]. Bromocriptine side effects seem to be less if the drug is taken with meals[85]. However, other side effects are much more serious. Strokes, seizures and death have been reported after the use of bromocriptine to inhibit lactation, and the US FDA has withdrawn its licence for this indication[86].

2. Lisuride

Lisuride is an antiparkinson agent of the iso-ergoline class, chemically related to the dopaminergic ergoline Parkinson's drugs and is used to lower prolactin[61]. In a double-blind randomized prospective study on 60 premenopausal women with premenstrual mastalgia, where the study and control groups consisted of 30 women each. The patients were given one tablet daily (0.2 mg) of lisuride maleate or placebo orally for 2 months. Severity of mastalgia was evaluated using the visual analog scale. Mastalgia subsided significantly in women receiving lisuride maleate compared with controls, and there were no significant side effects. Prolactin levels decreased significantly in the group receiving lisuride, which correlated well with pain resolution[87].

3. Quinagolide

Quinagolide is a selective, Dopamine receptor D_2 agonist that is used for the treatment of elevated levels of prolactin[61]. In a pilot clinical trial on 52 patients, 75 microg Quinagolide given once per day was administered for the treatment of CM. Linear analogue charts were used for the assessment of response. Decrease in breast pain, heaviness, tenderness and serum prolactin level on the one hand, and increases in the serum estradiol and progesterone levels on the other hand were noted after 3 and 6 months administration and were statistically significant. The beneficial effect of Quinagolide also lasted after the cessation of treatment. Adverse effects like nausea, low blood pressure, dizziness and constipation were rarely reported[88].

Selective Estrogen Receptor Modulators (S.E.R.M.)

1. Tamoxifen

Tamoxifen is an antagonist of the estrogen receptor in breast tissue via its active metabolite, hydroxytamoxifen and behaves as an agonist In other tissues such as the endometrium.. Hence tamoxifen may be characterized as a mixed agonist/antagonist[61]; and the use of it in large numbers of premenopausal women in breast cancer prevention trials has increased familiarity with this medication in younger women without breast cancer[89,90]. Tamoxifen 10 mg daily or danazol 200 mg daily should be considered when first-line treatments of mastalgia are ineffective[35]. Tamoxifen was found to be effective in reducing pain in women with CM and also, but to a lesser degree, in women with non-CM[80,91]. R. Grio et al, in a randamised controlled study on 88 women, aged 22–44 years, found that 8 months of tamoxifen increased the proportion of women who achieved complete recovery compared with

placebo (90% with tamoxifen verses 0% with placebo)[92]. Tamoxifen has a risk of potentially serious adverse effects, with the principal concerns being deep venous thrombosis and endometrial cancer. Also, hot flashes, nausea, menstrual irregularity, vaginal dryness or discharge, and weight gain have been associated with tamoxifen treatment[6].

Adverse effects occurred more frequently with tamoxifen 20 mg than with tamoxifen 10 mg between days 15 and 25 of the menstrual cycle[91]. And when comparing tamoxifen dosages and duration for breast pain, the 10 mg/d dosage of tamoxifen was as effective as the 20 mg/d dosage with fewer adverse effects[91]. One outpatient based randomized controlled trial (RCT) on 93 women with severe CM compared three treatments over 6 months: danazol 200 mg daily, tamoxifen 10 mg daily, and placebo. The RCT found that tamoxifen was more effective than danazol, both at the end of treatment and 12 months after treatment. However, 4 women taking tamoxifen withdrew from the study owing to adverse effects of treatment, compared with 3 of those taking danazol. Reported adverse effects included an increase in weight (31% with danazol v 0% with tamoxifen), deepening of the voice (13% with danazol v 0% with tamoxifen), menorrhagia (13% with danazol v 6% with tamoxifen), and muscle cramps (9% with danazol v 0% with tamoxifen), hot flushes (12% with danazol v 25% with tamoxifen), and vaginal discharge (9% with danazol v 16% with tamoxifen; P values not reported)[80]. Nonetheless, tamoxifen, like the other hormonal interventions, should be reserved for women with severe mastalgia refractory to other measures[6,8]. It should be administered under close supervision and for a limited period of time[8]. However, tamoxifen is contraindicated in pregnancy because of potential teratogenicity[93].

