

## **Modern concept of Benign Breast Disorders and its Endocrinological Background**

*Sandeep Kumar*

Consultant Surgeon, Scientist & Epidemiologist  
Professor of Surgery Ex, King George's Medical University  
Founder Director AIIMS Bhopal  
HIG 111, Sector E, Aliganj, Lucknow.

### **ABSTRACT**

Mastalgia and generalised breast nodularity where a discrete lump cannot be felt called **Aberration of Normal Development and Involution** (ANDI) is the most common condition leading to breast related consultations. The author's work on this clinical syndrome over the last 3 decades has led to documentation of its natural history, epidemiological study of ANDI, development of objective scales for clinical assessment of breast pain and nodularity, its endocrinological aetiopathogenesis, response prediction of treatment in cyclical mastalgia, a randomized controlled trial of an indigenous selective estrogen response modulator – ormeloxifene and finally a meta-analysis of treatment for this condition. This turned a full wheel bridging gaps in the knowledge of this disorder and led us to evolve an effective, inexpensive treatment of mastalgia with least side effect. The work is dedicated to Professors LE Hughes, Robert E Mansel and Anurag Srivastava.

---

*Correspondence :* Dr. Sandeep Kumar, Consultant Surgeon, Scientist & Epidemiologist, Professor of Surgery Ex, King George's Medical University, Founder Director AIIMS Bhopal. HIG 111, Sector E, Aliganj, Lucknow 226 024. Phone : +91 522 232 8899, Mobile : +91 93352 40880, E.mail : profsandeepsurgeon@gmail.com.

COL. SANGHAM LAL MEMORIAL ORATION delivered during NAMSCON 2015 at the All-India Institute of Medical Sciences, Patna.

## INTRODUCTION

Nine out of ten breast related consultation consists of benign breast disorders that present as pain, inflammation, nipple areola problems, discrete lump and nodularity are common. The epidemiology of benign breast disease was not much studied. With social, economical, educational and information evolution increasing number of women solicit medical opinion for simple pain and nodularity in breasts. There is a considerable morbidity amongst women in India on account of breast pain and nodularity. It is indeed a normal finding and a physiological aberration of normal development and involution. This fact is still not very well understood by the general practitioners, gynaecologists and surgeons involved in the care of breast disease. Unnecessary biopsies and cancer phobia is commonly generated on account of simple benign breast nodularity.

Breasts are composed of epithelial system of ducts and lobulo-alveolar secretary units embedded in adipose tissue with interspersed fibrous septae derived from mesenchymal tissue. Morpho-genesis of these tissues occurs with hormonal changes, genetic constitution and mutation that respond to the circulating hormones and milieu interior. Paracrine effects of locally derived factors affecting the epithelium and stromal relationship form the major basis of benign breast disorders mainly breast pain and nodularity. Histopathogenesis of painful nodularity of breasts was erroneously described (1-3).

The natural history in a large cohort of such subjects was described by the author (4). Two populations emerged; cyclical pronounced mastalgia (CPM) and non-cyclical mastalgia (NCM). The cyclical pain generally related to a hormonal event, started early in life and usually abated at menopause spontaneously. This condition was described as **ANDI or Aberration of Normal Development and Involution**. It has no histological basis except for hormonally mediated change characterized by lumpiness of the breast and varying degrees of pain and tenderness. Retrospective epidemiological studies from the hospital data showed that fibroadenoma was the commonest benign breast lesion to be operated (5). The prevalence of nodular breast in the community (10%) and hospital based population (20%) was first described by the author using a validated 5-point objective assessment of breast nodularity scale (6). The assessment of mastalgia requires a careful structured history and physical examination and assessment of at least 2 months filling of pain charts to determine whether it is cyclical pronounced mastalgia (CPM) or non-cyclical mastalgia (NCM). In a quarter of patients it may be difficult to clearly distinguish between the two patterns and empirical management could be adopted.

### Cyclical Pronounced Mastalgia (CPM):

The commonest pattern seen in about two third of the patients is cyclical pronounced pattern because of its

