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MANAGEMENT OF FIBROCYSTIC BREAST DISEASE: A COMPREHENSIVE REVIEW

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ABSTRACT

Fibrocystic breast disease (FBD) is the most commonly encountered entity among benign breast disorders (BBD) with features like mastalgia and nodularity or lumpiness. The objective of this article is to present a comprehensive review of FBD and mastalgia to highlight the essential points regarding the etiopathology and to give a brief account of the recent advances and evidences regarding the management. A comprehensive literature review was performed searching through the electronic databases as well as the standard textbooks of surgery and gynecology. It is revealed that FBD is histologically characterized by varying degrees of cyst formations, fibrosis, metaplasia and hyperplasia of epithelium, chronic inflammation and calcification which occurs as a result of aberration of normal process of development and involution in breast tissue in females of reproductive age-group under the influence of cyclical hormonal changes. Certain dietary and other factors are also linked with this condition. Certain proliferative histological changes, with or without atypia, may increase the relative risk of development of breast carcinoma. Though diagnosis is usually made on clinical grounds, ultrasonography, mammography, aspiration cytology and tissue biopsy may aid in doubtful cases. Management include both endocrine and non-endocrine treatments but usually starts with reassurance and counselling with advice of proper breast support and certain dietary changes like restricted consumption of saturated fats and caffeine. Evening primrose oil and flaxseed oil are recommended as first line of therapy by some authorities. Treatment with tamoxifen or danazol should be reserved for severe or refractory cases due to their serious side-effects.

Keywords: Fibrocystic breast disease; fibrocystic breast changes; mastalgia; evening primrose oil; tamoxifen; danazol.

1. INTRODUCTION

Benign breast disorders (BBD) constitute a major proportion of reported breast abnormalities, but are usually given less attention and detected incidentally in context of excluding breast carcinoma [1]. A wide range of conditions are included under the umbrella of BBD, many of which are a result of normal changes occurring during the development and involution of breast under the effect of cyclical endocrine changes and hence, are not treated as a disease entity [2]. The ANDI (Aberration of Normal Development and Involution) framework proposed by Hughes differentiates such changes into normal, disordered and diseased state [3]. Repeated stimulation of hormone-sensitive breast tissue during menstrual cycles leads to high prevalence of breast nodulation or lumpiness accompanied with varying degree of pain (mastalgia) and tenderness, especially during premenstrual phase. This clinical condition is usually termed as fibrocystic breast disease (FBD). It is the most commonly encountered entity among all benign breast conditions [2] Mastalgia may however appear separately from FBD but both are usually associated [4]. The ANDI framework describes cyclical mastalgia with nodularity as a disorder while incapacitating mastalgia as a disease among women of late reproductive age-group (25-40 years) while the development of macrocysts (which may also cause mastalgia) is common during involution period (35-55 years) [3]. Mastalgia is therefore an important feature and sometimes the sole cause for seeking the treatment. Multiple theories regarding etiology and management of FBD and mastalgia have been proposed with evidences in favour and against as well. Present article aimed at to present a comprehensive review of FBD and mastalgiato highlight the essential points regarding the etiology and pathology and to give a brief account of the recent advances and evidences regarding the management. A comprehensive literature review was performed searching through the electronic databases as well as the standard textbooks of surgery and

gynecology and the results are described in following sections.

2. EPONYMS AND NOMENCLATURE

FBD is known by more than 35 eponyms like Reclus' disease, Schimmelbusch's disease, Bloodgood's disease, Cooper's disease, cystic mastopathy, mammary dysplasia, mazoplasia, chronic cystic mastitis etc. [4, 5] but none of them was satisfactory to encompass the whole spectrum of clinical and histological features. Therefore, according to the recommendations of College of American Pathologists, the term "fibrocystic breast changes" (FBC) is usually preferred [5]. The tenth revision of International Statistical Classification of Diseases and Related Health Problems (ICD-10) include the condition under benign mammary dysplasia (category N60) and subclassify according to the component like diffuse cystic mastopathy (N60.1; for cystic breast), fibroadenosis (N60.2), fibrosclerosis of breast (N60.3; for cystic mastopathy with epithelial proliferation). Mastodynia is classified under separate category (N64.4) [4, 6].