2. *Toremifene*

Toremifene citrate is a S.E.R.M. which helps oppose the actions of estrogen in the body[61]. In a double-blind RCT, 104 patients with moderate to severe mastalgia received toremifene citrate, 30 mg daily, and 91 a placebo tablet for 3 menstrual cycles and were followed up for breast pain score and adverse events. All women recorded breast pain daily on a visual analogue scale chart. More women reported a reduction of 50% or more in pain scores with toremifene compared with placebo (69.2% v 31.9% $p < 0.001$). Among the patients with CM, the response rate for toremifen was 76.7% v 34.8% for placebo ($p<.001$). In contrast, the response rate of patients with non-CM was 48.1% for toremifene and 24.0% for placebo ($p= .09$). The RCT found that women in the toremifene group reported adverse effects (menses disturbances, dizziness, vaginal discharge, and nausea), slightly but not significantly higher than the placebo group (50.5% v 42.9% $p = 0.45$). Showing that toremifene effectively relieves moderate and severe CM and tends to exert a positive therapeutic effect on non-CM, without increasing the incidence of intolerable adverse event[94].

Gonadotropin-Releasing Hormone Agonists

A gonadotropin-releasing hormone agonist (GnRH agonist) is a synthetic peptide modeled after the hypothalamic neurohormone GnRH that interacts with the GnRH receptor to elicit the release of the pituitary hormones FSH and LH[61]. As a result, these agents reliably decrease estrogen levels in women. In addition, extremely low levels of progesterone, ovarian androgens, and prolactin result[95]. Although the use of GnRH agonists is promising, few data are currently available to support their clinical use for treatment of mastalgia. They have troublesome and potentially serious adverse effects that must be considered in future studies to define their therapeutic role for breast pain[6]. Adverse effects related to the hypoestrogenic state produced by these medications are frequent and often severe, including hot flashes, headaches, nausea, fatigue, depression, anxiety, irritability, vaginal dryness, and decreased libido. Decline in trabecular bone mineral density is as high as 6% within 6 months of treatment

with the GnRH agonist Buserelin. Although usually reversible, treatment duration is limited by this effect[96].

Other Considerations

The Thyrotropin-Releasing Hormone (TRH) Prolactin (PRL) Response Test (TRH Test)

Using serial measurements of prolactin plasma levels after an intravenous injection of TRH, (TRH test), patients were divided in two groups:

1- Patients with abnormal PRL response to TRH
2- Patients with normal PRL response to TRH

N. Rea et al found that bromocriptine treatment, 2.5 mg b.i.d. for 3-6 months, was effective in 73.6% of patients with abnormal TRH test and in 23.5% of patients with normal TRH test: the difference was statistically significant. On the other hand, 76.9% of patients with either normal TRH test or those resistant to bromocriptine therapy had a favorable response to percutaneous progesterone and systemic NSAIDs. These results seem to confirm the hypothesis that PRL response to TRH could be used to identify patients affected with CM that are likely to benefit by bromocriptine treatment[84].

Sodium Iodide, Protein-Bound Iodide, And Molecular Iodine

L. Patrick claims that although above the established safe upper limit of 1 mg, 3 to 6mg doses of iodine are safe and studies using these relatively high doses of iodine to treat fibrocystic breast disease may reveal an important role for iodine in maintaining normal breast tissue architecture and function. He also suggests that iodine may also have important antioxidant functions in breast tissue and other tissues that concentrate iodine via the sodium iodide symporter[97].

Conclusion

Fibrocystic changes of the breast commonly affect women in their third or forth decades and should not be considered a disease but rather a phase of breast development and involution. Fibrocystic changes are occasionally associated with breast pain. Mastalgia caused by fibrocystic changes has been treated by a vast array of remedies ranging from simple re-assurance and a change in lifestyle, to non-pharmacological and pharmacological agents, the latter may be associated with serious side effects. Some of these remedies are supported by good clinical evidence, while others continue to be used simply because the treating physician feels his/her patients respond to it. The ideal treatment for mastalgia caused by fibrocystic changes remains to be identified by sound recent randomized controlled clinical studies. These studies should be done on the simplest of remedies before being performed on the stronger remedies with considerable side-effects. Hopefully, the results revealed by these studies will open the path towards a systematic approach to the treatment of a common condition which many women suffer (or are deemed to suffer) from. Treatment should start with simple lifestyle changes and advance in a stepwise fashion to abstinence from certain substances to mild remedies and finally to stronger remedies only in those where other means fail. Only then can this condition be conquered with the least adverse effects.

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