temporal relationship with menstrual cycle. It is almost always premenstrual with a duration varying from 1 – 4 weeks. Many women experience 2 – 3 days premenstrual breast tenderness or heaviness and this should be regarded as normal. CPM almost invariably has nodularity of a varying degree associated with it. This nodularity is maximal in the upper outer quadrant and shows cyclical changes. Fine nodularity that begins a short time before menstruation and regresses postmenstrually should be regarded as normal. The symptoms are maximally seen in the 3<sup>rd</sup> and 4<sup>th</sup> decades of life. However, cyclical breast pain is also encountered in young girls, women who have had hysterectomies and in peri menopausal women. CPM is regarded significant clinically if its intensity is 'pronounced'. The pronounced cyclical mastalgia is defined either by duration of greater than one week per cycle or by severity using a pain chart. Severity of pain is indeed, like all assessment of pain in clinical practice, a subjective assessment. Obstructive features in life style, such as sleep loss, work disturbance, breast tenderness or interrupted sexual activities are additional pointers towards the diagnosis of pronounced cyclical mastalgia. Other characteristics of CPM are bilateral pain associated with nodularity, heaviness and tenderness to touch. The pain often radiates to axilla and down the medial aspect of the upper arm. Clinical examination reveals varying grades of tenderness and nodularity especially in the upper quadrant. Nodularity has to be differentiated from a discrete lump felt with the flat of the hand.

Occasionally there may be small mobile nodes in the axillae. Examination in the premenstrual period often reveals greater degree of tenderness and nodularity when compared to the examination in the post menstrual period of the same patient. A discrete lump can be associated with pronounced cyclical mastalgia and qualifies for independent assessment. However, specific attention should be given to thyroid examination, gynaecological examination and other endocrinological manifestation because of some quasi association of CPM in such conditions.

Careful history, physical examination and pain charts are usually enough in the work up of mastalgia patients. Detailed endocrinological investigation is warranted only in a research setting or in the presence of overt endocrinological features. Mammography has proven unhelpful in the assessment of CPM as the non-specific changes ascribed to fibroadenosis have so far been the main feature. No specific radiological appearance correlates with the site or side of pain. Mammography is often ordered by the physician to relieve anxiety and forge reassurance. Such use of mammography is unwarranted and can lead to unnecessary demand on the services and un-indicated mammography in women below 35 years of age who frequent for such a problem. Selective screening of patients with symptomatic breast has no scientific basis as mastalgia is not a known risk factor for breast cancer and use of mammography in this situation is not cost effective. The role of FNAC in

the assessment of CPM patients is limited only to associated discrete lumps.

### **Non-Cyclical Mastalgia (NCM) :**

A third of the patients with breast pain on detailed assessment of their clinical features and pain chart are distinguished principally by its lack of relationship with the menstrual cycle. This non-cyclical pain pattern is observed in both pre- and postmenopausal women. The NCM pattern differs in several other aspects from the cyclical. The pain tends to be well localised in the breast and is more frequently sub areolar or inner quadrant in location. A finger-pointing test may be present. Simultaneous and similar bilateral pain is uncommon and descriptive terms of burning, drawing or abscess like are used by the subject. Transient sharp, pricking or stabbing pain may be experienced by some subjects suffering from NCM. When assessed on the linear analogue scale, the non-cyclical pattern is scored by the patient at a lower intensity than the cyclical pattern. Physical examination may reveal discrete areas of tenderness within the breast that may demonstrate, 'trigger spot pain', implying continued complaint of pain after palpation of those areas. Nodularity is less prominent than in the cyclical group and there may be no palpable abnormality at the site of pain. The pain is reported maximally in the fourth decade of life. A minority of these patients may actually be having cyclical mastalgia and represent the overlap that can occur despite the evaluation of pain charts. The natural history study undertaken by the author

revealed that if untreated, non-cyclical mastalgia showed spontaneous remission in half the patients unrelated to hormonal events in the body. There were two groups, the first in which the pain lasted for few years and the other in which it continued for over twenty years. Endocrinological investigations are unhelpful and unnecessary. Mammography has been of some interest in this group of patients. Radiological changes of coarse calcification and ductal dilatation attributed to ductal ectasia or periductal mastitis have been commonly seen in this group. The role of FNAC is limited. A variety of distinct histological features may be associated with NCM. These include duct ectasia, or periductal mastitis, sclerosing adenosis, trauma, post biopsy, and miscellaneous breast lesions. A minority of patients with carcinoma breast may present with NCM. However, in approximately half the patients with NCM there may be no underlying histological change demonstrable.