3. INCIDENCE

FBD is a result of exaggerated response of breast tissue to cyclical hormonal changes and hence, is more commonly found in 3rd to 5th decade of life [1]. Real incidence of FBD is difficult to estimate but clinical and autopsy studies estimate a 50% incidence among the women of child-bearing age [7-9]. However, some authors estimate that approximately 90% of women demonstrate some degree of fibrocystic change during their reproductive age [10].

4. ETIOLOGY

Multiple theories regarding etiology of FBD and mastalgia have been proposed from time to time based on some observed associations with some endocrine and other factors or processes which are briefly described below:

4.1. Disturbances in Pituitary-Ovarian axis & Estrogen-Progesterone Interplay.

Various hormonal theories like progesterone deficiency in luteal phase [11], estrogen excess [12], change in estrogen/progesterone ratio [13], differences in sensitivity and expression of estrogen and progesterone receptors [14-15], alterations in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion [16], androgen deficiency [17] etc. have been implicated as cause of FBD and mastalgia but could not be proved in other studies [18]. Development of breast cysts has also been shown to be due to hyperestrogenism as increased mean levels of serum estradiol have been demonstrated in women with cysts formation in breasts [19] and it has been suggested that the acini remain in dilated state due to excess unopposed estrogen [20]. In general, the imbalance between estrogen and progesterone levels with hyperestrogenism (relative or absolute) and enhanced responsiveness of breast tissue to these hormones in a woman of reproductive age group [21] is considered as the most widely accepted etiology.

4.2. Role of Prolactin

Prolactin (PRL) is responsible for mammary development and milk secretion. The secretion of PRL is episodic and shows circadian rhythm, menstrual and seasonal variations and also increases during stress [18]. High PRL levels have been reported in cases of fibroadenosis and breast cysts [22-23] but no differences compared to controls have been noted in basal PRL levels in cases of cyclical mastalgia [15]. Raised PRL levels have however been demonstrated due to stimulation by thyrotropin releasing hormones (TRH) [24] and in association with increased levels of thyroid stimulating hormone (TSH) [25] in patients of mastalgia and FBD, thus suggesting a possible relation between PRL and hypothalamic or pituitary-thyroid axis respectively. Locally produced PRL has also been implicated as the probable cause of symptoms [15]. In addition, it is suggested that hyperprolactinemia is related to increased level of estrogen in FBD cases [26] and an impaired ability to counteract estrogen-induced PRL release is the cause of mastalgia [27].

4.3. Consumption of Methylxanthines and Nicotine

Methylxanthines are alkaloids found in high concentrations in tea, coffee and chocolate, caffeine being the most common example. Works by Minton and colleagues clarified that caffeine consumption stimulate the release of catecholamines which by activation of adenylate cyclase lead to an increase in cyclic adenosine monophosphate (cAMP) which further leads to cellular proliferation in the breast. They also reported higher levels of β-adrenergic receptors in symptomatic cases compared to asymptomatic. Therefore, a genetic predisposition was suggested in symptomatic patients with stimulatory effects of methylxanthines on β-adrenergic-adenylate cyclase system, thus triggering the

intracellular cAMP-mediated events leading to symptommatic ANDI [28-29]. Moreover, caffeine intake has also shown to increase PRL in animal studies [30].

Similar to methylxanthines, nicotine (*e.g.* in cigarettes), tyramine (*e.g.* in over-ripened fruits) and stress also enhances the catecholamine release, thus increasing the level of circulating catecholamines. Studies have shown higher levels of urinary as well as serum catecholamines (epinephrine and nor-epinephrine) in symptomatic cases of FBD [18, 29].