### **Aetiology of Benign Breast Disorder :**

As for aetiology of mastalgia and nodularity, in the past, benign breast disease for most doctors it has been regarded as synonymous with "fibroadenosis" or "fibrocystic disease". These terms were used for the syndrome of premenstrual pain and nodularity. This concept arose from the unfortunate fact that early workers described histological changes of fibrosis, adenosis, cyst formation and apocrine metaplasia and assumed a causative association(1). Subsequently it was well established that

these histological changes were normal features of the breast microanatomy and ubiquitous in nature. As such there are no histopathological changes ascribable to breast pain and nodularity described so far. After extensive studies and review of literature, the major concern towards the risk of subsequent cancer or the premalignant potential of fibrocystic disease was set aside (2). This led the authors to put forward the concept that fibrocystic disease was a non-disease i.e. it did not exist. Long term follow up of specific benign lesions on histology for their subsequent cancer risk were clearly described and showed no association with mastalgia (3). This concept is attractive in denying the supposed histological basis for the clinical condition of mastalgia. However, the problem of providing satisfaction to many women who suffer a variety of clinical symptoms of distressing severity remains. The morbidity both physical and psychological on account of nodularity and breast pain needs to be addressed. The present consensus is to regard mastalgia as a purely clinical symptom complex, which should be included as a part of a broad based nomenclature suggested by Hughes *et al* (1989) (3), "ANDI or Aberration of Normal Development and Involution". It is based on the fact that most benign breast disorders are relatively minor aberrations of normal process of development, cyclical hormonal response and involution that interact throughout a woman's life. The term "aberration" has been included because it also encompasses a spectrum from minor to marked changes. It covers the common,

major benign processes of the breast like pain and nodularity, duct ectasia or epithelial hyperplasias. The concept of ANDI can be extended to cover a full spectrum of severity - from normal variations to disease. It is simple and consistent with the current knowledge of aetiopathogenesis.

In the past decade systematic investigations have been undertaken to understand the aetiological basis of mastalgia. Astley Cooper started the trend of describing the mastalgia patient as being of nervous disposition. However, case control studies undertaken using validated psychoneurotic score questionnaire did not confirm this view and treatment trials with anti anxiety drugs were unsuccessful. Secondly, water retention or oedema as aetiological basis of mastalgia when investigated scientifically was not confirmed. There is no report in the literature suggesting that general oedema was associated with mastalgia. Therefore, there is no rational basis of treatment of mastalgia with diuretics. The beneficial effect seen in general practice from diuretic treatment is due to placebo effect. Thirdly and perhaps most appropriately earlier workers who did not have detailed knowledge of hormonal profiles have suggested a hormonal basis for mastalgia. The advent of accurate radioimmuno-assays for estimating the blood hormones resulted in a large number of studies that tried to look into the issue. Three main theories have thus emerged regarding the aetiology of painful nodular breasts:

1. Increased oestrogen secretion from the ovary.
2. Deficient progesterone production (or 'relative hyper-oestrogenism')
3. Hyper-prolactinaemia.

Several studies have been performed on the above three theories. The results for CPM are difficult to interpret because of the too often mixing of the pathological and clinical terms. The balance of evidence, however, suggests that the first two theories are unimportant as the steroids levels were no different in clinically well-defined patients and controls. The case of luteal defect although strongly supported by a French group was not seen in other studies. Random levels of prolactin showed no significant difference between patients with benign breast disorders and controls. A major problem here is that prolactin secretion in normal women is pulsatile and has diurnal variation. Therefore, random sampling of basal prolactin is inappropriate. Careful studies of daily sampling at a fixed time throughout the menstrual cycle reveal a small but statistically significant difference between women with breast disease and controls. Prolactin is secreted by the anterior pituitary and is tonically inhibited by dopamine secretion by the hypothalamus. However, prolactin secretion by the pituitary can be stimulated by the use of thyrotropin releasing hormone and dopamine antagonist agents like Metoclopramide and Domperidone.

Several other aetiological theories have been proposed. The over stimulation of breast cells due to interference with ATP degradation by methylxanthine has some biochemical evidence to support it. Excessive coffee intake, which is a rich source of methylxanthine, has been incriminated by one group in North America. Caffeine intake in Indian women with mastalgia is much lower and may not be relevant in India. Another hypothesis proposes an abnormality of prostaglandin synthesis due to deficient intake of essential fatty acids (EFA) in diet. The result of EFA deficiency, however, may be a representation of the amplification of prolactin effect on breast cells because of deficient production of prostaglandin E1.

#### **Author's Contributions :**

##### ***1. Natural History of Mastalgia :***

In order to document the natural history of mastalgia (4) in untreated subjects 258 patients with breast pain were re-studied 2 to 7 years after initial assessment in a special mastalgia clinic. Pain persisted at follow up in 65% of patients. Mastalgia was cyclical in 2/3<sup>rd</sup> mean duration of pain in patient experiencing complete relief before follow up examination was 6.8 years, while duration of pain persisting at follow up ranged from 2 to 30 years. In patients who had relief or substantial improvement in pain, the improvement was spontaneous in 22% and resulted from a hormonally related – menopause, pregnancy, or use of oral contraceptives –

in the remainder. Onset of cyclical pain before the age of 20 years was followed by a prolonged course. A quarter of the patient had non-cyclical pain. There were 2 population of patient in this group. One experienced relief after a mean of 3 years, and in the other pain still persisted after 2-20 years. Relief was spontaneous in one half, and rarely followed a hormonally related event. About 70% of the patients, with both cyclical and non-cyclical pain, considered that there pain had warranted active treatment. This study indicates that the type of pain and age at onset may allow some prediction of the course of the disease and may aid the choice of therapy.

## ***2. The Epidemiology (5) of Benign Breast Disorders (BBD):***

BBD was studied by the author both in the hospital and community. Experience with BBD has been analysed in 3 non-western populations: Hong Kong, India and Northern Nigeria. Similarities to and differences from Western experience are found, but of great interest are notable differences between these populations which, as yet, lack explanation. All show 'fibroadenosis' and fibroadenoma as common conditions, but the frequency with which phyllodes tumor is diagnosed varies between centers in India as well as between different racial groups. Tuberculosis is another interesting example – wide differences in the frequency in all 3 countries. The value of prospective studies was shown when mastalgia was studied in this way in India. Often considered a 'Western' affliction, we were able to study 112 cases of mastalgia

and found it to be at least twice as common as cancer as a presentation in hospital based practice in 1970s and 1980s. These differing experiences between populations have yet not been explored and must hold promise for unraveling some of the enigmas of benign breast disorders in all countries (5). Furthermore, in 2010 the author studied 784 Women (hospital 384; community 400) aged between 20 and 70 years (mean 31.9) who underwent physical breast examination by 2 experienced clinicians. Inter-observer matched nodularity grading in women attending hospital were Grade 0 in 123 (32.03%), grade 1 in 67 (17.44%), grade 2 in 54 (14.06%), grade 3 in 52 (13.54%) and grade 4 in 23 (5.99%) and in community it was grade 0 in 172 (43%), grade 1 in 88 (22%), grade 2 in 60 (15%), grade 3 in 28 (7%) and grade 4 in 14 (3.5%) women. There was very good agreement ( $\kappa \approx 0.7798$ ) across all grades in hospital subjects and excellent agreement ( $\kappa \approx 0.8659$ ) in community subjects. Both estimates of kappa coefficients were highly significant from population kappa coefficient of zero ( $p < 0.001$ ). Overall, 1/3<sup>rd</sup> normal women have absolutely smooth textured breasts (6).

## ***3. Lucknow Cardiff Breast Nodularity Scale:***

In the above study a **scale for clinical assessment of nodularity** (6) was also developed for the first time and published. Objective measurement of benign non-discrete lumpy breasts is not performed routinely that would lead to

disease measurement, inter-physician communication, therapeutic response assessment and a normative function of reducing unnecessary biopsies. A schematic 5-point ordinal visual analogue scale was conceptualised. Two blinded experienced clinicians graded breast nodularity on a pre-determined five point analogue scale (grades 0–4) to determine its inter-observer reliability after its face validity that excluded inflammatory, nipple, areola and discrete lump problems. User-friendly tool developed for objective evaluation of non-discrete lumpy breasts showed excellent reliability and validity. This tool should be useful for clinical drug trials in benign breast disorders and for wide routine clinical recording of patients.

#### ***4. Endocrinological Background and Aetiology of Benign Breast Disorders :***

It was generally known that there was no overt alteration in the circulating levels of various peptide and steroid hormones of adrenal and gonadal origin in benign breast disorders. The pituitary control of prolactin secretion by TRH stimulation and domperidone disinhibition in well-defined CPM patients and controls were examined. Several blood samples were collected at regular intervals from these subjects and careful radioimmunoassays for prolactin were carried out. These studies have shown that basal prolactin levels were not significantly different between the groups but stimulated prolactin response and peak prolactin release was significantly greater in CPM as opposed to NCM patients and controls. Similar results have

been reported by an earlier worker from Germany. These data strongly suggest that a functional or a subtle 'fine tuning' defect may be the primary problem in painful nodular breast disease. Interestingly, a similar defect has been demonstrated in the cyclical oedema syndrome that has many similarities to cyclical mastalgia although they are distinct conditions. The excitability of prolactin secretion provides the basis of successful treatment of cyclical mastalgia using the dopamine agonistic agent - Bromocriptine. The effectiveness of this drug has been shown in several controlled clinical trials (7).