4.4. Essential Fatty Acids

Studies have evaluated the role of fat-restricted diets in FBD and have found positive effects on increasing the ratio of unsaturated to saturated fats in diet [31]. It is assumed that affected women have low levels of omega-6 essential fatty acids (like GLA), probably due to blockage of delta-6-desaturase enzyme which catalyzes formation of GLA from linoleic acid [32-33]. This delta-6 desaturation step is limited by higher levels of saturated fats, catecholamines, glucocorticoids diabetes and high cholesterol levels, thus producing deficiency of essential fatty acids (EFA). EFA deficiency has been hypothesized to produce a supersensitive state of the membrane receptors in breast tissue and hence cause mastalgia [14, 18, 34]. In addition, GLA metabolites have also been shown to be involved in production of non-inflammatory prostaglandins (*e.g.* PGE1) while suppressing the formation of pro-inflammatory prostaglandins and cytokines [35], thus indicating a causal relationship of GLA deficiency with mastalgia.

4.5. Role of Iodine

Iodine deficiency has also been implicated as a causative factor of FBD. Animal studies have suggested the role of iodine in breast tissue with iodine deficiency resulting in hyper-responsiveness to estradiol [36-37] Ghent *et al.* also found iodine replacement therapy to be beneficial in FBD cases [38].

4.6. Improper Breast Support

Studies have shown that movement of breast tissue is associated with pain and hence, ill-fitting and non-supportive bras have also been reported to be associated with mastalgia [18, 39].

5. PATHOLOGY

FBD primarily affects the terminal duct lobular unit (TDLU), although the epithelial hyperplasia can also extend to larger ducts. The basic histopathological changes include cyst formation, apocrine metaplasia, epithelial hyperplasia, fibrosis, chronic inflammation, calcification (coarse type with calcium phosphate or oxalates) and fibroadenomatoid changes (least common). A great degree of variability is noted in gross and microscopic pathology based on which manifestation of the disease predominates [5].

Cysts may be of two types. Type I cysts are lined by apocrine epithelium with high K^+/ Na^+ ratio and higher pH of cyst fluid while type II cysts are simple, lined by flattened epithelium with low K^+/ Na^+ ratio and lower pH (< 7.4). While the latter is usually single and non-recurrent, former tends to be multiple, recurrent and carries a risk of carcinoma formation. Cyst formation may also vary in size, from microscopic to macroscopic [1, 2, 5, 18, 40, 41].

Epithelial hyperplasia of ductal and lobular epithelium of mild, moderate, florid or atypical type may occur. It is an important notable feature of FBD because of possible relation to carcinoma. While florid hyperplasia carries a 2-fold relative risk, atypical hyperplasia carries a 4-fold relative risk for cancer development. Though, hyperplasia is of mild degree in most cases, it may sometimes be severe enough to result in papillomatous growths [5, 18, 41]. Apart from this, varying degree of fibrosis is usually present, probably occurring secondary to rupture of cysts. Fibrous tissue replaces the fat and elastic tissue with infiltration of interstitium by chronic inflammatory cells (like lymphocytes, plasma cells, foamy histiocytes) [5, 41].

6. CLASSIFICATION

Based on pathological findings, fibrocystic changes may be classified into non-proliferative and proliferative changes. Changes like cyst formations, apocrine metaplasia, fibrosis, intraductal hyperplasia, calcifications and development of fibroadenomas and related lesions are considered as non-proliferative changes as they usually do not carry the risk of development of breast carcinoma. However, with positive family history of breast carcinoma, relative risk is about 1.6 [10, 42].

Proliferative changes, on the other hand, are again subdivided into changes without atypia (like florid ductal hyperplasia, sclerosing adenosis and intraductal papillomatosis) and with atypia (like atypical ductal or lobular hyperplasia). While the former carries a relative risk of two folds, the latter carries a 4-5 fold risk for the development of breast carcinoma [10, 42].

7. CLINICAL FEATURES

Common features of FBD include breast pain or mastalgia and lump, nipple discharge may however be present at occasions. Mastalgiaoccurs in about 50% patients and is of two types, cyclical and non-cyclical, based on its relationship with menstrual cycle [41]. Cyclical mastalgia (CM) is present in around 2/3rd cases and usually seen in third and fourth decade of life. It generally occurs in late luteal phase and is characterized by diffuse breast engorgement, pain, ache, heaviness and tenderness, often in both breasts but one side is usually more involved. Exact site is difficult to localize except in case of a rapid distension of a single cyst but usually starts in upper-outer quadrant [1, 2, 18]. Non-cyclical mastalgia (NCM), on the other hand, is usually less frequent and seen in fourth and fifth decade. It is usually unilateral and located in medial quadrant or peri-areolar region. It tends to be chronic and is often difficult to treat [1, 2, 18, 43].

Other important feature is diffuse nodularity due to multiple but inseparable nodular lesions (feels like surface of multiple peas on palpation) with multiple, mobile lumps (cystic dilatations) which may be compressible. Single, discrete, ballotable, larger cysts may also be noted. Bilateral involvement is common. Fluctuations in size with waxing and waning nature of the breast mass may also be noted [1, 2, 18, 43]. Nipple discharge may also be seen in some cases. A cloudy green or yellow or milky discharge from multiple ducts is usually benign but spontaneous, unilateral, persistent sanguineous discharge from single duct is pathologic and warrants diagnostic exploration. FBD is one of the causes of spontaneous non-milky discharge [1, 44].

8. DIAGNOSIS

Diagnosis of fibrocystic breast disease can usually be made on clinical grounds. Cyclical breast pain, nodularity, lumpiness with fluctuation in size of lumps, multiplicity of lesions and bilateral involvement are the key features to diagnose the disease clinically. However, in doubtful cases, ultrasonography (USG), mammography and fine needle aspiration cytology (FNAC) may aid to confirm the diagnosis. While USG can help in differentiating cystic lesions from a solid mass, the cytomorphology done by FNAC may help in differentiating the proliferative and non-proliferative variety [2]. On mammography, FBD is represented by a dense pattern (DY or dysplastic pattern, described by Wolfe) [45] owing to the connective tissue proliferation (fibrosis). Calcifications (both micro and macro) can be easily seen but epithelial proliferations and nodular changes only appear as darker specks amid white dense areas. However, this dense pattern is of value only in the presence of FBD symptoms as such pattern may also be present in premenopausal women without FBD [46]. In case a lesion appears suspicious on USG/ Mammography/ FNAC, tissue biopsy should be performed [2].

9. MANAGEMENT

By general convention, fibrocystic changes are considered as normal consequences of breast development and involution and hence, education and counseling should be the first line of treatment [47] in addition to the clinical examination and imaging of breast to rule out any major pathology. However, severity of pain, engorgement and lumpiness may result the women to seek a definitive treatment for relief. Various modalities for management of FBD are described below.

9.1. Mechanical Support and Dietary Supplementations and Changes

9.1.1. Breast support

Comfortable supporting brassieres during day and night hours are advised to provide support and reduce tension on supporting ligaments of breast. It alleviates the concomitant edema and inflammatory response of breast parenchyma [2]. Well-fitted sports bra has been studied to show good relief in pain by providing support [39, 47]. Day and night breast support has even shown better relief in symptoms (85% v/s 58%) than danazol in a randomized trial [48].

9.1.2. Fat-restricted Diet

Dietary fat restrictions has shown significant improvement in cyclic breast pain, tenderness and swelling [31, 49] but not in non-cyclic pain [49]. Studies show change in cholesterol levels in late luteal phase in CM cases suggesting associated cyclic aberrations in lipid metabolism [49]. However, strict dietary restriction is difficult to achieve and a high degree of compliance by patient is required.