Paraffin wax embedded formalin-fixed BBD tissue taken from 17 patients (15 with microcystic disease and 2 with fibroadenoma) was studied for the presence of tissue bound prolactin using a rabbit antiserum against human prolactin applied in conjunction with a highly sensitive modified version of the dinitrophenyl (DNP)-hapten sandwich staining (DHSS) procedure. Sections taken from 14 of 15 cases showing apocrine cystic changes exhibited strong prolactin staining restricted to the cytoplasm of metaplastic apocrine cells lining the cyst. Normal lobules and ducts and blunt duct proliferations were all negative, as were also the 2 cases of fibroadenoma. In contrast 6 out of 8 cases of breast cancer examined showed heterogeneously distributed cytoplasmic staining in the cancer cells. Maximal prolactin staining in the apocrine cells was observed at antiserum dilutions as high as 1:60,000. This compared favourably with

a 1:120,000 dilution that gave maximal levels of staining in the prolactotrophs present in serial sections taken from formalin fixed paraffin wax embedded post mortem human anterior pituitaries. In both types of tissues the specific staining was abolished by pre-absorption of the antiserum with human prolactin (10 micro gram ml<sup>-1</sup>). No staining was observed when the anti-prolactin serum was either omitted or substituted with DNP-labelled normal rabbit serum. Apocrine metaplasia in cystic disease of the breast has been found to be associated with an increased breast cancer risk. The strong and selective presence of immunohistochemically demonstrable prolactin in the metaplastic cells may be of significance in view of the hormone's known growth stimulating effect on the breast epithelium (8).

*Hypothalamic pituitary axis tests and prolactin (9-11) :*

Pituitary function was tested in predefined clinical groups of benign breast disease under strictly controlled clinical and laboratory conditions. Two different tests of prolactin storage and control mechanisms, direct stimulation by thyrotropin-releasing hormone (TRH) and inhibition of dopaminergic control by domperidone, indicate a significantly abnormality in patients with severe cyclical mastalgia and nodular breast disease ( $P<0.05$  and  $P<0.002$ ), but not in those with noncyclical mastalgia. No abnormalities of thyroid function were found (9). Furthermore, a generalized abnormality of hypothalamopituitary

function was found in 17 patients with cyclical pronounced mastalgia compared with 11 controls by using a combined thyrotrophin releasing hormone and gonadotrophin releasing hormone test. The release of prolactin, luteinizing hormone and follicle stimulating hormone was significantly greater in cyclical mastalgia patients than in controls. Basal thyrotrophin, T3 and T4 levels were within the normal range in both groups indicating normal thyroid status in benign breast disease. The single measurement of oestrogen and progesterone in the luteal phase was not abnormal. These data demonstrate an alteration in lactotroph and gonadotroph function in patients with cyclical mastalgia. It is unknown at present whether this represents an appropriate cellular response to altered central or peripheral signals. There is no evidence to suggest, however, that the anterior pituitary cell types are abnormal per se (10, 11).

*Corpus luteal function test—daily salivary progesterone (12) :*

Progesterone levels were measured in samples of saliva collected daily throughout the menstrual cycle in patients with pronounced cyclical mastalgia and breast nodularity. A control group matched for age, length of menstrual cycle and parity was also studied. No significant differences in progesterone levels were detected between the two groups for the luteal phase of cycle. These data indicate that cyclical mastalgia is not associated with significant luteal phase progesterone

insufficiency, as demonstrated by salivary levels and, by implication, serum levels of progesterone.

### **5. Prediction of Response to Endocrine Therapy in Mastalgia (13) :**

Many of the endocrine agents currently used to treat symptomatic BBD modify the action or secretion of prolactin. We have compared the responses to hormonal therapy with dynamic assessment of prolactin control in 29 patients with CM and 9 patients with NCM. The tests of prolactin release used were direct stimulation with TRH or dopaminergic blockade by domperidone carried out before treatment in mastalgia patients and 22 age-matched asymptomatic controls. The response to treatment was assessed using a special pain chart and visual linear analogue scale. Patients with cyclical mastalgia could be divided into two groups: those in whom the peak prolactin release was exaggerated (mU/l) and those in whom the prolactin release was less marked and similar to control subjects and patients with non-cyclical mastalgia. Patients in the cyclical mastalgia group with a high peak prolactin release responded to hormonal treatment significantly more frequently (90%) than those with a normal prolactin release (50%). Basal prolactin levels did not correlate with the response to treatment. In the non-cyclical mastalgia group, no patient had peak prolactin release was exaggerated (greater than 4000 mU/l) and none responded to therapy. This study indicates that dynamic tests of prolactin release in cyclical

mastalgia may be useful in predicting the subsequent satisfactory response to endocrine therapy if a high peak prolactin release is induced.

### **6. Benign Breast Tissue Characterization :**

#### *Prolactin receptors :*

In another study (14) an immunocytochemical method involving the application of polyvlonal antisera to human prolactin (PRL) followed by a highly sensitive and a modified version of dinitrophenyl (DNP) hapten sandwich staining procedure using anti-DNP IgM monoclonal antibody has been used to detect PRL binding in benign and malignant breast tissue. The technique was applied to 5 microns thick sections of paraffin embedded formalin fixed tissue. Out of 107 breast biopsies 40 were carcinomas, 41 were fibroadenomas, 18 were benign cystic disease and 8 were gynaecomastia. In cases of carcinoma positive staining was observed in 82.5% whereas in fibroadenoma the positivity was in 57% cases only. The positive reaction in fibroadenoma was mainly due to the presence of apocrine metaplasia associated with the tumor. Also PRL was present in greater proportion in postmenopausal patients as compared to premenopausal cancer patients. These findings suggest the presence of specific PRL binding sites in breast tissue. The staining was restricted to epithelial cells and background staining of the stroma was minimally seen in these cases. Positively stained breast carcinoma may

represent an apocrine subset of the carcinoma.

*Human Sodium Iodide Symporter (hNIS) (15) :*

Human sodium iodide symporter (hNIS), responsible for the active transport of iodine is an integral plasma membrane glycoprotein present in the thyroid cells and extrathyroid tissues like breast and salivary glands. If its functional form is unequivocally shown in benign or malignant breast tissues, then it may serve as a basis for diagnosis and treatment using radioactive iodine. With an aim to analyze the hNIS expression in a distinct benign breast condition of fibroadenoma, biopsy proven fibroadenoma tissues, normal non-lactating breast tissue and biopsy proven infiltrating duct carcinoma tissues were examined for hNIS expression using immunohistochemistry. Out of 20 biopsy proven fibroadenoma tissues, 19 (95%) showed positivity for hNIS protein and only one was negative. Of these 10% were mildly positive, 50% cases were moderately positive and (35%) showed intense positivity. None of the control tissue obtained from reduction mammoplasty specimens or normal breast tissues samples (5 cms away from the tumor) were positive. hNIS was also intensely positive in 9 out of 10 (90%) infiltrating duct carcinoma tissues and moderately positive in one case. These preliminary results show that hNIS was present in high frequency as demonstrated by immunohistochemistry in fibroadenoma breast.

**7. Treatment of Painful Benign Breast Nodularity and Meta-analysis :**

Pain breast nodularity is treated by a large number of agents. These include hormonal manipulation by Danazol, Bromocriptine, Tamoxifen and LH-RH analogue ZOLADEX. Non hormonal agents effective in mastalgia are Nonsteroidal anti-inflammatory gels, iodides, plant derivatives like evening primrose oil (EPO) and Vitus Agnus Castus and reflex therapy. There was a considerable debate about the choice of best agents for initial management of mastalgia. No meta-analysis was described to evaluate the most effective agent. A meta-analysis on published randomized trials of common agents used in the therapy was attempted (16).

Articles on randomized trials on treatment of mastalgia were searched using the electronic databases viz. Medline, Google Embase, textbooks of benign breast diseases and surgery. The search was performed using key words: mastalgia, mastodynia, breast pain, benign breast disease, therapy & treatment and was confined to articles published in the English language. The search was also restricted to randomised clinical trials where an active drug was compared with placebo or another drug along with the placebo. Trials without randomisation or without a placebo arm were excluded. This meta-analysis was done for 4 agents that are commonly used. The outcome of interest was reported as the mean pain score with the active drug and with placebo in some

studies while other studies have described the number of cases achieving clinical response (usually greater than 50% reduction in the mean pain score measured on a visual analogue scale or Cardiff breast pain scale). Hence the pooled estimates of standardised difference of mean pain score between active drug and placebo has been calculated. The point estimates and 95% confidence limits have been computed for Fixed effect models. The pooled risk ratio (RR) has been computed for studies reporting outcome as dichotomous data on a 2x2 table. The Meta-analysis has been performed on "REVMAN" Meta-analysis statistical package from Cochrane Collaboration.