9.1.3. Evening Primrose Oil (EPO) and Gamma-Linolenic Acid (GLA)

Owing to its rich content of omega-6 essential fatty acid, GLA, evening primrose oil has been an important treatment for FBD [33]. Early studies on EPO found a good response rate in patients with mastalgia and

nodularity and went on to recommend it as the first line therapy [50]. However, later studies [51-52] and meta-analysis [53] of trials found no significant difference between EPO and placebo. Therefore, EPO lacks in having adequate recommendations [47, 54] but is still considered for treatment of FBD due to its good response and safety profile compared with other common options.

9.1.4. Flaxseed oil

Flaxseed oil, a source of alpha-linolenic acid, has also been shown to reduce breast pain in randomized placebo-controlled trials [55-56]. Though not many studies have been carried out to establish its efficacy, some authorities have recommended it as the first-line therapy [47].

9.1.5. Restriction of Methylxanthines in Diet

Many studies have reported disappearance of symptoms (nodularity, pain, tenderness etc.) after reducing or eliminating methylxanthines from the diet of cases studied [28-29, 57-59]. However, other studies had demonstrated either no association between methylxanthine consumptions and symptoms of FBD [60] or no relief in symptoms on caffeine restriction when compared to a control or placebo group [61]. Despite of such conflicting evidence, caffeine (methylxanthine) restriction may be a considerable approach in view of its zero cost and other potential adverse effects of caffeine [18].

9.1.6. Use of Vitamins

Certain vitamins have been studied and suggested as being potentially beneficial in improving symptoms of FBD and mastalgia like Vitamin E [62] (being anti-oxidant or altering levels of androgens) [54] and B6 [63] (by inhibiting prolactin release by stimulating dopamine) [54]. However, other studies have failed to claim the benefits [64-65]. Similarly, vitamin A in high doses has also been studied with beneficial effects but serious side-effects have been noted [66]. Controlled trials have failed to demonstrate a role for vitamins in the treatment of breast pain.

9.1.7. Iodine Supplementation

Works by Ghent *et al*. [38] demonstrated the beneficial role of iodine supplementation in mastalgia. Kessler also showed a significant relief in mastalgia in a randomized multicenter trial with a novel formulation which generated molecular iodine [67] but substantial evidence is still needed to approve the therapy.

9.2. Hormones and Hormone-Modulating Therapy

9.2.1. Oral contraceptive pills (OCPs)

Earlier, some studies revealed that patients on an OCP regimen remained protected from development of FBD and related symptoms and the success rates of 70%-90% have been reported with OCPs [46]. Due to sensitivity of breast tissue to estrogen contents, modified pills with low estrogen and high progestin have also been tried with 88% success rate [46]. But, in a large case-control study, no significant beneficial effect of OCPs on FBD has been found [68]. Moreover, recurrence on discontinuance of treatment and serious adverse-effect profile of OCP regime render it undesirable for use in FBD.

9.2.2. Danazol

Danazol, a derivative of 17α-ethinyl testosterone (ethisterone), is an inhibitor of estrogen and progesterone receptors and ovarian hormones' genesis [18]. It is approved by U.S. Food and Drug Administration (FDA) for treatment of mastalgia [4]. Studies have reported beneficial effects in alleviating FBD symptoms with dosage of 200 and 400 mg/day; response being early with higher dosage but with more side effects and relapse being quicker with lower dosage [50, 69]. Reported side-effects include menstrual irregularities, amenorrhea, weight gain, acne, hot flashes, hirsutism, voice change, fluid retention, depression, headaches etc [18]. Because of side effects, low-dose regimen with gradual tapering were developed and tried but with 55% success only [70]. However, recommendations for danazol administration permit 100 mg twice daily for 2 months which may be increased to 200mg twice daily in case of no response with 100mg but should be discontinued if it still does not respond [71].

9.2.3. Gestrinone

It is a synthetic androgen derivative of nor-testosterone with action and side effects like danazol. In a randomized, multicenter, placebo-controlled trial on 105 patients, gestrinone produced improvement in 55% patients but complete resolution in 22% cases only [72].