The results showed heterogeneity for the trials on Bromocriptine, the Chisquare test of heterogeneity yielded a  $p=0.26$  indicating that the results of the 3 trials were not heterogeneous. For trials on Tamoxifen the test demonstrated no heterogeneity ;  $p=0.47$ . For trials on EPO the heterogeneity test yielded a  $p=0.53$ . Thus a fixed effect model was applied to all these trials. A summary recommendation from this meta analysis emerged as patients with pronounced cyclical mastalgia can be benefited by a number of agents. Danazol, Bromocriptine, Tamoxifen are all effective in ameliorating the breast pain. Since very few studies have compared more than one agent in a RCT, the best choice of drug is difficult to make from a statistical point of view. Both Danazol and Bromocriptine produce significant side effects, some of which are highly undesirable in young women (weight

gain, hair growth, menstrual irregularities, gastrointestinal upset, nausea and vomiting) hence their use is currently declining. Since the relative risk of pain relief with Tamoxifen is 2.11, tamoxifen should be the drug of first choice. The low dosage regimen of 10 mg daily for 3 months is shown to be as effective as a higher dose 20 mg, hence it should be tried first for 3 months as the initial drug treatment of mastalgia. A search for newer agent specially SERMs was envisaged (16).

#### **8. Randomised Control Trial with Ormeloxifene (17)—a SERM:**

Double blind randomized placebo controlled clinical trial of oral centchroman 30 mg (ormeloxifene); a SERM or placebo twice a week for 3 months in women (20-50 yrs) with pronounced breast pain with or without lumpiness were recruited after excluding discrete benign lump or cancer. Serial assessments of pain on a visual analogue scale and nodularity grade on a 5-point ordinal Lucknow-Cardiff scale were done. A total of 151 patients were randomly allocated to two interventions using blocks of size four. Participants and physicians were blinded to randomization. Of the 151 patients, 121 (active=57, placebo=64) were available for efficacy analysis. The mean pain level showed a systematic downward trend over five visits ( $F=105.23$ ,  $p<0.0001$ ), that significantly reduced in active group compared to placebo ( $F=18.66$ ,  $p<0.0001$ ). The patterns of variation in pain over time for the individual groups

differ from the overall mean pattern for two groups and thus from one another ( $F=44.43$ ,  $p<0.0001$ ). Cumulative frequencies of breast nodularity grades during the successive visits showed significant improvement ( $p=0.001$ ) compared to placebo at the end of third month. The effect of active drug persisted till the completion (6 months) of the treatment ( $p < 0.001$ ). At the last visit, 91.2% subjects in active group had grade 2 or lower nodularity as compared to 65.7% in the placebo. Oligomenorrhea alone was reported in 12 subjects. Centchroman showed significant efficacy for treating breast pain and nodularity.

### **Conclusion :**

Painful nodularity of female breasts is a common clinical presentation both in general and specialised practices. ANDI is now a distinctive clinical syndrome without any histopathological basis. Pronounced mastalgia causes morbidity and requires treatment. It is not a symptom of neurotic women. Reassurance against absence of cancer is the main stay of treatment. Increased cancer risk is unassociated in the absence dysplasia. It has two distinctive patterns of cyclical pronounced (CPM) and non-cyclical mastalgia (NCM). CPM is common during child bearing age. It is amenable to hormonal treatment and has an hormonal aetiopathogenesis. There are no overt changes in the circulating levels of hormones, however. A subtle hormonal abnormality both in the circulating levels and target tissue is possible.

A thorough history and physical examination of breast, ultrasound in younger subjects and x-ray mammography in women above 35 years should suffice the clinical work up in a usual case. It is further added by using a breast pain chart to document the intensity and the pattern of pain, its temporal relationship with menstrual cycle. Lucknow Cardiff breast nodularity scale developed above is a reliable scale on 5 points of 0 to 4 grades. Grade 3 to grade 4 nodularity is seen in the Indian community in about 10% normal subjects. Unnecessary biopsies must be avoided. Objective assessment of pain and nodularity will allow the clinicians to measure the response to treatment.

In summary, the hypothesis of neuroticism and water retention has not found support from experimental data. Extensive hormonal studies both as basal, month long salivary hormones and dynamic hypo-thalamic pituitary axis tests in CPM and NCM revealed normal basal levels of oestrogens, progesterons, thyroid hormones and prolactin. Pulsatile secretion of prolactin and / or gonadotropins are abnormal in painful nodular breast that provided a basis for hormonal treatment (7-17). Levels of oestrogen, the administration of which is known to cause symptoms of painful nodularity, does not seem to be abnormal in CPM patients. Progesterone deficiency due to inadequate corpus luteum function is unlikely to be present. Defect in the tissue response or an end-organ abnormality is so far partially studied and needs further elucidation (15-16).

A third of mastalgia patients solicited treatment. Hormonal manipulation was done by danazol, tamoxifen, bromocriptine, progesterone, oral contraceptive pill, LHRH analogue (17). Non hormonal agents include analgesics, plant extracts like fructus-agni-casti, evening primrose oil and GLA. Randomized controlled trial of centchroman (ormeloxifene-SERM) 30/mg/weekX2 for 3 months resulted in abrogation of nodularity (93%) and highly significant of amelioration of pain. A highly effective with least side effects agent – ormeloxifene is now in regular use in several clinics in the country (18).