9.2.4. Luteinizing Hormone–Releasing Hormone (LHRH) Agonist

LHRH agonists (*e.g.* goserelin) have anti-gonadotrophic action and inhibit ovarian hormones' genesis [18]. Though clinical efficacy has been demonstrated with intramuscular depot injections [73], serious side effects

like myasthenia, depression, vaginal dryness, decreased breast size, visual disorders, loss of trabecular bone etc. [18, 74] defer its preferability.

9.2.5. Progesterone

Based on the theory of luteal phase progesterone deficiency and case-control surveys demonstrating lower prevalence and severity of mastalgia in women receiving progesterone for contraception [75], progesterone (in form of 20 mg of medroxyprogesterone acetate during the luteal phase) has been tried but failed to show benefits in a randomized controlled trial [76].

9.2.6. Tamoxifen and Toremifene

These belong to the 'selective estrogen receptor modulator' (SERM) class of drugs. Tamoxifen has shown good efficacy in cyclical mastalgia (in 90% cases) in controlled trials with fewer side effects with 10 mg daily dosage [4, 77, 78]. In a randomized controlled trial, tamoxifen (10 mg daily) was found superior to danazol (200 mg daily) and placebo [79]. Major side effects include hot flashes, vaginal discharge, menstrual irregularities, weight gain etc. with more serious effects like deep vein thrombosis and endometrial cancer [4, 18]; owing to which, the drug should not be used as a first line therapy. However, a recent study showing improvement in FBD symptoms with the use of a topical gel of afimoxifene (a tamoxifen metabolite) with very low serum levels of the drug, no change in plasma hormone levels and no serious side effects [80] has opened a new frontier for its use.

Toremifene (30 mg daily) also exhibited better response rates for CM and NCM(76.7% and 48.1% respectively) compared with placebo (34.8% and 24%) and with less serious side effects [81] but reports of toremifene causing cardiac arrhythmias warrants caution [18].

9.3. Dopamine Agonists

Dopamine agonists like bromocriptine, lisuride, quinagolide and cobergoline act by lowering serum prolactin levels. Bromocriptine, which acts on hypothalamic-pituitary axis and suppress PRL secretion, has shown significant improvement in symptoms like pain, tenderness and heaviness in various studies [82-83] but serious side-effects like seizures, stroke and even death have resulted in its removal from recommended list of treatment [4, 18, 71]. Lisuride [84] (an anti-parkinson agent), quinagolide [85] (a dopamine receptor agonist) and cabergoline [86] (dopaminergic agent) have also reported significant improvement in symptoms with no significant adverse effects but further trials are needed.

9.4. Surgery

Surgical intervention should be the last option for patients with fibrocystic changes and should be offered only after significant counseling. It may be advised if a prominent nodule in the breast remains even after long days of treatment or if a large cyst continues to recur even after multiple aspirations. Ruling out the doubt of carcinomatous pathology should be in mind [18].

9.5. Psychiatric Approaches

Studies have suggested that patients with mastalgia show signs of psychological upsets, mood disturbances, anxiety and depression, the degree of which may be severe in some cases [87-88]. Hence, it has been suggested to include a psychiatric intervention for patients in whom standard pharmacological interventions fail to provide relief [89]. A study has even shown beneficial effects of listening to relaxation audio tapes in patients of cyclical mastalgia [90].

10. CONCLUSION

Fibrocystic breast changes and mastalgia are a result of aberration of normal cyclical changes but they may be severe enough in many women to demand a definitive treatment. Reassurance, counseling and advice to wear a properly supporting bra should be the first prescription. Though not enough recommendations are there but changes in diet pattern (low saturated fats) and abstinence from certain substances (caffeine, nicotine) can be advised and pharmacological interventions should begin with therapies like EPO which are safer than the hormonal or hormone-modulating drugs. Only in severe or refractory cases, treatment with tamoxifen or danazol may be tried but with proper caution and a beforehand explanation to patient about the possible side-effects.

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