Of the prevalent treatments used for this condition; breast supporting garments, NSAIDs, Vitamins B6 and E, methyl-xantine (coffee) withdrawal, gamma linolic acid (GLA), progestogens have not found to be effective or better than placebo in randomized trials. Hormonal manipulations with dopamine agnostic agent that suppresses prolactin responses like bromocriptine are effective but have side effects and expensive. Similarly, treatment with danazol – a testosterone derivative causes hirsutism, muscular pain and loss of breast durity. Treatment with GnRH, tamoxifen and ormeloxifene (centchroman) are effective. GnRH is expensive and difficult to administer, tamoxifen is more commonly used in cancer therefore ormeloxifene now marketed in India for benign breast disorder with its least side effects is the treatment of choice.

## REFERENCES:

1. Foote FW, Stewart FW (1945). Comparative studies of cancerous versus non-cancerous breasts. *Ann Surg* **6**: 121.
2. Love SM, Gelman RS, Silen W (1982). Fibrocystic disease of the breast – A non-disease. *New Eng J Med* **307**: 1010-1014.
3. Hughes LE (1989). Benign Breast Disorders – Introduction. Fibrocystic Disease ? Nondisease ? or ANDI ? *World JSurg* **13** : 667-668.
4. Wisbey JR, Kumar S, Mansel RE, Preece PE, Pye JK, Hughes LE (1983). Natural history of breast pain. *Lancet* **ii**: 672-674.
5. Shukla HS, Kumar S (1989). Benign Breast Disorders in Nonwestern Populations: Part II Benign Breast Disorders in India. *World JSurg* **13**: 747.
6. Kumar S, Rai R, Das V, Dwivedi V, Kumar S, Agrawal GG (2010). Visual analogue scale for assessing breast nodularity in non discrete lumpy breasts: The Lucknow Cardiff breast nodularity scale. *The Breast* **19** : 238–242.
7. Mansel RE, Preece PE, Hughes LE (1978). A double blind trial of the prolactin inhibitor bromocriptine in painful benign breast disease. *Br JSurg* **65**: 724.

8. Kumar S, Mansel RE, Jasani B (1987). Presence and possible significance of immunohistochemically demonstrable prolactin in breast apocrine metaplasia. *Br J Cancer* **55**: 307-309.
9. Kumar S, Mansel RE, Hughes LE, et al. (1984). Prolactin response to Thyrotropin - Releasing Hormone stimulation and dopaminergic inhibition in benign breast disease. *Cancer* **53**: 1311-1315.
10. Kumar S, Mansel RE, Hughes LE (1983). Secretory response of prolactin and TSH in benign breast disease before and after TRH stimulation. *Br J Surg (abstract)* **70**: 293.
11. Kumar S, Mansel RE, Scanlon MF, et al. (1984). Altered responses of prolactin, luteinizing hormone and follicle stimulating hormone secretion to thyrotropin releasing hormone / gonadotrophin releasing hormone stimulation in cyclical mastalgia. *Br JSurg* **71**: 870-873.
12. Kumar S, Mansel RE, Read GF, Truran PL, Wilson DW, Hughes LE (1986). Daily salivary progesterone levels in cyclical mastalgia patients and their controls. *Br JSurg* **73**: 260-263.
13. Kumar S, Mansel RE, Hughes LE, Edwards CA, Scanlon MF (1985). Prediction of response to endocrine therapy in pronounced cyclical mastalgia using dynamic tests of Prolactin release. *Clin Endocrinol (Oxford)* **23**: 699-704.
14. Agarwal PK, Tandon S, Agarwal AK, Kumar S (1989). Highly specific sites of Prolactin binding in benign and malignant breast tissue. *Ind J Exp Biol* **27**: 1035-1038.
15. Rai R, Shrivastava A, Godbole MM, et al. (2011). Human Sodium Iodide Symporter (hNIS) in Fibroadenoma Breast-an Immunohistochemical Study. *Ind J of Exp Biol* **49(2)**: 113-117.
16. Kataria K, Dhar A, Srivastava A, Kumar S, Goyal A (2013). A Systematic Review of Current Understanding and Management of Mastalgia. *Indian J Surg* **75**: 1-6.
17. Kumar S, Rai R, Agarwal GG, Dwivedi V, Kumar S, Das V (2013). A Randomised Double Blind Placebo Controlled Clinical Trial of Centchroman (Ormeloxifene) in Breast Pain and Nodularity (Benign Breast Disorder). *Nat Med J India* **26**: 69-74.